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Harald Edvard Mølmen Hansen

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Sammendrag

I denne oppgaven ble det undersøkt effekter av høyintensiv aerob intervall trening (AIT) blant personer med høyt blodtrykk og blant friske eldre og yngre personer.

AIT med høy intensitet (>90% av maksimal puls) er mer effektiv for å øke kondisjonen og redusere risikofaktorer for hjerte- karsykdom sammenlignet med trening ved moderat intensitet (-70% av maksimal puls). Dette er tidligere vist blant friske personer og pasienter med hjertesvikt, angina pectoris og metabolsk syndrom.

Høyt blodtrykk (hypertensjon) er en viktig risikofaktor for hjerneslag, hjerteinfarkt og hjertesvikt., ansvarlig for 7 millioner dødsfall pr. år på verdensbasis. Om lag 30 % av den voksne befolkningen har høyt blodtrykk.

I den første studien undersøkte vi effekten av trening ved høyt blodtrykk. AIT ble sammenlignet med en gruppe som trente ved moderat intensitet (MIT) og en kontrollgruppe. Begge treningsgruppene trente på tredemølle, 3 ganger per uke i 12 uker. Kontrollgruppen fikk standardiserte treningsråd, men ingen veiledet trening. Resultatene viste at begge treningsformer reduserte 24 timers blodtrykk og forbedret den systoliske (hjertets evne til å pumpe blod) hjertefunksjonen, men at AIT var mer effektiv til å senke systolisk blodtrykk (overtrykket), øke kondisjonen, forbedre kolesterolet og forbedre den diastoliske (hjertets evne til å fylle seg mellom hjerteslagene) hjertefunksjonen.

I den andre studien trente friske eldre (>70 år) AIT 3 ganger per uke i 12 uker, og kondisjonen ble forbedret med 15 % (lik relativ økning som vist hos yngre personer). Resultatene ble sammenlignet med yngre friske personer og eldre (> 70 år) toppatleter (Birkebeinerresultat). Den diastoliske hjertefunksjonen ble forbedret til samme nivå som de eldre toppatletene, men den var fortsatt svært redusert sammenlignet med yngre personer. Hjertet til de eldre ble kraftigere og større etter treningen, men var fortsatt mindre enn hos de eldre toppatletene.

I den tredje studien ønsket vi å undersøke hvilken treningsfrekvens som var best for å øke kondisjonen, lungefunksjonen og hjertefunksjonen. Friske unge personer ble enten satt til å trene AIT 3 ganger per uke i 8 uker (moderat frekvens gruppen, MF) eller 8 ganger per uke i 3 uker (høyfrekvensgruppen, HF). Begge treningsperioder ble etterfulgt av en detreningsperiode uten trening i 8 uker. MF gruppen økte kondisjonen, lungefunksjonen og hjertefunksjonen progressivt under treningen og denne gikk gradvis tilbake under detreningen. HF gruppen fikk i utgangspunktet en tendens til nedgang i kondisjonen og en signfikant nedgang i lungefunksjon og hjertefunksjon. Dette normaliserte seg etter detreningsperioden.

Konklusjonen på oppgaven er at høyintensiv aerob intervall trening er en trygg og effektiv metode for å øke kondisjonen, forbedre hjertefunksjonen og senke blodtrykket hos personer med høyt blodtrykk og blant friske eldre og yngre personer. For å unngå overtrening bør utrente personer trene med moderat frekvens, slik at kroppen får restituert seg mellom treningsøktene.

Acknowledgment

The work presented in this thesis was performed at the Norwegian University of Science and Technology, Department of Circulation and Medical Imaging, and financed by the EXTRA funds from Norwegian Foundation for Health and Rehabilitation through the Norwegian Heart and Lung Patient Organization (LHL). I want to thank Stig Slørdahl who gave me the opportunity to begin with scientific work before I received the funding from the abovementioned organizations.

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List of papers

Paper 1

Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Schjerve-Ekeberg I, Aunet-Tyldum G, Wisloff U, Ingul CB, Stoylen A:

High intensity aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients.

European Cardiovascular Journal of Prevention and Rehabilitation. Published online before print March 4, 2011.

Paper 2

Molmen-Hansen HE, Aamot IL, Wisloff U, Stoylen A, Ingul CB:

Aerobic interval training compensates age related decline in cardiac function. Scandinavian Cardiovascular Journal. Published online before print January 24, 2012.

Paper 3

Støbakk PK, Hatle H, Molmen-Hansen HE, Brønstad E, Tjønna AE, Steinshamn S, Skogvoll E, Wisløff U, Ingul CB, Rognmo Ø:

Effect of high and moderate frequency aerobic interval training on the oxygen transport chain.

Submitted.

Abbreviations

A	Peak late diastolic mitral flow velocity
a’	Peak late diastolic mitral annular velocity
AIT	Aerobic interval training
ABP	Ambulatory blood pressure
CO	Cardiac output
CVD	Cardiovascular disease
DecT	Deceleration time of early diastolic mitral flow velocity (E).
E	Early diastolic mitral flow
e’	Peak early diastolic mitral annular velocity
EF	Left ventricular ejection fraction
FMD	Flow mediated dilatation
HR	Heart rate
HRR	Heart rate recovery
LV	Left ventricle
SD	Standard deviation
S’	Peak systolic mitral annular velocity
TDI	Tissue Doppler imaging
VO_{2max}	Maximal oxygen consumption

Definitions

Physical activity: Any bodily movement produced by the skeletal muscles resulting in a substantial increase over the resting energy expenditure

Exercise: A physical activity which is planned, repetitive, structured and purposeful in the sense that improvement or maintenance of physical fitness is the objective.

Physical fitness: set of attributes that people have or try to achieve, related to the ability to perform physical activity, such as cardiorespiratory fitness, muscle strength, body composition, and flexibility. The term fitness is associated by a state of physiological well being. This approach can be health related, allowing one to meet the demands of daily life challenges, or it can be performance-related in providing the basis for sports activities.

Aerobic capacity:

Aerobic capacity is normally influenced by three different factors; VO_{2max}, lactate threshold and work economy

Introduction

The association between physical activity, health and longevity has been known for centuries. More than 2500 years ago Hippocrates stated that: “Speaking generally, all parts of the body which have a function, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if unused and left idle, they become liable to disease, defective in growth, and age quickly”.

The relation between regular physical activity and fitness status to both cardiovascular and all cause mortality is strong, independent, inverse and graded (1-6). Cardiovascular diseases (CVD) are the leading causes of death, counting for every third death worldwide (7). In industrialized countries the rate is higher, 49% of all deaths in Europe (8) and about 39 % in Norway (9). Physical fitness has been commonly accepted as one of the strongest associates of mortality reduction, compared to other known risk factors such as smoking, hypertension, elevated cholesterol, obesity and diabetes type 2 (10, 11). Moreover, there is evidence that physical active subjects have reduced risk of other chronic conditions, such as cardiovascular diseases (CVD), osteoporosis, some cancers (breast, colon) and dementia (2, 12). In addition, increased physical activity is associated with higher well-being and reduced risk of psychiatric disorders, such as depression and anxiety (2).

The relation between CVD risk reduction and physical activity has shown a clear dose-response pattern with continuously lower risk at higher levels of regular physical activity,

resulting in to a improved protection for the fit and the most active subjects (4, 13). This robust and independent association is apparent in healthy people and people with CVD, and is observed in youth, middle-aged and elderly populations (2, 14). Physical fitness is modifiable and physical activity improves fitness which is associated with reduced mortality from all-causes, and specifically, from CVD (15, 16). This association is independent of genetic factors (17). In patients with CVD, randomized studies have shown reduced risk with training (18). In healthy persons, there are no sufficiently large scale randomized studies showing definite risk reduction with increased physical activity, the evidence is still limited to surrogate end points and epidemiological associations. Additionally, there is evidence that heritability may influence the training response up to ~50% (19), and that the responsiveness to training may influence the effect on risk factors (20).

Physical activity

The profile of physical activity can be varied by different mode, frequency, intensity and duration. To define the amount of physical activity there exist an interrelation between dose and intensity of the activity. The dose of physical activity refers to the amount of energy used during physical activity, often measured as total amount of calories. Intensity reflects the rate of energy expenditure, either measured as absolute intensity, often measured as oxygen uptake, or relative intensity, referring to the percentage of maximal aerobic power during exercise expressed as percentage of maximal HR or VO_{2max}.

Maximal Oxygen Uptake (VO_{2max})

VO_{2max} is considered as the best measure of cardio-respiratory fitness, and refers to the maximum capacity of an individual's body to transport and use oxygen during incremental exercise (21). It is either expressed as an absolute rate in liters (volume) of oxygen per minute (L/min) or as a relative rate in milliliters of oxygen per kilogram of bodyweight per minute (ml/kg/min). The main factors that influence VO_{2max} are cardiac output reserve (CO_{max}) and the maximal arterio venous ($a\text{-}vO_2$) difference, i.e. the maximal extraction. This is defined by Ficks equation:

$$VO_{2max} = CO_{max} \times avO_{2diff\,max}$$

$$VO_{2max} = SV_{max} \times HR_{max} \times avO_{2diff\,max}$$

Every part of the oxygen supply transport chain, from the lungs to the mitochondria may affect the VO_{2max}. Although it has been debated, it is generally accepted that the main limiting factor of VO_{2max} in healthy subjects, is the ability of the cardio-respiratory system to deliver oxygen to the working musculatures (21, 22). Arterio-venous extraction is not higher in endurance trained athletes than sedentary controls (23). Since maximal heart rate (HR_{max}) is barely influenced by fitness status or physical activity level (24), SV is the main determinant of training induced increase in fitness. However, peripheral mitochondrial capacity is usually down regulated to match the central capacity in individuals with low fitness. Thus the limitation may be both central and peripheral (25).

Aging affects the aerobic capacity and a decline in VO_{2max} by about 10% per decade has been observed in the population after 30 years of age (23). The rate of decline seems to be independent of physical activity level, although individuals with high activity level has higher absolute VO_{2max} (26).

Resting heart rate and Heart Rate Recovery (HRR)

Resting HR correlates with mortality (27, 28). Regular physical activity and increased fitness level lowers resting HR (21). The mechanisms are not fully understood, but a regulation in the autonomic nervous system from a sympathetic to a more parasympathetic dominance is believed to occur (29). In addition, the myocardial SV increases and a lower HR is thus needed to maintain a sufficient CO. HR reserve (HR_{max} – HR rest) increases as HR_{max} changes minimally by training.

Heart rate recovery (HRR) is the decline in HR after cessation of a maximal exercise test, and refers to the difference in HR between HR_{max} and at one, and –or two minutes after terminating the test (30, 31). HRR is a predictor of mortality in both healthy individuals and patients referred to exercise testing (30, 31). Regular physical activity and increased fitness level increase HRR (29, 32).

Hypertension

High blood pressure is the most common risk factor for CVD, affecting about 1 billion people world wide (33). Essential hypertension can be defined as a rise in blood pressure

(BP) of unknown cause, increasing the risk of cerebral, cardiac and renal events (34). In hypertension there is a mismatch between cardiac output, the intravascular volume and vasoconstriction resulting in excessive arterial wall stresses that cause endothelial damage, atherosclerosis and end organ damage.

The global prevalence of hypertension is increasing and lifestyle factors are strongly associated in this development. In western countries about one third of the adult population has hypertension and the prevalence of hypertension increases with age (33). The life time risk of developing hypertension for an individual with normal BP at the age of 55 is set to be 90% during the remaining life time in both sexes (35).

It is estimated that 7 million deaths are attributed to hypertension, thus it stands out to be the top global risk factor for cardiovascular mortality. The major hazards of hypertension are increased risk of stroke, coronary heart disease and heart failure. The associations between BP level and these outcomes are strong, continuous, and independent (33). Mortality and morbidity double for every 20mmHg increase in systolic BP above 115mmHg and for every 10 mmHg increase in diastolic BP above 75 mmHg (36).

Hypertension has a multifactor origin, where more than 250 factors have been identified and influence upon the pathophysiological mechanisms of hypertension. The pathogenesis is complex and incompletely understood and involves interactions between genetic, environmental and demographic factors (37). Some of the major pathophysiological causes of hypertension include increased activation of the

sympathetic nervous system, and increased renin-angiotensin-aldosterone system (RAAS) activity (38). Other mechanisms include vascular and metabolic factors. Increased sympathetic nervous system activity increases renin angiotensin II secretion and increases noradrenaline release from the sympathetic nerve terminals which subsequently stimulates vasoconstriction (39). The kidneys are the main regulators of long term blood pressure by adjusting blood volume through urinary sodium and water excretion (40), whereas the short term regulation is mainly ensured by hormones, mechanical factors and neural reflexes (41). The baroreceptor in the arterial walls of the carotid sinuses and the aortic arch are sensitive to mechanical stimuli and provide an important feedback mechanism of BP regulation (42).

Classification of hypertension

Blood pressure has a skewed normal distribution in the population, and there is a continuous relation to CVD risk from as low as 110-115 mmHg and 75-70 mmHg at systolic and diastolic measurements, respectively (33). Earlier, the diastolic BP was emphasized as a predictor of future CVD, and systolic BP was not included in early guidelines and hypertension trials (43). However, in a large meta-analysis of observational data from 61 studies including almost 1 million persons without cardiovascular diseases, both systolic and diastolic BP were independently and similar predictive of CVD and all cause mortality (44).

Cut off values for classification of hypertension, may seem artificial, but are set to simplify treatment and diagnostic approaches in daily clinical life. In addition, the

terminology and different grades of hypertension is widely known and to avoid confusion, the classification of hypertension is retained in the latest guidelines (45).

The term hypertension should be considered as flexible and individual, being higher or lower based on the subjects total cardiovascular risk.

Table 1. Classification of hypertension, levels in mmHg

Category	Systolic		Diastolic
Optimal	<120	And	<80
Normal	120-129	And/or	80-84
High Normal	130-139	And/or	85-89
Grade 1 hypertension	140-159	And/or	90-99
Grade 2 hypertension	160-179	And/or	100-109
Grade 3 hypertension	≥180	And/or	≥110
Isolated systolic hypertension	≥140	And	≤90
Ambulatory day	<135	And/or	<85
Ambulatory night	<125	And/or	<80

24-hour Ambulatory Blood Pressure (ABP)

ABP allows a non-invasive measurement of the BP during the entire day and night during normal daily activities and nightly sleep. ABP provides additional information to office BP measurements, and is superior to the latter in respect of predicting new CVD events both in untreated and treated hypertensive patients (46, 47). It is also less affected by the "white coat phenomenon", thus being more representative for the individual's true BP. Therefore, ABP values correlates better to end organ damage such as left ventricular hypertrophy, compared to office BP (45).

In research, the ABP is superior to office BP due to enhanced objectivity and reproducibility. Although reproducibility of ABP is better than office blood pressure, day-to-day variations are reported in ABP measurements. The differences from one measurement to another may be substantial, and the HARVEST study revealed that in only one third of the patients there was less than 4/3 mmHg differences for mean ABP systolic and diastolic, respectively (48). The day to day variations are probably mainly caused by true biological variability, different activity pattern and measurement errors due to incorrect cuff size- and placements and arm- movements and position during the measurements (48). The reproducibility is incrementally increased by following a simple checklist including careful patient instruction (activity pattern, arm position and no arm movement during the measurements), sizeable cuff in position, testing the monitor before registration and a visual check of the registered 24-hour measurement.

Comparative studies of ABP equipment with mercury column sphygmomanometers are the gold standard for device validation. Validation of the accuracy with mercury sphygmomanometer show accuracy 5 mm Hg between readings (49). Blood pressure devices are regularly validated by the British Society of Hypertension's homepage, http://www.bhsoc.org/blood_pressure_list.stm and on http://www.dableducational.org/sphygmomanometers.html.

According to the new NICE (National Institute of Health and Clinical Excellence) guidelines (50) (51) , ABP is now recommended to verify hypertension diagnosis and to monitor treatment in primary care. This is the first time ABP has been included as a first step tool in the diagnosis and treatment of hypertension.

Hypertension and physical activity

There is a graded correlation between hypertension and physical fitness in the population, and hypertensive patients have a reduced aerobic capacity compared to their normotensive counterparts (52).

Physical activity is recommended in the prevention, treatment and management of hypertension, and the anti hypertensive effect of physical activity is generally accepted (53). In addition, physical activity has minimal costs and minimal side effects. Studies show conflicting results regarding training intensity, duration and frequency (54). In a meta analysis by Fagard and Corneliussen (55) it was reported an over all effect of

exercise on blood pressure in both hypertensive and normotensive subjects of 3.2 mmHg systolic and 2.5 mmHg diastolic BP. Among the hypertensive patients the BP reducing effect was more profound, with 6.4 mmHg systolic and 4.3 mmHg diastolic. If ABP is applied, the effect has been found to be smaller, and among hypertensive subjects there have been noted a reduction by 3.0 mmHg and 3.2 mmHg, systolic and diastolic BP, respectively (55).

Endothelial function

The endothelium forms the interface between the blood and the endovascular and cardiac surfaces (56). It covers an area of about 4-7000 square meters and consists of more than 10^{13} of cells, weighting approximately 1 kg (57). One important feature of the endothelium is the regulation of the vasomotor tone. It is able to respond to physical and chemical signals by production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation (56). In the endothelium several potent vasodilator substances are produced, including Prostacyclins, Epoxyeico-satrienoic acids (EETs), H_2O_2, Bradykinin and Nitric oxid (NO). On the other hand, the endothelium is the production site of different vasoconstrictors, such as endothelin-1 and is also the site for a small part of the conversion of angiotensin I to angiotensin II (renal endothelium).

NO is considered the most important vasodilator and reduced NO bioavailability is often considered as synonymous to endothelial dysfunction (58). One of the first signs in the pathologic process in atherosclerotic CVD is endothelial dysfunction, and has thus been

proposed as the primary mechanism of atherosclerosis. Endothelial dysfunction is often seen in hypertension, hypercholesterolemia and diabetes, and is associated with incremental risk for CVD. The endothelial production of NO promotes vasodilation, and inhibits inflammation, thrombosis and smooth muscle cell proliferation (59). It is also a smooth muscle relaxant in the arterial walls and causes enhanced relaxation rate in the cardiomyocytes (60).

Bradykinin and Achetylcholin are agonist substrates that lead to increased release of NO. Increased endothelial shear stress, due to increased blood flow, also increases NO release, with subsequent dilatation of the vessels (normalizing shear stress), a process termed "flow-mediated dilatation" (FMD) (61). Aerobic exercise training increases vascular shear stress by increasing blood flow, resulting in increased NO production and up regulation of the enzyme endothelial nitric oxide synthase (eNOS). Antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase. The antioxidant enzymes are involved in the scavenging of reactive oxygen species (ROS).

In clinical settings, FMD can be measured in the brachial artery by ultrasound technique (62, 63). Placing a sphygmomanometer either above the antecubital fossa or on the forearm ceases blood flow in the artery with the cuff inflated to a pressure well above the systolic artery pressure. After five minutes of occlusion the cuff of the sphygmomanometer is deflated and reactive hyperemia will occur in the artery. The FMD is the difference, measured in %, between the basal diameter and the diameter after deflation caused by the reactive hyperemia. This methodology has been debated because

the hyperemic response is probably partly confounded by ischemia-induced hypoxia in the area being imaged (64). The placement of the cuff is reported to affect the FMD measurements and new guidelines suggest placing the cuff distal to the probe, since this approach is thought to give a predominantly endothelium-dependent vasodilatation (64). However, several studies have demonstrated a prognostic significance of endothelial function using a proximal occlusion (65-67). A low FMD response to shear stress is considered as an indicator of endothelial dysfunction. There exist no general reference values for FMD, as mean FMD varies widely between different studies. This may be due to different populations (age, diseases) and measurement techniques (68).

Despite some debate, the general view is that the assessment of FMD represents the endothelium derived NO bioavailability in humans (64). If performed appropriately, FMD is an easy, relative reliable and gentle measurement of the endothelial function. It has shown to be a strong predictor of CVD risk in both healthy populations and in groups of patients with known CVD, including hypertension (67, 69-71). However, the method remains a population measure, with little diagnostic value in individual diagnoses. Reproducibility of FMD has been reported to be in the order of ±11.6%, ±8% and ±7% for intra-observer variability, inter-observer variability and repeatability respectively (72).

High intensity exercise

Recent studies have shown that exercise training with a high intensity (>90% of maximal heart rate) is more effective to reduce cardiovascular risk factors and improve physical

capacity than exercise training performed with a moderate intensity (73-75). This has been demonstrated in both healthy subjects and in different patient groups, such as heart failure, coronary artery disease, claudicatio intermittens and metabolic syndrome (76-79). The mechanisms of increased physical adaptation may be explained by the close relation of stroke volume and intensity. Stroke volume increases in concurrence with higher intensities, and the largest stroke volume is reached near VO_{2max}. In conclusion, high intensity training is probably the most effective training to improve stroke volume. Aerobic exercise also improves peripheral factors and high intensity exercise has been shown to improve endothelial function and antioxidant status significantly compared to training programs performed at lower intensities (76).

Risk of exercise

Although numerous studies have observed a protective role of regular exercise in the prevention of CVD and mortality, there is a definable risk of complications during exercise training. Most of the adverse effects are du to musculoskeletal injuries and have a non-fatal outcome. Serious cardiovascular events are less common risks, and include arrhythmia, sudden cardiac death and myocardial infarction. The risks of exercise are more likely to occur in vigorous activity compared to moderate and low intensity activities, especially in those who are least fit and least active (80). In younger individuals the risk for serious events is almost exclusively related to congenital diseases, whilst in older subjects (> 40 years) the risk is most associated to underlying atherosclerotic diseases (81). The risk of sudden death is estimated to one death per every

15000-18000 subject year (80, 82). In addition, regular physical activity protects against sudden cardiac death (2).

Echocardiography and Tissue Doppler Imaging

Real time two dimensional (2D) examination of the heart combined with Doppler technology allows a non-invasive assessment of cardiac anatomy, pathology, function and hemodynamics.

The first introduction of ultrasound in cardiology was by Edler and Hertz in Lund in Sweden in 1953 (83). The amplitude of the reflected signal at a certain depth can be displayed as the brightness of the reflector, called a B-mode (brightness) modality. Depth selectivity is achieved by time gating. By plotting repeated B-mode signals along the x-axis it is possible to record motion, an M-mode modality, which was the first modality to record moving reflections from the heart. By sweeping the ultrasound beam in successive sectors, two dimensional B-mode images can be created, built up by multiple B-mode lines.

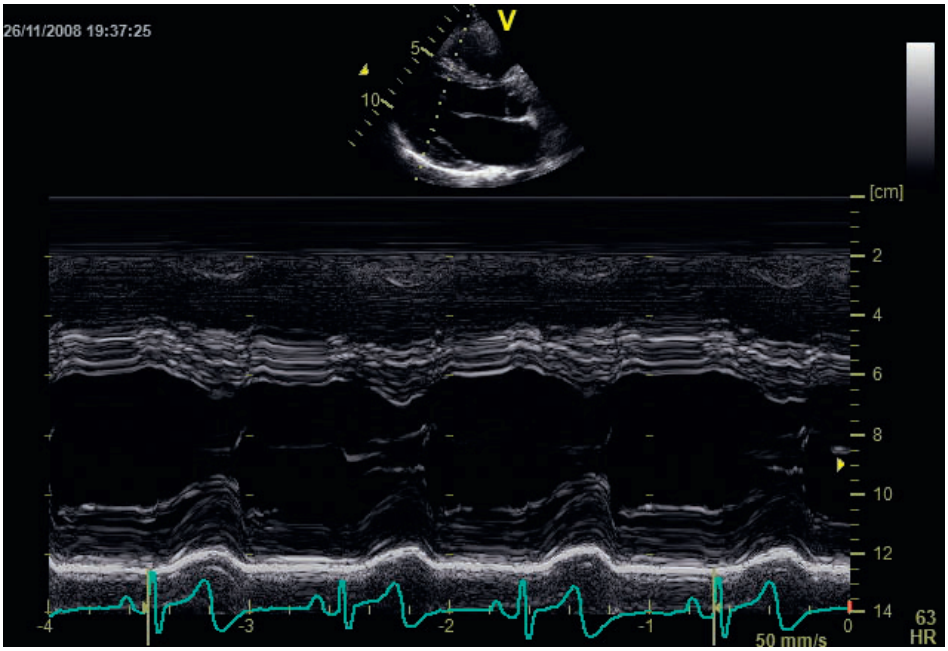

Figure 1. *Parasternal B-mode of the left ventricle, and M-mode image of the mitral valve.*

The number of lines displayed per second is limited by the ultrasound velocity. The time per line is increased if the depth is increased. As an image is built up by a number of lines sweeping across a sector, frame rate is also a function of the number of lines, which again is determined by the sector width and line density (84, 85). It is possible to increase the frame rate, i.e. in order to visualize high velocity moving objects such as the myocardial leaflets, but this will reduce the image resolution by reducing the line density.

2D echocardiography enables the measurement of LV volumes, stroke volume and ejection fraction. The most commonly used convention is Simpson's method (86). The

measurement of volumes is susceptible to artifacts due to shadows, poor endocardial definition, foreshortening and also lateral resolution due to reduced line density. The inter-observer reproducibility of volume measurements by B-mode echocardiography without contrast was investigated at our department, showing that the limits of agreement, were about -33.3 to 18.1 ml (end diastolic volume (EDV)), -23.5 to 16.5 ml (end systolic volume (ESV)) and -16.6 to 14.2% (ejection fraction (EF)) (87). Intra-observer reproducibility was not reported in this study. Thorstensen et al reported higher reproducibility for cardiac volumes with a coefficient of repeatability of 14 ml and 18 ml for EDV, 9 ml and 8.5 ml for ESV and 0.007 % and 0.006 % for EF (inter- and intra-observer analyses respectively)(88). However, the population in Thorstensen's study differed from the other study by its healthy, young subjects.

Doppler effect

The frequency of the transmitted ultrasound pulse changes when it is reflected from a moving object. The frequency will be higher if the object moves towards the probe and lower when the object moves away. The Doppler equation states that the velocity (v) of a moving reflector is given by

$$V = \frac{f_d \cdot c}{2 \cdot f_0 \cdot \cos\theta}$$

Where f_0 is the emitted frequency, f_d is the Doppler shift, c is the velocity of the ultrasound and θ is the angle between the emitted ultrasound and the velocity vector of the moving object.

Velocity measurements by the Doppler shift are thus sensitive to misalignment between the direction of the motion and the direction of the ultrasound. Angle correction cannot be used in cardiac measurements, because the directions of tissue and flow are difficult to predict and varies during the cardiac cycle. In blood vessels, the direction can be predicted from the vessels geometry and since flow direction is constant during the cardiac cycle.

Tissue Doppler imaging (TDI)

Tissue Doppler measurements are based on the same principle as blood flow Doppler measurements. Blood has higher velocities and lower amplitude, whereas tissue has lower velocities and higher amplitude. The low and high velocities may be filtered to measure the desired object.

The myocardial velocities progressively decrease from the base of the ventricles to the relatively stationary apex, and the placement of the sample volumes are of importance. Measurements in the mitral ring are thus assumed to reflect the general function of the entire ventricle (85). In our studies we had relatively healthy subjects with normal myocardial function, and we did not do any regional analysis. The Doppler technique is angle dependent and it is crucial to be parallel to the movement direction to avoid significant underestimation of the real velocity. Furthermore, the myocardial velocities assessed by pwTDI from the apical views do not detect radial and circumferential myocardial motion, which also contribute to the overall myocardial function.

The myocardial velocity profile created by TDI from the apical view is characterized by three wave forms; an apically directed systolic myocardial velocity (S'), early diastolic (e') and late (a') basally directed myocardial velocities.

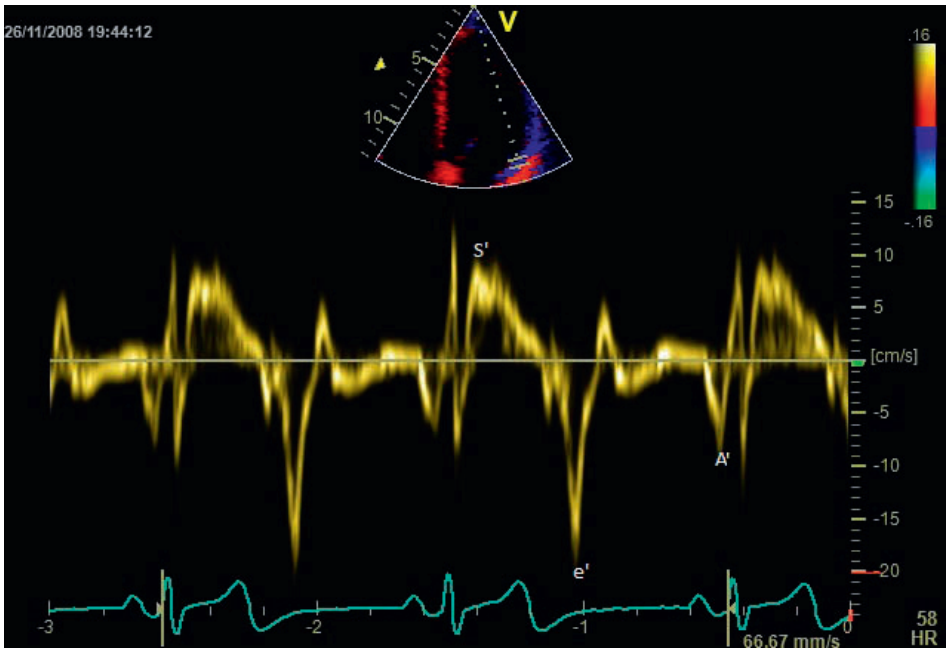

Figure 2. *Tissue Doppler imaging of a normal heart. Four chamber view with the sample size in the lateral corner.*

Two different methods are used to measure tissue velocities; pulse wave (PW) and color Doppler method (cTDI) (84). The whole frequency spectrum of the Doppler shift is displayed in the PW tissue Doppler method, resulting in a broad band of velocities, while in the cTDI method only the mean frequency of the Doppler shift are presented. cTDI

velocities corresponding to the middle of the spectrum, and are thus lower than the peak PW Doppler measurements.

During the last decade, TDI has been introduced as a more objective and quantitative method to assess the myocardial function (89-92). Tissue Doppler recordings are good markers of global diastolic and systolic function of the left ventricle (93), and both measurements can be obtained at the same time. With TDI it is theoretically possible to record tissue velocities anywhere in the myocardium, but for global evaluation of the LV, the movement of the atrio-ventricular plane is of most interest. The longitudinal velocities of the left ventricle decrease from the base toward the apex (94), since the apex virtually does not move.

The peak e' velocity reflects the early ventricular lengthening of the LV and is a measure of the LV relaxation. The e' velocity is related to the time constant of the isovolumic relaxation (tau) and elastic recoil. The load dependency of e' has been debated, but there has been growing support that this index is affected by different loading conditions (95-97). Decreased preload has shown to reduce e' in normal hearts, and vice versa, a higher preload leads to higher e' (96, 98). With increasing age there is a gradual decrease in the rate of myocardial relaxation and elastic recoil, thus leading to reduced e' velocity in older populations (99). Although e' has shown to be less dependent by HR (100), a recent study suggest that e' is also affected by HR (101).

The S' velocity reflects the systolic shortening of the ventricle in the longitudinal direction, and the peak systolic velocity provides information about the systolic function of the ventricle. The S' velocity recorded in the mitral and tricuspid annulus has shown to correlate with the left and right ventricular ejection fractions respectively (102, 103). The S' velocity is reduced during aging (99), and is inversely related to afterload (104).

Recently, our research group has tested the reproducibility of echocardiographic measurements in healthy persons (n=10, 7 men 30±6 years) (88). Inter-observer reproducibility (different recordings, different analyser) for systolic measurements were 6, 8, 7 and 4 % mean error for EF, S' (pwTDI), S' (cTDI) and mitral annulus excursion (MAE) (mm), respectively. For diastolic measurements; 22, 17, 8 % mean error for E/A, isovolumic relaxation rate (IVRT) and e' (pwTDI), respectively. Inter-analyser reproducibility (the same recordings, different analyser) for systolic measurements were 6, 3, 3, and 3 % mean error for EF, S' (pwTDI), S' (cTDI) and MAE (mm), respectively. For diastolic measurements; 10, 7 and 3 % mean error for E/A, IVRT and e' (pwTDI), respectively. Intra-analyser (same recordings, same analyser) for systolic measurements were 5, 2, 2 and 3 % mean error for EF, S' (pwTDI), S' (cTDI) and MAE (mm), respectively. For diastolic measurements; 5, 3 and 2 % mean error for E/A, IVRT and e' (pwTDI), respectively. Intra-analyser analyses showed that the reproducibility is fairly good. We examined relatively healthy persons and the results from Thorstensen et al. may be comparable to our studies.

Myocardial function and aerobic capacity

Acute hemodynamic changes occur from resting state to exercise, with increased HR and SV along with the increase in intensity and VO_{2max}. The relation between the increase in SV and V_{O2max} has been debated (105). The traditional view is that SV increases in untrained and less fit subjects by 20-30 % with progressively increasing workload, and then plateaus until exhaustion. However, some studies in well-trained subjects have shown that SV continue to increase linearly nearly up to VO_{2max} (106, 107). This may, however, be one of the mechanisms of training adaption in well-trained subjects.

Stroke volume may be influenced by ventricular volume, preload, myocardial contractility and afterload. During exercise there is increased venous return, caused by the peripheral muscle pump. This does not necessarily increase preload, as increased ventricular suction during exercise may be the sole mechanism for increased filling (108). This may be a result of both increased relaxation rate due to increased sympathetic tone, and increased elastic recoil due to increased systolic contraction (109). Increased myocardial contractility is caused by a shift in the activity of the autonomic nervous system from parasympathetic to sympathetic dominance, also causing increased circulating catecholamines. Peripheral resistance is reduced by a vasodilatation in the working muscles leading to a reduced afterload. Increased CO raises systolic BP, whereas the diastolic BP increases less, or even decreases due to the reduced peripheral resistance.

At prolonged exercise at moderate intensity (50-70% of VO_{2max}) HR progressively increases after 10 minutes, while SV and mean arterial and pulmonary pressures decrease

progressively. Cardiac output is held relatively constant (105), a situation referred to as cardiac drift.

If exercise is prolonged >45 minutes, VO_2 tend to decrease. The reasons are not fully elucidated, but according to Fick's equation the stroke volume or the a-vO_2 difference are involved. Several studies indicate that the latter is not the case, but rather a reduction in SV (110). This may be caused by reduction in preload due to greater cutaneous vasodilatation, dehydration and reduced plasma volume. The increased HR may in addition contribute to a shorter filling time and a reduced end diastolic volume (110). These factors may have implications in the use of HR as a measure of intensity.

Long term myocardial adaptations to exercise

Athletes participating in endurance exercise are primary exposed to a volume load on the myocardium, and to a lesser extend a pressure load as seen in isometric exercise such as weightlifting (111). The results are increased LV chamber size with a proportional increase in wall thickness, which is described as eccentric hypertrophy. Endurance trained athletes have a high CO and thus a high venous return which also cause an increase of the atria and the right ventricular chamber. Even though the athlete's heart increases in size, control mechanisms restrain "over growing", and keep the heart approximately in the same size. In humans, cardiac output can increase from resting state to 5, 6, or 8 times during exercise in athletes but the stroke volume never more than doubles. The end-diastolic volume increases only by about 50% and the end-systolic volume decreases by the same amount; whereas heart rate may increases from resting HR

to HR_{max} by two and a half times in the untrained to 5 times in the physically fit athlete (21). This, however, is due to a lower resting HR in athletes, as the maximal HR tends to be slightly lower in trained than in sedentary subjects. The main adaption in athletes is increased LV end diastolic volume, with normal or slightly increased wall thickness, hence increased LV mass (eccentric hypertrophy). The increased LV volume results in a higher LV stroke volume reserve. The wall thickness remains at, or slightly above upper normal limit (112). Functional parameters by tissue Doppler shows normal systolic and diastolic function, as opposed to pathological hypertrophy, although the discernment may be difficult in some cases (113).

Objectives and hypothesis

The primary aims of the studies were to:

Paper 1.

Compare the effect of high intensity aerobic interval training to moderate continuous training on blood pressure and myocardial function in hypertensive patients.

Hypothesis: Moderate continuous training reduces systolic blood pressure in hypertensive patients, but aerobic interval training reduces systolic blood pressure significantly more.

Paper 2.

Evaluate and compare the effect of aerobic interval training on myocardial function in a cohort of sedentary seniors, and to compare the results with a young healthy population and well trained seniors.

Hypothesis: Age related reduction in diastolic function is partially related to ageing, partially to inactivity. Thus, diastolic function is better in well trained seniors, but can be improved by exercise in healthy sedentary seniors.

Paper 3.

Compare the effect of high or low frequency of aerobic interval training on aerobic capacity and myocardial function in young healthy individuals.

Hypothesis: There is similar effect of high or low frequency training on VO_{2max} (and myocardial function) as long as total numbers of training sessions are equal.

Materials and Methods

Subjects

Paper 1

The first study was a randomized trial consisting of 88 patients (52.0±7.8 years, 39 women) with mild to moderate essential hypertension. The patients were recruited locally by an advertisement in the regional newspaper, Adresseavisen.

Inclusion criteria were essential hypertension grade 1-2 (mild to moderate) defined as systolic blood pressure (SBP) 140-179 mmHg and/or diastolic blood pressure (DBP) 90-109 mmHg (53), age <65 years. Patients with secondary hypertension, indications of end organ affection (left ventricular hypertrophy, retinal changes, micro albuminuria) or three or more risk factors for CVD (53), as well as patients using more than one antihypertensive drug were excluded. Before inclusion, 39 patients used an antihypertensive drug. This was terminated, and they were observed for a wash-out period of 1 month before inclusion to avoid influence of the medical treatment. The patients were randomized to either aerobic interval training (AIT, n=31), moderate continuous training (MIT, n= 28) or to a control group (C, n=29). To fulfill a study criterion of 90 % compliance to the training program we registered 6 drop outs in the AIT group, 5 in the MIT group and 4 patients in the C group. In the AIT group three patients did not fulfill the training program due to a lack of motivation and three patients because of pain. In the MIT group three patients lost their motivation and did not complete the training program, whilst one patient had to quit due to a myocardial non-ST-elevation infarction he sustained at home, and the last patient had to quit because her blood

pressure rose during the study period and exceeded the inclusion criteria. In the C group three patients lost their motivation and one started intense training on his own initiative and thus had to be excluded from the analysis.

The total patient population for analysis was done with 25 patients in AIT, 23 in MIT and 25 in C.

Paper 2

In the second paper,19 healthy sedentary seniors (73 3 years, 8 women) were recruited through the regional newspaper, Adresseavisen. The participants performed AIT for twelve weeks. Inclusion criteria were age > 70 years and not exercising more than twice per week for the last two years. Persons with any chronic illness or chronic use of any medication, regular smoking, or any metabolic or cardiovascular abnormality were excluded. Three patients dropped out, one because of a leg muscle injury and two for reasons not related to the study. The drop outs were lost to follow up.

The results of the male seniors were compared to 11 senior Master Athletes (74 2 years, all males) who were recruited from the top ten results of a national ski content (Birkebeinerrennet, Rena-Lillehammer, distance 54 km)(from two different subsections, 70-75 years old and from 75 years and older). All of them had exercised regularly (>5 times/week) the last 25 years and the majority of the participants were still competing at the top national or international level for their age group. They were all still physical active, maintaining an exercise frequency of at least 5 times per week.

The results were also compared to 10 healthy male sedentary students (23±2 years) that were recruited from the Norwegian University of Science and Technology, who also participated in study 3.

Paper 3

In the third study, 21 healthy sedentary students (23.0 ± 2.1 years, 10 females) were randomized from Norwegian University of Science and Technology to high intensity interval training, either at a high frequency program of 8 sessions per week for three weeks (n=11 female/male=6/5), or to a moderate frequency program consisting of 3 sessions per week (n=10, f/m=4/6) for eight weeks. Thus both groups accomplished an equal number of AIT training sessions. There were no drop outs in either group.

Inclusion criteria were healthy, non-smoking students that were not exercising more than twice weekly the last year and with a $VO_{2max} \leq 50$ ml/kg/min for women and 60 ml/kg/min for men (measured at our laboratory at baseline).

Ambulatory blood pressure measurement

Ambulatory blood pressure monitoring in study 1 was performed with an oscillometric TM-2430 Recorder (A&D Co LTD, Tokyo, Japan. This device is validated for clinical and research use, ranked with a top rating, A/A, classified by the British Society of Hypertension (114, 115). The inter-observer reproducibility has been reported to be

0.6±2.6 mmHg for systolic and 0.2±2.2 mmHg for diastolic BP measurements, respectively (114).

The cuff was fixed to the non-dominant arm. BP measurements were done every 15 minutes during daytime, defined as 7.00 am to 10.00 pm, and every 30 minutes during night time, defined as 10.00 pm to 7.00 am. The recordings were accepted if at least 75% of the recordings were obtained. Values were deleted if SBP >240 mmHg and <80mmHg, and/or DBP >140 and <40mmHg, and/or if pulse pressure >110mmHg or <20 mmHg. The devices were programmed to do another measurement if there was a change between consecutive readings of SBP >50mmHg DBP >40mmHg and pulse pressure>50 mmHg. If the ABP failed to measure the BP, another ABP was performed. The values used in the analysis were average values, and variation displayed as SD.

Exercise testing

In all three papers we measured VO_{2max} by the same test protocol. The test situation and the exercise sessions were performed fairly similar, with the subjects walking or running uphill on a treadmill (Figure 3). We believed that this would be an advantage as the situation would be known for the study participants, and it would further reflect a true VO_{2max} rather than local fatigue related to the use of other less used musculature, as has been reported as a problem when bicycle testing has been used (21). Jogging or running uphill involves large muscle groups necessary to reach VO_{2max}. This method has been found to achieve about 5 % higher VO_{2max} compared to stationary bike cycle testing in untrained individuals (21).

Maximal oxygen uptake was measured by Cortex Metamax II portable metabolic test system (Cortex Biophysics GmbH, Leipzig, Germany). This device has been validated against the Douglas Bag method, which is thought of as the gold standard (116, 117) (mean differences of measured VO_2 was 0.03, 0.02, and 0.04 $L \cdot min^{-1}$ for 100, 200, and 250 Watt, respectively). Reproducibility is accurate if the system is calibrated and tested regularly, intra-class reliability has been found to be 0.984 (± 0.2ml $L \cdot min^{-1}$) for VO_2 measurements (116).

We used an individualized graded ramp protocol. After a 10 minutes warm-up, a facemask was placed on the subject's face for ventilatory analysis. Incline was constant at 10% and band speed increased every minute until VO_2 leveled off (< 2 ml/kg/min increase) despite further increased work load, and a respiratory exchange ratio >1.10 was reached. The test was completed within 8-12 minutes.

Figure 3. *Exercise testing in our laboratory.*

Maximal heart rate, heart rate recovery and resting heart rate

HR_{max} was measured during the VO_{2max} test procedure. The maximal heart rate obtained during the test was always reached during the final minute of the test. True HR_{max} is reached after several repeated intervals of maximum effort, and after several minutes at the last interval. The heart rate obtained at the end of the test is thus usually lower than

HR_{max}. To obtain an estimate of HR_{max}, we added 5 beats per minute to the HR at peak exercise.

In paper one, we measured heart rate recovery, defined as the reduction in heart rate from peak exercise to one and two minutes after terminating the test (118). The subjects in paper one were patients with essential hypertension and it was assumed that the exercise training would involve a reduction in the sympathetic nervous tone. In papers two and three the subjects were healthy, and HRR was not measured, as it would probably not give additional information more than the progression of training status.

Resting heart rate was measured in all three studies during the resting echocardiography examination. The measurements were calculated by the mean of three heart beats. In general, the subjects had rested about 10 minutes at that time.

Training intervention

Training at high intensity, >90 % of HR_{max} has significantly shown increased VO_{2max} and reduced CVD risk factors, compared to training at lower intensities in both healthy people and in different patient groups (76, 79, 117). The high intensity is only possible to maintain in short periods, as it is above the anaerobic threshold. In our study we chose four minutes intervals (>90% of HR_{max}), performed four times with three minutes active breaks in between (70% of HR_{max}) to eliminate lactic acid. The training sessions always started with a ten minutes warm-up and rounded off with a three minutes cool down.

Total time was set to 38 minutes. Intensity (speed or incline) was increased during the intervention period to keep HR at the same level, in order to maintain relative intensity as fitness increased. This has been proven to be an effective method (Figure 4), clearly demonstrated by our department in several recent studies (76, 77, 79, 117, 119).

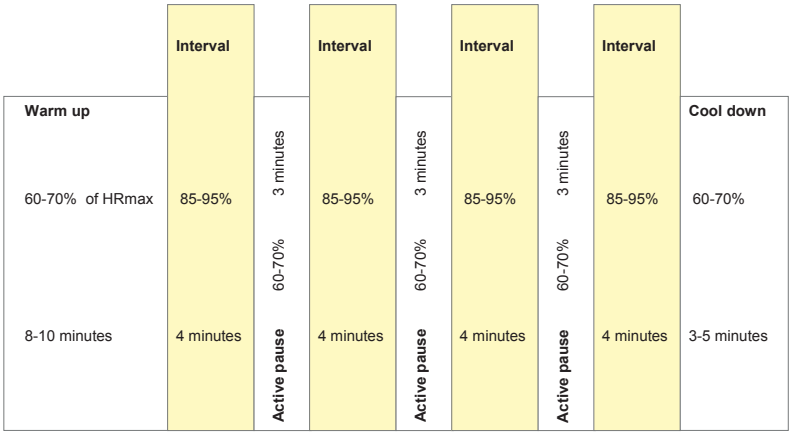

Figure 4. *Aerobic interval training model.*

In paper one, we compared if the AIT was more effective to lower blood pressure than isocaloric continuously training at a moderate intensity (MIT) at ~ 70% of HR_{max}. The MIT was performed as walking/running for 47 minutes, being isocaloric to AIT (117). In general, the moderate intensity training applied in our study is referred to as high intensity training in the existing literature and has shown to have a documented antihypertensive effect (52). Both training forms were performed on uphill treadmill walking or running. To ensure that the required intensity was maintained, the participants monitored their HR with Polar HR monitors (Polar, Kempele) and were controlled,

backed up and supervised by a personal trainer. The training sessions were performed three times a week for twelve weeks.

In paper two and three no other training method than AIT was applied. In paper two we were interested to study if seniors aged >70 years, could improve their VO_{2max} to the same relative extent as seen in young populations and if it could to some degree reverse the age related impairments of the left ventricular function. AIT was performed three times a week for twelve weeks.

The rate of adaptations has been questioned, and we aimed to study if the effect of AIT could be achieved in a shorter time by increasing training session frequency. In paper three, the healthy young students completed 24 sessions of AIT either in three weeks or in eight weeks.

Endothelial function

In paper one and three, we measured endothelial function as FMD of the brachial artery, using high resolution vascular ultrasound (12MHz echo Doppler probe, Vivid 7 system, GE Vingmed Ultrasound, Horten, Norway). The procedure followed in paper one is described by Coretti et al (62), and the cuff for occlusion of the artery was placed proximal to the ultrasound probe. In paper three we placed the cuff distal to the probe to exclude any influence of ischemic processes (64). No difference where observed in paper one after NO was administrated sublingually, indicating that the response reflected the bioavailability of NO in both methods.

The lumen diameter of the artery was measured at three consecutive R-waves times and an average was used as baseline values and after one minute after cuff release. The percent change in diameter was used as FMD. All measurements were done in a quiet room after >8 hours fasting from food, caffeine, tobacco and alcohol. The participants were told to avoid strenuous activity 24 hours before the measurements.

Echocardiography

In paper one only 51 patients obtained an echocardiogram due to capacity problems. In addition, recordings were performed at rest only. In paper two and three all patients were examined by echocardiography at rest and during exercise. In paper three, echocardiography was done at baseline, after the training period and after the detraining period. In all three papers we used a Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway) with a phased array transducer (3MS probe).

The resting echocardiography examinations were done with the subjects in the left lateral decubitus position. Three consecutive cardiac cycles from the three standard apical views (4-chamber, 2 chamber and long axis) as well as short axis (basal, mid-papillary and apical) were recorded by conventional two-dimensional (2D) harmonic grey scale mode and in colour tissue Doppler mode. The loop with the best quality was chosen for the analysis. B-mode recordings were done with an average of 53-54 frames per second and tissue Doppler with 150-154 frames per second. M-mode recordings were done in parasternal short axis view. Pulsed Doppler flow recordings of the mitral inflow were

obtained with the sample volume between the tips of the mitral leaflets. Measurements included early diastolic filling (E) and late diastolic filling (A). Isovolumic relaxation time (IVRT) was measured with the sample volume between the aortic and the mitral annulus, imaging the aortic valve closure click as well as the start of the mitral inflow. Stroke volume (SV) and cardiac output (CO) was calculated by Doppler flow measurement in the left ventricular outflow tract (LVOT) together with LVOT diameter and HR. LV volumes and ejection fraction (EF) were calculated from apical recordings by modified biplane Simpson's method (86).

PwTDI velocities were recorded with the sample volumes placed in the mitral ring in the septal and lateral position of the four-chamber plane, and the anterior and inferior positions in the two-chamber plane. In all three papers we used the average velocity of the four positions as global measures.

Exercise echocardiography was obtained in paper two and three (additional information regarding paper 3; exercise data not sent for publication). Recordings were done sitting upright on a stationary bike at rest and during exercise at ~70% of HR_{max} (calculated from the VO_{2max} test). During upright stress testing, it is difficult to make accurate measurements due to the movements of the subject. Therefore we used cTDI to record myocardial tissue velocities, and analyses were done in post processing, measuring values of the mitral ring as described for resting echocardiography. Doppler flow recordings were obtained from four-chamber view and cTDI recordings was obtained in four-chamber and two-chamber view. The average value of four points was used in the

analysis. These values are lower than pulsed tissue Doppler velocities since cTDI velocities represent the mean instantaneous velocities (85). Due to a fusion of early diastolic tissue velocity and late diastolic tissue velocity during exercise, only the highest value was used as a measurement of e'. Blood pressure was measured conventionally at rest, sitting in a chair, according to standard procedures (53) and at submaximal exercise, sitting on bike, to assess hemodynamic changes.

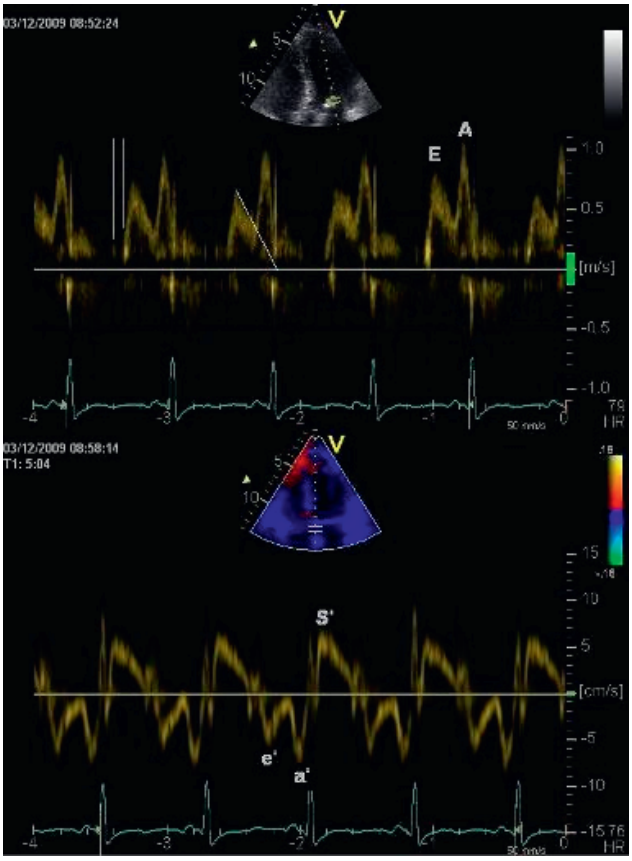

Figure 5. *Patient with hypertension and diastolic dysfunction. The image at top shows reduced E/A ratio, prolonged IVRT and prolonged deceleration time. The image below shows reduced tissue Doppler velocity, e' (85).*

Blood samples

In paper one and three the following blood samples were analyses were done at St Olavs University Hospital with standard procedures: Serum triglycerides, glucose, high-density lipoprotein (hdl), low-density lipoprotein, total cholesterol, hemoglobine, sodium, potassium and creatinine. Blood were obtained after at least 8 hours of fasting from food, caffeine, nicotine and alcohol.

Statistics

Data are presented as mean (SD). All statistical analyses were done with SPSS (SPSS, Inc, Chicago).

In all three papers we applied independent or paired t-test to discover within group differences. Analysis of variance was used in paper two to discover differences between the three male groups. One way analysis of covariance (ANCOVA) which is the preferred approach for analyzing randomized trials with baseline and follow up measurements (120) was used to discover between group differences in paper one and three. Covariance was used to avoid influence of different baseline values among the subjects, but in both study one and three this was not strictly necessary with the primary

outcome since baseline values were not significantly different. Post-hoc adjustment with Bonferroni correction and a two sided $p<0.05$ was regarded as marker of statistical significance in all three papers.

Summary of results

Paper 1.

The principal outcome was ABP. AIT reduced systolic ABP by 12 mmHg ($p<0.001$) and diastolic ABP by 8.5 mmHg ($p<0.001$), whilst MIT reduced systolic ABP by 4.5 mmHg ($p<0.01$) and diastolic ABP by 3.5mmHg ($p<0.05$) (Figure 6). There was a significant difference comparing the effect on the systolic ABP between the two training groups ($p<0.05$). No changes were seen in the control group. In the control group there was a non significant trend for BP reduction during observation by 2 mmHG both for systolic and diastolic pressure. Although not significant, this may be the order of magnitude of regression towards the mean, as the selection criterion was the same as the primary outcome.

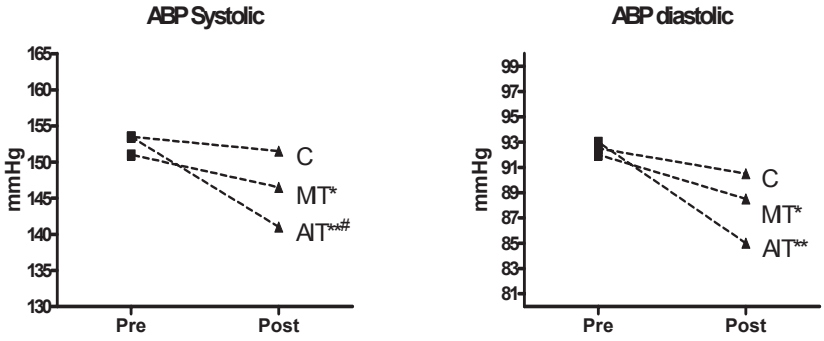

Figure 6. *24-hour ambulatory blood pressure.*

*Graphs display average reduction in ABP for **AIT**: Aerobic interval training group, **MIT**: Moderate continuous training group, **C**: Control group.*

** indicates: p-value<0.05 compared to control group. ** indicates p-value<0.001 compared to control group. # indicates p-value<0.05 AIT group compared to MIT group.*

Secondary outcomes were VO_{2max}, HRR after one and two minutes, mean HR-24 hours, endothelial function, myocardial function, total peripheral resistance, quality of life and Hdl cholesterol. AIT improved VO_{2max} by 15 % ($p<0.001$) and MIT 5% ($p<0.01$) (group difference $p=0.001$). Only the AIT group achieved a significant improvement in heart rate recovery with 7 beats/min ($p=0.01$) and 8 beats/min ($p=0.04$) recorded one and two minute post-exercise, respectively. Only the AIT group achieved a reduction in HR_{mean}, with 3.8 beats/min/24-hours ($p<0.01$). Endothelial function improved only after AIT ($p<0.01$ within group, between group differences, $p=0.02$). Endothelial-independent dilatation did not change. Only the AIT group improved left ventricular ejection fraction (6.5 %points (11.2% relative increase), $p<0.001$), stroke volume (11%, $p=0.02$), systolic flow velocity (9.3%, $p=0.03$), end-diastolic volume (11%, $p=0.01$), and early diastolic mitral annulus tissue velocity, E' (14%, $p<0.001$). Systolic mitral annulus tissue velocity, S' increased by 15% ($p<0.001$) after AIT and 8% ($p=0.04$) after MIT. No significant changes were seen on conventional diastolic markers (E, A, DT). The isovolumic relaxation time decreased significantly in the AIT group only, with 16% ($p<0.01$). TPR decreased by 18.4% ($p=0.03$) in AIT and 12.8% ($p=0.06$) in MIT. Hdl-cholesterol increased in AIT group with 5.3% ($p=0.04$), all other general clinical parameters remained unchanged in all groups. AIT improved QL in three sub domains: general

health (p=0.02), social function (p=0.04) and physical function (p=0.02). MIT showed improvement in general health (p=0.03). No changes were seen in the control group.

Table 2. Physiological measurements

	AIT (n=25)			MIT (n=23)			C (n=25)		
	Baseline	Follow up	p-value	Baseline	Follow up	p-value	Baseline	Follow up	p-value
VO_{2max}, ml/kg/min	36.3±8.8	41.5±10.6	<0.01*	34.0±7.0	35.8±6.9	<0.01	34.7±7.8	35.7±7.6	0.06
FMD, % dilatation	6.49±3.71	10.66±5.00	<0.01*	6.50±5.01	7.11±5.10	0.70	8.01±4.62	8.91±5.20	0.39
HR red 1 min, b/min	149.7±13.9	143.1±14.9	0.01*	149.4±11.0	151.4±9.8	0.35	149.5±16.0	149.3±14.5	0.90
HR red 2 min, b/min	128.9±16.2	120.9±14.9	0.04	129.0±10.5	126.6±12.1	0.86	123.6±16.7	127.5±12.9	0.24
Peak HR b/min	184.0±9.7	180.0±9.9	0.02	181.5±7.8	182.5±9.2	0.65	180.0±12.1	182.5±11.9	0.06

Table published in European Journal of Cardiovascular Prevention and Rehabilitation (121).

Data are mean (SD). **VO_{2max}:** *maximal oxygen uptake.* **FMD:** *flow mediated dilatation.* **HR red 1 min and HR red 2 min:** *heart rate recovery/reduction after 1 and 2 minutes after test, respectively.* **Peak HR:** *peak heart rate.*

* indicates p-value ≤0.05 between AIT and MIT. Comparison between training groups and control group is not displayed.

Table 3. Echocardiographic measurements

	AIT			MIT			C		
	Baseline	Follow-up	P-value within group	Baseline	Follow-up	P-value within group	Baseline	Follow-up	P-value within group
EF, %	58.0±4.5	64.5±6.7	<0.001*	59.5±7.6	61.0±8.7	0.25	59.0±9.3	58.0±7.8	0.50
EDV, ml	110±31	122±31	0.01	116±22	117±24	0.79	120±21	123±25	0.55
SV, ml	72.1±11.7	80.1±14.8	0.02	68.3±15.4	71.1±18.2	0.48	75.3±16.7	72.2±13.1	0.29
CO, L/min	4.6±0.7	5.2±0.9	0.05	4.5±1.1	5.0±1.3	0.09	5.3±1.27	5.0±1.04	0.25
HR at rest, b/min	65.0± 6.0	66.5± 9.0	0.50	65.5±11.0	72.0±12.0	0.11	71.0±10.0	69±8.0	0.45
IVRT, m/s	96.5±11.5	81.0±13.6	0.02	91.0±29.9	89.0±23.3	0.59	102±13.7	97.0±10.1	0.12
E, m/s	0.74±0.15	0.77±0.16	0.40	0.67±0.14	0.66±0.15	0.74	0.70±0.21	0.69±0.18	0.69
A, m/s	0.62±0.09	0.62±0.09	0.91	0.65±0.11	0.68±0.17	0.49	0.68±0.22	0.64±0.21	0.22
S' cm/s	6.89±0.90	7.90±1.30	<0.001	7.40±1.20	7.99±1.36	0.03	7.52±1.50	7.07±2.13	0.53
E', cm/s	8.06±1.60	9.26±1.80	<0.001*	8.93±2.11	8.62±2.27	0.42	8.70±1.81	8.27±1.90	0.24
TPR, dynes*sek*cm^{-1}	2050±295	1669±361	0.03	2120±541	1846±599	0.06	1863±580	1891±416	0.80

Table published in European Journal of Cardiovascular Prevention and Rehabilitation (121).

Data are mean (SD). **EF:** *ejection fraction*. **EDV:** *end diastolic volume*. **SV:** *stroke volume*. **CO:** *cardiac output*. **HR:** *heart rate differs from table 1 and 2, as this is measured during the echocardiographic examination,. Mainly in order to evaluate other echo measurements.*. **IVRT:** *isovolumic relaxation time*. **S:** *systolic peak flow velocity in left ventricular outlet tract.* **E:** *peak mitral inflow velocity during early filling*. **A:** *peak mitral inflow during atrial systole*. **E':** *peak annulus tissue velocity during early filling*. **TPR:** *total peripheral resistance.*

*indicates p-value <0.05 between AIT and MIT. Comparison between training groups and control is not displayed.

Paper 2.

Study two consists of three different parts. Firstly, a cross sectional study were performed where a group of healthy, sedentary seniors, were compared to well trained seniors (old Master athletes) and to a group of young, sedentary students. Among the Master athletes, we were only able to recruit men and therefore the comparison between the three groups was done with males only to avoid gender effects. This comparison shows that old males regardless of fitness status have a reduced diastolic function, as measured by e', compared to young males. However, the old Master Athletes had a trend to 23% higher e' than the sedate seniors ($p=0.08$).

Secondly, a prospective training intervention was performed in the sedentary seniors, including both men and women, to assess the training effects of short term training in sedentary seniors. The diastolic function, measured by e', improved in the sedate seniors ($p<0.05$) after the intervention (both genders). VO_{2max} increased by 15% ($p<0.01$). After the intervention, the male portion of the senior training group was compared to the master athletes to assess the training effects of short term versus life long training among healthy seniors. The e' increased by 11% ($p<0.05$) among the sedate seniors after the intervention and equalized the difference compared to the old Master Athletes ($p=0.20$). Secondary outcomes such as VO_{2max}, EDV and e' measured during exercise increased by 11.5 % ($p<0.01$), 22% ($p<0.01$) and 7.5% ($p<0.01$) respectively, but was still different from the Master Athletes.

Table 4. The effect of intervention, comparison seniors versus Master athletes. Males only.

	Seniors (N=10)			Master Athletes (N=11)	Comparison **Seniors-versus Master Athletes**	
	Pre	Post	P-value within group	Baseline	P-value pre-values	P-value post-values
$VO_{2max,}$ ml/min/kg	35.0±5.0	39.0±7.2	<0.01	49.5±4.5	<0.01	0.01
EDV, ml	102±13	124±15	<0.01	142±21	<0.01	0.05
SV, ml	79±13	87±11	<0.01	102±26	0.03	0.20
E/A	0.92±0.27	1.35±0.36	0.06	1.33±0.70	0.10	0.92
e', cm/s	6.9±1.5	7.5±1.3	0.10	9.0±2.1	0.03	0.20
S',cm/s	7.3±0.8	7.6±1.1	0.45	8.2±1.60	0.10	0.30
HR submax	126±7	128±7	0.94	118±10	0.06	0.04
SV_{submax}, ml	88±16	106±20	<0.01	132±26	<0.01	0.02
CO_{submax}, l	10.7±2.2	13.4±2.7	<0.01	14.5±1.9	<0.01	0.40
e'_{submax} cm/s	12.1±2.1	13.0±2.2	0.12	14.4±1.4	0.03	0.05
S'_{submax} cm/s	8.4±1.5	10.8±1.6	<0.01	11.9±1.2	<0.01	0.20

Data are mean (SD). **VO_{2max}:** *Maximal oxygen uptake*, **EDV**: *end diastolic volume*, **SV:** *stroke volume*, **E/A:** *E/A ratio Early diastolic mitral inflow/late diastolic mitral inflow*, **e:** *early diastolic*

tissue velocity, **S':** *systolic tissue Doppler velocity*, **e'$_{submax}$:** *early diastolic tissue velocity during stress test*, **S'$_{submax}$:** *systolic tissue velocity during stress test*

Paper 3.

The primary outcome in paper three was VO_{2max}. Both groups increased their VO_{2max}, but VO_{2max} peaked varied at different time points indicating different adaptation rate. Independent of time point measurements, the moderate frequency (MF) group increased peak VO_{2max} by 12.1% ($p<0.01$)(day four after training cessation) and the high frequency (HF) group increased peak VO_{2max} 7.1 % ($p<0.01$, between group differences, $p= 0.319$) (day 12 after the training cessation). Initially, there was a non-significant decline in the HF group after the training period. However, there was no difference in the magnitude of VO_{2max} improvements when comparing the two groups during the study period.

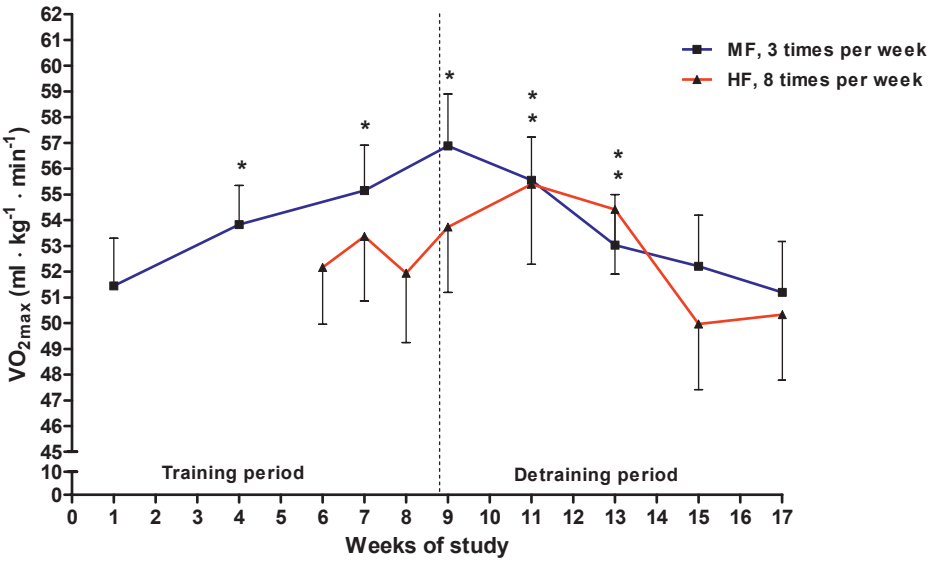

Figure 7. *Time points of VO_{2max} measurements.*

Mean values and standard error of the mean of VO_{2max} for the two groups during the training and the detraining period are shown. Vertical dotted line states the last day of training. Echocardiography was obtained at baseline, between test 3 and 4 and at week 17.

*Indicates significant differences from baseline within groups.

The secondary outcomes were myocardial systolic and diastolic function, lung diffusion capacity, endothelial function and blood samples. After the training period we observed an increased SV and EF measured at rest in the MF group only ($p<0.05$). EF measured at rest decreased in the HF group ($p<0.01$). EDV and SV increased after the detraining period in the HF group. All cardiac measurements were normalized to baseline values in the MF group after the detraining period. The lung diffusion capacity was increased in the MF group after the training period, whilst a reduction was observed in the HF group.

Lung diffusion capacity was normalized to baseline values in both groups during the detraining. There were no changes in either groups regarding endothelial function or among the blood samples analyzed. We concluded that the two training programs yielded different cardiopulmonary adaptations; a moderate frequency program caused a progressive cardiopulmonary adaptation during the training program and conversely a progressive loss of adaptation in the detraining period. On the other hand, a high frequency program induced a transient fatigue that initially depressed the cardiopulmonary function, but resulted in a super compensation during the detraining period and had a longer lasting effect.

Additional information not included in the paper: Exercise echocardiography supports our cardiac findings at rest showing that S' measured during exercise decreased in the HF group after the training period. This was compensated after the detraining and tended to increase from baseline measurement.

Discussion

An effective treatment strategy of essential hypertension

Study one demonstrates that the antihypertensive effect of endurance training in essential hypertension may be intensity dependent (Figure 6). The AIT group reduced average and night time systolic ABP more than the MIT group, and only the AIT group reduced the average HR during 24 hour.

The blood pressure reducing effect of dynamic aerobic training is generally accepted (53) and according to the American College of Sports Medicine, categorized as evidence A (52). Numerous studies have shown that endurance training has an antihypertensive effect (52, 55, 122). The correlation between exercise intensity and BP reducing effect has been debated and there are conflicting results in the literature (52, 55, 123). Most reviews have concluded that low intensity training is as effective in lowering blood pressure as training at higher intensities (45, 55). However, the majority of these studies have investigated the effect of exercise intensity training below 85% of maximal heart rate (HR_{max}), and few studies have compared different intensities directly (54). In studies where two or more training regimens are compared there have often been different intensity, duration and exercise mode (54). Fagard and Cornelissen performed a well designed cross-over study to investigate the role of intensity on the BP reducing effect of endurance training (124). Two groups were randomized to either a training program with 33% of heart rate reserve or 66% of heart rate reserve (corresponding to 59% and 79% of HR_{max} respectively). They could not find any relation between intensity and systolic BP, but the higher intensity group reduced diastolic BP more than the lower intensity group. However, in their study, only five of the participants had hypertension while the others had normal BP. Further, they observed the largest effect among those with the highest baseline BP. Our patients were all classified as moderate hypertensive patients with mean systolic ABP by 152 mmHg. In addition, both training groups in Cornelissen and Fagard's study performed continuous training where the applied intensities were fairly similar to our continuous moderate group. Their results correspond to the findings observed in the MIT group in paper one. To our knowledge there has not been performed studies with

hypertensive subjects prescribed to exercise at an intensity >85% of HR_{max}. As the relation between VO_{2max} and the magnitude of BP reduction is well established (54), the most effective training program to increase VO_{2max} would thus expect to result in largest BP reduction. In a short term view, this would favour training with a high intensity (117). Our results seem to substantiate this.

In paper two, AIT reduced office systolic and diastolic BP among healthy seniors. Aging causes changes in the vasculature that in part may be comparable to hypertension, with increased stiffness, intimal wall thickening and reduced compliance. As the walls of the arteries stiffen, central systolic arterial pressure increases, whilst the diastolic arterial pressure decreases. A widened pulse pressure is an independent risk factor for future CVD events (125). Isolated systolic hypertension is the most common form of hypertension after the age of 50 (126). Among young persons the BP is mainly determined by the peripheral vascular resistance (TPR), but in older subjects it is determined to a greater extend by increased stiffness in the central arteries (127). Also, it has been proposed that increased vascular stiffness precedes the development of hypertension (128). This suggests that hypertension may primarily be a disease of the arterial wall, causing structural changes in the vasculature, and those compensatory mechanisms to normalize BP fails during ageing. As an example is the observation of the marked reduction in endothelial function, measured by FMD, at the 6.th decade (129). This means that structural changes are normalized by functional compensatory mechanisms, but when these functional mechanisms fail, such as reduced production of eNos, hypertension will develop.

Acute effects of exercise on blood pressure

During the first minutes of endurance training, elevated oxygen demand creates an initial increase in CO due to a reduction in parasympathetic activity. This is gradually followed and replaced by an increased sympathetic activity (130). Increased CO and vasoconstriction of the non-exercising vascular beds result in elevated systolic BP, but the working muscles increase local blood flow and the net result is a reduction in TPR. Diastolic BP is reduced or slightly elevated (caused by the occlusion of blood flow by the forceful contractions of the exercising muscle). After exercise has been terminated, there has been observed a reduction of plasma catecholamines, CO, plasma volume and TPR (52, 131). The phenomena of the acute effect of BP reduction after a single bout of exercise was discovered in 1897 by Hill (132) and is referred to as post exercise hypotension (PEH). The effect of PEH has been observed to last from 2 to 22 hours (52). The transient effect is thought to accumulate and may be responsible for some or even most of the chronic BP reduction seen after endurance training (131, 133). Lately there has been growing literature suggesting a relation between intensity and PEH (133-135). One recent study by Pescatello and Eicher et al demonstrates that training sessions performed near 100% of VO_{2max} provides the largest BP reduction in hypertensive patients compared to training at lower intensities (133). Their results are in accordance to our results, showing a reduction of systolic ABP by 11.0 mmHg.

Chronic effects of exercise on blood pressure

The exercise induced BP regulation is complex and a variety of mechanisms have been observed with aerobic endurance training. This include changes of the autonomic nervous system, circulating catecholamine's, endothelial function, blood lipids, blood volume, total peripheral resistance, renin-angiotensin system and insulin resistance (55).

The autonomic nervous system plays a central role in the hypertensive pathology. Exercise has been shown to reduce sympathetic nerve activity as shown by reduced circulating catecholamines (54), reduced activity in the postganglionic nerve activity from the peroneal nerve measured by microneurography (136). These studies areconsistent with our findings with reduced resting HR and increased HRR after maximal exercise.

HR recovery after an exercise test is proven to be an index of the inhibitory effect on the vagal reactivation in the heart after the termination of the sympathetically activated state of exercise (118). Reduced HR after exercise is in accordance to many other studies (55, 136, 137) suggesting an increased vagal tone and a reduced sympathetic drive (138). HR at rest and HR recovery after exercise testing are used as prognostic markers for CVD and mortality (32). In our study, however, the effect on HR recovery and HR_{mean} was limited to the AIT group. The mechanisms behind the modulation of the autonomic nervous system may be multiple. Blood volume has been shown to increase in response to exercise training (139) and is believed to stimulate baroreceptors in the right atrium (130) which subsequently lead to a reduced sympathetic vasomotor tone(140).

Several studies have demonstrated a reduction of the plasma renin activity after exercise (55). In addition to reduced vasomotor tone, this may cause structural changes in the vasculature, since angiotensin II has a trophic effect on the smooth musculature. Trained subjects have an increased ratio of capillary lumen to intima media (141). In conclusion, this would contribute to a reduced TPR as seen in paper one.

The hypertensive pathology leads to endothelial dysfunction with increased risk of thrombosis, cell proliferation of intima and smooth muscles and changes in the coagulation-fibrinolytic pathways. Several studies have demonstrated increased FMD and improved endothelial function after aerobic exercise in patients with CVD, including patients with hypertension, dyslipidemia and diabetes type II (142-144). High intensity aerobic interval training has shown in some studies to improve FMD and endothelial function more than exercising at lower intensities (76, 79), but the effect has been equal in other studies (145, 146) . In our study, endothelial function improved only in the AIT group. We have no explanation to the lack of improvement of FMD in the MIT group, which was unexpected. Although we did not measure FMD in paper two, regular aerobic exercise appears to slow down the age-related progression of central artery stiffening (144). There has been growing literature proving that high intensity training improves blood lipids more than training at lower intensities (12, 79, 147). In our study, only the AIT group improved Hdl cholesterol.

The implications of AIT as treatment for patients with hypertension might be considered to be of clinical importance. Only small reductions of blood pressure have substantial

effects on morbidity and mortality of CVD. It has been estimated that a 2-mm Hg reduction of SBP results in a 6% reduction in stroke mortality and a 4% reduction in mortality attributable to coronary heart disease. For a 5-mmHg decrease of systolic BP the reduction in stroke and ischemic heart mortality was 14% and 9%, respectively (148).

An effective method to increase aerobic capacity

In all three studies AIT increased VO_{2max} profoundly. In study one AIT improved VO_{2max} more than MIT (15.0% vs 5.0%, group difference $p<0.01$). Our results are in line with other studies (75, 76, 79, 117, 149) reflecting the importance of intensity to increase VO_{2max}. In paper one the AIT group increased VO_{2max} by 0.15 ml/kg/min or 0.42% per training session. Large epidemiological studies show that higher levels of physical activity and physical fitness are associated with a continuous and graded reduction in the incidence of hypertension. Training at high intensity should therefore be efficient, not only to treat hypertension as seen in paper one, but also to prevent development of hypertension among healthy subjects. Physical activity is generally low in western countries and the incidence of hypertension is estimated to increase in the future. Aerobic capacity is a strong predictor of morbidity and mortality in healthy people and patients with CVD (11) and patients with hypertension (150). The results in paper one suggest that high intensity aerobic interval training is an effective approach to increase aerobic capacity and to reduce overall cardiovascular risk in hypertensive patients.

Demographic patterns are changing in western countries, with a pattern of increased life expectancy and a reduced birth rate. The need of self-reliant among elderly is

importunate, and physical activity is a key element to achieve successful aging (151). During ageing there is a marked reduction of physical activity in leisure time, and especially high intensity exercises. Changes in behaviour to include more physical activity, and especially to include physical activity at higher intensities has shown to reduce the risk for future CVD events and increase longevity (152). A recent study by Kokkinos et al showed that aerobic fitness is a strong predictor of mortality also in a population of healthy older men (14). In paper two, the baseline value of VO_{2max} among the seniors was 32.5 ml/kg/min, which is higher than an average value in the normal population for this age class (21). The AIT method increased VO_{2max} in healthy seniors by 0.13 ml/kg/min per training session (a total of 14.0%) and is considerable taken the high baseline values into account. The effect of a vigorous training program in elderly people has been shown earlier, and our results are consistent with previous work (153). In our study, the compliance to the training program was high and suggests that AIT is a well tolerated training method among elderly healthy subjects.

In paper three we observed a similar increase of VO_{2max} in the moderate frequency group, with an average increase by 0.23 ml/kg/min per training session. The increase in the high frequency group was smaller, however not significant different from the moderate frequency group, with an average increase by 0.13 ml/kg/min (between group difference p=0.32). Immediately after terminating the training program we observed a non-significant decline in VO_{2max} in the HF group. This may suggest a lack of compensatory response due to a fatigue. Whether this fatigue was muscular, cardiopulmonary or central nervous is unclear. The subjects in the HF group were not able to achieve their HR_{max} and

felt exhausted and complained about a general fatigue throughout the training period and especially at the end of the training period. During the detraining period where sufficient restitution was obtained, we observed an increased VO_{2max} in the HF group with their peak 12 days after terminating the training program.

Our results suggest that improved VO_{2max} among healthy non-exercising subjects is similar (relative change), regardless of age and training status. In addition, the improvements may be independent of the length of the training programme. Our results suggest that it is the numbers of training sessions that are of importance. However, our sample sizes in the different studies are limited by small sample sizes and of short duration.

In paper three, the MF group improved VO_{2max} almost double of what the HF group did, although not significantly different. We believe that longer duration of the training programme or a larger sample size, a significant difference would have occurred between the two groups. This is further supported by the initial reduction in the myocardial function and lung diffusion capacity seen in the high frequency group immediately after the training period. We would therefore suggest that the high frequency training is not advisable to untrained subjects.

An effective method to improve myocardial function

Regular aerobic endurance training induces several functional and structural changes in the heart muscle, characterized by increased LV cavity size and mass, referred to as the

athlete's heart (154). This was first described in 1897 by Henschen, a Swedish physician, by percussion of the thorax of cross-country skiers. He observed an enlargement of the heart and stated that "Skiing causing an enlargement of the heart which can perform more work than the normal heart". Cross sectional studies demonstrate that endurance trained athletes have larger LV cavities and increased LV mass (154). Longitudinal studies of sedentary people starting aerobic endurance training support that myocardial changes occur in response to training (154-156). In all our three studies we confirm the same findings. Table 5 summarizes the effect of aerobic endurance training on myocardial function in *our* studies.

Table 5. Echocardiography, effect of exercise

	Hypertensive AIT	Hypertensive MIT	Seniors	MF after training	HF after training	MF after detraining	HF after detraining
EDV, ml	↑	→	↑	↑	↑	→	↑
SV, ml	↑	→	↑	↑	→	→	↑
EF, %	↑	→	↑	↑	↓	→	→
E/A, ratio	→	→	↑	→	→	→	→
IVRT, ms	↓	→	↓	↓	↓	→	↑
e', cm/s	↑	→	↑	→	→	→	→
S', cm/s	↑	↑	↑	↑	→	→/↑	→
$e'_{exercise,}$ cm/s			↑	↑	↑	→	→
$S'_{exercise,}$ cm/s			↑	↑	↑	→	↑
$HR_{rest,}$	↓	→	↓	→	↓	→	→

b/min							
HR_{max}, b/min	→	→	→	↓	↓	→	→

EDV*; end diastolic volume,* **SV***; stroke volume,* **EF***; ejection fraction,* **E/A***; ratio of early diastolic mitral inflow velocity/late diastolic mitral inflow,* **IVRT***; isovolumic relaxation time,* **e'**; *early diastolic tissue velocity measured at rest,* **S'***; systolic tissue velocity measured at rest*, $\mathbf{e'_{exercise}}$*; early diastolic tissue velocity measured during exercise,* $\mathbf{S'_{exercise}}$*; systolic tissue velocity measured during exercise, ,* $\mathbf{HR_{rest}}$*; Heart rate measured at rest during echocardiographic examination,* $\mathbf{HR_{max}}$*; Maximal heart rate measured during maximal oxygen uptake test.*

In paper one AIT had a superior effect to increase myocardial systolic function compared to training at lower intensity. The positive effect of high intensity exercise on myocardial function in other CVD has been well documented in previous studies (76, 78, 119), but this is, to our knowledge, the first time it has been studied in a hypertensive population. Our study demonstrated increased stroke volume, end diastolic volume and ejection fraction in the AIT group. This is in accordance with the findings in paper two among the sedentary seniors and in paper three in the MF group. The effect on cardiac systolic performance correspond to earlier studies in aged populations (157). However, increased circulating blood volume in response to endurance training has earlier been reported after endurance training (139), and the effect is similar between moderate intensity continuous training and high intensity interval training (158). Increased EDV with a simultaneous increased SV, without increased LV wall thickness may thus reflect eccentric remodeling

as a response to training. In the high frequency group in paper three, EDV increased after the training period while resting SV was unchanged and EF was thus reduced. Systolic function measured by S' increased at rest in the MF group, while no difference was observed in the HF group. The number of participants in this study is limited and the SV and S' is similar in both groups after the training intervention. The baseline differences may be a question of coincidence, and a type 2 error can not be ruled out. On the other hand, we observed a reduced lung diffusion capacity and a small and non-significant decline in VO_{2max} in this group. This may indicate a temporary cardiopulmonary depression induced by the strenuous training program as been demonstrated before (159). After the detraining period (9 weeks), the increased EDV was sustained and SV had increased and EF was normalized to baseline value. This suggests that the restitution was inadequate and more rest was needed to induce compensatory cardiac adaptations, but that the cardiac effect was maintained for a longer time. The differences might have been more profound earlier in the detraining period, but can not be ruled out since the first measurements were initiated 8 weeks after termination of the training.

In paper one, the changes in systolic tissue Doppler measurements were highly significant, while only borderline in the MIT group. There was a trend towards increased S' in the MF group in paper three, but not among the seniors or the HF group in paper two and three. S' is a relatively early event in systole and has been shown to correlate to contractility (160). However, S' is inversely related to afterload (104) and correlates to HR (99). The population in paper one was hypertensive patients and both training groups reduced systolic BP and TPR which may have contributed to the increased S'. Among the

seniors we also observed a reduction in afterload, with unchanged resting S', but the effect on S' may have been counteracted by a significant reduction in resting HR.. Nevertheless, S' measured during exercise increased significantly in this group despite similar BP measurements during exercise. This may indicate an increased systolic function and an increased cardiac reserve independently of different loading conditions. Animal studies performed at our laboratory have reported incremental effect on contractility in isolated myocytes from rats after AIT compared to MIT. This supports an enhanced systolic function per se after AIT (161), not only improvement due to reduced load. However, increased plasma volume in response to training may have inferred our measurements and contributed to greater utilization of the Frank Starling effect which may have increased S' during exercise.

Additional information, not sent for publication; In the HF group in paper three, we observed a reduced S' measured during exercise after the training period, but this normalized after the detraining and tended to increase compared to baseline values, although not significantly (p=0.09). During exercise measurements, systolic BP and HR was similar in the HF group at baseline and follow up, which may indicate that there was a myocardial effect per se and not only an effect of different loading conditions.

In conclusion our studies indicate that AIT enhances systolic cardiac performance in hypertensive patients as well as healthy aged and young subjects.

Diastolic function, measured by echocardiography, improved among the AIT group in paper one and among seniors in paper two, but not among any of the young subjects in paper three. Young sedentary subjects have a normal diastolic function, which is capable to meet increased physical demands (162, 163). Thus it is less probable that this increases with training.

A normal diastolic function allows the LV to fill without increasing the filling pressure. Diastolic dysfunction refers to increased filling pressures, and is a common finding in hypertension, but the population in paper one was within the normal range when indexed for age (99, 164). However, we did not perform stress echocardiography testing in paper one, which may have unmasked diastolic abnormalities during exercise despite a normal diastolic function at rest. In a recent study, Tan et al demonstrated that subjects with well-monitored essential hypertension and absence of LVH had diastolic dysfunction during exercise, despite a normal diastolic function at rest (165). As for hypertension, aging causes changes in the diastolic function with increased left ventricular stiffness, fibrosis and reduced calsium handling in the cardiomyocytes (166). Tissue Doppler velocities are markedly reduced during aging, and e' is reduced by 1 cm/second each decade after the age of 30 years (167). The aged myocardium contains less myocytes that are slightly increased in size, and in the extracellular matrix there is increased connective tissue due to degradation of matrix proteins (127). In paper two, the sedentary seniors had a mean value of e' by 6.9 cm/second which is comparable to their age class in normal studies (99). Although debated, e' is demonstrated to be useful as a less load dependent measure of left ventricular relaxation rate compared to traditional flow parameters (168). E'

corresponds to tau, the rate constant of pressure versus time (dP/dT) in the LV isovolumic relaxation. The shortened IVRT among the AIT group in paper one and the seniors in paper two after AIT supports the finding of improved LV relaxation. The LV relaxation is, on the molecular level, determined by the rate of calcium reuptake in to the sarcoplasmatic reticulum by the sarcoplasmatic reticulum calcium ATPase (SERCA2). Animal studies have shown that calcium handling and SERCA2 activity are increased in older sedentary animals after participating in exercise programs (169-171). Increased relaxation rate with exercise is also demonstrated in isolated myocytes, thus showing that there are myocardial effects, not only effects due to reduced load (172) The mechanism for the improved e' in our studies may be similar.

Improved diastolic function among highly trained elderly subjects compared to sedentary controls has previously been demonstrated (173, 174). The improvement has been modest, and remains far below values observed in young sedate persons. An important drawback with echocardiographic measurements is that their values are a result of mixed influences of relaxation, stiffness and filling pressures. Levine et al has earlier proposed that lifelong endurance training improves LV compliance and not LV relaxation (174). LV compliance is a measure of change in volume over the change in pressure (dV/dP) and is the reciprocal of LV stiffness. LV compliance is determined by myocardial viscoelastic properties and ventricular-arterial coupling. LV compliance is measured correct by invasive LV pressure-volume loops, and is measured as the LV end diastolic pressure volume relation. Thus, reduced compliance is less relevant for the rate of *early* relaxation. However, in a recent study, Levine et al also found improved LV relaxation

after training intervention among sedate seniors (175). In this study, 9 sedentary men (70.6±3 years, 6 men, 3 women) exercise regularly for one year and progressively increased intensity and duration during the training period. Their results were compared to old Master Athletes (MA). Concordant to our study they found improved E/A ratio and a shortened IVRT after the training period, but conversely they found reduction of e', which also differed from their other echocardiographic measurements. They speculate if their contradictory results show that LV relaxation did not actually improve, and that Doppler flow measurements increased only due to plasma volume expansion after training. Invasive measurements in the same study demonstrated that LV compliance did not improve after one year of training. On the other hand, our study revealed clear and concordant results for both flow and tissue Doppler measurements. Both early and late diastolic filling improved in our study. Both studies are small, and the differences may be explained by the differences between the groups.

In paper one and two we found improved e' and IVRT after the training intervention. This has previously been demonstrated (76, 119) and supports the beneficial effect of AIT on diastolic function. In addition, systolic BP decreased during the training period and thus reduced the afterload among the hypertensive patients and the seniors. The LV diastolic function is not isolated from the systolic function as LV recoil is affected. This is not only seen as a change in LV stiffness, but also the amount of systolic contraction, which again is afterload dependent. Arterial compliance is known to increase after training interventions (176). A reduced afterload causes less resistance to the systolic contraction, increasing the total amount, causing more recoil and a greater diastolic

suction. Heart rate has a significant influence on the traditional diastolic flow markers and may be partly responsible for the increased E/A ratio of the mitral flow (177) seen in our studies. Although tissue Doppler velocities have shown to be less dependent by HR (100), a recent study suggest that e' is also affected by HR (101) which may have contributed to the increased e' measured at rest among the seniors in paper two.

During exercise the increased CO, which can increase as much as eight times from rest to maximal exercise (21), must be matched by enhanced LV diastolic filling. The need for an optimal diastolic function is thus crucial. The filling time of the LV has to be reduced to match the increased HR. Filling time decreases from ~ 0.55 sec at a HR of 70 beats per minute to about 0.12 sec at a HR at 195 beats per minute (108, 178). In a recent study it was suggested that the key difference between sedentary seniors and Master athletes during submaximal exercise was the ability to augment the diastolic suction of the left ventricle (179). In paper two, we measured diastolic performance during stress with color tissue Doppler measurements of e' and a'. Unfortunately, we measured e' and a' together (fusion) and not separately, which makes it difficult to differentiate between early active relaxation and static compliance. This is a limitation since we are not able to distinguish between the two measurements and thus unable to draw any conclusion of the early relaxation of the LV.

The measurements before and after the training period were obtained at the same intensity and are nonetheless a measure of the diastolic function. Likewise, the results are in line with our other echocardiographic measurements. Among the seniors the diastolic

tissue Doppler velocity increased significantly (12.9±1.9 cm/s to 14.3±2.2 cm/s, $p<0.01$) and was different from the MA at baseline, but not after the training period (14.4±1.4 cm/s, $p<0.01$ at baseline and $p>0.90$ at follow up). This indicates that cardiac diastolic reserve is trainable and that only three months of high intensity interval training may equalise life long endurance training in some subjects. However, the difference in diastolic function was larger between MA and young subjects than seniors and MA.

Several cross sectional studies have observed an enhanced diastolic function among endurance trained individuals compared to sedentary controls (162), whilst some studies have not seen any differences (162). In longitudinal studies there exists limited data of alterations in diastolic function after training interventions. One study have shown that exercise capacity is closely linked to diastolic function (107). Based on our studies, it is not possible to determine the most important component to improve VO_{2max} as both systolic and diastolic properties increased simultaneously after AIT. Our studies were not designed to elucidate the mechanisms behind the improved diastolic function. Further studies are required to answer this question.

In conclusion our studies indicate that AIT enhances diastolic cardiac performance in hypertensive patients and healthy aged sedentary subjects, where diastolic function is reduced at the outset. The latter group, however, only to the level of trained counterparts of the same age, is far below the level of young subjects. Where diastolic function is absolutely normal, as in the young subjects, there is less effect of training.

Limitations and future directions of studies

The main limitation in all training studies is that the studies primarily recruits the subjects most motivated for training. The potential of training as treatment is thus limited in the general population.

Paper 1

The patients in study 1 were recruited locally by an advertisement in the regional newspaper, Adresseavisen. This may potentially have resulted a selection bias as mentioned above, but our population is comparable to other, larger trials (54).

This small study have to be considered as experimental and as an example of what is possible to achieve in an optimal laboratory setting, measuring only the physiological effects of training. The effect of AIT as treatment is dependent on factors such as how applicable the training regimen is in a multi-center setting, the number of patients it is possible to recruit, compliance and, the adherence to training as permanent lifestyle after the first intervention. Our study lacks long time follow-up data on the patients. Another limitation is the impossibility to blind the patients in regard to the training method and intensity. Psychological factors affect blood pressure and knowledge of the training intensity may have influenced the results, especially in the control group. Finally, we cannot completely rule out the possibility that some patients took blood pressure medication during the intervention period.

The strengths of the study is the strict training program which is easy to monitor, allowing the study of the physiological effects of the training interventions, and measure the progression according to any improvement in aerobic capacity.

In a future setting, a multicenter study should be performed in order to validate the reproducibility of results at different centers, as well as larger number to do intention-to-treat. As the long term adherence to training may be influenced by the degree of fitness improvement, long term follow up should be done to see if different training regimens might result in different adherence. Also, more focus should be emphasized on the drop-outs to identify factors and distinguish between those subjects achieving a successful or unsuccessful training period. To reveal more of the antihypertensive mechanisms investigators should consider measurements of the sympathetic nervous system, heart rate variability, renin, vascular stiffness (tonometry) and blood volume. In addition, measurements of physical activity outside the study and dietary registrations should be easily obtained by validated questionnaires.

Paper 2

The group of healthy seniors consisted of highly motivated and healthy persons and does not represent the general population >70 years. This has to be kept in mind as the translation to the general population may not be transferable.

The study is limited by its small number of participants and has a skew gender allocation in both the intervention group and among the master athletes. The seniors recruited to our

study were free of diseases, motivated and had a very high baseline $VO_{2max.}$ Our results may therefore not be transferable to the general age related population. Future recommendations to studies would include long term follow-up, recruit more patients from other patient populations and consider measurements of endothelial function, ABP, blood volume and artery stiffness.

Paper 3

The main limitation is the limited number of participants which affects the power of the secondary outcome measurements. In addition, in our study we observed inadequate restitution, but with a modification of the exercise design allowing more days without training, the results may have been different. Future studies should search to identify an "overtraining factor" and a "restitution factor" that may lead to an individual tailored advice for athletes to achieve an optimal progression of training adaptations.

References

1. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical Fitness as a Predictor of Mortality among Healthy, Middle-Aged Norwegian Men. N Engl J Med. 1993;328(8):533-7.

2. Physical Activity Guidelines Advisory Committee Report, 2008. Centers for Disease Control and Prevention: U.S Department of Health & Human Services 2008.

3. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239-46. Epub 2008/06/06.

4. Lee. Physical activity and all-cause mortality: what is the dose-response relation? Medicine and science in sports and exercise. 2001;33(6):S459-S71.

5. Paffenbarger RS, Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med. 1986;314(10):605-13. Epub 1986/03/06.

6. Blair SN, Kohl HW, III, Barlow CE, Paffenbarger RS, Jr, Gibbons LW, Macera CA. Changes in Physical Fitness and All-Cause Mortality: A Prospective Study of Healthy and Unhealthy Men. JAMA. 1995;273(14):1093-8.

7. Organization WH. Global Burden of Disease, 2004 update. 2008.

8. Sophie Petersen VP, Mike Rayner, Jose Leal, Ramon Luengo-Fernandez, Alastair Gray. European Cardiovascular Diseases Statistics. British Heart Foundation Health Promotion Research Group, Department of Public Health, University of Oxford. 2005.

9. Deaths by underlying cause of death. The whole country. 1991-2009. Statistisk Sentralbyrå. 2009.

10. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. Br J Sports Med. 2009;43(1):1-2. Epub 2009/01/13.

11. Jonathan Myers MPR, Victor Froelicher, Dat Do, Sara Partington, Edwin Atwood. Exercise Capacity and Mortality Among Men Reffered for Exercise Testing. New England Journal of Medicine. 2002;346(11):793-801.

12. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39(8):1423-34. Epub 2007/09/01.

13. Kesaniemi YK, Danforth E, Jr., Jensen MD, Kopelman PG, Lefebvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc. 2001;33(6 Suppl):S351-8. Epub 2001/06/28.

14. Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, et al. Exercise Capacity and Mortality in Older Men. A 20-Year Follow-Up Study. Circulation. 2010. Epub 2010/08/11.

15. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. Circulation. 2011;124(23):2483-90. Epub 2011/12/07.

16. Erikssen G, Liestol K, Bjornholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. Lancet. 1998;352(9130):759-62. Epub 1998/09/16.

17. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality: the Finnish twin cohort. JAMA. 1998;279(6):440-4. Epub 1998/02/18.

18. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2011(7):CD001800. Epub 2011/07/08.

19. Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J, et al. Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. J Appl Physiol. 1999;87(3):1003-8. Epub 1999/09/14.

20. An P, Perusse L, Rankinen T, Borecki IB, Gagnon J, Leon AS, et al. Familial aggregation of exercise heart rate and blood pressure in response to 20 weeks of endurance training: the HERITAGE family study. Int J Sports Med. 2003;24(1):57-62. Epub 2003/02/13.

21. Aastrand P.O RK. Textbook of work physiology: Physiological bases of exercise. Human Kinetics Publishers. 1986.

22. Levine BD. .VO2max: what do we know, and what do we still need to know? J Physiol. 2008;586(1):25-34. Epub 2007/11/17.

23. Ogawa T, Spina RJ, Martin WH, 3rd, Kohrt WM, Schechtman KB, Holloszy JO, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. Circulation. 1992;86(2):494-503. Epub 1992/08/01.

24. Bassett DR, Jr., Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc. 2000;32(1):70-84. Epub 2000/01/27.

25. PD. W. New ideas on limitations to VO2 max. Exerc Sport Sci Rev. 2000;28:10-4.

26. Aspenes ST, Nauman J, Nilsen TI, Vatten LJ, Wisloff U. Physical activity as a long-term predictor of peak oxygen uptake: the HUNT Study. Med Sci Sports Exerc. 2011;43(9):1675-9. Epub 2011/03/03.

27. Zhang GQ, Zhang W. Heart rate, lifespan, and mortality risk. Ageing Res Rev. 2009;8(1):52-60. Epub 2008/11/22.

28. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011;306(23):2579-87. Epub 2011/12/22.

29. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. Sports Med. 2003;33(1):33-46. Epub 2002/12/13.

30. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med. 1999;341(18):1351-7. Epub 1999/10/28.

31. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med. 2000;132(7):552-5. Epub 2000/04/01.

32. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biological Psychology. 2007;74(2):224-42.

33. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23. Epub 2005/01/18.

34. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet. 2007;370(9587):591-603. Epub 2007/08/21.

35. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA. 2002;287(8):1003-10. Epub 2002/02/28.

36. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet. 2001;358(9294):1682-6. Epub 2001/12/01.

37. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. Circulation. 2000;101(3):329-35. Epub 2000/01/25.

38. Seravalle G, Cattaneo BM, Giannattasio C, Perondi R, Saino A, Grassi G, et al. RAA system and cardiovascular control in normal subjects, hypertensives and patients with congestive heart failure. J Hum Hypertens. 1993;7 Suppl 2:S13-8. Epub 1993/08/01.

39. Grassi G, Quarti-Trevano F, Dell'oro R, Mancia G. Essential hypertension and the sympathetic nervous system. Neurol Sci. 2008;29 Suppl 1:S33-6. Epub 2008/07/17.

40. Cowley AW, Jr., Roman RJ. The role of the kidney in hypertension. JAMA. 1996;275(20):1581-9. Epub 1996/05/22.

41. Esler M, Rumantir M, Kaye D, Jennings G, Hastings J, Socratous F, et al. Sympathetic nerve biology in essential hypertension. Clin Exp Pharmacol Physiol. 2001;28(12):986-9. Epub 2002/03/21.

42. Kirchheim HR. Systemic arterial baroreceptor reflexes. Physiol Rev. 1976;56(1):100-77. Epub 1976/01/01.

43. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet. 1990;335(8692):765-74. Epub 1990/03/31.

44. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13. Epub 2002/12/21.

45. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens. 2007;25(9):1751-62. Epub 2007/09/01.

46. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. JAMA. 1983;249(20):2792-8. Epub 1983/05/27.

47. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med. 2003;348(24):2407-15. Epub 2003/06/13.

48. Palatini P. Reliability of ambulatory blood pressure monitoring. Blood Press Monit. 2001;6(6):291-5. Epub 2002/06/11.

49. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, O'Malley K, et al. The British Hypertension Society protocol for the evaluation of automated and semi-

automated blood pressure measuring devices with special reference to ambulatory systems. J Hypertens. 1990;8(7):607-19. Epub 1990/07/01.

50. Excellence NIfHaC. Hypertension: clinical management of primary hypertension in adults. 2011; CG127.

51. Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM. Comparison of interleukin-6 and C-reactive protein for the risk of developing hypertension in women. Hypertension. 2007;49(2):304-10. Epub 2006/12/13.

52. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc. 2004;36(3):533-53. Epub 2004/04/13.

53. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007;14 Suppl 2:S1-113. Epub 2007/11/06.

54. Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. Eur J Cardiovasc Prev Rehabil. 2007;14(1):12-7. Epub 2007/02/16.

55. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension. 2005;46(4):667-75. Epub 2005/09/15.

56. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007;115(10):1285-95. Epub 2007/03/14.

57. Wolinsky H. A proposal linking clearance of circulating lipoproteins to tissue metabolic activity as a basis for understanding atherogenesis. Circ Res. 1980;47(3):301-11. Epub 1980/09/01.

58. Green D. Point: Flow-mediated dilation does reflect nitric oxide-mediated endothelial function. J Appl Physiol. 2005;99(3):1233-4; discussion 7-8. Epub 2005/08/17.

59. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999;340(2):115-26. Epub 1999/01/14.

60. Brutsaert DL, De Keulenaer GW, Fransen P, Mohan P, Kaluza GL, Andries LJ, et al. The cardiac endothelium: functional morphology, development, and physiology. Prog Cardiovasc Dis. 1996;39(3):239-62. Epub 1996/11/01.

61. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, et al. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation. 1995;91(5):1314-9. Epub 1995/03/01.

62. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39(2):257-65. Epub 2002/01/15.

63. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340(8828):1111-5. Epub 1992/11/07.

64. Harris RA, Nishiyama SK, Wray DW, Richardson RS. Ultrasound assessment of flow-mediated dilation. Hypertension. 2010;55(5):1075-85. Epub 2010/03/31.

65. Gokce N, Keaney JF, Jr., Hunter LM, Watkins MT, Menzoian JO, Vita JA. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. Circulation. 2002;105(13):1567-72. Epub 2002/04/03.

66. Gokce N, Keaney JF, Jr., Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO, et al. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol. 2003;41(10):1769-75. Epub 2003/05/28.

67. Neunteufl T, Heher S, Katzenschlager R, Wolfl G, Kostner K, Maurer G, et al. Late prognostic value of flow-mediated dilation in the brachial artery of patients with chest pain. Am J Cardiol. 2000;86(2):207-10. Epub 2000/07/29.

68. Bots ML, Westerink J, Rabelink TJ, de Koning EJ. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurement on the FMD response. Eur Heart J. 2005;26(4):363-8. Epub 2004/12/25.

69. Muiesan ML, Salvetti M, Paini A, Monteduro C, Galbassini G, Poisa P, et al. Prognostic role of flow-mediated dilatation of the brachial artery in hypertensive patients. J Hypertens. 2008;26(8):1612-8. Epub 2008/07/16.

70. Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation. 2001;104(2):191-6. Epub 2001/07/12.

71. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation. 2007;115(18):2390-7. Epub 2007/04/25.

72. Magda SL, Ciobanu AO, Florescu M, Vinereanu D. Comparative reproducibility of the noninvasive ultrasound methods for the assessment of vascular function. Heart and vessels. 2012. Epub 2012/01/14.

73. Kemi OJP, Wisloff UP. High-Intensity Aerobic Exercise Training Improves the Heart in Health and Disease. [Review].

74. Wenger HA, Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. Sports Med. 1986;3(5):346-56. Epub 1986/09/01.

75. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. Am J Cardiol. 2006;97(1):141-7. Epub 2005/12/27.

76. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115(24):3086-94. Epub 2007/06/06.

77. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2004;11(3):216-22. Epub 2004/06/05.

78. Slordahl SA, Wang E, Hoff J, Kemi OJ, Amundsen BH, Helgerud J. Effective training for patients with intermittent claudication. Scand Cardiovasc J. 2005;39(4):244-9. Epub 2005/08/25.

79. Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation. 2008;118(4):346-54. Epub 2008/07/09.

80. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA, 3rd, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation. 2007;115(17):2358-68. Epub 2007/05/01.

81. Foster C, Porcari JP. The risks of exercise training. J Cardiopulm Rehabil. 2001;21(6):347-52. Epub 2002/01/05.

82. Shaper AG, Wannamethee G, Walker M. Physical activity, hypertension and risk of heart attack in men without evidence of ischaemic heart disease. J Hum Hypertens. 1994;8(1):3-10. Epub 1994/01/01.

83. Fraser AG. Inge Edler and the origins of clinical echocardiography. Eur J Echocardiogr. 2001;2(1):3-5.

84. Angelsen B. Ultrasound Imaging. Waves, signals and signal processing. 2000:Chapter 1.

85. Stoylen A. Homepage. 2011:http://folk.ntnu.no/stoylen/strainrate/index.html#diastolic_function.

86. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. Eur J Echocardiogr. 2006;7(2):79-108. Epub 2006/02/07.

87. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. J Am Coll Cardiol. 2004;44(5):1030-5. Epub 2004/09/01.

88. Thorstensen A, Dalen H, Amundsen BH, Aase SA, Stoylen A. Reproducibility in echocardiographic assessment of the left ventricular global and regional function, the HUNT study. Eur J Echocardiogr. 2010;11(2):149-56. Epub 2009/12/05.

89. Goodman JM, Liu PP, Green HJ. Left ventricular adaptations following short-term endurance training. J Appl Physiol. 2005;98(2):454-60. Epub 2004/09/28.

90. McDicken WN, Sutherland GR, Moran CM, Gordon LN. Colour Doppler velocity imaging of the myocardium. Ultrasound Med Biol. 1992;18(6-7):651-4. Epub 1992/01/01.

91. Fleming AD, Palka P, McDicken WN, Fenn LN, Sutherland GR. Verification of cardiac doppler tissue images using grey-scale M-mode images. Ultrasound Med Biol. 1996;22(5):573-81. Epub 1996/01/01.

92. Sutherland GR, Stewart MJ, Groundstroem KW, Moran CM, Fleming A, Guell-Peris FJ, et al. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. J Am Soc Echocardiogr. 1994;7(5):441-58. Epub 1994/09/01.

93. Alam M, Wardell J, Andersson E, Samad BA, Nordlander R. Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects. J Am Soc Echocardiogr. 1999;12(8):618-28. Epub 1999/08/11.

94. Wilkenshoff UM, Sovany A, Wigstrom L, Olstad B, Lindstrom L, Engvall J, et al. Regional mean systolic myocardial velocity estimation by real-time color Doppler

myocardial imaging: a new technique for quantifying regional systolic function. J Am Soc Echocardiogr. 1998;11(7):683-92. Epub 1998/08/06.

95. Nagueh SF. Search for non-invasive load-independent indices of left ventricular relaxation. Clin Sci (Lond). 2003;105(4):395-7. Epub 2003/07/11.

96. Pela G, Regolisti G, Coghi P, Cabassi A, Basile A, Cavatorta A, et al. Effects of the reduction of preload on left and right ventricular myocardial velocities analyzed by Doppler tissue echocardiography in healthy subjects. Eur J Echocardiogr. 2004;5(4):262-71. Epub 2004/06/29.

97. Hsiao SH, Huang WC, Sy CL, Lin SK, Lee TY, Liu CP. Doppler tissue imaging and color M-mode flow propagation velocity: are they really preload independent? J Am Soc Echocardiogr. 2005;18(12):1277-84. Epub 2005/12/27.

98. Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, et al. The Effects of Aging and Physical Activity on Doppler Measures of Diastolic Function. The American Journal of Cardiology. 2007;99(12):1629-36.

99. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging. 2010;3(5):614-22. Epub 2010/06/29.

100. Yu CM, Lin H, Ho PC, Yang H. Assessment of left and right ventricular systolic and diastolic synchronicity in normal subjects by tissue Doppler echocardiography and the effects of age and heart rate. Echocardiography. 2003;20(1):19-27. Epub 2003/07/10.

101. Burns AT, Connelly KA, La Gerche A, Mooney DJ, Chan J, MacIsaac AI, et al. Effect of heart rate on tissue Doppler measures of diastolic function. Echocardiography. 2007;24(7):697-701. Epub 2007/07/27.

102. Vinereanu D, Khokhar A, Tweddel AC, Cinteza M, Fraser AG. Estimation of global left ventricular function from the velocity of longitudinal shortening. Echocardiography. 2002;19(3):177-85. Epub 2002/05/23.

103. Miller D, Farah MG, Liner A, Fox K, Schluchter M, Hoit BD. The relation between quantitative right ventricular ejection fraction and indices of tricuspid annular motion and myocardial performance. J Am Soc Echocardiogr. 2004;17(5):443-7. Epub 2004/05/04.

104. Borlaug BA, Melenovsky V, Redfield MM, Kessler K, Chang HJ, Abraham TP, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol. 2007;50(16):1570-7. Epub 2007/10/16.

105. Rowland T. Endurance athletes' stroke volume response to progressive exercise: a critical review. Sports Med. 2009;39:687-95.

106. Zhou B, Conlee RK, Jensen R, Fellingham GW, George JD, Fisher AG. Stroke volume does not plateau during graded exercise in elite male distance runners. Med Sci Sports Exerc. 2001;33(11):1849-54. Epub 2001/11/02.

107. Gledhill N, Cox D, Jamnik R. Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. Med Sci Sports Exerc. 1994;26(9):1116-21. Epub 1994/09/01.

108. Stoylen A, Wisloff U, Slordahl S. Left ventricular mechanics during exercise: a Doppler and tissue Doppler study. Eur J Echocardiogr. 2003;4(4):286-91. Epub 2003/11/13.

109. Opdahl A, Remme EW, Helle-Valle T, Lyseggen E, Vartdal T, Pettersen E, et al. Determinants of left ventricular early-diastolic lengthening velocity: independent contributions from left ventricular relaxation, restoring forces, and lengthening load. Circulation. 2009;119(19):2578-86. Epub 2009/05/06.

110. Wingo JE, Lafrenz AJ, Ganio MS, Edwards GL, Cureton KJ. Cardiovascular drift is related to reduced maximal oxygen uptake during heat stress. Med Sci Sports Exerc. 2005;37(2):248-55. Epub 2005/02/05.

111. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. Ann Intern Med. 1975;82(4):521-4. Epub 1975/04/01.

112. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. N Engl J Med. 1991;324(5):295-301. Epub 1991/01/31.

113. Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, Fraser AG. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. Am J Cardiol. 2001;88(1):53-8. Epub 2001/06/26.

114. Palatini P, Frigo G, Bertolo O, Roman E, Da Corta R, Winnicki M. Validation of the A&D TM-2430 device for ambulatory blood pressure monitoring and evaluation of

performance according to subjects' characteristics. Blood Press Monit. 1998;3(4):255-60. Epub 1999/04/23.

115. O'Brien E, van Montfrans G, Palatini P, Tochikubo O, Staessen J, Shirasaki O, et al. Task Force I: methodological aspects of blood pressure measurement. Blood Press Monit. 2001;6(6):313-5. Epub 2002/06/11.

116. Meyer T, Davison RC, Kindermann W. Ambulatory gas exchange measurements--current status and future options. Int J Sports Med. 2005;26 Suppl 1:S19-27. Epub 2005/02/11.

117. Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc. 2007;39(4):665-71. Epub 2007/04/07.

118. Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, Prakash M, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol. 2001;38(7):1980-7. Epub 2001/12/12.

119. Amundsen BH, Rognmo O, Hatlen-Rebhan G, Slordahl SA. High-intensity aerobic exercise improves diastolic function in coronary artery disease. Scand Cardiovasc J. 2008;42(2):110-7. Epub 2008/03/28.

120. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323(7321):1123-4. Epub 2001/11/10.

121. Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. Eur J Cardiovasc Prev Rehabil. 2011. Epub 2011/04/01.

122. Kokkinos PF, Giannelou A, Manolis A, Pittaras A. Physical activity in the prevention and management of high blood pressure. Hellenic J Cardiol. 2009;50(1):52-9. Epub 2009/02/07.

123. Nemoto K, Gen-no H, Masuki S, Okazaki K, Nose H. Effects of high-intensity interval walking training on physical fitness and blood pressure in middle-aged and older people. Mayo Clin Proc. 2007;82(7):803-11. Epub 2007/07/04.

124. Veronique A. Corneliessen JA, Paul Holvoet, Robert H. Fagard. Influence of exercise at lower and higher intensity on blood pressure and cardiovascular risk factors at older age

Journal of Hypertension. 2009;27:753-62.

125. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, et al. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in Men. Hypertension. 2000;36(5):801-7. Epub 2000/11/18.

126. Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. N Engl J Med. 1993;329(26):1912-7. Epub 1993/12/23.

127. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation. 2003;107(1):139-46. Epub 2003/01/08.

128. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, et al. Arterial stiffness and the development of hypertension. The ARIC study. Hypertension. 1999;34(2):201-6. Epub 1999/08/24.

129. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. J Am Coll Cardiol. 1994;24(2):471-6. Epub 1994/08/01.

130. O'Sullivan SE, Bell C. The effects of exercise and training on human cardiovascular reflex control. J Auton Nerv Syst. 2000;81(1-3):16-24. Epub 2000/06/28.

131. Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. Med Sci Sports Exerc. 2001;33(6 Suppl):S438-45; discussion S52-3. Epub 2001/06/28.

132. Hill L. Arterial pressure in man while sleeping, resting, working and bathing. *J Physiol Lond* 1897;22.

133. Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J. 2010;160(3):513-20. Epub 2010/09/10.

134. Quinn TJ. Twenty-four hour, ambulatory blood pressure responses following acute exercise: impact of exercise intensity. J Hum Hypertens. 2000;14(9):547-53. Epub 2000/09/12.

135. Forjaz CL, Cardoso CG, Jr., Rezk CC, Santaella DF, Tinucci T. Postexercise hypotension and hemodynamics: the role of exercise intensity. J Sports Med Phys Fitness. 2004;44(1):54-62. Epub 2004/06/08.

136. Grassi G, Seravalle G, Calhoun D, Bolla GB, Mancia G. Physical exercise in essential hypertension. Chest. 1992;101(5 Suppl):312S-4S. Epub 1992/05/01.

137. Jennings G, Nelson L, Nestel P, Esler M, Korner P, Burton D, et al. The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity. Circulation. 1986;73(1):30-40. Epub 1986/01/01.

138. Collier SR, Kanaley JA, Carhart R, Jr., Frechette V, Tobin MM, Bennett N, et al. Cardiac autonomic function and baroreflex changes following 4 weeks of resistance versus aerobic training in individuals with pre-hypertension. Acta Physiol (Oxf). 2009;195(3):339-48. Epub 2008/09/09.

139. Hagberg JM, Goldberg AP, Lakatta L, O'Connor FC, Becker LC, Lakatta EG, et al. Expanded blood volumes contribute to the increased cardiovascular performance of endurance-trained older men. J Appl Physiol. 1998;85(2):484-9. Epub 1998/08/04.

140. Tanaka H, Davy KP, Seals DR. Cardiopulmonary baroreflex inhibition of sympathetic nerve activity is preserved with age in healthy humans. J Physiol. 1999;515 (Pt 1):249-54. Epub 1999/02/02.

141. Dinenno FA, Tanaka H, Monahan KD, Clevenger CM, Eskurza I, DeSouza CA, et al. Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. J Physiol. 2001;534(Pt 1):287-95. Epub 2001/07/04.

142. Higashi Y, Sasaki S, Kurisu S, Yoshimizu A, Sasaki N, Matsuura H, et al. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. Circulation. 1999;100(11):1194-202. Epub 1999/09/14.

143. Linke A, Erbs S, Hambrecht R. Effects of exercise training upon endothelial function in patients with cardiovascular disease. Front Biosci. 2008;13:424-32. Epub 2007/11/06.

144. Di Francescomarino S, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. Sports Med. 2009;39(10):797-812. Epub 2009/09/18.

145. Inga E Schjerve GAT, Harald Edvard Mølmen Hansen, Arnt E Tjonna, Tomas Stølen, Ulrik Wisløff. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults
Clinical Science. 2008(115):283-93.

146. Stensvold D, Tjonna AE, Skaug EA, Aspenes S, Stolen T, Wisloff U, et al. Strength training versus aerobic interval training to modify risk factors of metabolic syndrome. J Appl Physiol. 2010;108(4):804-10. Epub 2010/01/23.

147. Cornelissen VA, Verheyden B, Aubert AE, Fagard RH. Effects of aerobic training intensity on resting, exercise and post-exercise blood pressure, heart rate and heart-rate variability. J Hum Hypertens. 2010;24(3):175-82. Epub 2009/06/26.

148. Mansia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press. 2007;16(3):135-232. Epub 2007/09/12.

149. Gormley SE, Swain DP, High R, Spina RJ, Dowling EA, Kotipalli US, et al. Effect of intensity of aerobic training on VO2max. Med Sci Sports Exerc. 2008;40(7):1336-43. Epub 2008/06/27.

150. Kokkinos P, Manolis A, Pittaras A, Doumas M, Giannelou A, Panagiotakos DB, et al. Exercise capacity and mortality in hypertensive men with and without additional risk factors. Hypertension. 2009;53(3):494-9. Epub 2009/01/28.

151. Baker J, Meisner BA, Logan AJ, Kungl AM, Weir P. Physical activity and successful aging in Canadian older adults. J Aging Phys Act. 2009;17(2):223-35. Epub 2009/05/20.

152. Talbot LA, Morrell CH, Fleg JL, Metter EJ. Changes in leisure time physical activity and risk of all-cause mortality in men and women: the Baltimore Longitudinal Study of Aging. Prev Med. 2007;45(2-3):169-76. Epub 2007/07/17.

153. Hickson RC, Bomze HA, Holloszy JO. Linear increase in aerobic power induced by a strenuous program of endurance exercise. J Appl Physiol. 1977;42(3):372-6. Epub 1977/03/01.

154. Naylor LH, George K, O'Driscoll G, Green DJ. The athlete's heart: a contemporary appraisal of the 'Morganroth hypothesis'. Sports Med. 2008;38(1):69-90. Epub 2007/12/18.

155. Green DJ, Naylor LH, George K. Cardiac and vascular adaptations to exercise. Curr Opin Clin Nutr Metab Care. 2006;9(6):677-84. Epub 2006/10/21.

156. Rodrigues AC, de Melo Costa J, Alves GB, Ferreira da Silva D, Picard MH, Andrade JL, et al. Left ventricular function after exercise training in young men. Am J Cardiol. 2006;97(7):1089-92. Epub 2006/03/28.

157. Ehsani AA, Ogawa T, Miller TR, Spina RJ, Jilka SM. Exercise training improves left ventricular systolic function in older men. Circulation. 1991;83(1):96-103. Epub 1991/01/01.

158. Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, Taylor DA, et al. Blood volume expansion and cardiorespiratory function: effects of training modality. Med Sci Sports Exerc. 2004;36(6):991-1000. Epub 2004/06/05.

159. Aslani A, Babaee Bigi MA, Moaref AR. Effect of extreme exercise on myocardial function as assessed by tissue Doppler imaging. Echocardiography. 2009;26(9):1036-40. Epub 2009/06/30.

160. Thorstensen A, Dalen H, Amundsen BH, Stoylen A. Peak systolic velocity indices are more sensitive than end-systolic indices in detecting contraction changes assessed by echocardiography in young healthy humans. Eur J Echocardiogr. 2011;12(12):924-30. Epub 2011/09/24.

161. Kemi OJ, Haram PM, Loennechen JP, Osnes JB, Skomedal T, Wisloff U, et al. Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. Cardiovasc Res. 2005;67(1):161-72. Epub 2005/06/14.

162. George KP, Naylor LH, Whyte GP, Shave RE, Oxborough D, Green DJ. Diastolic function in healthy humans: non-invasive assessment and the impact of acute and chronic exercise. Eur J Appl Physiol. 2009. Epub 2009/10/13.

163. Obert P, Nottin S, Baquet G, Thevenet D, Gamelin FX, Berthoin S. Two months of endurance training does not alter diastolic function evaluated by TDI in 9-11-year-old boys and girls. Br J Sports Med. 2009;43(2):132-5. Epub 2007/12/12.

164. Marwick PMMaT. Assesment of diastolic function: what the general cardiologist needs to know. Heart. 2005;91:681-95.

165. Tan YT, Wenzelburger F, Lee E, Heatlie G, Frenneaux M, Sanderson JE. Abnormal left ventricular function occurs on exercise in well-treated hypertensive subjects with normal resting echocardiography. Heart. 2010;96(12):948-55. Epub 2010/06/12.

166. Cain BS, Meldrum DR, Joo KS, Wang JF, Meng X, Cleveland JC, Jr., et al. Human SERCA2a levels correlate inversely with age in senescent human myocardium. J Am Coll Cardiol. 1998;32(2):458-67. Epub 1998/08/26.

167. Innelli P, Sanchez R, Marra F, Esposito R, Galderisi M. The impact of aging on left ventricular longitudinal function in healthy subjects: a pulsed tissue Doppler study. Eur J Echocardiogr. 2008;9(2):241-9.

168. Gulati VK, Katz WE, Follansbee WP, Gorcsan J, 3rd. Mitral annular descent velocity by tissue Doppler echocardiography as an index of global left ventricular function. Am J Cardiol. 1996;77(11):979-84. Epub 1996/05/01.

169. Kemi OJ, Ellingsen O, Smith GL, Wisloff U. Exercise-induced changes in calcium handling in left ventricular cardiomyocytes. Front Biosci. 2008;13:356-68. Epub 2007/11/06.

170. Tate CA, Taffet GE, Hudson EK, Blaylock SL, McBride RP, Michael LH. Enhanced calcium uptake of cardiac sarcoplasmic reticulum in exercise-trained old rats. Am J Physiol. 1990;258(2 Pt 2):H431-5. Epub 1990/02/01.

171. Tate CA, Helgason T, Hyek MF, McBride RP, Chen M, Richardson MA, et al. SERCA2a and mitochondrial cytochrome oxidase expression are increased in hearts of exercise-trained old rats. Am J Physiol. 1996;271(1 Pt 2):H68-72. Epub 1996/07/01.

172. Kemi OJ, Ceci M, Condorelli G, Smith GL, Wisloff U. Myocardial sarcoplasmic reticulum Ca2+ ATPase function is increased by aerobic interval training. Eur J Cardiovasc Prev Rehabil. 2008;15(2):145-8. Epub 2008/04/09.

173. Baldi JC, McFarlane K, Oxenham HC, Whalley GA, Walsh HJ, Doughty RN. Left ventricular diastolic filling and systolic function of young and older trained and untrained men. J Appl Physiol. 2003;95(6):2570-5. Epub 2003/07/29.

174. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, et al. Effect of aging and physical activity on left ventricular compliance. Circulation. 2004;110(13):1799-805. Epub 2004/09/15.

175. Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. Circulation. 2010;122(18):1797-805. Epub 2010/10/20.

176. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. Circulation. 2003;107(2):346-54. Epub 2003/01/23.

177. Galderisi M, Benjamin EJ, Evans JC, D'Agostino RB, Fuller DL, Lehman B, et al. Impact of heart rate and PR interval on Doppler indexes of left ventricular diastolic filling in an elderly cohort (the Framingham Heart Study). Am J Cardiol. 1993;72(15):1183-7. Epub 1993/11/15.

178. Rowell LB. Human Circulation: Regulation during physical stress. New York, Oxford University Press. 1986.

179. Popovic ZB, Prasad A, Garcia MJ, Arbab-Zadeh A, Borowski A, Dijk E, et al. Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. Am J Physiol Heart Circ Physiol. 2006;290(4):H1454-9. Epub 2005/11/15.

Paper 1

Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients

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Paper 2

Aerobic interval training compensates age related decline in cardiac function

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Paper 3

Effect of high and moderate frequency aerobic interval training on the oxygen transport chain

Running head: High vs. moderate frequency aerobic interval training

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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.

1997

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

1998

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

2000

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.

2001

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

2002

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

2003

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

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

2004

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

2005

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

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

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS

280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM

306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS
324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN
326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1* GENE MUTATION
327. Ingebjørg S. Juel : INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97
334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING

335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA
342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT
350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION
352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY
354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.
362. Kjetil Høydal : EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.

363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS
368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES
379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM
383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES
393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION

395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS
399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY
410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA
412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS
415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?
422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH

424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?
425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE
433. Lars Adde: PREDICTION OF CEREBRAL PALSY IN YOUNG INFANTS. COMPUTER BASED ASSESSMENT OF GENERAL MOVEMENTS
434. Magnus Fasting: PRE- AND POSTNATAL RISK FACTORS FOR CHILDHOOD ADIPOSITY
435. Vivi Talstad Monsen: MECHANISMS OF ALKYLATION DAMAGE REPAIR BY HUMAN AlkB HOMOLOGUES
436. Toril Skandsen: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. MAGNETIC RESONANCE IMAGING FINDINGS, COGNITION AND RISK FACTORS FOR DISABILITY
437. Ingeborg Smidesang: ALLERGY RELATED DISORDERS AMONG 2-YEAR OLDS AND ADOLESCENTS IN MID-NORWAY – PREVALENCE, SEVERITY AND IMPACT. THE PACT STUDY 2005, THE YOUNG HUNT STUDY 1995-97
438. Vidar Halsteinli: MEASURING EFFICIENCY IN MENTAL HEALTH SERVICE DELIVERY: A STUDY OF OUTPATIENT UNITS IN NORWAY
439. Karen Lehrmann Ægidius: THE PREVALENCE OF HEADACHE AND MIGRAINE IN RELATION TO SEX HORMONE STATUS IN WOMEN. THE HUNT 2 STUDY
440. Madelene Ericsson: EXERCISE TRAINING IN GENETIC MODELS OF HEART FAILURE
441. Marianne Klokk: THE ASSOCIATION BETWEEN SELF-REPORTED ECZEMA AND COMMON MENTAL DISORDERS IN THE GENERAL POPULATION. THE HORDALAND HEALTH STUDY (HUSK)
442. Tomas Ottemo Stølen: IMPAIRED CALCIUM HANDLING IN ANIMAL AND HUMAN CARDIOMYOCYTES REDUCE CONTRACTILITY AND INCREASE ARRHYTHMIA POTENTIAL – EFFECTS OF AEROBIC EXERCISE TRAINING
443. Bjarne Hansen: ENHANCING TREATMENT OUTCOME IN COGNITIVE BEHAVIOURAL THERAPY FOR OBSESSIVE COMPULSIVE DISORDER: THE IMPORTANCE OF COGNITIVE FACTORS
444. Mona Løvlien: WHEN EVERY MINUTE COUNTS. FROM SYMPTOMS TO ADMISSION FOR ACUTE MYOCARDIAL INFARCTION WITH SPECIAL EMPHASIS ON GENDER DIFFERECES
445. Karin Margaretha Gilljam: DNA REPAIR PROTEIN COMPLEXES, FUNCTIONALITY AND SIGNIFICANCE FOR REPAIR EFFICIENCY AND CELL SURVIVAL
446. Anne Byriel Walls: NEURONAL GLIAL INTERACTIONS IN CEREBRAL ENERGY – AND AMINO ACID HOMEOSTASIS – IMPLICATIONS OF GLUTAMATE AND GABA
447. Cathrine Fallang Knetter: MECHANISMS OF TOLL-LIKE RECEPTOR 9 ACTIVATION
448. Marit Følsvik Svindseth: A STUDY OF HUMILIATION, NARCISSISM AND TREATMENT OUTCOME IN PATIENTS ADMITTED TO PSYCHIATRIC EMERGENCY UNITS
449. Karin Elvenes Bakkelund: GASTRIC NEUROENDOCRINE CELLS – ROLE IN GASTRIC NEOPLASIA IN MAN AND RODENTS
450. Kirsten Brun Kjelstrup: DORSOVENTRAL DIFFERENCES IN THE SPATIAL REPRESENTATION AREAS OF THE RAT BRAIN
451. Roar Johansen: MR EVALUATION OF BREAST CANCER PATIENTS WITH POOR PROGNOSIS

452. Rigmor Myran: POST TRAUMATIC NECK PAIN. EPIDEMIOLOGICAL, NEURORADIOLOGICAL AND CLINICAL ASPECTS
453. Krisztina Kunszt Johansen: GENEALOGICAL, CLINICAL AND BIOCHEMICAL STUDIES IN *LRRK2* – ASSOCIATED PARKINSON'S DISEASE
454. Pål Gjerden: THE USE OF ANTICHOLINERGIC ANTIPARKINSON AGENTS IN NORWAY. EPIDEMIOLOGY, TOXICOLOGY AND CLINICAL IMPLICATIONS
455. Else Marie Huuse: ASSESSMENT OF TUMOR MICROENVIRONMENT AND TREATMENT EFFECTS IN HUMAN BREAST CANCER XENOGRAFTS USING MR IMAGING AND SPECTROSCOPY
456. Khalid S. Ibrahim: INTRAOPERATIVE ULTRASOUND ASSESSMENT IN CORONARY ARTERY BYPASS SURGERY – WITH SPECIAL REFERENCE TO CORONARY ANASTOMOSES AND THE ASCENDING AORTA
457. Bjørn Øglænd: ANTHROPOMETRY, BLOOD PRESSURE AND REPRODUCTIVE DEVELOPMENT IN ADOLESCENCE OF OFFSPRING OF MOTHERS WHO HAD PREECLAMPSIA IN PREGNANCY
458. John Olav Roaldset: RISK ASSESSMENT OF VIOLENT, SUICIDAL AND SELF-INJURIOUS BEHAVIOUR IN ACUTE PSYCHIATRY – A BIO-PSYCHO-SOCIAL APPROACH
459. Håvard Dalen: ECHOCARDIOGRAPHIC INDICES OF CARDIAC FUNCTION – NORMAL VALUES AND ASSOCIATIONS WITH CARDIAC RISK FACTORS IN A POPULATION FREE FROM CARDIOVASCULAR DISEASE, HYPERTENSION AND DIABETES: THE HUNT 3 STUDY
460. Beate André: CHANGE CAN BE CHALLENGING. INTRODUCTION TO CHANGES AND IMPLEMENTATION OF COMPUTERIZED TECHNOLOGY IN HEALTH CARE
461. Latha Nrugham: ASSOCIATES AND PREDICTORS OF ATTEMPTED SUICIDE AMONG DEPRESSED ADOLESCENTS – A 6-YEAR PROSPECTIVE STUDY
462. Håvard Bersås Nordgaard: TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS – A CLINICAL AND EXPERIMENTAL STUDY

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

2011

463. Marte Helene Bjørk: DO BRAIN RHYTHMS CHANGE BEFORE THE MIGRAINE ATTACK? A LONGITUDINAL CONTROLLED EEG STUDY
464. Carl-Jørgen Arum: A STUDY OF UROTHELIAL CARCINOMA: GENE EXPRESSION PROFILING, TUMORIGENESIS AND THERAPIES IN ORTHOTOPIC ANIMAL MODELS
465. Ingunn Harstad: TUBERCULOSIS INFECTION AND DISEASE AMONG ASYLUM SEEKERS IN NORWAY. SCREENING AND FOLLOW-UP IN PUBLIC HEALTH CARE
466. Leif Åge Strand: EPIDEMIOLOGICAL STUDIES AMONG ROYAL NORWEGIAN NAVY SERVICEMEN. COHORT ESTABLISHMENT, CANCER INCIDENCE AND CAUSE-SPECIFIC MORTALITY
467. Katrine Høyer Holgersen: SURVIVORS IN THEIR THIRD DECADE AFTER THE NORTH SEA OIL RIG DISASTER OF 1980. LONG-TERM PERSPECTIVES ON MENTAL HEALTH
468. MarianneWallenius: PREGNANCY RELATED ASPECTS OF CHRONIC INFLAMMATORY ARTHRITIDES: DISEASE ONSET POSTPARTUM, PREGNANCY OUTCOMES AND FERTILITY. DATA FROM A NORWEGIAN PATIENT REGISTRY LINKED TO THE MEDICAL BIRTH REGISTRY OF NORWAY
469. Ole Vegard Solberg: 3D ULTRASOUND AND NAVIGATION – APPLICATIONS IN LAPAROSCOPIC SURGERY
470. Inga Ekeberg Schjerve: EXERCISE-INDUCED IMPROVEMENT OF MAXIMAL OXYGEN UPTAKE AND ENDOTHELIAL FUNCTION IN OBESE AND OVERWEIGHT INDIVIDUALS ARE DEPENDENT ON EXERCISE-INTENSITY
471. Eva Veslemøy Tyldum: CARDIOVASCULAR FUNCTION IN PREECLAMPSIA – WITH REFERENCE TO ENDOTHELIAL FUNCTION, LEFT VENTRICULAR FUNCTION AND PRE-PREGNANCY PHYSICAL ACTIVITY
472. Benjamin Garzón Jiménez de Cisneros: CLINICAL APPLICATIONS OF MULTIMODAL MAGNETIC RESONANCE IMAGING
473. Halvard Knut Nilsen: ASSESSING CODEINE TREATMENT TO PATIENTS WITH CHRONIC NON-MALIGNANT PAIN: NEUROPSYCHOLOGICAL FUNCTIONING, DRIVING ABILITY AND WEANING
474. Eiliv Brenner: GLUTAMATE RELATED METABOLISM IN ANIMAL MODELS OF SCHIZOPHRENIA

475. Egil Jonsbu: CHEST PAIN AND PALPITATIONS IN A CARDIAC SETTING; PSYCHOLOGICAL FACTORS, OUTCOME AND TREATMENT
476. Mona Høysæter Fenstad: GENETIC SUSCEPTIBILITY TO PREECLAMPSIA : STUDIES ON THE NORD-TRØNDELAG HEALTH STUDY (HUNT) COHORT, AN AUSTRALIAN/NEW ZEALAND FAMILY COHORT AND DECIDUA BASALIS TISSUE
477. Svein Erik Gaustad: CARDIOVASCULAR CHANGES IN DIVING: FROM HUMAN RESPONSE TO CELL FUNCTION
478. Karin Torvik: PAIN AND QUALITY OF LIFE IN PATIENTS LIVING IN NURSING HOMES
479. Arne Solberg: OUTCOME ASSESSMENTS IN NON-METASTATIC PROSTATE CANCER
480. Henrik Sahlin Pettersen: CYTOTOXICITY AND REPAIR OF URACIL AND 5-FLUOROURACIL IN DNA
481. Pui-Lam Wong: PHYSICAL AND PHYSIOLOGICAL CAPACITY OF SOCCER PLAYERS: EFFECTS OF STRENGTH AND CONDITIONING
482. Ole Solheim: ULTRASOUND GUIDED SURGERY IN PATIENTS WITH INTRACRANIAL TUMOURS
483. Sten Roar Snare: QUANTITATIVE CARDIAC ANALYSIS ALGORITHMS FOR POCKET-SIZED ULTRASOUND DEVICES
484. Marit Skyrud Bratlie: LARGE-SCALE ANALYSIS OF ORTHOLOGS AND PARALOGS IN VIRUSES AND PROKARYOTES
485. Anne Elisabeth F. Isern: BREAST RECONSTRUCTION AFTER MASTECTOMY – RISK OF RECURRENCE AFTER DELAYED LARGE FLAP RECONSTRUCTION – AESTHETIC OUTCOME, PATIENT SATISFACTION, QUALITY OF LIFE AND SURGICAL RESULTS; HISTOPATHOLOGICAL FINDINGS AND FOLLOW-UP AFTER PROPHYLACTIC MASTECTOMY IN HEREDITARY BREAST CANCER
486. Guro L. Andersen: CEREBRAL PALSY IN NORWAY – SUBTYPES, SEVERITY AND RISK FACTORS
487. Frode Kolstad: CERVICAL DISC DISEASE – BIOMECHANICAL ASPECTS
488. Bente Nordtug: CARING BURDEN OF COHABITANTS LIVING WITH PARTNERS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE OR DEMENTIA
489. Mariann Gjervik Heldahl: EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER BASED ON MR METHODOLOGY
490. Lise Tevik Løvseth: THE SUBJECTIVE BURDEN OF CONFIDENTIALITY
491. Marie Hjelmseth Aune: INFLAMMATORY RESPONSES AGAINST GRAM NEGATIVE BACTERIA INDUCED BY TLR4 AND NLRP12
492. Tina Strømdal Wik: EXPERIMENTAL EVALUATION OF NEW CONCEPTS IN HIP ARTHROPLASTY
493. Solveig Sigurdardottir: CLINICAL ASPECTS OF CEREBRAL PALSY IN ICELAND. A POPULATION-BASED STUDY OF PRESCHOOL CHILDREN
494. Arne Reimers: CLINICAL PHARMACOKINETICS OF LAMOTRIGINE
495. Monica Wegling: KULTURMENNESKETS BYRDE OG SYKDOMMENS VELSIGNELSE. KAN MEDISINSK UTREDNING OG INTERVENSJON HA EN SELVSTENDIG FUNKSJON UAVHENGIG AV DET KURATIVE?
496. Silje Alvestad: ASTROCYTE-NEURON INTERACTIONS IN EXPERIMENTAL MESIAL TEMPORAL LOBE EPILEPSY – A STUDY OF UNDERLYING MECHANISMS AND POSSIBLE BIOMARKERS OF EPILEPTOGENESIS
497. Javaid Nauman: RESTING HEART RATE: A MATTER OF LIFE OR DEATH – PROSPECTIVE STUDIES OF RESTING HEART RATE AND CARDIOVASCULAR RISK (THE HUNT STUDY, NORWAY)
498. Thuy Nguyen: THE ROLE OF C-SRC TYROSINE KINASE IN ANTIVIRAL IMMUNE RESPONSES
499. Trine Naalsund Andreassen: PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENETIC ASPECTS OF OXYCODONE TREATMENT IN CANCER PAIN
500. Eivor Alette Laugsand: SYMPTOMS IN PATIENTS RECEIVING OPIOIDS FOR CANCER PAIN – CLINICAL AND PHARMACOGENETIC ASPECTS
501. Dorthe Stensvold: PHYSICAL ACTIVITY, CARDIOVASCULAR HEALTH AND LONGEVITY IN PATIENTS WITH METABOLIC SYNDROME
502. Stian Thoresen Aspenes: PEAK OXYGEN UPTAKE AMONG HEALTHY ADULTS – CROSS-SECTIONAL DESCRIPTIONS AND PROSPECTIVE ANALYSES OF PEAK OXYGEN UPTAKE, PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK FACTORS IN HEALTHY ADULTS (20-90 YEARS)

503. Reidar Alexander Vigen: PATHOBIOLOGY OF GASTRIC CARCINOIDS AND ADENOCARCINOMAS IN RODENT MODELS AND PATIENTS. STUDIES OF GASTROCYSTOPLASTY, GENDER-RELATED FACTORS, AND AUTOPHAGY
504. Halvard Høilund-Kaupang: MODELS AND METHODS FOR INVESTIGATION OF REVERBERATIONS IN NONLINEAR ULTRASOUND IMAGING
505. Audhild Løhre: WELLBEING AMONG SCHOOL CHILDREN IN GRADES 1-10: PROMOTING AND ADVERSE FACTORS
506. Torgrim Tandstad: VOX POPULI. POPULATION-BASED OUTCOME STUDIES IN TESTICULAR CANCER
507. Anna Brenne Grønskag: THE EPIDEMIOLOGY OF HIP FRACTURES AMONG ELDERLY WOMEN IN NORD-TRØNDELAG. HUNT 1995-97, THE NORD-TRØNDELAG HEALTH STUDY
508. Kari Ravndal Risnes: BIRTH SIZE AND ADULT MORTALITY: A SYSTEMATIC REVIEW AND A LONG-TERM FOLLOW-UP OF NEARLY 40 000 INDIVIDUALS BORN AT ST. OLAV UNIVERSITY HOSPITAL IN TRONDHEIM 1920-1960
509. Hans Jakob Bøe: LONG-TERM POSTTRAUMATIC STRESS AFTER DISASTER – A CONTROLLED STUDY OF SURVIVORS' HEALTH 27 YEARS AFTER THE CAPSIZED NORTH SEA OIL RIG
510. Cathrin Barbara Canto, Cotutelle with University of Amsterdam: LAYER SPECIFIC INTEGRATIVE PROPERTIES OF ENTORHINAL PRINCIPAL NEURONS
511. Ioanna Sandvig: THE ROLE OF OLFACTORY ENSHEATHING CELLS, MRI, AND BIOMATERIALS IN TRANSPLANT-MEDIATED CNS REPAIR
512. Karin Fahl Wader: HEPATOCYTE GROWTH FACTOR, C-MET AND SYNDECAN-1 IN MULTIPLE MYELOMA
513. Gerd Tranø: FAMILIAL COLORECTAL CANCER
514. Bjarte Bergstrøm: INNATE ANTIVIRAL IMMUNITY – MECHANISMS OF THE RIG-I-MEDIATED RESPONSE
515. Marie Søfteland Sandvei: INCIDENCE, MORTALITY, AND RISK FACTORS FOR ANEURYSMAL SUBARACHNOID HEMORRHAGE. PROSPECTIVE ANALYZES OF THE HUNT AND TROMSØ STUDIES
516. Mary-Elizabeth Bradley Eilertsen: CHILDREN AND ADOLESCENTS SURVIVING CANCER: PSYCHOSOCIAL HEALTH, QUALITY OF LIFE AND SOCIAL SUPPORT
517. Takaya Saito: COMPUTATIONAL ANALYSIS OF REGULATORY MECHANISM AND INTERACTIONS OF MICRORNAS

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

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

2012

524. Hans H. Wasmuth: ILEAL POUCHES
525. Inger Økland: BIASES IN SECOND-TRIMESTER ULTRASOUND DATING RELATED TO PREDICTION MODELS AND FETAL MEASUREMENTS
526. Bjørn Mørkedal: BLOOD PRESSURE, OBESITY, SERUM IRON AND LIPIDS AS RISK FACTORS OF ISCHAEMIC HEART DISEASE
527. Siver Andreas Moestue: MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF BREAST CANCER THROUGH A COMBINATION OF MR IMAGING, TRANSCRIPTOMICS AND METABOLOMICS
528. Guro Aune: CLINICAL, PATHOLOGICAL, AND MOLECULAR CLASSIFICATION OF OVARIAN CARCINOMA

529. Ingrid Alsos Lian: MECHANISMS INVOLVED IN THE PATHOGENESIS OF PRE-ECLAMPSIA AND FETAL GROWTH RESTRICTION. TRANSCRIPTIONAL ANALYSES OF PLACENTAL AND DECIDUAL TISSUE
530. Karin Solvang-Garten: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 – THE ROLE AS A SCAFFOLD PROTEIN IN BASE EXCISION REPAIR AND SINGLE STRAND BREAK REPAIR
531. Toril Holien: BONE MORPHOGENETIC PROTEINS AND MYC IN MULTIPLE MYELOMA
532. Rooyen Mavenyengwa: *STREPTOCOCCUS AGALACTIAE* IN PREGNANT WOMEN IN ZIMBABWE: EPIDEMIOLOGY AND SEROTYPE MARKER CHARACTERISTICS
533. Tormod Rimehaug: EMOTIONAL DISTRESS AND PARENTING AMONG COMMUNITY AND CLINIC PARENTS
534. Maria Dung Cao: MR METABOLIC CHARACTERIZATION OF LOCALLY ADVANCED BREAST CANCER – TREATMENT EFFECTS AND PROGNOSIS
535. Mirta Mittelstedt Leal de Sousa: PROTEOMICS ANALYSIS OF PROTEINS INVOLVED IN DNA BASE REPAIR AND CANCER THERAPY
536. Halfdan Petursson: THE VALIDITY AND RELEVANCE OF INTERNATIONAL CARDIOVASCULAR DISEASE PREVENTION GUIDELINES FOR GENERAL PRACTICE
537. Marit By Rise: LIFTING THE VEIL FROM USER PARTICIPATION IN CLINICAL WORK – WHAT IS IT AND DOES IT WORK?
538. Lene Thoresen: NUTRITION CARE IN CANCER PATIENTS. NUTRITION ASSESSMENT: DIAGNOSTIC CRITERIA AND THE ASSOCIATION TO SURVIVAL AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ADVANCED COLORECTAL CARCINOMA
539. Berit Doseth: PROCESSING OF GENOMIC URACIL IN MAN AND MOUSE
540. Gro Falkenér Bertheussen: PHYSICAL ACTIVITY AND HEALTH IN A GENERAL POPULATION AND IN CANCER SURVIVORS – METHODOLOGICAL, OBSERVATIONAL AND CLINICAL ASPECTS
541. Anne Kari Knudsen: CANCER PAIN CLASSIFICATION
542. Sjur Urdson Gjerald: A FAST ULTRASOUND SIMULATOR
543. Harald Edvard Mølmen Hansen: CARDIOVASCULAR EFFECTS OF HIGH INTENSITY AEROBIC INTERVAL TRAINING IN HYPERTENSITIVE PATIENTS, HEALTHY AGED AND YOUNG PERSONS