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Cardiovascular changes in diving: from human response to cell function

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Kardiovaskulære endringer under dykking: Fra menneskelig respons til cellulær funksjon.

Menneskekroppen er evolusjonsmessig tilpasset et liv på land, men etter at dykking med komprimert luft ble allment tilgjengelig så har mennesket kunnet utforske verdenshavene på en helt ny måte. Imidlertid må kroppen raskt tilpasse seg et økende trykk under nedstigning og for at lungene ikke skal kollapse må luft alltid tilføres under høyt trykk. Avhengig av dybde og tid vil kroppen ta opp en viss mengde gass og ved retur til overflaten kan overmetning av gass føre til dannelse av gassbobler og mulig trykkfallsyke. Samtidig vil det kardiovaskulære systemet bli utsatt for betydelige påkjenninger under de ulike fasene av et dykk, og hovedmålet med dette arbeidet har vært å evaluere om kunnskap fra dyrestudier kan bidra til økt forståelse av de fysiologiske endringer man finner hos mennesket og dermed minimalisere risikoen for skader forbundet med dykking.

Denne avhandlingen er basert på tre studier hvor den første studien evaluerte hvilke effekter dyp luftdykking hadde på lunge og hjertefunksjon og varigheten av disse symptomene. Ved bruk av ultralyd ble det stadfestet at symptomer på interstitiell lunge ødem (ultralyd lungekometer (ULC)) forsvant etter 2-3 timer etter påfølgende dykk, og symptomer på nedsatt hjertefunksjon ble dokumentert etter hvert dykk. I dag blir slike målinger på menneske kun utført i forkant av- og etter dykking da det ikke finnes utstyr for å gjøre målinger under selve dykket. For å få økt forståelse av hvordan det kardiovaskulære systemet blir påvirket av dykking ved ulike tidspunkt og dermed en bedre forståelse av de endingene som er observert hos mennesket etter dykk, ble det andre studiet initiert. Her ble kardiovaskulære endringer hos anesteserte rotter kontinuerlig evaluert med et trykk volum kateter (PV-loop) i venstre ventrikkel og femoral arterien. Rottene ble utsatt for et simulert dykk i trykk-kammer og resultatene viste at de mest framtredende endringer fant sted under kompresjonsfasen og gradvis returnerte til utgangsverdier under dekompresjon og etter dykk. I tillegg undersøkte vi om en moderat nedkjøling under dekompresjonsfasen og oppvarming igjen etter dykk ville endre utfallet av dykket. Vi fant ingen økt risiko for trykkfallsyke, men observerte en overrakende nedgang i slagvolum og minuttvolum etter re-varming. I den tredje studien undersøkte vi om immersjon (nedsenking i vann) i kombinasjon med et simulert dykk kunne gi cellulære endringer i hjertet og dermed økt risiko for trykkfallsyke sammenliknet med hyperbart dykk uten immersjon (tørt dykk). Effekten av immersjon på det kardiovaskulære system ble funnet å vedvare over tid. De dyr som hadde oppholt seg i vann før det simulerte dykket fikk nedsatt hjertecelletfunksjon samt økt boblegrad sammenliknet med de dyr som ikke hadde vært nedsenket i vann. Hvorfor dykk i vann resulterer i økt risiko for trykkfallsyke enn dykk i tørre omgivelser er uklart, men det viser at man ikke bør direkte overføre prosedyrer fra tørre dykk til dykk i vann.

Kandidat: **Svein Erik Gaustad**
Institutt: **Institutt for sirkulasjon og bildediagnostikk**
Veiledere: **Professor Alf O. Brubakk og professor Ulrik Wisløff**
Finansieringskilder: **Norwegian Petroleum Directorate, Norsk Hydro, Esso Norge and Statoil from the start, and later by Gassco, ExxonMobil and Statoil through the Frame contract for Diving, Pipeline repair, Contingency and Modification Services.**

Overnevnte avhandling er funnet verdig til å forsvares offentlig for graden Philosophiae Doctor i Molekylærmedisin.
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Contents

Acknowledgments

The studies presented in this thesis were carried out during the years 2006-2010 at the following three institutions: 1) Faculty of Medicine, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, 2) Department of Physiology, University of Split School of Medicine, Croatia and 3) Department of Medical Physiology, Institute Medical Biology, University of Tromsø, Norway. The work has been financially supported by Norwegian Petroleum Directorate, Norsk Hydro, Esso Norge and Statoil from the start, and later by Gassco, ExxonMobil and Statoil through the Frame contract for Diving, Pipeline repair, Contingency and Modification Services.

First of all, I want to thank my supervisor Alf Ottar Brubakk. His enormous enthusiasm, motivation and great knowledge has been of invaluable importance for this work. Under his supervision I have always been allowed to pursue my ideas, get in contact with his vast international network and gain a comprehensive understanding of dive physiology.

I also want to thank my co-supervisor, Ulrik Wisløff. He has contributed significantly to this work and his always good mood and motivating comments have been highly appreciated. He has also become a good friend and we have had a lot of fun on our diving trips.

As the first and only PhD student in this international PhD program I was enrolled in spring 2006. After 3 months at NTNU I went to the Medical College of Wisconsin (MCW), where I attended graduate school for 1 year. MCW's physiology department is ranked as nr 1 in the US, and with only 8 selected students from all over the world in my class, I experienced a comprehensive and professional curriculum at the highest scientific level. I am thankful to Allen Cowley and Hubert Forster who accepted me into the MCW program and especially to Julian Lombard who kindly enrolled me in his research group. Highly appreciated is also all the hours in the laboratory with Lynn Dondlinger and thanks to Zeljko Bosnjak for taking care of the administrative challenges. I also want to thank all my class mates, the rest of the Lombard lab and off course Domagoj Mladinov for a nice time at MCW. But most importantly, I want to thank Jasna Marinovic Ljubkovic and Marko Ljubkovic. Your support and extreme patience having me around your house 24-7 is admirable and I truly appreciate our close friendship.

My second stay in the US was at the Mayo Clinic College of Medicine, Rochester, Minnesota. I am grateful to Gary Sieck for incorporating me into his research group. At Mayo I also met Torkjel Tveita, and our mutual interest for science resulted in a 4 months stay in Tromsø where study II was carried out with a lot of help from Timofei Kondratiev. I also want to thank Zeljko Dujic at Split School of Medicine for introducing me to human dive trials and Daniele Catalucci at the Istituto Tecnologie Biomediche for performing Western blots.

Finally I want to thank all the fantastic colleagues and friends here at the Department of Circulation and Medical Imaging. Additionally, I want to thank my best friends, Arve Jørgensen and Kai Arne Smeby-Lerstad and of course my always supporting family.

Svein Erik Gaustad, Trondheim, December 2010.

List of papers

The studies presented in this thesis were carried out during the years 2006-2010 at the following three institutions: 1) Faculty of Medicine, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, 2) Department of Physiology, University of Split School of Medicine, Croatia and 3) Department of Medical Physiology, Institute Medical Biology, University of Tromsø, Norway. The included papers listed below will be referred to by their roman numerals in this thesis.

Paper I.

Ultrasonic evidence of acute interstitial lung edema after SCUBA diving is resolved within 2-3 hours. *Marko Ljubkovic, Svein Erik Gaustad, Jasna Marinovic, Ante Obad, Vladimir Ivancev, Nada Bilopavlovic, Toni Breskovic, Ulrik Wisloff, Alf O. Brubakk, Zeljko Dujic.* Respiratory Physiology & Neurobiology. 2010 Apr; 171(2):165-170**.**

Paper II.

Dynamic changes in cardiovascular function during diving and decompression at different core temperatures. *Svein Erik Gaustad, Timofei Kondratiev, Andreas Møllerløkken, Ulrik Wisløff, Alf O. Brubakk and Torkjel Tveita.* In manuscript.

Paper III.

Immersion before dry simulated dive reduces cardiomyocyte function and increases mortality after decompression. *Svein Erik Gaustad, Alf O. Brubakk, Morten Høydal, Daniele Catalucci, Gianluigi Condorelli, Zeljko Dujic, Jasna Marinovic, Marko Ljubkovic, Andreas Møllerløkken and Ulrik Wisløff .* Journal of Applied Physiology. 2010 Sept; 109 (3): 752-757.

Abbreviations

APE	Acute pulmonary edema
ATA	Atmosphere absolute
Ca^{2+}	Calcium
$[Ca]^{2+}$	Intracellular calcium concentration
CO	Cardiac output
DCS	Decompression sickness
DLCO	Diffusion lung capacity of carbon monoxide
He	Helium gas
HR	Heart rate
kPa	Kilopascal
LV	Left ventricle
LV dP/dtmax	Maximal velocity of LVP rise
LV-EDV	Left ventricular end-diastolic volume
LV-EDP	Left ventricular end-diastolic pressure
LV-ESP	Left ventricular end-systolic pressure
LV-ESV	Left ventricular end-systolic volume
LVP	Left ventricular pressure
MAP	Mean arterial pressure
MSW	Meter of seawater
N_2	Nitrogen gas
NCX	Na^+/Ca^{2+} exchanger
NT-proBNP	N-terminal prohormone brain natriuretic peptide
O_2	Oxygen gas
PA	Pulmonary artery
PLN	Phospholamban
PLN 16P	Serine-16 site of Phospholamban
PLN 17P	Threonine-17 site of Phospholamban
PO_2	Partial pressure of oxygen
proANP	Pro-atrial natriuretic peptide
RV	Right ventricle
SCUBA	Self contained underwater breathing apparatus
SERCA2a	Sarcoplasmatic reticulum calcium ATPase, isoform 2a

SR	Sarcoplasmatic reticulum
SV	Stroke volume
SVR	Systemic vascular resistance
TRP	Total peripheral resistance
TTP_{50}	Time to peak 50% shortening
ULC	Ultrasonic lung comets
VGB	Venous gas bubble

Definitions

Afterload: The load the ventricle has to overcome during contraction.

Calcium handling: The ability of the cardiomyocyte to regulate intracellular calcium levels during contraction and relaxation.

Cardiomyocyte shortening: The shortening of a cardiomyocyte from end-diastole to end-systole, divided by end-diastolic length.

Immersion: The organism is submersed in water.

Inert gas: Biochemically inactive gas that is not involved in metabolic processes. In diving inert gas is usually N_2/H_2 and is the main contributor to decompression bubbles.

Mean arterial pressure: Diastolic pressure + 1/3 of pulse pressure.

Nitrox: Gas mixture (N_2/O_2) with oxygen levels higher than air.

Preload: The load present before ventricular contraction has started, at the end of diastole. It reflects the venous filling pressure that fills the left atrium, which in turn fills the left ventricle during diastole.

Pulse pressure: Systolic pressure – diastolic pressure.

Total peripheral resistance: Mean arterial pressure/Cardiac output.

Trimix: Gas mixture ($He/N_2/O_2$) used for diving.

Ultrasonic lung comet (ULC) detection: Ultrasonic lung imaging to estimate the severity of extravascular lung water by counting the number of ULCs.

Background

Although not adapted to the underwater environment, man has always had the urge to explore the possibilities and mysteries of the deep. Compared to other mammals that are able to perform breath-hold dives up to 1500 meter of seawater (msw) [1], humans have considerable limitations. Due to the invention of self contained breathing apparatus (SCUBA), new possibilities emerged and today diving is a popular world wide activity both at the recreational and professional level. However, diving demands rapid physiological adaptations and in order to prevent the lungs from collapsing at increased ambient pressure, air must be supplied under high pressure. The amount of gas taken up in a diver's body increases with depth and time, and unlike oxygen (O_2) and carbon-dioxide (CO_2) which are metabolized, inert gases are biologically inactive and are absorbed in tissues. Various depths require different breathing gas compositions and at greater depths the inert nitrogen (N_2) gas is often substituted with the inert helium gas (He) due to its advantages over nitrogen [2]. Nevertheless, diving can be harmful and the major risk relates to formation of gas bubbles upon return to the surface [3]. Along with environmental factors such as immersion and temperature, these bubbles can induce long term depressive alteration of the cardiovascular system in humans, lasting up to several days [4]. The mechanisms behind these observations are unclear and in addition it is still an enigma why there is a large individual variation in susceptibility for bubble formation. To gain a more comprehensive understanding of the clinical signs observed after diving, translational research is needed. Combining cellular and molecular data from animal studies with human data is crucial for improved safety and treatment strategies after a dive.

Vascular gas bubbles and pathophysiological effects

Vascular gas bubbles are observed after nearly all decompressions [5] and these bubbles are considered to be the initiators of the pathophysiological cascade leading to decompression sickness (DCS). Haldane proposed that DCS would be avoided if bubbles were not present and that bubbles would not occur after decompression if supersaturation did not exceed a critical value [6]. Supersaturation occurs when ambient pressure is reduced at a faster rate than gas can be elimination from the tissues. The mechanisms for bubble production are still not completely understood but today it is generally held that bubbles do not directly form *de novo* from supersaturation but from pre-existing gas nuclei [7]. Although no direct

observations exist, it has been hypothesized that these nuclei attach and grow on the endothelial lining of the vessel wall [3] and that the number and size is affected by the surface tension in the blood [3].

Intravascular gas bubbles are more likely to form on the venous side of the circulation due to lower gas tension and blood pressure on the arterial side [8]. In most cases these bubbles do not lead to any clinical signs of DCS and are thus named "*silent bubbles*" [9]. However, DCS risk appears to be higher in the presence of bubbles [10] and assessment of bubbles by ultrasound imaging is widely used to quantify decompression stress. The lung has a good filter capability for gas bubbles but bubbles may gain access to the arterial circulation due to gas overload in the lung [11] or patent foramen ovale (PFO). PFO is present in approximately 30% of adult humans and its occurrence is shown to be related to neurological DCS [12].

The innermost layer of the vessel wall, the endothelium, is a crucial modulator of the vascular tone. Various physiological stimuli triggers its release of multiple vasoactive substances, including nitric oxide (NO), which influences upon e.g blood flow, blood coagulation and angiogenesis [13]. This fragile layer seems to play an important role for gas bubble production but it can also be damaged or get reduced function in response to gas bubbles in a dose dependent manner [14, 15]. This will active inflammatory responses such as leucocytes and platelets [16, 17], cogulation system [18] and the complement cascade [19]. Also, oxidative stress in the vessel wall is associated with the generation of reactive oxygen and nitrogen species (ROS/NOS), causing vasoconstriction and impaired NO-dependent vasodilatation [20, 21]. All these above mentioned factors will reduce the bioavailability of NO and may stimulate bubble growth due to incased adhesiveness of the endothelial surface [3]. Subsequently, these changes will pose significant challenges and alterations on the heart -and lung function, which will be outlined in the next sections.

Cardiovascular function

The heart is a muscular pump organized in four pumping chambers and the cardiac cycle constitutes of two major phases: the systolic contraction -and the diastolic relaxation phase. Systole is initiated when an action potential (AP) spreads along the bundle of His, the Purkinje fibers and transverse (T)-tubules. The complex T-tubules network ensures that the AP is propagated to the interior of the cardiomyocytes for synchronized Ca^{2+} release and

contraction [22, 23], which is crucial to overcome the hydraulic load imposed on the ventricle during ejection (afterload). When the contraction is ended, the cardiomyoctes start to relax and enters the diastolic phase where the myocardial wall is stretched in response to the hemodynamic load from the venous return (preload). Thus, the amount of blood that is ejected is dependent by afterload, preload and the inotropic state of the myocardium [24-26]. Since the human heart is adapted to a normobaric atmospheric pressure at 1 ATA, significant cardiovascular changes will occur during diving to ensure proper circulatory function.

Cardiovascular changes during diving

A diver faces several challenges such as increased ambient pressure and breathing gas density, enhanced partial pressures of gases, immersion, exercise, psychological stress, and thermal conditions [2, 27-30]. This elicits several cardiovascular changes such as bradycardia, changes in stroke volume (SV), reduction in cardiac output (CO) and increased vascular resistance [4, 31-35]. Bradycardia is triggered by the "diving response" through parasympathetic nerve activation [36, 37] but may also be attenuated by sympathetic nerve activation due to psychological stress [38]. While descending during a dive, increased PO_2 in the inspired breathing gas significantly decreases heart rate [34] and induces vasoconstriction and hence increased systemic vascular resistance (SVR) [39]. The mechanisms for hyperoxia induced vasoconstriction are unclear but there are indications that the nitric oxide (NO) pathway is altered [40].

Today no equipment exists to measure hemodynamic changes and ejection properties of the heart during SCUBA, thus measurements are performed after the dives or in hyberbaric chambers. After open sea dives, studies show a decreased SV and CO in the presence of increased systemic vascular resistance [4, 31, 41]. Systolic performance is not impeded only by an increased afterload but also due to altered diastolic function seen as a reduction in preload up to 2 hours after a dive [42]. One must emphasize that these measurements are performed after a dive and are a result of significant hemodynamic changes that have occurred during a dive. Although no hemodynamic data during SCUBA exist, increased central blood volume due to cold water immersion [43] is accompanied with diuresis [44, 45] and hence reduced preload after a dive. Hemodynamic changes can be seen up to 48 hours after a dive [4] and open sea dives are likely to increase DCS risk compared to dry dives [46]. This indicates that results obtained in hyperbaric chambers differ from in water dives and

more focus should be addressed to hemodynamic changes induced by immersion, exercise and temperature.

Assessments of cardiac function in *in-vivo* animal studies show an increased cardiac contractility and left ventricular pressure under hyperbaric exposures [47-49]. This is in accordance with increased myocardial blood flow, indicating enhanced cardiac oxygen consumption (work rate) under hyperbaric pressure [49-51]. Additionally, repeated dives seem to induce cardiac hypertrophy since increased ventricular mass has been observed [52]. This is likely to suppress systolic function, as observed in the diseased heart [26] compared to an athlete's heart [53], since a decreased CO is observed at high pressure [54] together with an altered excitation-contraction coupling [55]. Effects on the vasculature show varying results, where some authors do not see changes in mean arterial pressure (MAP) [48, 49] whereas others observe increased MAP under exposure to increased environmental pressure [56]. Cardiovascular changes are reported to sustain after decompression since CO, SV and right ventricular wall thickening decreased along with increased SVR [56]. However, it is also reported that cardiovascular changes are restored only a few minutes after decompression [48]. In order to interpret the significance of these cardiovascular changes, translation research is needed. Since cardiac contractile dysfunction is heavily dependent on intracellular Ca^{2+} handling and excitation contraction coupling, the next section will explain the mechanisms of cardiomyocyte function during systole and diastole.

Excitations contraction coupling and intracellular Ca^{2+} handling

Basic mechanisms

The working heart is dependent on the ability of the cardiomyocytes to contract and relax. Contraction of the cardiomyocytes is initially activated when an action potential (AP) depolarizes the sarcolemma membrane and activates the process named "Ca^{2+}-induced Ca^{2+} release" (CICR). Ca^{2+} enters through voltage gated L- type Ca^{2+} channels and results in a locally increase of $[Ca^{2+}]_i$ that subsequently activates the ryanodine receptors (RYR) located on the sarcoplasmatic reticulum (SR) membrane [57]. RYR are in close physical proximity to the L-type Ca^{2+} channels and it appears that each L-type Ca^{2+} channel controls only one RYR receptor [58]. A summation of individual CIRC events leads to a significant increase of

$[Ca^{2+}]_i$ which in turn binds to Tropnin C on the thin filaments of the sarcomeres. This initiates the adenosine triphosphate (ATP) dependent cross-bridge cycling in the myofilaments and contraction occurs (inotropic phase) (Figure 1). After the contraction has subsided, the cardiac muscle enters the relaxation phase (lusitropic phase). During relaxation Ca^{2+} is sequestered within the cytostol or extruded over the sarcolemmal membrane and out of the cell. The main component of Ca^{2+} removal is the sarcoplasmatic reticulum Ca^{2+} - ATP-ase (SERCA2a), accounting for a removal of 70% in humans and 92% in rats into the SR [59]. SERCA2a is regulated by phospholamban (PLN); unphosphorylated PLN binds to SERCA2a and inhibits its activity, whereas phosphorylation removes PLN from SERCA2a and increases Ca^{2+} uptake rate. Mainly, PLN is phosphorylated by cAMP-dependent protein kinase A (PKA) at serine (Ser)-16 and by Ca^{2+}/calmodulin-dependent kinase II (CaMKII) at threonine (Thr)-17 [60]. The remaining $Ca2^{+}$ is mainly removed out of the cell by the Na^{+}/Ca^{2+} exchanger (NCX) [59], and sarcolemmal Ca^{2+}-ATP-ase channel (PMCA), or pumped into the mitochondrial compartment.

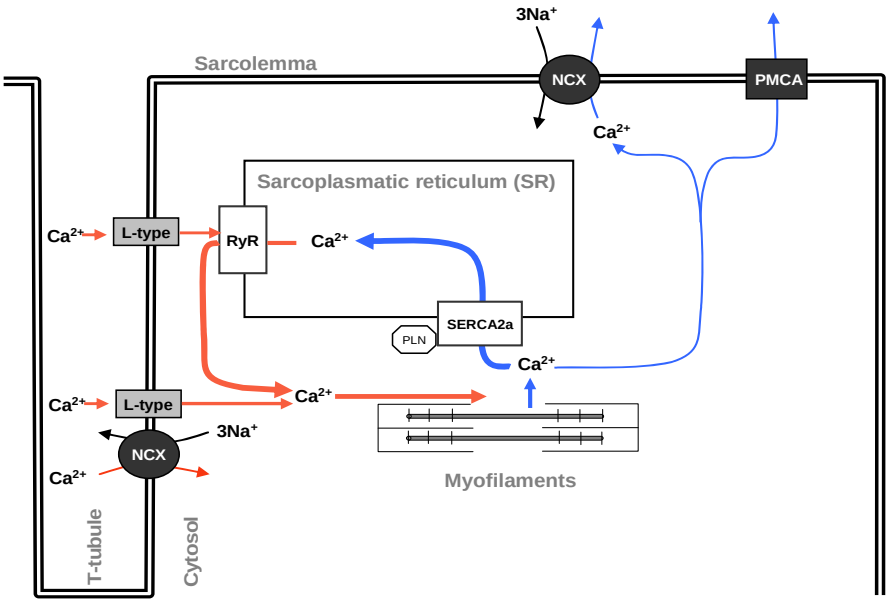

Figure 1. Depiction of Ca^{2+} fluxes in the cardiomyocyte. This simplified version explains the parameters measured in paper III. Red lines show Ca^{2+} fluxes towards myofilaments during contraction in systole after depolarization of the sarcolemma, while blue lines show Ca^{2+} fluxes into sarcoplasmatic reticulum (SR) and over sarcolemma during relaxation in diastole. The following pumps, channels and proteins are involved in the Ca^{2+} fluxes: L-type; Voltage gated Ca^{2+} channel, NCX; Na^{+}/Ca^{2+} exchanger, PMCA; Sarcolemmal Ca^{2+} - ATP-ase, RyR; Ryanodine receptor, SERCA2a; Sarcoplasmatic reticulum Ca^{2+} - ATP-ase, PLN; Phospholamban. This figure is modified from [61].

Cellular changes during diving

There are many elements within the cell that may be altered in response to changes in ambient pressure and hence may explain altered myocardial cell function. This includes structural changes of the phospholipid bilayer in the cell membrane [62, 63], ion channels and ion transporters and pumps [64-66] and membrane bound enzymes [67]. However, most studies have been performed at very high ambient pressures (> 100 ATA) *in vitro* to solely examine the effect of pressure, and significant research remains before a comprehensive understanding of ambient pressure effects on cellular and molecular changes during diving can be declared.

High pressure seems to have both positive and negative inotropic effect on the cardiac muscle [64], but there is limited information how diving affects Ca^{2+} signaling and excitation contraction coupling. The contraction force seems to be transiently increased in response to increased pressure [68, 69] but restored to baseline values after decompression [69]. Previously it has been suggested that these dive induced effects may be due to altered Ca^{2+} sensitivity, SERCA2a and NCX activity [64, 66]. The positive inotropic effect may be explained by the increased duration of action potential observed in cardiac tissue under hyperbaric conditions [70], since a prolongation of the action potential may enforce a greater release of Ca^{2+} from the SR. Additionally, recordings of Purkinje fibers to 150 ATA showed reduction in spontaneous beating frequency due to slowed diastolic depolarization [71]. To my best knowledge, there exist no studies that have studied the cellular and molecular mechanisms behind these observations.

Cardiopulmonary function

The entire CO from the right ventricle is carried in the pulmonary artery (PA) for gas exchange in the lungs. The pulmonary artery pressure (PAP) is significantly lower than the systemic artery pressure, which is reflected in the size and wall thickness of the right ventricle. In the lungs, the PA divides into numerous tiny arterioles that track along the alveoli, the smallest air filled components of the lung where gas exchange occurs. An efficient gas exchange is ensured due the high number and vast surface area of the alveoli (approximately 300 million and 75m^2, respectively), the vast alveolar capillary bed meshwork and the short distance between the alveoli and the capillaries [72]. The re-oxygenated blood is eventually collected in the pulmonary vein (PV) and directed to the left heart. Insufficient lung function and gas exchange may occur due to various lung diseases that will not be

described here, but emphasis will be addressed physiological and pathophysiological events in response to the hyperbaric and diving environment.

Pulmonary changes during diving

During diving, proper ventilation of the lung is dependent of the ability to overcome the increased airway resistance and elastic loads [73]. The increased inspired gas density during decent is the primary factor for enhanced airway resistance and is reported to affect lung function by reducing forced expiratory volume, maximum expiatory flow and maximum voluntary ventilation [74, 75]. Additionally, increased ventilatory work may also be a result of the resistance of the breathing apparatus. During immersion, the elastic load (compliance) of the lung is heavily influenced by static lung loading (SLL), which is comprehensively outlined by Lundgren [76]. Both blood redistribution from immersion and body position (increased distance between the regulator and the chest in upright position will cause negative SLL, whereas the opposite occurs in head down position) will affect ventilatory work. Positive SLL have been reported to increase vital capacity and expiratory respiratory volume (ERV) whereas negative SLL seems to decrease ERV and increase dyspnea [77]. Thus, to minimize the work constrains of the lung and ensure proper ventilation, breathing gas is supplied at high pressure. However, although the breathing gas in most dives are hyperoxic, the most common respiratory abnormalities in diving is insufficient ventilation of the alveoli with a resulting hypercapnia [78]. This is due to either hypoventilation or/and elevated dead space and can be further reviewed in [73, 78].

To ensure efficient gas exchange, the blood-gas barrier (BGB) has to be very thin but also strong enough to cope with high capillary pressure. These conflicting requirements may be problematic during diving since previously clinical symptomatic and asymptomatic occurrence of acute pulmonary edema (APE), such as cough, dyspnea, hemoptysis, hypoxemia and reduced lung diffusing capacity for carbon monoxide (DLCO), have been reported after swimming and SCUBA [79-82]. APE occurs as a result of increased pulmonary capillary permeability (non-cardiogenic pulmonary edema) or when the pulmonary capillary hydrostatic pressure exceeds the plasma oncotic pressure (cardiogenic pulmonary edema) [83]. This will subsequently lead to extravasation of fluid, cells and proteins into the interstitium. The exact mechanism for APE during diving is unclear, but factors such as increased central blood flow during immersion, cold exposure, increased PAP, increased wall

stress and venous gas bubbles are likely to be involved [84-86]. Although symptoms of APE have been reported after diving, the symptoms are in the majority of cases spontaneously resolved within 5 minutes to 24 hours after a dive or with β_2-adrenergic agonist or diuretic therapy, but can also be fatal [73, 83]. Additionally, the prevalence for APE is rather rare, which was confirmed in a Swiss survey conducted on 1250 SCUBA divers, where only 5 individuals out of 460 responders had a history suggestive of APE 1.1% [87]. However, although the susceptibility for APE is relatively low, one should have in mind that the number of potential individuals that could be at risk of developing APE is substantial since there are millions of recreational and professional divers worldwide.

Environmental challenges during diving

Immersion

Although the atmospheric pressure is the same whether a dive is performed in a hyperbaric chamber or immersed in water, immersion causes significant hemodynamic changes due to the "anti-gravity" effect on the body [78]. The anti-gravity effect can also be observed on land where a supine position will reduce the gravity dependent pooling of blood in the legs that occurs in a vertical position (Figure 2). However, during immersion an increasing pressure from the water column in an upright posture will diminish the hydrostatic pressure in the veins of the lower part of the body. When the water level reaches the diaphragm (xiphoid) and the hydrostatic indifference point [88], there is a counterbalance between the hydrostatic pressure of the water and the veins of the abdomen and the lower parts of the extremities, offsetting pooling of blood in the dependent regions [89]. At this point, blood volume in the heart is almost identical as supine position on land, whereas increased water level to the neck increases the blood flow into the heart and thorax that leads to increased central venous pressure, increased diastolic filling, stroke volume and further distention of the heart [89-92]. The increased filling of the cardiac chambers activates cardiac mechanoreceptors which induces reflex adjustments of renal water and electrolyte excretion [93] but it seems that plasma volume, SV and CO remain elevated throughout 6 to 12 hours of immersion [43].

During diving the effect of immersion is prominent but will naturally differ dependent of the duration of the dive. However, another aspect that is of great importance is the effects on the

cardiovascular system after immersion. After immersion, hemodynamic effects such as reduced preload and CO, have been reported to be sustained for up to 16 hours after immersion [94], while several cardiac changes are not fully reversed up to 48 hours after SCUBA [95]. Until now there is sparse data that describe the long term cardiovascular effect of immersion and physiological performance in the recovery phase after immersion.

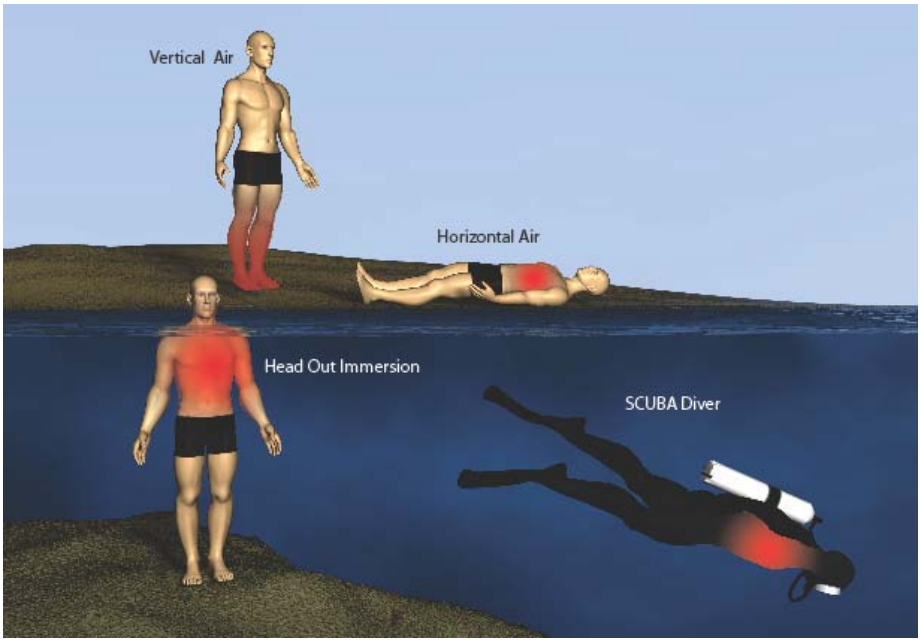

Figure 2. Depiction of blood distribution at different body positions in air and during water immersion. Upper left shows a person in vertical position on land where blood pressure is highest in the legs due to gravity. Upper right shows a person in a supine position on land where more blood is allocated to the heart/thorax. Bottom left shows a person vertically immersed to the neck where gravity is abolished and more blood is allocated to the heart/thorax. Bottom right shows a SCUBA diver with approximately the same blood distribution as vertical immersion. Made by MGS studios.

Temperature

Thermal problems, whether it is hyperthermia or hypothermia, and especially the latter, is a well known problem in diving. Hyperthermia is most likely to occur in waters above thermoneutral temperature (34-35 ºC) [93] or in hot water suits [96], but since most of the waters in the world are below human thermoneutral temperature, this section will focus on diving in cold environments. Due to the high thermal conductance and capacity of water [97], diving imposes great demands on the human thermoregulatory system. The metabolism increases in proportion with the reduction in skin and core temperature [98] as a result of the depth and duration of the dive and the status of thermal protection.

Diving in cold conditions is believed to increase the risk of DCS [99]. The mechanisms are still unclear but since gas uptake and removal are primary determent by perfusion [100], cold induced vasoconstriction through sympathetic nerve activation [45] is likely to have a significant effect on the outcome of a dive. There have been observed fewer incidences of paresthesia, pruritus and skin rash in areas of skin with added thermal protection [101] and according to U.S Navy dive procedures, longer decompressions are required when the divers are *exceptionally cold* during a dive [102]. Additionally, during diving it is beneficial to have an optimal thermal status at different phases of a dive and specifically it has been observed that cold conditions at the bottom time and warm conditions during decompression and post diving reduces DCS risk [103-105]. The opposite situation, which is the case in most dive scenarios, with warm conditions during bottom time and cold during decompression should result in increased perfusion and gas uptake at the bottom and less perfusion and prolonged duration for desaturation of nitrogen during decompression [30]. Technical approaches with heated undergarments could prevent the latter situation, but at this point this not widely used due to high costs and insufficient technical quality. Although there is some literature regarding diving and cold temperatures, there is no solid evidence providing a causal relationship between temperature and dive risk [29, 99]. Thus, to improve dive safety, comprehensive knowledge regarding cold water diving is needed and will be of increasing interest due to the rapid expanding activity in the northern areas.

Aims and hypotheses

The main purpose was to examine dive induced cardiopulmonary changes through a translational perspective in order to obtain a more comprehensive understanding of human adaptations and responses after dive under various environmental conditions. The specific aims were:

I. To determine the significance and duration of acute interstitial lung edema after SCUBA with the hypothesis that asymptomatic acute pulmonary edema will disappear within 2-3 hours after SCUBA in healthy individuals.

II. a). To continuously investigate cardiovascular changes at all time points during a dive with the hypothesis that cardiovascular changes observed after a dive is a result of hemodynamic changes occurring at all time points during a dive and not solely during the decompression phase.

b). To determine the effect of cold exposure during decompression and post dive on bubble grade and DCS risk with the hypothesis that cold decompression and post dive period will decrease off-gassing and hence increase bubble production and DCS.

III. To determine the effect immersion prior to a dive had on cardiomyocyte function and DCS risk with the hypothesis that immersion induces prolonged cardiovascular changes that will promote bubble production and DCS risk.

Methodological considerations

Animal protocols

In study II & III Sprague Dawley female rats were used. We chose this strain and gender since our research group has considerable experience in using these rats in hyperbaric experiments [106-109]. The experimental protocols were approved by the Norwegian Council for Animal Research, and all experimental procedures conformed with the European Convention for the Protection of Vertebrate Animals used for Experimental And Other Scientific Purposes.

Human trial

All experimental procedures were conducted in accordance with the Declaration of Helsinki, and were approved by the Ethics Committee of the University of Split School of Medicine. Each method and potential risks were explained to the participants in detail and they gave their written informed consent before the experiment. The participants were experienced divers of the Croatian Search and Rescue Unit (CRS). No subject developed decompression sickness (DCS), but in case of emergency the dive site was in close proximity to a recompression chamber.

Ethical considerations

The purpose of the animal experiments was to obtain improved knowledge of biological and medical issues related to human or animal health. In study II & III we used animals to obtain a more comprehensive understanding of cardiovascular events that have been reported after SCUBA diving. We always strive for alternative solutions that do not involve animals but when animal experiments are the only alternative we ensure proper animal welfare by focusing on the three R's - replacement, reduction and refinement [110].

The human trial in study I showed bubble grades up to grade IV, but there was a considerable difference in bubble production between the individuals. This raises an ethical dilemma, should we advise the "high bubblers" not to dive? Obviously today's decompression

procedures are not good enough, but the only way to improve dive safety is to increase our knowledge. This can be done by performing controlled human trials. Study I was done in collaboration with the Split Medical School in Croatia due to their vast experience on human dive trials [4, 41, 46, 95, 111]. Some people may disagree and claim that we should terminate this testing, but we mean on the contrary, it is unethical not to continue. Since the millions of divers use the guidelines made by researchers, we must validate and be certain that our recommendations are reliable.

Dry hyperbaric diving

The most used approach is to expose animals to diving conditions in simulated dry dives in a hyperbaric chamber. The chamber is easily pressurized and de-pressurized with air and hence tightly controlled dives can be performed. Although certain elements such as e.g. immersion, water current, exercise and temperature differ from open water dives, physiological and cellular adaptations to high atmospheric pressure can be elaborated. In the non-anesthetized rats in study III, we used a dive profile that has previously been widely used in our group [107, 108, 112]. This protocol is appropriate to study individual response to diving since female rats at 270-300 grams get both high bubble scores (grade 3-5) or low bubble scores (grade 0-2). A less stressful dive would not induce significant physiological responses and thus it would be impossible to target the mechanisms behind the vast interspecific discrepancy in bubble production and DCS risk. In study II however, rats were exposed to a less stressful dive since pilot studies and unpublished work (Jørgensen et. al) have shown that anesthetized animals are more prone to bubble production and DCS risk. To minimize possible anesthesia induced effects such as insufficient gas exchange, altered breathing pattern and thermal status, we performed several pilot studies to ensure that spontaneous breathing rats on an electric heat pad had normal blood gas values throughout the experiment. Since the purpose of this paper was to observe dynamic cardiovascular changes at different core temperatures during a dive, it was crucial that the rats survived the dive protocol. The decompression procedures and interventions are more thoroughly described in the papers.

Open seawater diving

Field studies require a great deal of logistics and planning. In the trimix field study we established a fully equipped field laboratory in proximity to the dive site. When entering the

laboratory, the divers had to follow a tightly controlled schedule which enabled rapid and time matched measurements. The participants had a professional attitude and considerable dive experience which is of importance when analyzing and evaluating individual human response to diving. Due to similar skill levels, factors such as buoyancy control and physiological stress were minimized. Decompression profiles were determined using V-planner software according to Varying Permeability Model (VPM-B) [113]. During the dive, breathing mixtures of O_2 (16-17%), He (44-46%) and N_2 (37-39%) (trimix) were used up to 21 m. At 21 m the divers changed from trimix to nitrox mix (50% N2/50% O_2) in order to keep the partial pressure of oxygen (PO_2) at 160 kPa [114]. Exceeding the recommended levels of [PO_2] can lead to several toxic effects that may lead to fatal events [40]. A group leader validated the gas mixtures in each diver and controlled the decent rate, duration of the dive and decompression rate. Each dive profile was downloaded from the computers and used to calculate the probability of DCS (P_{DCS}) as an index of severity of exposure [115].

Bubble detection and analysis

Compared to ultrasonic Doppler measurements which can be challenging in respect to proper monitoring and analysis [5], ultrasonic imaging is a well suited and cost-effective technique for detection of decompression bubbles even for personnel with limited previous experience [116]. The 2- dimensional (2D) ultrasonic scanning (B-mode imaging, brightness mode) is today the most widely used imaging technique for detection of intravascular gas bubbles [117]. In all studies, decompression bubbles from 2D ultrasonic images were graded from 0 to 5 according to the following criteria: 0 = no bubbles; 1 = an occasional bubble; 2 = at least one bubble every 4^{th} heart cycle; 3 = at least 1 bubble in each heart cycle; 4 = continuous bubbling, at least one bubble/cm^3 in all frames; 5 = individual bubbles are absent ("white-out) and are most often seen animals [5] and only once reported in humans [118].

Vascular bubbles observed after decompression are most likely formed on the venous side (VGB) of the circulation due to higher gas tension and lower blood pressure than the arterial side [3, 8]. VGB will pass the right ventricle (RV) and pulmonary artery (PA) for gas elimination in the lungs and therefore we imaged VGB as high intensity echoes in the RV and the PA [119]. To make sure that we measured the correct number of VGB, 2D scanning was performed for at least 30 seconds with a transducer at 10 MHz frequency in study II & III and

1.5-3 MHz frequency in study I. Previous experience has shown that these frequencies give the best penetration and resolution in the investigated structures.

The main challenge using 2D scanning is to obtain high quality images with accurate VGB scores [117]. The pulmonary circulation is a well suited detection area but there may be a chance that we underestimate that actual number of gas bubbles since some bubble may be trapped as stationary bubbles. Although Daniels *et al* [120] have developed a technique to measure stationary and moving bubbles with high resolution ultrasound imaging, the method is not developed further, and can therefore not obtain accurate and reliable measurements of stationary bubbles. Recently, a technique named Second-order UltRasound Field Imaging (SURF) [121] shows promising results in improving ultrasound imaging and may be well suited for future detection of stationary decompression bubbles.

Cardiomyocyte isolation and measurements

In cardiovascular research cardiomyocyte measurements are widely used to study cellular function of the left ventricle (LV). This is in contrast to dive related research where cellular data to support *in vivo* findings are limited. Cardiac changes from diving have been observed in man [4, 31, 42], and in order to understand the mechanism behind these observations we isolated cardiomyocytes from the LV. Immediately after the dive protocol was ended in study III, the hearts were quickly put into ice-cold Krebs buffer to prevent hypoxic events and connected to the aortic cannula of a standard Langendorff retrograde perfusion system as described in [122]. To ensure stable physiological conditions, the hearts were perfused with Krebs buffer and collagense at a rate of 7,5ml/min. After proper digestion of the myocardium, cardiomyocytes from the LV were isolated and deposited on coverslips for cell measurements. Contractile properties and Ca^{2+} handling were recorded by electrically stimulating the cells on an inverted epi-fluorescence microscope (Nikon eclipse – TE 2000-S, Tokyo, Japan). To avoid bias and only use healthy cells, rod shaped cells without blebs or other visible morphological damages were tested to 2 Hz before recordings started. In study III all measurements were obtained at room temperature at 2 Hz.

The FURA-2AM is a high affinity Ca^{2+} indicator that responds to Ca^{2+} by shifting wavelengths while maintaining strong fluorescence. The fluorescent signals from FURA-2AM are obtained by exciting the cardiomyocytes at a wavelength at 340 nm and 380 nm

with an emission wavelength at 510 nm. The ratiometric fluorescence intensities detected at 510 nm give an estimate of the intracellular Ca^{2+} levels in the cardiomyocytes [123]. Since this is a sensitive fluorescent dye that may affect cardiomyocyte shortening [124], loading was performed under the same environmental conditions: i.e 20 minutes at room temperature in a dark room with a FURA-2AM concentration of 2 μM.

Protein analysis

Western immunoblotting, a semi-quantitative technique for protein detection, was performed to support our cardiomyocyte measurements. Western blot is a reliable and common stepwise technique where proteins are separated on the principle of gel-electrophoresis. Next, the proteins of interest can be detected by adding specific antibodies. In study III we examined proteins known to be involved in Ca^{2+} handling during diastole. Protein expression levels were measured in isolated cardiomyocytes instead of a tissue sample prior the isolation. Although a tissue sample would have gained more protein than isolated cardiomyocytes and hence facilitated the protein analysis, we wanted to measure protein expression under the same conditions as the actual recordings were performed. Protein analysis was performed by an Italian collaborator due to the difficulty in performing western blots on low protein amounts. The protein analysis protocol is further described in paper III.

Pressure volume loop (PV-loop) analysis

During the cardiac cycle *pressure* is generated and ejects a *volume* of blood [26], following the *Frank-Starling Law of the Heart* [125, 126]. Accurate assessment of systolic and diastolic ventricular function is possible via PV-loop analysis [24]. Study II investigated left ventricular (LV) mechanical properties with a Millar PV-loop catheter and this section will explain hemodynamic events from the LV. A 2.0 French catheter was used (designation of the spacing between the sensors of the record unit (9 mm)). We experienced that this is the maximal catheter size that should be used to obtain reliable volume signals without the sensor tip exceeding the internal ventricle length in rats of 240-280 grams. Additionally, one Millar catheter was inserted into the left femoral artery to measure mean arterial pressure (MAP). The catheter insertion into the LV is a sensitive technique and pilot studies showed that increased ambient pressure could result in compression of the chest and thus the sensor tip touching the myocardial wall. To ensure reliable PV-loop recordings, the catheter tip must at

all times be in the center of the ventricle without touching the myocardial wall and experiments that did not meet this inclusion criterion were not included in the study.

Figure 3 illustrates the instrumental setup and PV-loop diagram (bottom right). At point A, the onset of systole, depolarization of the heart occurs initiating the *isovolumic contraction*. In this period left ventricular pressure (LVP) rises with unchanged volume, mitral valve closes while aortic valve is also closed due to higher aortic pressure (AoP). At point B, LVP exceeds AoP, the aortic valve is opened and blood is ejected until the heart reaches the maximum activates state at point C. Ejection is now ended and the heart enters *isovolumic relaxation*, where LVP declines at a constant left ventricular volume (LVV) due to closed aortic –and mitral valve. At point D, filling of the ventricle begins when LVP decreases atrial pressure and hence mitral valve opens. By analyzing changes in the shape of the PV-loop diagram during the cardiac cycle, we were able to assess how pressure changes in diving affects the cardiovascular system. Detailed description of analysis procedures is available in Burkhoff *et al* [24].

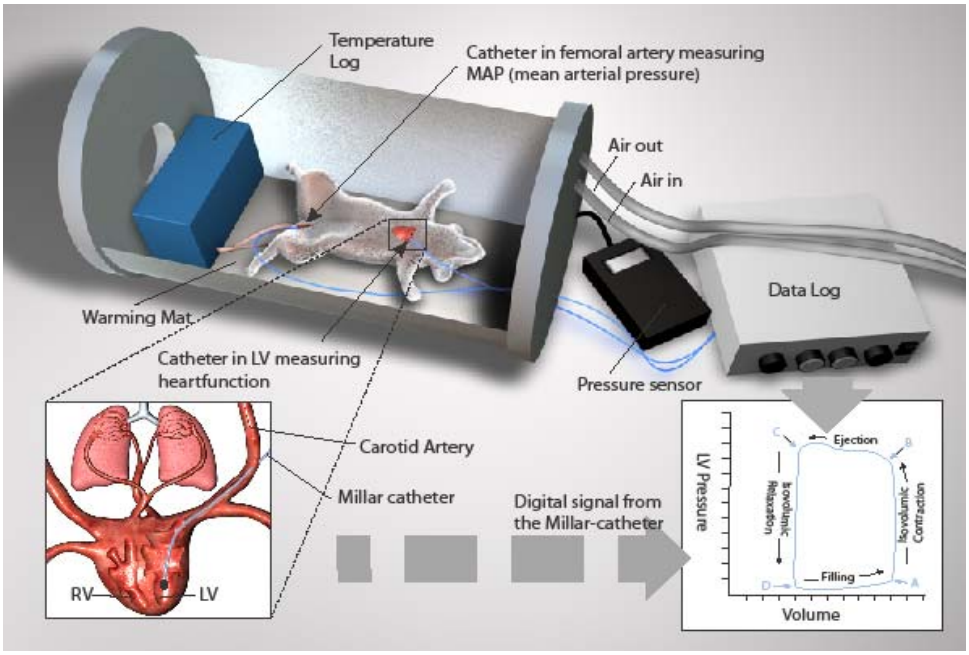

Figure 3. Depiction of the pressure volume loop (PV-loop) recordings in an anesthetized rat. By inserting a Millar catheter into the left ventricle and femoral artery, recordings of cardiovascular changes in response to hyperbaric exposure at different temperatures are possible. Made by MGS studios.

Assessment of pulmonary edema

Measurements of pulmonary function consisted of spirometry and single breath lung diffusing capacity for carbon oxide (DLCO) pre –and post diving. DCLO is a technique to measure gas diffusion between the alveoli and the blood and can be viewed in detail in paper I. DCLO is reduced when fluid is redistributed from the capillary lumen into the alveolar interstitium, an event that leads to acute pulmonary edema (APE) [127, 128]. Based on previous reports that have shown reduction in DLCO up to 60-80 minutes after dives [41, 82], we wanted in study I to evaluate if pulmonary depression was persistent for several hours after dives. Since there is a large variation in individual physiological response to diving, each diver was tested in the same order and time point after each dive.

Chest x-ray is the gold standard to assess extravascular lung water (EVLW) but it is inappropriate for field studies due to the need of radiology facilities and specific reading expertise [129]. Therefore, in study I we examined the lung for the presence of extravscular lung water by counting the number of ultrasonic lung comets (ULC) [130] with a portable ultrasonic scanner (Vivid i). The ULC, generated by the difference in acoustic impedance between air and water, is defined as an echogenic, coherent, wedge-shaped signal with a narrow origin arising from the hyperechogenic pleural line and extending to the far edge of the viewing area. Although the lung is considered poorly accessible to ultrasound, images of ULC for EVLW measurements have been proven to correlate well with other methods including chest x-ray, computerized tomography (CT) and thermodilution [129, 131, 132]. The number of ULC were assessed from 61 predetermined chest sites on the anterior and posterior chest wall [133] and expressed as the sum of all chest scanning areas. The reproducibility of our approach was tested by performing the ULC assessment at two time points in the same day in absence of a dive.

Cardiac function by echocardiography and blood samples

Thorough examination of both right and left ventricles was examined by 2D echocardiography pre –and post dive according to the previously described protocol [95]. Since there is limited information available regarding consecutive trimix diving, bubble production and DCS risk, cardiac measurements were critically evaluated along with bubble

score and ULC before and after each dive. Based on these continuous measurements none of the divers were excluded from the study.

Paralleled with the non-invasive methods to assess dive induced cardiopulmonary strain, quantitative protein concentrations in blood of N- terminal pro-brain natriuretic peptide (NT-proBNP) and pro-atrial natriuretic peptide (proANP) were analyzed with highly protein sensitive commercial immunoassay kits. The blood samples were taken approximately one hour after the dives, thus NT-proBNP was chosen over BNP since the half-time of NT-proBNP is longer than BNP [134]. Also, due to NT-proBNP and proANP's effect in electrolyte and volume homeostasis [135, 136] and hence dehydration following the dives, the amount of peptides was corrected for increased albumin concentrations.

Statistics

In both study II & III data have been presented as mean ± standard error of the mean (SEM), while in study I we presented mean ± standard deviation (SD). In paper III a one way ANOVA test using LSD as post-hoc test was used to evaluate the cardiomyocyte parameters in the different groups. For evaluating the differences in bubble formation, a Mann-Whitney U test was used as in paper II, while Friedman test was used in paper I. In study II, comparisons between the groups in respect of hemodynamics and blood parameters were performed with two-tailed independent Student's test. In study I, after normality of the distribution was confirmed for all parameters using Kolmogorov-Smirnov test, pre –and post dive values for a single dive were assessed by Student's test for paired samples. We evaluated the changes from baseline values and response to diving at different time points by repeated measures ANOVA with Dunnett's test in study II and with Bonferroni post hoc test in study I. Differences were considered significant at $P<0.05$.

Results and discussion

The present thesis reports that both *in vivo* and cellular data from animal studies are of great importance to obtain a comprehensive understanding of the dive induced cardiopulmonary changes seen in humans (Study I-III). In most cases it seems that diving induces transient changes since symptoms of EVLW and cardiac strain in study I came back to baseline values between repetitive dives and in study II where cardiovascular parameters came back to baseline after the dive exposure. However, environmental factors such as temperature and immersion are likely to induce prolonged effect on the cardiovascular system since in study II SV and CO significantly dropped after rewarming whereas in study III the effect of immersion significantly influenced upon the outcome of a subsequent dive.

Hemodynamic changes and impact on venous gas bubble production

The vast individual variation in susceptibility for bubble production and DCS after identical dives indicates that some individuals are better adapted to diving than others. Since there is also an intra-individual difference in bubble production after identical dive procedures, it is likely that daily physiological status plays a significant role. Even in animal studies, where physiological parameters are tightly controlled, there are big intra –and inter-specific differences. Thus, to minimize influence from external factors, the divers had to strictly follow the same procedures. It was emphasized that the divers had to restrain from exercise before diving, during decompression and after the dives since these conditions have been reported to reduce venous gas bubbles after dives [137-139]. In recent years, especially exercise prior to a dive has gained a lot of attention due to its precondition effect on bubble production [106, 137, 140]. The exact mechanisms are unclear but it is strongly believed that exercise influences bubble production through the nitric oxide (NO) pathway [106, 107] and thereby reducing the probably of nuclei adhering to the endothelium [3]. The most effective precondition effect has been reported after strenuous exercise 24 hours before a dive. Although rats in study III were faced very light swimming prior a dive, a possible exercise induced effect was offset by the time point and magnitude of exercise and the significant effect of immersion. However, in study I the divers performed moderate exercise during the bottom phase (up to 40% of max HR) while abstaining from exercise during decompression

stops. Exercise alters the blood flow to body compartments with increased perfusion of the skeletal muscles [141, 142]. Perfusion is recognized to be the main factor affecting uptake and removal of inert gas [100], thereby controlling bubble production and DCS risk. This implicates that the trimix divers had increased gas uptake during bottom time while reduced gas elimination during decompression. This may have contributed to increased bubble production since increased work load during decompression is proven to reduce venous gas bubble production [138, 143].

During diving, hemodynamics are affected by additional environmental factors such as immersion and cold temperature which may influence upon the increased bubble production seen after open sea dive versus dry hyperbaric dives [46]. Thus, this indicates that dry dive protocols should not be directly implemented into wet dive protocols. It is well known that immersion has an anti gravity effect which leads to increased central blood volume but there is sparse information regarding the long term effects of immersion and why wet dives produce more bubbles. In study III we observed that a hyperbaric exposure preceded by one hour immersion depressed heart function and increased mortality and bubble production after decompression. Since there was no significant drop in core temperature, the changes were likely due to hemodynamic changes. One could only speculate why this will produce more bubbles but the increased blood flow could impose mechanical shear stress and hence detachment of bubbles from the vessel wall. Additionally, immersion induced hypervolemia could be the cause of increased release of pro-atrial natriuretic peptide (proANP) in the trimix divers, which is often paralleled with increased naturesis and diuresis [93, 144]. This could alter the surface tension in the blood and promote bubble grown since a decreased surface tension is likely to stimulate bubble growth [145].

Based on previous studies that report increased bubble production and risk of DCS under cold conditions and cold decompression [104, 105], we carried out study II to investigate how cardiovascular function continuously changes during a dive at different temperatures and what impact these changes have for the outcome of a dive. Our study mimicked a dive scenario where the divers are constantly warm (W/W) or become cold during decompression and post dive (W/C), but our results showed no significant increase in bubble production and DCS risk where cold decompression was present. Thus, our finding do not support the hypothesis that cold decompression should result in decreased perfusion and off-gassing and hence increased bubble production [30], but are in line with others who state that there are no solid evidence

demonstrating a causal relationship between temperature and diving [29, 99]. However, one should have in mind that our study was performed on anesthetized rats under dry hyperbaric conditions and were not affected by immersion and exercise that are know to affect perfusion and bubble production [46, 146]. We chose a maximum reduction in core temperature of 2ºC in the rats since a core temperature below 35 ºC is defined as accidental hypothermia in humans [147, 148], but due to species differences a 2ºC temperature drop may not be that critical for rats. In study II we observed no cold induced vasoconstriction since mean arterial pressure (MAP) and total peripheral resistance (TPR) did not differ between the experimental groups during decompression and post dive. This indicates that perfusion was not restricted and inert gas removal in the W/C group followed the same pattern as in the W/W group. Our results are in contrast to Mack and Lin [30] who found a significant reduction in nitrogen elimination and washout rate constant (k) in hypothermic unanesthetized rats (33 ºC). The contrary results may be due to various physiological effects of anesthesia. Anesthesia is known to offset the thermoregulatory control and induce hypothermia [149], but since the rats in our study were heated on an electrical heat pad we were able to maintain constant core temperature. During core cooling, the lack of vasoconstriction may be due to the initial anesthesia induced vasodilation facilitating core to peripheral redistribution of blood [150] and since we had a short observation period the subsequent thermoregulatory vasoconstriction did not occur.

The significance of dive induced asymptomatic pulmonary edema

Based on previous reports that have observed asymptomatic signs of APE such as EVLW and reduced DLCO after diving [82, 85], study I was carried out to evaluate the persistence of EVLW by ULC measurements. We found that EVLW returned to baseline values between the dives and was resolved within 2-3 after each dive, which is in contrast to [85] where EVLW did not return to baseline during the course of repetitive dives. Due to the limited number of studies and since APE is only reported with a prevalence ranging from 1.1% to 1.8 % in swimmers and divers [81, 87], the physiological mechanisms contributing to this phenomenon are still unclear. A key factor may be immersion induced increase in venous return, resulting in 700 mL increased intrathoracic blood volume during head out immersion which corresponds to the PAP increase of 12 mmHg [91]. Consequently this may lead to increased pulmonary blood volume and transmural capillary pressure that may lead to capillary stress failure, extravasation and alveolar fluid flooding [151]. Symptoms of EVLW (swimming

induced pulmonary edema) have also been observed in studies conducted on swimmers and triathletes [81, 152]. The central pooling of blood is reinforced due to cold-induced peripheral vasoconstriction which further contributes to ANP secretion and increased vascular permeability [153]. In our study cold was probably a minor effect since divers faced a minimum water temperature at 14-15 ºC in well insulated dry suits. However, the divers had to perform moderate exercise to overcome various water current velocities which may be of importance since strenuous exercise increases pulmonary blood flow and may promote pulmonary edema [154]. In addition to the aforementioned factors that could affect EVLW and the pulmonary circulations is hyperoxia, which can induce pulmonary inflammatory responses and endothelial damage that will contribute to interstitial edema [155, 156]. Demchenko et al. [156] observed that even hyperoxic breathing <1.5 ATA resulted in destruction of the alveolar-capillary barrier and edema and this scenario could have occurred in the trimix divers who were exposed to a breathing gas with O_2 partial pressure up to 150 kPa. They did not exceed the recommended levels of [PO_2] since that can lead to several toxic effects that may lead to fatal events [40].

In the trimix study, venous gas bubbles were seen after each dive and this may contribute to development of APE due to pulmonary microembolisations that cause inflammatory responses and breaks in the thin capillary endothelial layer [14, 15, 56]. This could lead to blood redistribution and overperfusion of pulmonary capillaries in dependent regions, which is in close resemblance to the inhomogeneous hypoxic vasoconstriction occurring in high-altitude PE [151]. Previously, venous gas bubbles have been seen in parallel with increased PAP [85] and reduced DCLO [41, 82] but the significance of bubbles are unclear since we found no correlation between bubbles and APE. The discrepancy may be due insufficient bubble detection but also to the time points for DCLO measurements. It has been shown that reduced DCLO lasts for up to 80 minutes and our recordings of unchanged DCLO at 120-180 minutes indicate that physiological signs of symptomatic APE are transient. However, although we found no spirometric decrements, Skogstad et al. [157] found a reduction in spirometric parameters for up to two hours after dives to 10 and 50 meters. The reason for this discrepancy is unclear and thus further research is needed to evaluate the significance of asymptomatic APE under different dive protocols.

Finally, since the EVLW accumulation is affected by the dive induced left ventricular changes seen in all the paper in this thesis, one must consider the significance of the observed cardiac

changes for EVLW buildup. The observed decrease in left ventricular EF and FS along with increased end-systolic volume (ESV) and end-diastolic volume (EDV) in study I are indicative of reduced left ventricular contractility, which was also observed in the cardiomyocytes in study III. Increased LV EDV and end-diastolic pressure (EDP) could facilitate EVLW since this would result in increased LV atrium pressure that propagates into the pulmonary circulation and hence induces edema. However, since we did not see an increase in LV EDP in the rats in study II, implying that PAP was unchanged, edema was most likely less prominent in this study. These contrary results have also been seen in other studies where increased PAP is found after open sea dives [4] whereas no increase in PAP is found after dry dives [158].

Dive induced changes of left ventricular function

In this thesis dive induced LV changes were examined from a translational research point of view. Study I examined changes in humans after a dive, study II examined changes during the whole time span of a dive in an *in vivo* animal model, whereas study III examined some of the cellular mechanisms behind the cardiac changes. The divers in study I showed signs of cardiac strain due to increased plasma levels of NT-proBNP and proANP and reduced LV function (Table 1). The trimix divers maintained constant core temperature during the dive but when compared to the rats with constant core temperature in study II (W/W), cardiac parameters differed significantly. Study II was performed under dry hyperbaric conditions and all recorded cardiac parameters in the W/W group returned to baseline post diving, indicating pronounced immersion induced hemodynamic changes in the human trial. Likely, centralization of blood resulted in increased wall stress (increased proANP and NT-proBNP) but also increased EDV (preload). Due to the Frank-Starling relationship [125, 126], increased preload should normally increase the volume of blood ejected during the systole. However, this refers to a healthy heart at normobaric pressure. Our study along with previous findings shows that diving is also associated with increased ESV [85, 95], indicating that an increased preload is not necessarily correlated with increased SV. We report no change in SV which is contrary to previous observations after air SCUBA dives [4, 31]. The reason for our observation is unclear but may be due to successful rehydration at the time of ECHO assessment (120-180 minutes after the dive). In addition to preload, SV is determined by afterload and the inotropic state of the myocardium. Human trials give valuable information how heart function is altered after a dive, but it does not give us the whole picture of diving

since several important changes may have occurred prior to the measurements and at the cellular level.

Table 1. Parameters of left ventricular function.

	Dive 1		Dive 2		Dive 3	
	Predive	**Postdive**	**Predive**	**Postdive**	**Predive**	**Postdive**
FS, %	35.3 ± 1.8	34.0 ± 1.5†	36.0 ± 0.6	33.6 ± 1.3*	36.0 ± 1.2	33.1 ± 1.1*
EF, %	64.1 ± 2.6	62.4 ± 2.0	65.2 ± 1.0	62.3 ± 1.4*	65.4 ± 1.5	61.7 ± 1.2*
SV, ml	73.7 ± 10.6	76.9 ± 12.0	76.5 ± 12.3	74.7 ± 12.4	74.9 ± 12.8	75.9 ± 12.6
EDV, ml	114.4 ± 16.7	123.1 ± 20.3*	117.3 ± 18.9	106.3 ± 27.6	114.4 ± 19.4	123.2 ± 19.7*
ESV, ml	40.9 ± 6.9	46.3 ± 8.6*	41.0 ± 6.8	45.0 ± 6.7*	39.6 ± 6.9	47.2 ± 7.1*
HR, bpm	61.1 ± 6.9	66.6 ± 6.7	64.0 ± 4.2	66.1 ± 8.2	64.0 ± 5.0	67.6 ± 9.2
CO, l/min	4.5 ± 0.7	5.1 ± 0.6*	4.9 ± 0.6	5.0 ± 1.0	4.8 ± 1.0	5.1 ± 0.7

The performance of the left heart was evaluated ultrasonographically before diving and 120-180 min after surfacing. FS; endocardial fractional shortening, EF; ejection fraction, SV; stroke volume, EDV; end-diastolic volume, ESV; end-systolic volume, HR; heart rate, CO; cardiac output. *P<0.05 *versus* baseline value obtained on a same day. † = 0.078 *versus* Predive on the same day.

The cellular data in study III may give a more comprehensive understanding of the reduction in left ventricular contractility in study I (decreased FS and EF). In rats exposed to immersion prior to a dive we observed a decreased cardiomyocyte shortening (% contractility) in the presence of increased intracellular systolic [Ca^{2+}] and [Ca^{2+}] amplitude (Figure 4 A-C). Normally decreased shortening is paralleled with insufficient systolic $[Ca^{2+}]_i$, since failing cardiomyocytes have reduced contractility [122, 159] and since $[Ca^{2+}]_i$ - amplitude is strongly correlated with cardiomyocyte contraction [160]. However, an increased $[Ca^{2+}]_i$ appears to be involved in the short- and long term compensatory mechanisms maintaining CO in physiological and pathological conditions, but an inappropriate excess of $[Ca^{2+}]_i$ may eventually contribute to heart failure [161]. In our study there may be two plausible explanations for depressed contractility in the presence of high $[Ca^{2+}]_i$; 1) Since we did not measure cardiomyocyte length, the cardiomyocytes might be slightly pre-contracted prior to recording and thus further contraction was impaired and/or 2) the Ca^{2+} sensitivity may be reduced. The mechanisms behind altered Ca^{2+} sensitivity are complex and not fully understood, but in failing hearts multiple biochemical alterations of the contractile proteins including changes in the Troponin complex (TnT, TnC, TnI) [162], suppression of α and increased β-myosin heavy chain expression [163] have been reported.

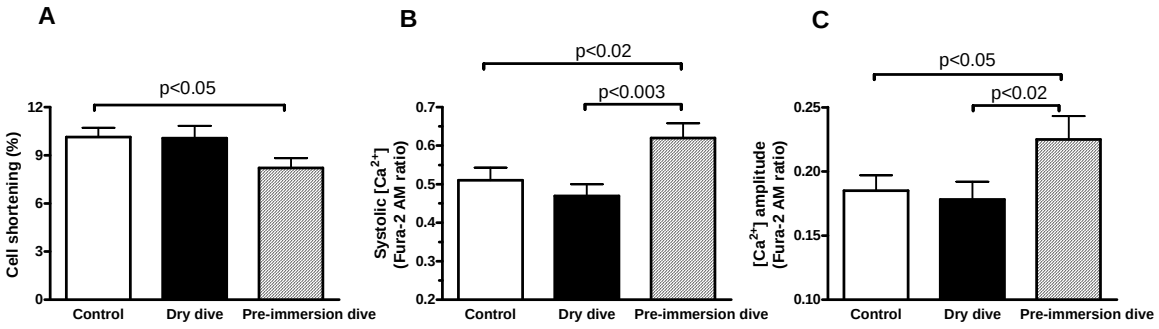

Figure 4. Systolic parameters in cardiomyocytes electrically stimulated at 2 Hz. White bars represent control animals. Black bars represent dry hyperbaric dive. Striped bars represent dry dive preceded by immersion. **A**: Cell shortening (%). **B**: Intracellular systolic [Ca^{2+}]. **C**: [Ca^{2+}] Amplitude.

The increased diastolic $[Ca^{2+}]_i$, increased diastolic relaxation time and altered protein expression levels in study III (Figure 5 A-F) may address cellular explanations of depressed LV function in study I and previous reported impairment of diastolic function up to 2 hours after dives [31, 42]. Although study III investigated the physiological effects of immersion prior to a simulated dry dive, the findings can be related to the studies evaluating the effects of immersion during SCUBA diving. Of specific interested is the duration of immersion induced changes, since study III showed that the effects were present after getting out of the water. Study I showed impaired LV function up to 3 hours after a dive, and Boussuges and colleagues have shown that hemodynamic changes did not return to baseline values 16 hours after prolonged water immersion [94]. The sustained immersion induced allocation of blood to the heart and thorax [78, 89] with increased stretch of the myocardial wall due to increased EDV during diving may be the cause for impaired diastolic function. Figures 5 A-F show important cellular determinants for cardiac muscle relaxation and underlines that diastolic function is significantly depressed after diving. Prolonged relaxation is well described in failing hearts and may be partly explained by reduced protein levels of SERCA2a and decreased phosphorylation of PLN [164]. However, reduced SERCA2a activity seen in study III will normally lead to reduced re-uptake of Ca^{2+} into SR during diastole and subsequently lower Ca^{2+} SR-content and Ca^{2+} amplitude. Additionally, in the rats exposed to immersion prior to a dive we observed increased diastolic $[Ca^{2+}]_i$ due to reduced reuptake of Ca^{2+} into the SR (Figure 5 D&F) and/or leakage through RYR [165, 166] and may be a explanation for reduced LV function since increased diastolic $[Ca^{2+}]_i$ is reported to enhance myocardial stiffness [167]. Since there is sparse information on how diving alters Ca^{2+} signaling in cardiomyocytes, further studies are needed to verify these results. The results from both

studies I and III indicate that immersion has a significant effect of LV function, but at this point we can not elaborate about the significance of the changes.

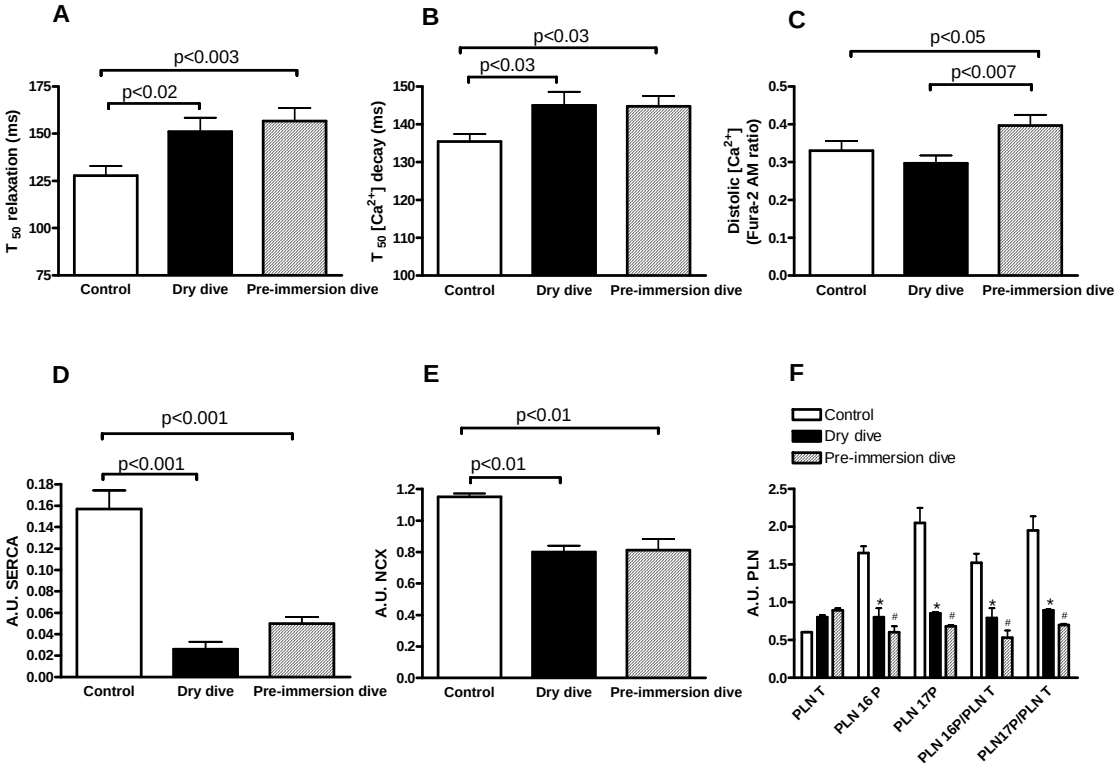

Figure 5. All figures represent diastolic properties in cardiomyocytes electrically stimulated at 2 Hz. * refers to significant difference between dry dive and control. # refers to significant difference between pre-immersion dive and control. Upper panel; **A**: time to baseline (T_{50} relaxation, ms), **B**: [Ca^{2+}] decay (T_{50} decay, ms), **C**: Intracellular diastolic [Ca^{2+}] levels. Lower panel; **D**: protein levels of sarcoplasmic reticulum calcium ATPase (SERCA2a), **E**: protein levels of Na^{+}/Ca^{2+} exchanger (NCX) and **F**: phosphorylation of phospholamban (PLN).

Human trials report increased ESV, ESP and TPR resistance after diving [4, 33, 85] and these changes are good indicators of increased afterload. Clinical trials probably give the most correct assessments to evaluate human physiological adaptations to SCUBA, but today's technology is not suitable for underwater measurements. This results in a lack of valuable measurements during the dive and thus we initiated the *in vivo* study to evaluate at which time point crucial cardiovascular changes occurred and if these changes could be of importance for interpreting the observed changes after a dive. In study II we observed that the most conspicuous cardiovascular changes occurred during bottom time before gradually declining during decompression and returning to base line post diving. From figure 6 A-C it was apparent that afterload was significantly increased, underlining that increased atmospheric pressure mainly impaired LV systolic function and hardly LV diastolic function under dry dive conditions. The increase in afterload was likely due to increased [P_{O2}], causing well

known hyperoxia induced vasoconstriction [21, 168]. As seen in figure 6B, this affected ejection of blood from the LV and since HR remained unaltered, reduced CO was due to reduced SV (Figure 7 A). This is in accordance with previous reports [27] stating that decreased CO was due reduced SV under dry hyperbaric conditions, but due to decreased HR in subject immersed to the neck under hyperbaric conditions. Then an important question arises, can continuous hemodynamic measurements under dry conditions, as in study II, supplement the changes observed after open water dives? Probably to a certain extent, but in order to better understand why open water dives produce more gas bubbles compared to dry dives [46] and result in the impaired LV function seen in study I, a more comprehensive PV-loop animal model under immersed conditions should be implemented.

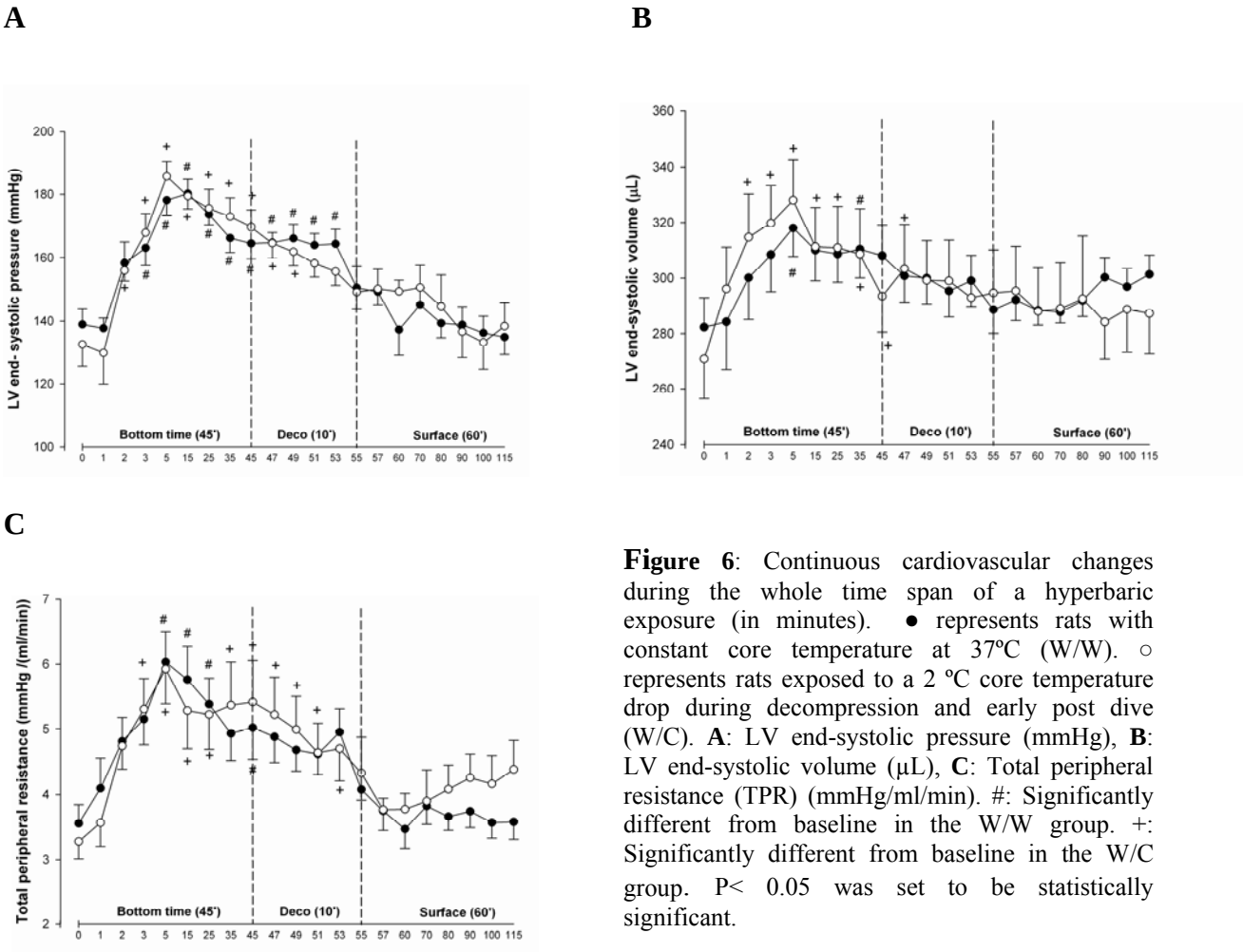

Figure 6: Continuous cardiovascular changes during the whole time span of a hyperbaric exposure (in minutes). ● represents rats with constant core temperature at 37ºC (W/W). ○ represents rats exposed to a 2 ºC core temperature drop during decompression and early post dive (W/C). **A**: LV end-systolic pressure (mmHg), **B**: LV end-systolic volume (µL), **C**: Total peripheral resistance (TPR) (mmHg/ml/min). #: Significantly different from baseline in the W/W group. +: Significantly different from baseline in the W/C group. P< 0.05 was set to be statistically significant.

Our temperature intervention in study II did not increase bubble production and risk of DCS, and at most time points during the dive, cardiovascular parameters followed the same pattern in both the W/W and W/C group. However, we observed a significant drop in SV and CO in

the W/C group during rewarming to 37 ºC (Figure 7 A&B). It was rather surprising that this short lasting modest temperature intervention caused hemodynamic changes since reduction in CO has previously been reported after cooling and rewarming rats from profound hypothermia [169]. This was likely not due to reduced contractile properties since LV ESV and preload recruitable stroke work remained at baseline values. Likely there were alterations in the peripheral vasculature since there was a tendency of increased TPR (Figure 6C) and one can only speculate if the decreased SV was due to vascular escape and pooling in some capillaries. Since we only observed the rats for one hour post diving we can not evaluate the duration of these changes. This is of specific interest in repetitive SCUBA diving where indications of cumulative cardiopulmonary changes have been reported [85]. Since study II was performed under dry conditions, and thus lacks the prolonged immersion induced cardiovascular changes [42, 94], it is tempting to believe that a rat model including immersion and hypothermia would result in increased bubble production and risk of DCS, as seen in human trials [104]. Further, the significance of a combination of stressors was also seen in study III, where neither solely immersion nor dry hyperbaric dive resulted in impaired cardiac function, only a combination of immersion and dry dive did.

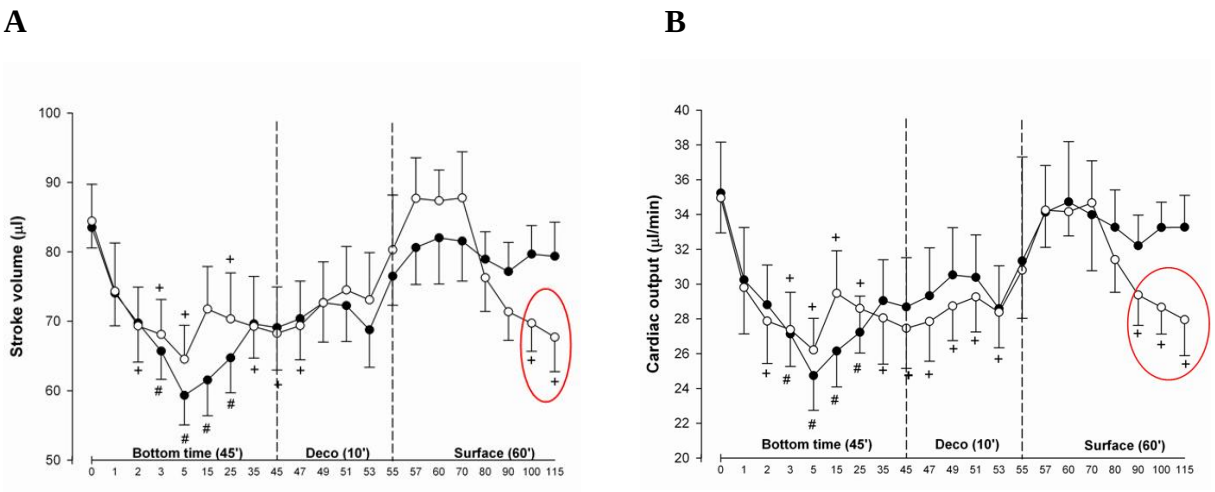

Figure 7: A: Changes in stroke volume (µL) during diving. **B**: Changes in cardiac output (µL /min) during diving. ● represents rats with constant core temperature at 37ºC (W/W). ○ represents rats exposed to a 2 ºC core temperature drop during decompression and early post dive (W/C). Red circles highlight significant changes during rewarming from 35ºC to 37ºC. #: Significantly different from baseline in the W/W group. +: Significantly different from baseline in the W/C group. $P < 0.05$ was set to be statistically significant.

Further perspectives

In most dive scenarios the human body is able to rapidly adapt to the altered environmental challenges imposed by diving. Due to modern SCUBA equipment and by following standard decompression procedures, millions of dives are performed worldwide with no reported clinical abnormalities. However, based on the cardiopulmonary alterations found on a small number of divers in study I, diving induced cardiopulmonary changes are most likely significantly underreported. Additionally, the test subjects in study I were all fit, experienced search and rescue personnel which is in great contrast to the average recreational dive population that no longer include only young and fit people. Although the ascent rate upon return to the surface is the main factor controlling DCS risk, it has been shown that young, slim aerobic fit divers produced less bubbles than divers with the opposite characteristics [170]. The solubility of N_2 is higher in pure fats and oils than in water [28] and blood [171], thus removal of greater amounts of N_2 stored in the lipid tissue of unfit people would require extended decompression time. In study I, the trimix divers planned the dive according to the Varying Permeability Model (VPM-B), which is a model that calculates dive risk on a theoretical and mathematical basis. Models are evolving and have recently begun to incorporate individual physiological parameters for more accurate risk analysis [172], but still there is a substantial work ahead before we understand the vast individual variation in bubble production and risk of DCS in man. Data from human trials give valuable insight to how the organism responds diving, but in order to understand why some individuals are more "biologically adapted" to diving, there is a need for substantial translational research. Animal studies are a powerful tool to investigate mechanisms and etiologies that control the physiological responses during a dive, and further investigation of the finding in study II & III may result in improved treatment strategies and decompression procedures under various dive conditions. Study II & III proved that further research should be addressed cardiovascular changes in response to immersion and hypothermia. There is sparse knowledge regarding the long tem effect of immersion and its significance has also caught interest in other scenarios, such as triathlon, were it is speculated that increased number of swim-related deaths can be linked to swimming induced pulmonary edema (SIPE) [152]. Finally, due to the increased interest of exploiting the northern areas, improved treatment strategies and decompression profiles during cold exposures will be of increasing interest and importance.

Main conclusions

I. In healthy individuals performing repetitive trimix diving in three consecutive days, asymptomatic acute pulmonary edema (APE) came back to baseline values between each dive and resolved within 2-3 hours after each dive exposure. The physiological mechanisms of APE are still unclear and should be addressed more attention in the medical community since the growing dive population do not only include fit and young divers.

II. a) Continuous measurements of cardiovascular function in a dry hyperbaric exposure showed that the most conspicuous changes in left ventricular function occurred at high atmospheric pressure before gradually decreasing during decompression and returning to baseline post diving. This model could not explain the depressed cardiovascular changes seen in humans after dives and should be further developed to better mimic open water dives.

b) Cold exposure during decompression and early post dive period did not increase venous gas bubble production and risk of DCS. The lack of temperature induced cardiovascular changes during the dive indicates that tissue perfusion was unaltered and hence resulted in unchanged gas uptake and removal at different time points. However, rewarming induced a significant drop in SV and CO and further studies are needed to elaborate the long term effect of these changes.

III. Immersion before a dry simulated dive resulted in reduced cardiomyocyte function, increased bubble production and mortality. The reduced cardiac function was likely due to immersion induced hemodynamic changes and support the hypothesis that immersion results in prolonged cardiovascular changes that promote bubble production and risk of DCS.

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PAPER I

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Ultrasonic evidence of acute interstitial lung edema after SCUBA diving is resolved within 2–3 h

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ABSTRACT

Recently, an increase in extravascular lung water (EVLW) accumulation with diminished left ventricular contractility within 60 min after SCUBA diving was reported. We have observed previously that diving was associated with reduced diffusing lung capacity for carbon monoxide (DLCO) and arterial oxygen pressure for up to 60–80 min postdive. Here we investigated whether increased EVLW persists 2–3 h after successive deep dives in a group of seven male divers. The echocardiographic indices of pulmonary water accumulation (ultrasound lung comets (ULC)) and left ventricular function, respiratory functional measurements and arterial oxygen saturation (SaO_2) were assessed 2–3 h post diving, while venous gas bubbles (VGB) and the blood levels of NT-proBNP and proANP were analyzed 40 min after surfacing. Spirometry values, flow-volume, DLCO, SaO_2 and ULC were unchanged after each dive, except for significant increase in ULC after the second dive. Left ventricular function was reduced, while NT-proBNP and proANP levels were significantly elevated after majority of dives, suggesting a cardiac strain.

1. Introduction

Symptomatic acute pulmonary edema (APE) following self-contained underwater breathing apparatus (SCUBA) diving, breath hold diving and endurance swimming is a rather rare complication (Wilmshurst et al., 1989; Pons et al., 1995; Koehle et al., 2005; Liner and Andersson, 2008). In a Swiss survey conducted on 1250 SCUBA divers, only 5 individuals out of 460 responders had a history suggestive of APE (1.1%) (Pons et al., 1995). Having in mind that there are millions of recreational and professional divers worldwide, the number of potential individuals that could be at risk of developing this clinical syndrome is still substantial. Therefore, although of rare occurrence, the APE syndrome deserves attention of the medical community, especially in countries with strong diving tourism and industry. A recent analysis of 60 cases of SCUBA-related APE by Koehle et al. (2005) revealed that affected individuals are typically healthy (although 5 were hypertensive) but that increasing age poses an additional risk. The most common clinical manifestations of APE were cough, dyspnoea and hemoptysis, and in the majority of cases the symptoms resolved within 5 min to 24 h after the dive. Dive depth varied from 2.9 to 42 m of both salt and fresh water with water temperature ranging from 4.7 to 19 °C (Koehle et al., 2005).

As with any other clinical disorder, APE after diving may be asymptomatic and much more frequent than reported due to the large functional reserve in respiratory gas exchange. In a recent study performed during a series of successive dives with trimix (breathing mixtures composed of helium, nitrogen and oxygen), we observed an enhanced accumulation of extravascular lung water (EVLW) using technique of ultrasonic lung comet detection (Agricola et al., 2005; Picano et al., 2006; Marinovic et al., 2009b). This was paralleled by an augmented mean pulmonary artery pressure (PAP), diminished left ventricular contractility and increased release of N-terminal part of the pro-brain natriuretic peptide (NT-proBNP), suggesting a significant cardiopulmonary strain. The number of ultrasonic lung comets (ULC) and PAP values did not return to baseline during the course of repetitive dives, indicating a possible cumulative effect with increasing risk for APE.

The blood–gas barrier between the pulmonary capillaries and alveoli is very thin allowing for rapid exchange of respiratory gases during rest and exercise. The permeability of this barrier is usually expressed as a lung diffusing capacity for carbon monoxide (DLCO). DLCO is reduced during extravasation of fluid, cells and proteins from the vascular space that is a major pathophysiological event leading to APEs. We have previously reported that simulated chamber air dives are followed by significant arterial hypoxemia and reduction of DLCO lasting up to 60–80 min after dives (Dujic et al., 1993). This was later confirmed in the field dives (Dujic et al., 2005a).

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Based on our previous finding of a transient DLCO reduction following the simulated air dives (Dujic et al., 1993), we hypothesized that most of the physiological signs of asymptomatic APE (increased ULC, reduced DLCO and arterial oxygen saturation) will disappear within 2–3 h after diving with trimix in healthy individuals.

2. Methods

2.1. Study population

Seven certified male SCUBA divers were enrolled in the study. They were 40.2 ± 9 years old, with average height of 1.8 ± 0.1 m and 84.5 ± 11.1 kg weight. All participants were experienced divers of the Croatian Search and Rescue Unit (CSR) and were all non-smokers. All subjects completed the study and were included in analysis, and no one developed decompression sickness (DCS) or associated symptoms. During the study period, the divers showed no signs of acute or chronic illness and did not use any medication. All experimental procedures were conducted in accordance with the Declaration of Helsinki, and were approved by the Ethics Committee of the University of Split School of Medicine. Each method and potential risks were explained to the participants in detail and they gave their written informed consent before the experiment.

2.2. Study design

Divers performed a total of three SCUBA dives in 3 consecutive days at the diving depths ranging from 63 to 65 m of sea water. They used a breathing mixture of oxygen (16–17%), helium (44–46%) and nitrogen (37–39%) (trimix) for a descent and an ascent up to 21 m. During ascent at 21 m they switched to a breathing mixture containing oxygen (50%) and nitrogen (nitrox mixture). The bottom times varied between 13.5 and 16.5 min and total dive time including decompression varied between 59 and 83 min. Water temperatures were 19–20 °C at the surface and 14–15 °C at a bottom. Divers wore dry suits, a SCUBA apparatus and Galileo dive computer (Uwatec, Johnson Outdoors Inc., Racine, WI, USA). Decompression profiles were determined using V-planner software according to Varying Permeability Model (VPM-B) (Yount and Hoffman, 1986). Each dive profile was downloaded from the dive computers to a PC for analysis of the dive's depth and duration as well as the heart rate (HR). Individual dive profiles were used to calculate the probability of DCS (P_{DCS}) as an index of severity of exposure (Gerth and Vann, 1997). The divers restrained from exercise 24 h before diving, during decompression stop or after dives since these conditions were reported to reduce venous gas bubbles (VGB) (Dujic et al., 2004, 2005b, 2006a). Subjects did not perform other dives between predive testing and our postdive measurement and were allowed to drink water ad libitum immediately after surfacing.

2.3. Timeline of measurements

The pulmonary function assessment and echocardiography (bubble grade (BG), lung comets and left ventricular function) were performed 30–40 min prior to all dives, and then repeated approximately 120–180 min after surfacing (except for the BG that was measured at 60 min postdive). Blood levels of NT-proBNP, pro-atrial natriuretic peptide (proANP) and albumin were assessed from venous blood samples taken 30–40 min before and immediately after surfacing on days 1 and 3.

2.4. Spirometry, flow-volume and lung diffusing capacity measurements

Measurements of pulmonary function consisted of spirometry and single breath lung diffusing capacity (DLCO). For spirometric tests, three satisfactory maneuvers were collected each time. The instrument used was the computerized Quark PFT (Cosmed, Rome, Italy) that was calibrated daily by volume calibration with a 3 l hand pump and by automatic checking of the proper gas mixture for DLCO measurements. Forced vital capacity (FVC) and forced expired volume in 1 s (FEV_1) were taken as the highest readings obtained. The maximal expiratory flow rates (MEF) at 75%, 50%, and 25% of FVC expired and forced mid-expiratory flow rate were taken from the best test defined by the highest sum of FVC and FEV_1 (Anonymous, 1995).

DLCO was determined in duplicate by the single breath method, which requires the subjects to make maximal inspiration from the residual volume of a gas mixture containing 21% O_2, 0.3% carbon monoxide and 0.3% methane balanced with nitrogen. Concentrations of carbon monoxide were measured using an infrared analyzer (Quark PFT, Cosmed, Rome, Italy). DLCO was adjusted for changes in hemoglobin (Hb) and carboxyhemoglobin (HbCO) as follows:

$$\mathrm{DLCO_{corr}} = \mathrm{DLCO\ measured} \times f(\mathrm{Hb}) \times f(\mathrm{HbCO}),$$

where $f(\mathrm{Hb}) = (10.22 + \mathrm{Hb})/1.76\mathrm{Hb}$. This adjusts DLCO to a standard Hb value of 146 g/l as reported by Cotes (1979). In order to correct for DLCO measurements, blood hemoglobin was measured directly by modified hemoglobincyanide method on Abbot Cell-Dyn System 3700 (Abbot Diagnostics Division, Santa Clara, CA, USA). Alveolar volume (V_A) was measured by the single breath methane dilution and $DLCO/V_A$ was calculated. Arterial oxygen saturation (SaO_2) was assessed with pulse oxymeter (504, Criticare Systems, Waukesha, WI, USA).

2.5. Echocardiographic monitoring and venous gas bubbles detection

The subjects were placed in supine position and an echocardiographic investigation with a phase array probe (1.5–3.3 MHz) using Vivid 3 Expert ultrasonic scanner (GE, Milwaukee, USA) was conducted by an experienced cardiologist (AO). VGB were observed as high intensity echoes in the right heart and the pulmonary artery (Masurel, 1989). Monitoring was performed at 60 min postdive with divers at rest and after performing two coughs. Images were graded from 0 to 5 according to the previously reported method (Eftedal and Brubakk, 1997) and data expressed as median (25–75% quartile range). Detailed information about this technique is presented elsewhere (Dujic et al., 2004).

2.6. Assessment of extravascular lung water

The presence of extravascular lung water was probed with lung ultrasound by counting the number of B-lines or ultrasound lung comets (ULC) (Lichtenstein et al., 1997). The ULC is defined as an echogenic, coherent, wedge-shaped signal with a narrow origin arising from the hyperechogenic pleural line and extending to the far edge of the viewing area. This method of EVLW measurement was found to correlate well with other methods including chest X-ray, computerized tomography and thermodilution (Jambrik et al., 2004; Agricola et al., 2005; Picano et al., 2006). The number of ULC was assessed from 61 predetermined chest sites on the anterior and posterior chest wall (Frassi et al., 2007) and expressed as the sum of all chest scanning areas. The reproducibility of our approach was tested by performing the ULC assessment at two time points in the same day in absence of a dive.

2.7. Assessment of left ventricular function

Two-dimensional echocardiographic studies were performed using standard examination protocol as previously described (Obad

et al., 2007) and the following parameters were derived: end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and ejection fraction (EF). SV was derived from EDV and ESV using Teichholz's formula: SV (ml) = EDV − ESV (Teichholz et al., 1976). EF was calculated from the following equation: EF (%) = 100 × [(EDV − ESV)/EDV], and was used as an index of cardiac systolic function. Endocardial fractional shortening (FS) is calculated from the left ventricular inner diameters measured in systole (LVIDs) and diastole (LVIDd) as follows: FS (%) = 100 × (LVIDd − LVIDs)/LVIDd.

2.8. Assessment of circulating NT-proBNP and proANP

The NT-proBNP was measured in blood samples using a commercial kit Elecsys proBNP Immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA), the pro-atrial natriuretic peptide (proANP) concentration was assessed using a commercial kit for proANP(1-98) enzyme immunoassay (Biomedica Medizinprodukte GmbH & CoKG, Wien, Austria), and the albumin concentration was measured on Olympus Automatic Analyzer AU 2700 with Olympus Reagent for Albumin photometric color test (Olympus Life Science Research Europe GmbH, Munich, Germany). Concentrations of proANP and NT-proBNP were corrected for increase of albumin after diving to account for the effect of dehydration following the dives.

2.9. Statistical analysis

Data are given as mean ± standard deviation (SD). Normality of the distribution was confirmed for all parameters using Kolmogorov–Smirnov test. All the comparisons of parameters measured for a single dive (pre- and postdive values) were performed using Student's *t*-test for paired samples. Bubble grades were compared using Friedman's test. In order to examine whether the parameters changed over the course of consecutive dives (potential cumulative effects), the ANOVA for repeated measures with Bonferroni *post hoc* analysis was used. The limit of significance was set at $P < 0.05$. All analyses were done using Statistica 7.0 software (Statsoft, Inc., Tulsa, OK, USA).

3. Results

3.1. Bubble grade and the heart rate

All divers successfully completed three dives without any symptoms of DCS or APE. The calculated P_{DCS} ranged from 1.9% to 3.3%. Venous gas bubbling was found after each dive in all subjects (3 (3–4), 3 (2–3) and 3 (0.5–3) for the first, second and the third dive, respectively). HR increased from baseline to about 35–40% of maximal HR (HR_{max}, calculated as 220 − age) at the bottom phase of each dive and to about 20% of the HR_{max} during the decompression stop at 6 m.

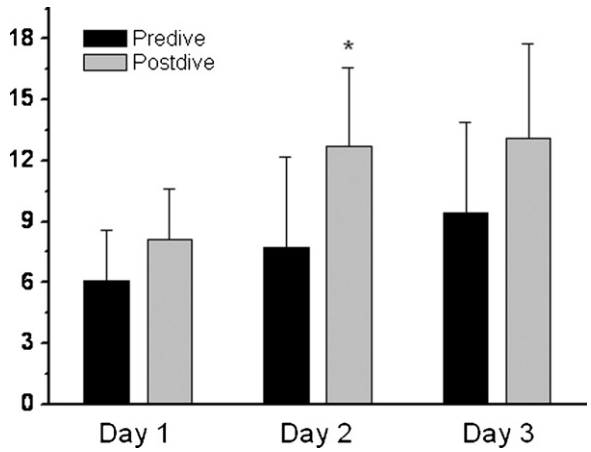

Fig. 1. Accumulation of extravascular lung water indicated by ultrasound lung comets. Shown are the means of ultrasound lung comets (ULC) number before and after a dive on days 1, 2 and 3. *$P < 0.05$ *versus* predive value on the same day.

3.2. Pulmonary functional measurements

Table 1 shows spirometry, flow-volume, DLCO and SaO_2 data for 7 divers collected 30–40 min predive and 120–180 min postdive for dives 1–3. No statistically significant differences between pre- and postdive were found in spirometry (FVC, FEV_1, FVC/FEV_1, $FEF_{25-75\%}$), flow-volume curves ($MEF_{75\%}$, $MEF_{50\%}$, $MEF_{25\%}$), DLCO ($DLCO_{corr}$, $DLCO_{corr}/V_A$) and SaO_2.

3.3. Ultrasonic lung comets

As displayed in Fig. 1, the sum of ULC significantly increased after the second dive from 7.7 ± 4.5 to 12.7 ± 3. 9 ($P = 0.015$), with similar non-significant trends for the first 6.1 ± 2.5 *versus* 8.1 ± 2.5 ($P = 0.18$) and the third dive 9.4 ± 4.5 *versus* 13.1 ± 4.7 ($P = 0.11$) (predive and postdive values, respectively). Moreover, the ULC predive value was higher in dive 3 compared to that detected in dive 1, but the statistical significance was not reached ($P = 0.12$).

3.4. Left heart function

Assessment of the left ventricular function revealed a decreased FS and EF with increased ESV and EDV after each dive (Table 2). No

Table 1
Parameters of pulmonary function.

	Dive 1		Dive 2		Dive 3	
	Predive	Postdive	Predive	Postdive	Predive	Postdive
FVC (% predicted)	119.0 ± 18.1	117.3 ± 13.4	117.8 ± 14.3	116.9 ± 15.3	117.7 ± 14.1	119.0 ± 11.6
FEV_1 (% predicted)	109.2 ± 11.3	107.5 ± 9.7	107.6 ± 10.3	109.4 ± 8.1	106.5 ± 9.5	108.3 ± 6.9
FVC/FEV_1 (%)	95.3 ± 9.8	96.6 ± 8.7	95.1 ± 8.8	97.0 ± 9.2	94.5 ± 8.5	94.6 ± 8.5
$FEF_{25-75\%}$ (% predicted)	83.4 ± 17.0	83.7 ± 15.1	81.0 ± 14.4	85.4 ± 14.5	79.5 ± 14.0	19.8 ± 13.8
$MEF_{75\%}$ (% predicted)	90.0 ± 15.0	92.9 ± 13.3	89.8 ± 14.2	92.6 ± 12.6	88.7 ± 14.2	88.5 ± 12.0
$MEF_{50\%}$ (% predicted)	86.3 ± 21.9	84.2 ± 17.5	81.5 ± 15.3	85.5 ± 17.0	78.4 ± 12.7	78.2 ± 14.7
$MEF_{25\%}$ (% predicted)	74.1 ± 17.2	76.2 ± 15.8	74.1 ± 17.2	80.8 ± 20.3	72.6 ± 17.1	77.1 ± 17.9
$DLCO_{corr}$ (ml/min/mm Hg)	34.4 ± 3.8	34.4 ± 4.4	34.2 ± 4.6	32.4 ± 4.1	31.5 ± 3.7	32.5 ± 3.5
$DLCO_{corr}/V_A$ (ml/min/mm Hg/l)	4.4 ± 0.5	4.5 ± 0.5	4.3 ± 0.5	4.4 ± 0.5	4.3 ± 0.5	4.4 ± 0.5
SaO_2 (%)	97.8 ± 0.8	97.7 ± 0.7	98.1 ± 0.4	98.4 ± 0.7	98.1 ± 0.9	97.6 ± 0.7

Spirometry, flow-volume, carbon monoxide diffusing capacity and arterial oxygen saturation were assessed before and 120–180 min after each dive. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; $FEF_{25-75\%}$, forced mid-expiratory flow; MEF, maximal expiratory flow rates measured at 75%, 50%, and 25% of FVC; $DLCO_{corr}$, lung diffusing capacity for carbon monoxide corrected for changes in hemoglobin and carboxyhemoglobin; V_A, alveolar volume; SaO_2, arterial oxygen saturation.

Table 2
Parameters of left ventricular function.

	Dive 1		Dive 2		Dive 3	
	Predive	Postdive	Predive	Postdive	Predive	Postdive
FS (%)	35.29 ± 1.8	34.0 ± 1.5†	36.0 ± 0.6	33.6 ± 1.3*	36.0 ± 1.2	33.1 ± 1.1*
EF (%)	64.1 ± 2.6	62.4 ± 2.0	65.2 ± 1.0	62.3 ± 1.4*	65.4 ± 1.5	61.7 ± 1.2*
SV (ml)	73.7 ± 10.6	76.9 ± 12.0	76.5 ± 12.3	74.7 ± 12.4	74.9 ± 12.8	75.9 ± 12.6
EDV (ml)	114.4 ± 16.7	123.1 ± 20.3*	117.3 ± 18.9	106.3 ± 27.6	114.4 ± 19.4	123.2 ± 19.7*
ESV (ml)	40.9 ± 6.9	46.3 ± 8.6*	41.0 ± 6.8	45.0 ± 6.7*	39.6 ± 6.9	47.2 ± 7.1*
HR (bpm)	61.1 ± 6.9	66.6 ± 6.7	64.0 ± 4.2	66.1 ± 8.2	64.0 ± 5.0	67.6 ± 9.2
CO (l/min)	4.5 ± 0.7	5.1 ± 0.6*	4.9 ± 0.6	5.0 ± 1.0	4.8 ± 1.0	5.1 ± 0.7

The performance of the left heart was evaluated ultrasonographically before diving and 120–180 min after surfacing. FS, endocardial fractional shortening; EF, ejection fraction; SV, stroke volume; EDV, end-diastolic volume; ESV, end-systolic volume; HR, heart rate; CO, cardiac output.

* $P < 0.05$ *versus* baseline value obtained on a same day.

† $P = 0.078$ *versus* Predive on the same day.

Table 3
Concentration of vasoactive hormones.

	Dive 1		Dive 3	
	Predive	Postdive	Predive	Postdive
NT-proBNP (pmol/l)	6.4 ± 0.3	7.4 ± 1.8	6.0 ± 0.9	6.9 ± 1.0*
ProANP (nmol/l)	0.6 ± 0.3	2.4 ± 1.2*	0.4 ± 0.3	2.3 ± 0.5*
Albumin (g/l)	46.7 ± 1.2	48.7 ± 1.9*	43.9 ± 2.3	46.6 ± 2.6*

The levels of N-terminal part of the pro-brain natriuretic peptide (NT-proBNP), pro-atrial natriuretic peptide (proANP) and albumin were measured in blood samples taken ~40 min before and after dives 1 and 3.

* $P < 0.05$ *versus* baseline on a same day.

changes in SV, HR and cardiac output were found. No differences in predive values between any of the days were found.

3.5. Vasoactive hormones

When compared to baseline values, NT-proBNP levels were significantly increased after dive 3 with similar trend after dive 1 (Table 3). Plasma ProANP was significantly elevated after both dive 1 and 3. Both dives resulted in a significant hemoconcentration, as evidenced by the increased postdive blood albumin levels. No differences in predive albumin concentration between dives 1 and 3 were found.

4. Discussion

4.1. Accumulation of EVLW and cardiac function

In our previous study with repetitive deep trimix dives we observed a threefold increase in ULC number at 40 min after each assessed dive (Marinovic et al., 2009b). A similar trend of ULC increase was also reported after apnea dives (Frassi et al., 2008), in patients undergoing hemodialysis (Noble et al., 2009), as well as in the heart failure patients (Frassi et al., 2007). In the current study we examined whether the ULC increase persists 2–3 h after a dive. We found that most of the ULC increase was not present at that time, although a slight increase by 20–30% still persisted. Since this effect was detected in all individuals after every dive, these data suggested that most of the pulmonary changes including EVLW accumulation lasted only for a short time after a dive. However, while the respiratory function completely returned to its predive levels, the cardiac function remained altered. Due to technical reasons, we were unable to measure all physiological parameters at each and every time point after diving and hence we cannot claim with complete certainty that increased ULC were indeed present immediately after diving. However, since we measured BG, proANP, NT-proBNP and albumin concentration 40 min after dives and all variables changed as expected (an increase in all parameters), we believe that the formation of interstitial lung edema immediately after diving likely occurred as previously reported (Marinovic et al., 2009b) and that at the 2–3 h after the dives the excess EVLW was already largely resolved.

The physiological mechanism(s) leading to the symptomatic and asymptomatic APE in SCUBA diving is (are) unknown, but can involve several factors: (a) immersion-induced blood centralization due to enhancement of venous return and increased cardiac preload (Marabotti et al., 2009). The consequential increase in pulmonary blood volume and transmural capillary pressure may lead to capillary stress failure, extravasation of plasma and alveolar fluid flooding (Sartori et al., 2007); (b) cold-induced peripheral vasoconstriction, resulting in increased cardiac afterload; (c) increased intrathoracic negative pressure due to increased breathing resistance during SCUBA diving (Ronnestad et al., 1994), causing a further increase in venous return; (d) an increased vascular permeability elicited by the enhanced ANP secretion due to right atrial stretch (caused by diving-induced blood centralization) (Brenner et al., 1990); (e) moderate exercise during the dive, since high level endurance exercise has previously been reported to rarely induce transient APE (McKenzie et al., 2005); (f) exposure to elevated oxygen level during a dive, which is associated to an endothelial damage in the pulmonary capillaries and alveoli, resulting in interstitial and alveolar edema (Crapo, 1986; Clark and Thom, 2003); and (g) VGB, since diving is regularly associated with various extent of venous gas bubbling that can contribute to development of APE by causing pulmonary microembolisations and damage to the pulmonary vascular endothelium in animal and human model (Hlastala et al., 1979; Butler et al., 1996; Nossum et al., 2002; Brubakk et al., 2005). Previously, we have shown that even a single air chamber dive caused a significant bubble production and a reduction in DLCO and arterial oxygen partial pressure (Dujic et al., 1993). Thus, there is evidence that VGB could be a contributing factor to the EVLW accumulation. However, in the current study, as well as in our previous study (Marinovic et al., 2009b) with moderate bubble loads, we found no correlation between the bubble grades and ULC, suggesting that development of APE is complex and still poorly understood clinical problem.

In addition to the above-mentioned factors that could possibly contribute to EVLW accumulation during and after a dive, we also observed changes in cardiac function that may play a part in the EVLW buildup. A postdive decrease in the left ventricular EF and FS with increased ESV and EDV are indicative of a reduced left ventricular contractility that could further promote an increase in the pulmonary blood volume and resulting capillary stress. These findings are similar to those from our previous studies (Dujic et al., 2006b; Obad et al., 2007; Marinovic et al., 2009a). An absence of changes in stroke volume, heart rate and, consequently, cardiac output that were previously reported after air SCUBA diving (Boussuges et al., 2006; Dujic et al., 2006b) may be

ascribed to a successful rehydration by the time of the ECHO assessment (120–180 min) or an increase in cardiac contraction elicited by greater ventricular filling (as evidenced by elevated EDV) which may offset a reduction in contractility (indicated by a diminished EF).

4.2. Concentration of NT-proBNP and proANP

In addition to echocardiographic changes detected after diving, hormonal indices of atrial (proANP) and ventricular (NT-proBNP) wall stress were also increased. This confirms previous finding of a postdive increase in the plasma levels of NT-proBNP that was recently reported by our group (Marinovic et al., 2009b) and others (Gempp et al., 2005). Furthermore, elevated levels of plasma proANP levels were previously found during water immersion (Epstein et al., 1987) and saturation dives (Tao et al., 1992). These hormonal changes were most likely caused by the increased cardiac preload and afterload during and after diving. Cardiac release of natriuretic peptides could also potentiate the accumulation of the EVLW since ANP augments the endothelial permeability and leads to increased extravascular fluid and albumin accumulation in the pulmonary circulation (Curry, 2005).

4.3. Spirometry and lung diffusing capacity

The finding of unchanged spirometric and flow-volume parameters 2–3 h after each trimix dive is in accordance to our previous study in which 8 recreational divers performed a single air dive to 39 m for 30 min and spirometric testing was done 90 min after a dive (Dujic et al., 2005a). However, the final conclusion is still unresolved since others have found FVC reduction after ocean dives to 10 m (53 min) or to 50 m (38 min) (Skogstad et al., 1996). Tetzlaff et al. (2001) reported a FVC reduction only after a cold dive exposure to 50 m, but not following dive at 50 m at ambient water temperature nor cold water exposure at 10 m. In a study with larger number of recreational divers comparing wet *versus* dry hyperbaric chamber exposures to 0.6 MPa (51 m water) for 15 min, no significant changes were observed in spirometric values or DLCO at 3 and 24 h postdive (Tetzlaff et al., 1999). Thus, wet exposure and immersion alone may not be responsible for changes in pulmonary function, but bronchoconstriction due to cold was suggested to be the likely causal factor. With relatively moderate summer water temperatures at Croatian coast, a cold water effect is unlikely in this study.

In the present study, no change in postdive (120–180 min) DLCO values was found. Previous studies have reported diminished DLCO following both dry and wet dives in which venous gas bubbles were detected (Dujic et al., 1993, 2005a; Thorsen et al., 1995). Following a dry dive to 45 m for 25 min, DLCO was reduced significantly in proportion to maximal bubble grade (Dujic et al., 1993), and a similar finding was subsequently shown for wet dive to 39 m (30 min) (Dujic et al., 2005a). Since this effect persisted only for 60–80 min after dry or wet dive, the current finding of unchanged DLCO at 120–180 min after emersion is in accordance with previous reports (Dujic et al., 2005a). Furthermore, a recent study showed unchanged DLCO and V/Q ratio at least 1 h after a dry chamber dive (Moore et al., 2009).

4.4. Study limitations

The findings of the present study have to be viewed with caution due to a small number of subjects. However, the strength of this work was improved by the repeated intra-individual measurements (predive and postdive) thus facilitating detection of any potential changes in the measured physiological parameters. Furthermore, as described above, future research on cardiovascular effects of repetitive SCUBA dives should be done with recreational divers and not with experienced divers. One limitation of the current study was that ULC were measured only at one time point, 120–180 min following a dive. Although ideally we would have measured ULC at additional timepoints (i.e. within 60 min after a dive), this was not possible due to the technical reasons (measurement of other parameters at that time point such as VGB and taking the blood samples). A detailed assessment of time-resolution of ULC is planned in the future.

5. Conclusion

In accordance to our hypothesis, the presence of interstitial lung edema after recreational SCUBA diving with trimix mixture lasts very shortly with renormalization of respiratory gas exchange, transfer of water between vascular and interstitial spaces, and arterial saturation within 2–3 h after diving. This study suggests that, besides the significant impact on cardiac function, deep dives of modest severity do not cause major pulmonary gas exchange alterations. However, one should bear in mind that these phenomena were studied in relatively limited number of experienced Search and Rescue divers that are frequently exposed to variety of environmental stressors such as high and low pressure, hypoxia and hyperoxia, cold and warm temperatures, extreme exercise or breathing of dense air mixture. It is therefore possible that they are non-specifically preconditioned to any stress such as a combination of diving and moderate exercise and consequently do not represent the average diving population. Therefore, future work on this topic should be done on a larger number of recreational healthy divers and individuals with common cardiovascular abnormalities (such as arterial hypertension) in order to analyze the risk for developing asymptomatic or symptomatic APE.

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12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.

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

1989

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

1990

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

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.

66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

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

1993

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

1994

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

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

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

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

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.

134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

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

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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

193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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