Doctoral theses at NTNU, 2012:147

Guri Kaurstad

Cardiomyocyte function and calcium handling in animal models of inborn and acquired maximal oxygen uptake

Doctoral Thesis

Guri Kaurstad

ISBN 978-82-471-3580-8 (printed version)
ISBN 978-82-471-3581-5 (electronic version)
ISSN 1503-8181

NTNU – Trondheim
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology
Thesis for the degree of Philosophiae Doctor
Faculty of Medicine
Department of Circulation and Medical Imaging

Doctoral theses at NTNU, 2012:147

NTNU – Trondheim
Norwegian University of
Science and Technology

NTNU

Guri Kaurstad

Cardiomyocyte function and calcium handling in animal models of inborn and acquired maximal oxygen uptake

Thesis for the degree of Philosophiae Doctor

Trondheim, May 2012

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

NTNU – Trondheim
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the degree of Philosophiae Doctor

Faculty of Medicine
Department of Circulation and Medical Imaging

ISBN 978-82-471-3580-8 (printed version)
ISBN 978-82-471-3581-5 (electronic version)
ISSN 1503-8181

Doctoral theses at NTNU, 2012:147

Printed by Skipnes Kommunikasjon as

‘All parts of the body which have a function, if used in moderation and exercised in labours in which each is accustomed, become thereby healthy, well-developed, and age more slowly, but if unused and left idle they become quickly liable to disease, defective in growth, and age more quickly’

Hippocrates, 460 BC-370 BC

Hjertemuskelcellefunksjon og kalsiumhåndtering i dyremodeller med medfødt og ervervet maksimalt oksygenopptak

Hjerte-karsykdommer er i dag årsaken til flest dødsfall i Europa. Selv om det er kjent at et høyt maksimalt oksygenopptak kan virke beskyttende mot hjerte-karsykdom både hos friske og de med økt risiko, vil studier av de underliggende mekanismene bidra med verdifull informasjon til utvikling av fremtidige retningslinjer for behandling og forebygging av hjerte-karsykdom. Maksimalt oksygenopptak er hos de fleste av oss avhengig av hjertets slagvolum som igjen bestemmes av hjertemuskelcellenes kontraksjonsevne. For at hjertemuskelcellene skal kunne kontrahere kraftig er kalsiumhåndteringen i cellene avgjørende. Ett av de proteinene som er med bidrar til å styre dette er kalsium/ kalmodulin avhengig protein kinase II (CaMKII). CaMKII aktiviteten øker når hjertefrekvensen øker og det ser ut til at den økte aktiviteten er viktig for treningsresponsen i hjertemuskelcellene, mens hos hjertesvikt er det motsatt og den økte aktiviteten fører til funksjonsnedsettelse.

De overordnede formålene med denne doktorgradsavhandlingen var å undersøke betydningen av et høyt medfødt oksygenopptak på hjertets remodellering etter infarkt, eventuelle forskjeller i treningsrelaterte tilpasninger i hjertemuskelceller fra rotter med ulik medfødt evne til å respondere på trening og om CaMKII er nødvendig for treningsrelaterte forbedringer i maksimalt oksygenopptak, hjertemuskelcellens kontraksjon og kalsiumhåndtering.

Resultatene viste at rotter med høyt og rotter med lavt medfødt maksimalt oksygenopptak fikk like stor remodellering av hjerte og funksjonsnedsettelse etter infarkt, men at et høyt utgangspunkt fungerte som en ”buffer” på funksjonsnedsettelsen. Videre fant vi at høy intensitets aerobe intervaller ikke forbedret maksimalt oksygenopptak, hjertemuskelcellefunksjon eller kalsiumhåndtering i rotter med lav medfødt respons til trening. Dette indikerer at mangel på plastisitet i hjertet bidro til å hindre treningsrespons på maksimalt oksygenopptak. Det siste studiet viste at i friske mus er CaMKII nødvendig for å opprettholde kalsiumhomeostase i hjertemuskelcellene og for å oppnå optimal treningsrespons på hjertemuskelcellehypertrofi, funksjon og kalsiumhåndtering. Men paradoksalt nok førte CaMKII inhibering allikevel til en større økning i maksimalt oksygenopptak.

Guri Kaurstad

Institutt for sirkulasjon og bildediagnostikk, Det medisinske fakultet, NTNU
Veiledere: Ulrik Wisløff og Tomas O. Stølen (biveileder)
Finansieringskilde: Norges Forskningsråd (Program for yngre fremragende forskere, Ulrik Wisløff), Samarbeidsorganet (HMN-NTNU) og stiftelsen K.G. Jebsen

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden PhD i molekylær medisin
Disputas finner sted i Auditoriet, Medisinsk teknisk forskningssenter, NTNU
Onsdag 23. mai 2012, kl. 12.15

CONTENTS

ACKNOWLEDGEMENTS **5**

SUPPORTING GRANTS **7**

PREFACE **8**

DEFINITIONS **9**

FREQUENTLY USED ABBREVIATIONS **11**

BACKGROUND **12**

MAXIMAL OXYGEN UPTAKE 12
VO_{2max} as a predictor of health *13*
FACTORS INFLUENCING VO_{2MAX} 13
Intrinsic and acquired elements of VO_{2max} *13*
Exercise training to improve VO_{2max} *14*
Myocardial infarction, cardiac function and VO_{2max} *15*
CELLULAR MECHANISMS OF ALTERATIONS IN VO_{2MAX} 16
Cardiomyocyte hypertrophy *16*
Cardiomyocyte contractile function *17*
Cardiomyocyte Ca^{2+} handling *18*
Ca^{2+} handling in healthy cardiomyocytes 18
Ca^{2+} handling in healthy exercise-trained cardiomyocytes 20
Ca^{2+} handling in failing cardiomyocytes 20
Ca^{2+} handling in exercise-trained failing cardiomyocytes 21
Transverse-tubule network 21

AIM OF THE THESIS AND HYPOTHESIS **23**

METHODOLOGICAL CONSIDERATIONS **24**

ANIMAL MODELS 24
Artificial selection of rats *24*
High and low capacity runners (HCR/LCR) 24
High and low responders to training (HRT/LRT) 25
Chronic CaMKII inhibition in mice *26*
EXPERIMENTAL INTERVENTIONS 27
Exercise training program *27*
Induction of myocardial infarction *28*
EXPERIMENTAL PROTOCOLS 28
Testing of maximal oxygen uptake *28*
Echocardiography in rats and mice *30*
Cardiomyocyte experiments *31*
Cardiomyocyte isolation 31
Cardiomyocyte contractile function and Ca^{2+} handling 32
SR Ca^{2+} leak 34
T-tubule density and synchrony of Ca^{2+} release 35
Cell dimension *36*
MOLECULAR ANALYSIS 37
Immunohistology *37*
Western immunoblotting *37*
STATISTICS 38

SUMMARY OF RESULTS **39**

DISCUSSION **42**

INBORN VO_{2MAX} AND CARDIAC REMODELLING AFTER MI (PAPER I) 42
Inborn VO_{2max} and cardioprotection *42*
Echocardiography of cardiac function and dimension *43*
Cardiomyocyte pathological hypertrophy *44*
Cardiomyocyte contractile function *45*
Cardiomyocyte Ca^{2+} handling *46*
Diastolic SR Ca^{2+} leak 46

ADAPTATIONS TO EXERCISE TRAINING IN HIGH AND LOW RESPONDER RATS AND CHRONIC CAMKII INHIBITED MICE 47
High intensity interval training did not improve VO_{2max} in LRT rats *47*
Chronic CaMKII inhibition enhanced VO_{2max} exercise response *48*
Echocardiography of cardiac function in CaMKII inhibited mice *49*
Pathological-like hypertrophy in LRT cardiomyocytes *49*
Cardiomyocyte hypertrophy with exercise training *50*
Cardiomyocyte contractile function *51*
Cardiomyocyte Ca^{2+} handling *52*
CONCLUSIONS **54**
REFERENCES **55**

ACKNOWLEDGEMENTS

First of all I would like to show gratitude to my supervisor Professor **Ulrik Wisløff** for trusting me with a position as his PhD student. For that I am eternally grateful. Ulrik had great ideas to get me started and introduced me to the field of cellular physiology. He has a unique ability to motivate, and his own research and accomplishments are inspiring.

My co-supervisor, **Tomas O. Stølen,** has been of great importance during these years. His helping hand was extended and we have had many scientific discussions that have taught me a lot throughout my PhD studies, as Tomas always seem to have an answer to everything. His cooperation has been much appreciated.

In the laboratory **Ragnhild Røsbjørgen, Trine Skoglund, Marcia Alves** and **Natalie Rolim** have been indispensable. It has felt as the word *no* is not a part of their vocabulary, especially during hectic periods of data collections. Thanks to **Morten A. Høydal** for teaching me about epifluorescence microscopy and scientific cooperation, **Ole J. Kemi** for scientific cooperation, and **Jose Bianco** and **Luiz Boiz** for western blot analysis.

I started this PhD studies coincident with **Anne Berit Johnsen**, the one and only problem solver, always laughing and spreading joy, putting her own problems aside to help others. Thanks for all the valuable discussions during these years and for our unforgettable conference trip to Beijing. “Its not that you aren’t smart AB you are just a bit slow☺”. **Anne Marie Ormbostad** has been a great colleague and lab partner, a dear friend and climbing partner, your contributions in both scientific and personal manners have been greatly appreciated! Together with **Marianne Havnes** the four of us have discussed science and approximately everything else throughout priceless hours of “knitting” gatherings and lunches. Thanks also to **Dorthe Stensvold**, one of the most caring person I have ever met, for clever comments and tips especially during the final stages.

Office mates and colleagues are all warmly acknowledged for their various contributions **Anne Berit, Anne Marie, Dorthe, Trine M., Ragnhild, Nina, Eva, Anja, Natalie, Inga, Marcia, Trine S., Siri Marte, Bjarne, Tomas, Javaid, Øivind, Eivind, Arnt Erik, Stian,** and **Morten;** it has been a great working environment both academically and socially. We are

fortunate enough to have an incredible collection of people working here at CERG. I am grateful to have been a part of this environment and will miss you all a lot!

I wish to thank my father, **Per Otto**, for encouragement in pursuit of my PhD studies and for always telling his children that they could achieve everything they put their minds to. You taught us not to quit which was a saving grace in the most difficult of times. I would also like to thank the rest of my **family** and my **in-laws** for their support, encouragement and consideration.

Most of all, I am utmost grateful to my great love **Martin**, your endless positivity, understanding and enormous patience is highly appreciated. I am forever indebted to you for this dissertation. Thank you for all your love and support!

SUPPORTING GRANTS

Samarbeidsorganet (HMN-NTNU)

The Norwegian Research Council Funding for Outstanding Young Investigators (YFF)

The Norwegian Council on Cardiovascular Disease

The K.G. Jebsen Foundation

Simon Fougner Hartmanns Family foundation

Foundation for Cardiovascular Research at St. Olav University Hospital

The Blix Fund for the Promotion of Medical Science

Arild and Emilie Bachkes Foundation

Dr. Fürsts Medical Laboratory Fund for Clinical Chemistry and Clinical Physiology Research

PREFACE

The thesis is based on the three papers listed below, referred to by their roman numerals throughout the document. The studies of this thesis were carried out at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology during the years 2008-2011.

Paper I

Morten A. Høydal, Guri Kaurstad, Natale Rolim, Anne Berit Johnsen, Marcia N. Alves, Jose Bianco, Luiz Bozi, Lauren G. Koch, Steven L. Britton, Tomas O. Stølen, Godfrey L. Smith, and Ulrik Wisløff. *High inborn aerobic capacity does not counteract deterioration of cardiac function and calcium handling after myocardial infarction.* Submitted.

Paper II

Guri Kaurstad, Tomas O. Stølen, Jose Bianco, Luiz Bozi, Ragnhild Røsbjørgen, Anja Bye, and Ulrik Wisløff. *Aerobic exercise response is dependent of cardiac plasticity.*

Paper III

Guri Kaurstad, Marcia N. Alves, Ole J. Kemi, Natale Rolim, Morten A. Høydal, Helene Wisløff, Tomas O. Stølen, and Ulrik Wisløff. *Chronic CaMKII inhibition blunts the cardiac contractile response to exercise training.* Eur J Appl Physiol. 2012;112(2):579-588.

DEFINITIONS

Aerobic fitness: The ability of the circulatory and respiratory system to supply oxygen during sustained physical activity.

Cardiovascular disease: A disease of the heart and/or blood vessels.

Calcium handling: The handling of calcium fluxes in the cardiomyocyte leading to the transient changes in intracellular calcium concentration during contraction and relaxation of the cardiomyocyte.

Contractile function: The intrinsic capacity of the myocardium/cardiomyocyte to contract, independent of changes in pre- or after load, or other "external factors".

Ejection fraction: The fraction of blood pumped out of the left ventricle with each stroke (stroke volume/ left ventricle end-diastolic volume).

Excitation- contraction coupling: The process from electrical excitation of the myocyte to contraction of the heart.

Fractional shortening: The decrease in cardiomyocyte length from end-diastole to end-systole divided by end-diastolic length.

Heart failure: The hearts inability to generate adequate pumping of blood to the peripheral organs in order to meet their metabolic demand.

Maximal oxygen uptake: The highest oxygen uptake that can be achieved by an individual during exercise with dynamic use of a large muscle mass; considered as the best indication of cardio respiratory capacity.

Myofilament calcium sensitivity: The myofilament contractile response to a given amount of activating calcium in the cardiomyocyte.

Ventricular remodelling: Most commonly refers to changes in the hearts size, shape and/or function following myocardial infarction.

FREQUENTLY USED ABBREVIATIONS

Ca^{2+}:	calcium
CaMKII:	calcium/calmodulin-dependent protein kinase II
CVD:	cardiovascular disease
ECC:	excitation- contraction coupling
HCR:	high capacity runners
HRT:	high responder training
Hz:	hertz
LCR:	low capacity runners
LRT:	low responder training
LTCC:	L-type calcium channel
LV:	left ventricle
MI:	myocardial infarction
NCX:	sodium/calcium - exchanger
PLB:	phospholamban
PKA:	protein kinase A
RyR2:	ryanodine receptor type 2
SERCA-2a:	sarcoplasmic reticulum calcium ATPase
SR:	sarcoplasmic reticulum
T-tubules:	transverse tubules
VO_{2max}:	maximal oxygen uptake

BACKGROUND

As early as the 1970s low aerobic fitness was recognized as a significant prognostic marker in patients with cardiovascular disease (CVD) (1). Since then substantial evidence has confirmed that aerobic fitness is a major independent predictor of morbidity and mortality (2-15) in both asymptomatic (3,16-18) and symptomatic men and women (9,13,19-22). Physical activity is also associated with reductions in CVD risk factors (10,14,23,24), however, aerobic fitness is shown to be the strongest predictor (6,17,21,25,26). For instance, Lee et al (17) recently reported that being fit but less active resulted in higher protection against mortality compared to being unfit and more active.

Considering the importance of aerobic fitness in health and longevity, studying the underlying mechanisms of aerobic fitness may provide valuable information for developing future guidelines for CVD prevention and treatment.

Maximal oxygen uptake

Maximal oxygen uptake (VO_{2max}) is considered the single best indicator and golden standard measure of aerobic fitness. VO_{2max} was defined by Hill and Lupton (27) in 1923 as "the oxygen intake during an exercise intensity at which actual oxygen intake reaches a maximum beyond which no increase in effort can raise it", and is a precise measure of whole-body capacity to transport and utilize oxygen during severe dynamic exercise with large muscle mass (28-30). VO_{2max} is a physiological characteristic, expressed by the Fick equation:

$$VO_{2max} = (HR \cdot SV) \cdot a\text{-}vO_2 \text{ difference},$$

where HR indicates heart rate, SV indicates stroke volume, and $a\text{-}vO_2$ indicates arterio-venous oxygen difference (31). Stroke volume is the major determinant of improvements in cardiac output and therefore VO_{2max}, as maximal heart rate remains unchanged or slightly decreased after long-term exercise training (32,33).

According to Hills postulate, VO_{2max} is limited by the cardiorespiratory systems' capacity for oxygen transport to the working muscle mass, thus, VO_{2max} is supply limited (27). This allegation has raised numerous disputes ever since, however today there seems to be a general

consensus of the original paradigm by Hill for healthy individuals. This is evidenced by the much larger capacity for oxygen extraction and utilization in the peripheral muscles compared to the central oxygen transport capacity in healthy individuals (31,34-37). However, some patients and untrained humans seem to be demand limited, making VO_{2max} dependent on "peripheral factors" (37).

VO_{2max} as a predictor of health

VO_{2max} reflects several important prognostic markers for CVD. These markers include cardiac function, pulmonary function, endothelial function, oxygen-carrying capacity and utilization, and the autonomic nervous system (5,18), together this markers makes VO_{2max} a valuable prognostic evaluator for morbidity and mortality (3,5,18). Recent studies suggest that holding a moderate to high VO_{2max} prevents development of several life-style related diseases (6,17,38). Rats artificially bread for high and low capacity running (HCR and LCR) has provided proof for this concept. LCR rats have higher scores on CVD risk factors that constitute the metabolic syndrome (39) and also decreased longevity (24 vs. 32 months, respectively) compared to HCR rats (40). However, in humans even a small increase in VO_{2max} of 1 metabolic equivalent (3.5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$) is sufficient to elicit substantial improvements in cardiovascular health and reductions in risk factors (6,41), whereas a decrease in VO_{2max} of 5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ corresponds to almost 56% higher prevalence of CVD risk factor clustering (42). Moreover, Aspenes et al (42) recently reported a VO_{2max} threshold level of 44 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ in men and 35 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ in women, whereupon values below the threshold was associated with an unfavourable CVD risk profile. However, a association between VO_{2max} and conventional CVD risk factors were still present in subjects above the threshold and those considered being fit (42).

Factors influencing VO_{2max}

Intrinsic and acquired elements of VO_{2max}

Inherited components cause large variations in intrinsic and acquired (exercise response) VO_{2max} among individuals (43-47). In healthy individuals VO_{2max} has a heritability of ~50% even when data are adjusted for age, sex, body mass and body composition (44,48). VO_{2max} response to exercise training also has a heritability of ~50% when adjusted for the parameters

mentioned above (45,49). Still, different combinations of genes appear to determine intrinsic VO_{2max} (48,50,51) and exercise responsiveness (43,45,46,49,51), although, some studies have suggested the contrary (52,53). However, among the 720 healthy participants in the large HERITAGE Family Study, age, gender, race, and baseline VO_{2max} combined contributed to only 11% of the variance in VO_{2max} exercise response after 20 weeks of exercise training (45,46). Moreover, variations in VO_{2max} response to standardized exercise programs has been shown to range from no gain to a doubling of VO_{2max}, regardless of baseline values (43,46). Thus, the idea that more exercise produces greater response is not always true, even though exercise training is considered the main principal for improvements in VO_{2max} (43,45,49,54).

Although genetic components are known to determine a large portion of both intrinsic and acquired VO_{2max} (50,55), the majority of studies on exercise training focus on mean effects and group results, ignoring the individual variability and the significance of these. Recently, some studies have focused on targeting genomic predictors of VO_{2max} response to exercise for the purpose of genotyping human exercise responsiveness to promote genotype-tailored interventions to prevent and treat life-style related diseases in low responders (54,56). This is an important contribution; however, some basic physiological questions still remain. For example it is acknowledged that VO_{2max} level is more related to morbidity and mortality than general physical activity, but the effect of intrinsic VO_{2max} on cardioprotection is currently unknown. In addition, it is known that there are large individual differences in VO_{2max} response to standardized exercise programs, but the cardiac mechanisms underlying exercise response have not been investigated despite the strong association between cardiac function and VO_{2max}.

Exercise training to improve VO_{2max}

Exercise training regimes have been extensively studied to determine the duration, intensity and frequency that provide the most optimal results on performance and health. High intensity interval training has been increasingly acknowledged to produce larger aerobic and cardiovascular improvements in both healthy individuals (57,58), patients with CVD and metabolic syndrome (22,23,59-61) compared to moderate intensity exercise. However, health recommendations of exercise intensity still vary from 40% to 90% of VO_{2max} (62).

The basic principle of increasing VO_{2max} through high intensity interval training was established in the early 1970s (63-65), and is physiologically based on the fact that, especially in endurance trained subjects, stroke volume does not plateau but rather increase up to intensities close to VO_{2max} (28,32,37,66). Cardiac adaptations to high intensity exercise in healthy individuals include physiological hypertrophy of the heart, increased cardiac output due to improved systolic emptying rate, and enhanced diastolic filling, providing increased oxygen transport to the working muscles (14,58,67). High intensity exercise training (85-90% of VO_{2max}) is bound to be performed as interval training as lactic acid starts accumulating after a few minutes, eventually resulting in fatigue of the skeletal muscles. Using intermittent active recovery periods at 50-60% of VO_{2max} accumulated lactic acid is effectively removed and exercise intensity can be maintained for the remaining interval periods (68). Hence, the optimal interval duration to improve VO_{2max} is suggested to be 3-5 minute intervals with active recovery periods in between (28,69).

Myocardial infarction, cardiac function and VO_{2max}

Myocardial infarction (MI) is a common form of CVD. MI reduces oxygen supply to the cardiomyocytes, which in turn results in reduced stroke volume and insufficient oxygen supply to peripheral tissue. These MI-induced changes in cardiac and peripheral function also cause a reduction in VO_{2max}. MI is most often caused by atherosclerotic plaque formation in one or more major coronary arteries, resulting in occlusion of the arteries. The subsequent ischemia results in MI which causes apoptosis if perfusion is not restored (70). The endocardium dies faster than the epicardium, as it is more vulnerable to energy-starvation, and the extent of MI is determined mainly upon how distal the occlusion occurs (71). MI induces ventricular remodelling that involves changes in ventricular structure, shape, and size, such as myocardial wall thinning, expansion of the infarcted area, and left ventricle (LV) chamber dilatation (72,73). These progressive changes contribute to the overall process of chamber enlargement due to pathological hypertrophy with elongation and widening of cardiomyocytes. The extent of remodelling is directly proportional to infarct size (74). Reduced LV contractile function after MI causes decreased systolic blood pressure and increased LV end-diastolic pressure, leading to a rightward-shift of the diastolic pressure-volume relationship and subsequent reduced VO_{2max} (73,75).

Cellular mechanisms of alterations in VO_{2max}

Although cardiomyocytes only account for ~20% of the total cardiac cell population they account for 70-90% of the myocardial mass (33,76), and have been widely used to study the cellular basis of ventricular function. Exercise-induced improvements in VO_{2max} partly derive from alterations in cardiomyocyte function (77) as cardiomyocyte dimension, contractility and calcium (Ca^{2+}) handling are associated with whole-body VO_{2max} (69,77-80).

Cardiomyocyte hypertrophy

Chronic endurance exercise training is often associated with functional and morphological changes in the heart such as physiological hypertrophy, a beneficial mechanical adaptation that contributes to increased stroke volume in response to increased demands (81). Physiological hypertrophy involves proportional eccentric (elongation) and concentric (widening) cardiomyocyte growth, LV chamber enlargement and proportional change in wall thickness and mass (82-84). The magnitude of hypertrophy appears to be intensity-dependent as high intensity interval training is known to induce larger hypertrophic response than moderate intensity training (67,69,85). The Insulin-like Growth Factor 1 (IGF1)/Akt pathway has been proposed as the significant signalling pathway in physiological hypertrophy, demonstrated by complete absence of exercise-induced hypertrophy when the IGF1/Akt signalling cascade was disrupted (86,87). Physiological hypertrophy regresses when exercise training is terminated (77).

Pathological hypertrophy is initially a compensatory response to chronic overload that normalizes wall stress and permits normal cardiac function. Pathological remodelling occurs after cardiac injury including myocardial infarction, pressure overload, inflammatory disease and volume overload that increase the mechanical stretch placed on the cardiomyocytes (88). The extent of hypertrophy after MI is related to the magnitude of initial damage to the myocardium, infarct healing, and ventricular wall stress (89). The most significant pathways for pathological hypertrophy include activation MAPK-kinases and several fetal gene programs, and release autocrine and paracrine humoral factors such as; angiotensin II, endothelin 1 and IGF1 (for detailed review see Bernardo et al (88)) (90). In time, pathological hypertrophy becomes detrimental, associated with contractile dysfunction, increased interstitial fibrosis, apoptosis (cell death), and potentially dilation of the hypertrophied heart that may ultimately lead to heart failure (91). During the transition from compensatory

hypertrophy to decompensation, increased activation of calcineurin and Ca^{2+}/calmodulin dependent protein kinase II (CaMKII) is prominent features that may cause arrhythmic events (92-97). Nuclear CaMKII (together with PKD) can activate myocyte enhancer factor 2 (MEF2) and cause hypertrophy (98,99). The significance of CaMKII in pathological hypertrophy is demonstrated by the reduced remodelling during pressure overload in CaMKII inhibited mice (97,100). Moreover, exercise training has been shown to attenuate cellular hypertrophy in failing cardiomyocytes from post MI rats (79,101). Preliminary data suggest that exercise reduce cardiomyocyte volume in an intensity dependent manner (unpublished work). However, the cellular mechanisms for exercise-induced attenuation of pathological hypertrophy remain unclear.

Cardiomyocyte contractile function

Improved systolic and diastolic functions of the heart are central features associated with regular exercise training (32,33). Exercise-induced adaptations in cardiomyocyte function provide the cellular rationale for improved stroke volume with enhanced ejection of blood at systole and improved relaxation and filling rate during diastole. A widely held hypothesis is that exercise-induced alterations in cardiomyocyte contractile function are intensity-dependent (69,77,79,80,102-104). This hypothesis is supported by Kemi et al (69) who reported larger effect on cardiomyocyte contractile function after high intensity exercise (85-90% of VO_{2max}) compared to moderate intensity exercise (65-70% of VO_{2max}). There are also a few studies that report unaltered cardiomyocyte contractile function after exercise training (105,106). However, this discrepancy is most likely explained by differences in exercise intensity.

Cardiomyocytes from failing hearts have reduced contraction and slowed relaxation compared to healthy cardiomyocytes. This contractile dysfunction in failing ventricles is caused by a combined effect of abnormal loading *in vivo* (107) and intrinsic properties of the cardiomyocytes (108). In rats, exercise training has been demonstrated to restore cardiomyocyte contractility from failing hearts to levels comparable to sham-operated rats, both after high intensity aerobic interval training and high intensity sprint training (79,109).

Cardiomyocyte Ca^{2+} handling

Ca^{2+} handling in healthy cardiomyocytes

Cardiomyocyte contractile function is closely related to Ca^{2+} handling (108,110) and contraction can be changed either by altering amplitude or duration of Ca^{2+} transients or altering myofilament Ca^{2+} sensitivity (110). The process from electrical excitation of the myocyte to cardiomyocyte contraction, excitation-contraction coupling (ECC) (Figure 1), is mainly regulated by Ca^{2+} (110,111). Depolarization of the sarcolemma and the transverse (T-) tubules during action potential cause Ca^{2+} entry through the voltage-dependent L-type Ca^{2+} channels (LTCC). In addition a small amount of Ca^{2+} enters the cell through the Na^{+}/Ca^{2+} exchanger (NCX) in reverse mode (112). These Ca^{2+} currents activates the ryanodine receptor type 2 (RyR2) and triggers the release of larger amounts of Ca^{2+} from the sarcoplasmic reticulum (SR) through RyR2, termed Ca^{2+} induced Ca^{2+} release. This raises the cytosolic Ca^{2+} concentration, and Ca^{2+} binds to troponin C activating the myofilaments leading to the cardiomyocyte contraction (systole).

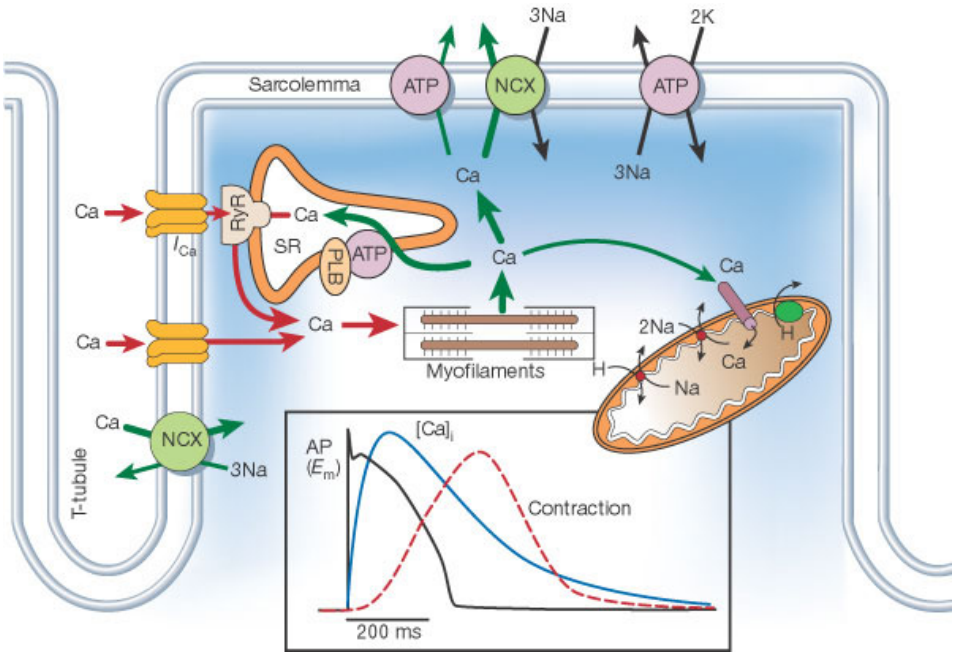

Figure 1. Ca^{2+} cycling during excitation- contraction coupling. Inset; the time course of an action potential (AP), Ca^{2+} transient ($[Ca]_i$) and contraction. NCX, $Na+/Ca^{2+}$ exchange; ATP, ATPase; PLB, phospholamban; SR, sarcoplasmic reticulum. Reprinted by permission from Macmillian Publishers Ltd: Nature (110), copyright 2002.

Relaxation (diastole) occurs when the cytosolic Ca^{2+} is removed (110,113,114). To maintain Ca^{2+} homeostasis the same amount of Ca^{2+} that entered the cell must also be removed out of the cell. Ca^{2+} is transported back to the SR by the SR Ca^{2+} ATPase (SERCA-2a), or is extruded across the sarcolemma by the NCX. A small amount of Ca^{2+} is also removed by the sarcolemmal Ca^{2+} ATPase (PMCA) and the mitochondrial Ca^{2+} uniport (110).

CaMKII is a key mediator fine-tuning ECC that has drawn a lot of attention the recent years (111,115,116). CaMKII is a serine-threonine kinase that is activated by increased intracellular Ca^{2+} and is expressed abundantly in the heart (For detailed review, see (111,115,117)) (115,116). There are four different CaMKII isoformes (α, β, γ, δ), with the δ isoform predominant in the heart (115,117-119). CaMKII becomes autophosphorylated at threonine $(Thr)^{287}$ and by oxidation of a pair of methionines 281/282 at the regulatory domain. When CaMKII is autophosphorylated it remains active after Ca^{2+}/calmodulin has dissociated from its binding region. Once in the autophosphorylated state, dephosphorylation by protein phosphatases and reversed oxidation by methionine sulfoxide reductase A is necessary for complete inactivation (111). By phosphorylation of several Ca^{2+} handling proteins in the cardiomyocyte, including the LTCC, RyR2 and phospholamban (PLB) on the SERCA-2a, CaMKII can regulate/dysregulate Ca^{2+} cycling in health and disease (Figure 2) (111,115,116).

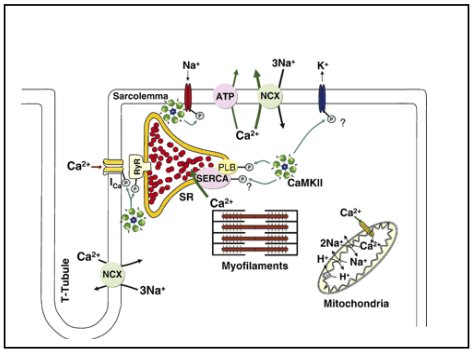

Figure 2. Effects of CaMKII on excitation-contraction coupling. CaMKII phosphorylates several Ca^{2+} handling proteins, including phospholamban (PLB), possibly SR Ca^{2+} ATPase (SERCA), SR Ca^{2+} release channels (RyR), L-type Ca^{2+} channels (I_{Ca}), Na^{+} channels and K^{+} channels. Maier LS & Bers DM 2007 (111), by permission of Oxford University Press.

Ca^{2+} handling in healthy exercise-trained cardiomyocytes

Exercise training is generally proven to enhance Ca^{2+} handling, in conjunction with improvements in cardiomyocyte contractility. Kemi et al (69) observed an association between faster contraction-relaxation rates that corresponded with faster Ca^{2+} rise and decay of twitch transients in exercised cardiomyocytes. Several possible mechanisms have been suggested to explain the increased rate of rise in Ca^{2+} transients after exercise training, including a more effective coupling between LTCC and RyR2 Ca^{2+} release (106), and greater Ca^{2+} entry across the plasma membrane due to prolonged action potentials (121). The faster diastolic Ca^{2+} decay is at least partly explained by improved SERCA-2a activity through increased SERCA-2a levels and increased SERCA-2a/PLB ratio after exercise training (79,80,103,122). This contributes to increased relaxation and improves contraction by facilitating SR Ca^{2+} uptake, making more Ca^{2+} available for the next contraction (33,103,110). Furthermore, when the inhibition of SERCA-2a by phosphorylation of the PLB by protein kinase A (PKA) or CaMKII is relived SERCA-2a can increase its activity two- to threefold (123-126). The importance of exercise-induced increase in CaMKII activity is currently unknown and might be an indirect effect of increased intracellular Ca^{2+} cycling (103,127). Moreover, the exercise-induced increase in myofilament Ca^{2+} sensitivity in cardiomyocytes that enhances Ca^{2+} handling and thus cardiomyocyte contractility (79,80,103), might be related to increased CaMKII activity. Interestingly, acute CaMKII inhibition after an exercise training intervention has been found to substantially blunt the exercise-induced improvements in cardiomyocyte inotropy and lusitropy (103). This indicates that CaMKII is potentially necessary for exercise-induced adaptations in cardiomyocytes. Despite these findings, there exists no further literature to support this hypothesis, and whether the outcome of regular exercise training is dependent on CaMKII activation is currently not known.

Ca^{2+} handling in failing cardiomyocytes

Alternations in normal cardiomyocyte Ca^{2+} handling are associated with contractile dysfunction (128,129), increased propensity for cardiac arrhythmias and sudden cardiac death in failing cardiomyocytes (96,108,128,130-135). Abnormal Ca^{2+} handling is caused by defective Ca^{2+} handling by sarcolemma and/or SR channel proteins, and include prolonged Ca^{2+} transients, depressed SR Ca^{2+} content and/or SR Ca^{2+} release and reduced SERCA-2a activity (128,130-132,136-138). Recent studies have shown that CaMKII has a functionally effect on myocardial pathology (139-141). CaMKII expression and activity is increased in

failing hearts (142,143) promoting dysregulation of Ca^{2+} homeostasis and disruption of ECC (97,117,119,143-146), playing an important role in arrhythmogenesis (94,96,143,147).

Increased diastolic SR Ca^{2+} leak is a common feature in failing cardiomyocytes (143,148,149). Spontaneous Ca^{2+} release from RyR2 cause delayed after-depolarization that give rise to a transient inward Ca^{2+} current during the diastolic period (150), increasing the propensity for cardiac arrhythmias and sudden cardiac death (108,130,151). Chronic hyperphosphorylation of RyR2 by PKA (149) and CaMKII (152-154) cause increased diastolic SR Ca^{2+} leak via RyR2 by increasing RyR2 Ca^{2+} sensitivity and open probability (143,152,155,156). Combined with effects of depressed SERCA-2a activity (143), and increased NCX activity (132,157,158) diastolic SR Ca^{2+} leak reduces SR Ca^{2+} load, thereby reducing Ca^{2+} transient amplitude in failing cardiomyocytes (132). Due to the crucial role for CaMKII activity on diastolic SR Ca^{2+} leak (143,152,153,155) inhibition of CaMKII may serve as a therapeutic prevention of heart failure progression (95,97).

Ca^{2+} handling in exercise-trained failing cardiomyocytes

Exercise training produces several positive effects on a failing heart (22,58,79,159,160). These effects include decreased diastolic Ca^{2+} levels, increased systolic Ca^{2+} release and normalization of β–adrenergic response, myofilament Ca^{2+} sensitivity, faster rise and decay of intracellular Ca^{2+} transient, and increased SERCA-2a expression (22,33,58,79,161-163). Studies on animal models with pathologically increased CaMKII activity report a reduction in CaMKII activity after exercise training, associated with improved cardiomyocyte function linked to increased SERCA-2a activity and reduced SR Ca^{2+} leak through RyR2 (104,127). Interestingly, CaMKII inhibition restores Ca^{2+} homeostasis, normalizes ECC function and reduces myocardial pathological remodelling by improving a complicated mixture of CaMKII regulated pathways, somewhat similar to the effect of exercise training (94,95,97,119,139,147,148,164-172). However, the effect of combining pharmacological CaMKII inhibition and exercise training has not been explored.

Transverse-tubule network

T-tubules in mammalian ventricle myocytes are invaginations of the plasma membrane along the Z-line regions along the longitudinal axis forming a complex network that facilitates

coordinated contractions and efficient ECC with uniform depolarization across the whole cell (173,174). Important proteins for ECC such as LTCC and NCX are concentrated at the T-tubules, while RyR2 and SERCA-2a are located in close proximity at the junctional SR (174). Local Ca^{2+} signalling complexes, called couplons, are present at the junction between sarcolemma (both T-tubules and surface) and the SR (110). There is ~20,000 couplons in the cardiomyocyte whereupon each couplon consist of 10-25 LTCCs and 100-200 RyR2s (175). All couplons are under local control, and activated by action potentials and subsequent inward Ca^{2+} currents (175). Synchronous contraction of the cell requires simultaneous stimulation of all couplons.

T-tubules become disorganized and reduced in density in CVD (176,177) causing disruption of the ECC with reduced Ca^{2+} release synchrony (104,177). The structural remodelling of T-tubules starts at the LV and penetrates to the right ventricle as disease progresses (176). The reduced T-tubule density might reflect a differential organization in relation to additional sarcomeres caused by pathological hypertrophy or a true loss of T-tubules in the given area. However, a recent study indicated that T-tubule density may be independent of cell size as exercise-induced physiological hypertrophy did not reduce relative T-tubule density (160). Moreover, high intensity exercise training has been demonstrated to partly restore T-tubule density and T-tubule function after cardiac remodelling following cardiomyopathy and MI (104,160), supporting the idea that T-tubules have a degree of plasticity (177).

AIM OF THE THESIS AND HYPOTHESIS

The overall aims of the thesis were 1) to determine the role of intrinsic VO_{2max} upon cardiac remodelling after MI and 2) to determine exercise-induced adaptations in cardiomyocytes from rats with different in-born ability to respond to endurance training, 3) to determine whether CaMKII is important in defining the exercise-induced improvements in VO_{2max}, cardiomyocyte contractile function and Ca^{2+} handling.

We hypothesized that;

1) the higher aerobic capacity in HCR rats would yield a cardioprotective effect after MI compared to the LCR rats that already have established risk for CVD.
2) high intensity exercise training would improve VO_{2max}, cardiomyocyte contractility and Ca^{2+} handling and induce cardiac hypertrophy in high responder rats (HRT) but not in low responder rats (LRT).
3) chronic CaMKII inhibition would abolish the normal cardiac exercise response for VO_{2max} and cardiomyocyte function.

The specific aims of the individual papers were:

Paper I: Determine the role of intrinsic VO_{2max} on cardiac contractile function and Ca^{2+} handling in LCR vs. HCR rats after induction of MI by ligation of the left anterior descending coronary artery.

Paper II: Determine the exercise response on VO_{2max}, cardiomyocyte dimensions, function and Ca^{2+} handling in the HRT/LRT model after a high intensity interval training program.

Paper III: Determine the effect of chronic CaMKII inhibition upon VO_{2max} and cardiomyocyte function during the course of an exercise training program in healthy mice.

METHODOLOGICAL CONSIDERATIONS

The following section contains considerations about the main methodologies used in the different studies that are included in this thesis. Detailed method descriptions are presented in the original papers.

Animal models

In-dept studies of cardiomyocyte function in experimental settings require use of animal models. In the present studies we chose to use rat and mice models that are supposed to mimic human physiology. All *in-vivo* interventions were done during the animals' dark cycle, as rodents are normally active at night. The experiments were approved by the Norwegian Council for Animal Research, which was in accordance with *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health Publication No. 85-23, revised 1996).

Artificial selection of rats

Two rat models have been established by artificial two-way, selective breeding for high and low capacity runners (HCR/LCR) (55,178), and for high and low responders to training (HRT/LRT) (51). The initial hypothesis for these rat models was that functional alleles at multiple interacting loci affecting intrinsic properties would be enriched or fixed between the extreme ends of selection within each animal model. Both rat models are derived from genetically heterogeneous rats obtained from the National Institute of Health, USA, (N:NIH stock). To maintain the heterogeneous genetic lines a rotational mating paradigm has been used that minimizes inbreeding (1.25% per generation) (178). In comparison to inbred strains, outbred selected lines maintain genetic complexity (179). Finally, HCR/ LCR and HRT/ LRT lines may serve as reciprocal controls for unknown environmental changes due to the concurrent breeding of each line in both rat models.

High and low capacity runners (HCR/LCR)

In paper I we examined the effect of intrinsic VO_{2max} on cardiac remodelling after MI. For this purpose we used female HCR and LCR rats from the 22^{nd} generation, described in detail elsewhere (178). In brief, rats were selected for breeding based on their intrinsic treadmill running capacity. The HCR rats represents a ~400% higher inborn maximal running distance

and a ~30% higher inborn VO_{2max} than the LCR rats (Figure 3A & B). As a consequence of selecting purely upon running capacity this model gave LCR rats that had a high-risk cardiovascular profile (39,180,181). These data obtained from a contrasting heterogeneous model system provide strong evidence that genetic segregation for aerobic exercise capacity can be linked with cardiovascular disease and is useful for deeper mechanistic exploration.

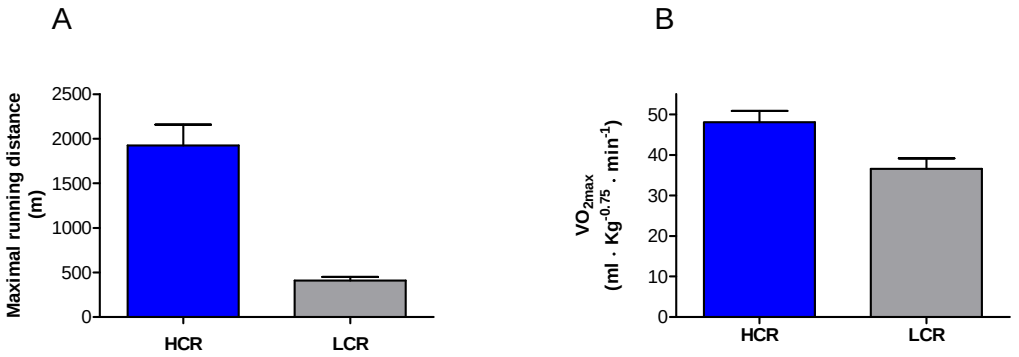

Figure 3. Intrinsic running capacity measured as maximal running distance (A) and as VO_{2max} (B) in high capacity runners (HCR) and low capacity runners (LCR), data presented as mean values ± SD.

High and low responders to training (HRT/LRT)

Female rats from the 7th generation of artificial selection for high or low response to training were included for experiments on cardiac exercise response and from the 9th generation for experiments on cardiac protein expression and histochemistry in paper II. In contrast to HCR/LCR, the HRT/LRT rat model is based on selection for extreme ends of response to exercise training measured as change in maximal treadmill running distance after 24 days of modest treadmill exercise training (Figure 4) (51). The exercise program resembled the general guidelines prescribed for man (moderate brisk walking or jogging for 30 minutes, 3 times a week) to make sure that all rats were able to complete the entire program independent of strain or sex (55). The six highest and six lowest responding rats of each sex was selected to mate for the next generation. Over generations these rats have developed contrasting phenotypes and gene networks providing a powerful tool to determine mechanisms of response to exercise training.

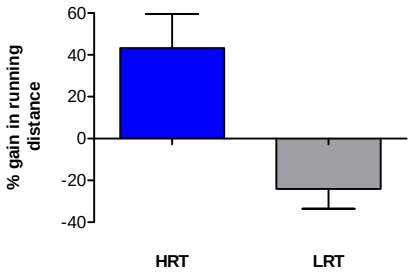

Figure 4. Relative gain in running distance as response to exercise training in high responders to training (HRT) and low responders to training (LRT), data presented as mean values ± SD.

Chronic CaMKII inhibition in mice

To examine the impact of CaMKII on normal function and exercise-induced alterations in the heart we chronically inhibited CaMKII in C57 BL/6J mice (Møllegaard Breeding Center, Lille Skensved, Denmark) in paper III. CaMKII inhibition was obtained by use of the potent, selective and cell-permeable KN-93 (2-[N-(2-Hydroxyethyl)-N-(4-methoxybenzenesulfonyl)] amino-N-(4-chlorocinnamyl) –N-methylbenzylamine; Alexis-Biochemical, Enzo Life Science, PA). KN-93 was first generated as a synthesized methoxybenzenesulfonamide compound in the early 1990s, and has been widely used to study CaMKII ever since. KN-93 inhibits CaMKII by competing for the calmodulin binding site on the regulatory domain (182). The dosage administered in paper III was based on previous studies which reported a dose-dependent effect of KN-93 on CaMKII inhibition (97,167). Daily injections of 10 µmol/kg KN-93 have been reported to produce similar effect on LV contraction measurements as the genetically CaMKII-inhibited AC3:I mice (97,147).

Potential non-specific effects of KN-93 have been noticed, such as acting as CaMKII-independent ion channel antagonists, and affecting glucose-induced and forskolin-stimulated insulin release. Most important for our study were the potential inhibitory effects on the LTCC (167,183,184). We did not control for this side effect, but Sossalla et al (165) have controlled for the effect of KN-93 on LTCC against autocamtide-2 related inhibitory peptide (AIP) effects and found no change in LTCC current. Moreover, studies reporting LTCC inhibition were acute cell experiments, and other studies applying KN-93 injections *in vivo* have not reported any specific side effects (97,147). KN-93 was diluted in dimethyl sulfoxide (DMSO; C_2H_6OS; Sigma-Aldrich, St. Louis, MO), which also has minor concentration-

dependent adverse effects (185). These side effects were minimized by administering small dosages of DMSO in paper III (0.04- 0.05 mL per injection). To control for potential side effects of DMSO sham mice were injected with the same amount of DMSO. Therefore, it is unlikely that DMSO influenced the observed differences between the groups. Urine sticks were used to test for glucose in the urine; there were no indications of such in any of the groups. These results suggest that KN-93 did not affect glucose-induced insulin release in the present study. After euthanasia mice were sent for pathological examinations of the vital organs at the Norwegian Veterinary Institute, Oslo, Norway to control for side effects of chronic KN-93 injections on aerobic fitness and cardiac function. All vital organs (including hearts) were examined to exclude that any major side effects had influenced the results. In brief, necropsy was performed on 17 of the animals, specimens from heart, liver, kidney, spleen, intestine and brain were fixed in 4 % neutral buffered formaldehyde and processed routinely for light microscopy. Sections were cut at 5 µm and stained with hematoxylin and eosin. The pathologist made no observations that would have altered aerobic fitness (except from discomfort from injections) or cardiac function. To minimize potentially negative effects of the injections on exercise performance, injections were administered after the exercise session.

Experimental interventions

Exercise training program

To optimize the effect of exercise training, high intensity aerobic interval training was performed on rats and mice in paper II and III. Animals were trained 5 days/week for 6 weeks, running uphill (25˚) on a treadmill. Training sessions consisted of a 10-minute warm up at 50-60% of VO_{2max}, whereupon exercise then alternated between 4-minute intervals and 2-minute active breaks at 85-90% and 50-60% of VO_{2max}, respectively, for 90 minutes in paper II and 60 minutes in paper III. VO_{2max} was measured at the beginning of every training week to ensure that the desired exercise intensity was obtained and to adjust for exercise-induced improvements in VO_{2max} and running economy (67,85). Sedentary animals were only tested before and after the exercise training period. This model of high intensity aerobic interval training was established by Wisløff et al (67), and has been proven efficient for inducing cardiovascular adaptations in both clinical and experimental studies (22,58,60,69,80,85,104,186,187).

Induction of myocardial infarction

To induce acute MI in paper I, we used ligation of the descending coronary artery through thoracotomy. This is a well described and recognised experimental method that provides quite reproducible infarct sizes and serves as a rodent simulation of human MI (71,73,188,189). Ligation causes an MI in the LV free wall typically characterized by pathological remodelling such as increased lumen, dilated LV, thinning of the non-infarcted posterior wall and hypertrophy (190). Subsequent depressed contraction, slowed relaxation and impaired Ca^{2+} handling is most pronounced one week after MI is induced, followed by a partial recovery towards the fourth week, whereupon it remains unchanged but impaired for several weeks (78). Scar formation, as fibroblast proliferation and collagen deposition is completed within six weeks, and additional augmentation in ventricular volume will proceed until three months even in moderate sized infarctions (20-40% of the LV)(89).

Although the histological evolution and scar formation are comparable in humans and rats (71,190), there are some notable limitations to this rat MI model in comparison to human MI. Experimental rat MI models and human MI naturally divert in origin (191). MI is usually induced in relatively young rats that does not reflect the analogous pathogenesis of coronary disease and subsequent MI normally seen in humans, which likely results from symptoms evolved over several years due to atherosclerosis, obesity, diabetes or hypertension (189). However, rats in paper I were close to one year at MI induction, and LCR rats possessed some of the symptoms above, providing a closer association to human MI (39). Moreover, variability in induced MI size among rats is inevitable and affects the remodelling process. In large MI (>40-50% of LV circumference) symptomatic signs of heart failure will develop over time (189,190,192), whereas hypertrophy of surviving myocardium in small MI (<20% of LV circumference) may normalize LV wall stress resulting in minimal pathological remodelling (192). All experiments were performed after completion of the acute remodelling phase.

Experimental protocols

Testing of maximal oxygen uptake

Aerobic fitness was measured as VO_{2max}, which represents the upper limit of aerobic exercise capacity (28). VO_2 increases with power output in dynamic work with large muscle masses up

to a level where it reaches a plateau despite increasing workloads. VO_{2max} was assessed before, during and after the exercise training period in paper II and III. In paper I VO_{2max} was tested prior to cardiomyocyte experiments.

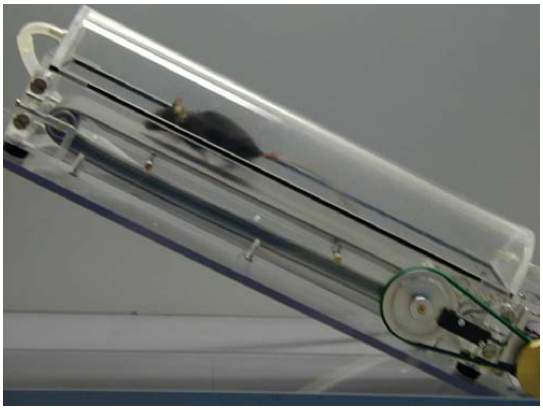

Figure 5. Illustration of VO_{2max} testing of mice.

We determined VO_{2max} by uphill (25°) treadmill running until exhaustion in a specialized metabolic chamber that allows us to register and control the amount of air volume passing through the chamber and analyse the fractions of oxygen and carbon dioxide (Figure 5). The use of inclination simplifies the assessment of animals' VO_{2max} and ensures reaching maximal work intensity, since performance is not limited by running speed (67,85). Such a full-body exercise taxes the cardiovascular system and VO_2 maximally. Tests were started at low-moderate intensity (0.10 $m \cdot sec^{-1}$ for mice, and 0.12 $m \cdot sec^{-1}$ for rats), whereupon running speed was increased by approximately 0.03 $m \cdot sec^{-1}$ every second minute until the animals were not able to maintain velocity and VO_2 levelled off despite increasing work loads. This method has been thoroughly tested, and found reliable on rats and mice (67,85,186). To consider differences in body weight, VO_{2max} was expressed in relation to body weight raised to the power of 0.75 in paper I and III (193).

Familiarization to the treadmill is essential for exercise training and testing outcomes since it reduces stress associated with the treadmill and handling procedures. Prior to VO_{2max} tests and exercise training rats and mice were allowed a gentle introduction to the treadmills, where they were kept on the treadmill at rest and subsequent low speeds. There is an electrical gird at the end of the running lanes giving electrical pulses of 0.2 mA causing discomfort but not pain. During the familiarization period this gird was turned off and when applied, animals

learned quickly to avoid the electrical gird, and thus, exercise intensity could be carefully controlled.

Echocardiography in rats and mice

Global adaptations on cardiac morphology and work was evaluated by echocardiography on animals in paper I and III using a single-element mechanical transducer with a center frequency of 30 MHz (Vevo 770, VisualSonics, Toronto, Canada) and digital ultrasonic system. Echocardiography is considered a feasible method for obtaining good-quality measurements of cardiac morphology and physiology in both rats and mice (192,194-199). Echocardiography is also validated for characterization of pathological hypertrophy in hearts (79,192), whereas the value in determining exercise-induced physiological hypertrophy has been questioned and currently measurements of isolated cell dimension are considered more accurate. Body composition and anatomical properties might limit echocardiography recording quality, and a future high-resolution echocardiography is necessary to obtain better quality measurements of exercise-induced hypertrophy comparable to post-mortem and isolated cell dimension measures.

Echocardiography in conscious animals has minimal effect on measurements of cardiac function (196,199), however it requires substantial training of animals to minimize stress, and is also difficult to practice in rats, due to size. To control for potential cardiodepressive effects of anesthesia on echocardiography measurements standardizing the anesthetic protocol is essential. We performed echocardiography in self-breathing rats and mice exposed to a mixture of isoflurane and oxygen. Isoflurane anesthesia lowers breathing rate in a concentration-dependent manner, but the effect on cardiac function is considered to be small, and isoflurane is preferred over injectable anesthetics (197,200). During echocardiography, respiration and heart rate were closely monitored, and the amount of isoflurane (2%) was kept stable for all experiments. It is therefore unlikely that anaesthesia would have influenced the observed differences between groups. Following echocardiography, animals awoke almost immediately, indicating a light anaesthesia.

Cardiomyocyte experiments

Significant correlation between cardiomyocyte contractile function and *in vivo* cardiac function facilitates the use of isolated cardiomyocytes in studies on cellular mechanisms of aerobic fitness and CVD (69,77-80). In the present thesis cardiomyocyte experiments were performed in paper I, II and III.

Cardiomyocyte isolation

Animals were anesthetized with isoflurane and heparinised hearts were rapidly removed and placed in an ice-cold perfusion buffer. Different perfusion buffers were used when isolating cardiomyocytes from rats and mice as described in detail in the respective papers. This is because mice cardiomyocytes are more sensitive to Ca^{2+} concentrations during the isolation process than rat cardiomyocytes. In brief, rat cardiomyocytes were isolated as previously described with a modified Krebs- Henseleit Ca^{2+} free buffer (67,80,201), whereas mice cardiomyocytes were isolated in a HEPES-based physiological solution, also previously described (202,203). Aorta was connected to an aortic cannula on a standardized Langendorff retrograde perfusion system and the hearts were cleaned by perfusion of Krebs buffer in paper I and II and Hepes buffer containing ethylene glycol tetra acetic acid (EGTA) in paper III. When the hearts were clean the perfusion solution was switched to a Krebs (paper I and II) or HEPES-based (paper III) solution (zero Ca^{2+}) containing the enzyme collagenase II (Worthington, NJ, USA) and bovine serum albumin (Sigma Aldrich, MO, USA). Collagenase breaks down the peptide connections in the collagen, enabling separation of the cells. Hearts were removed from the perfusion system before the LV was separated and cut into small pieces. The tissue was lightly shaken for 10 minutes and the non-digested tissue filtered out by a nylon mesh. Cells were centrifuged at 600 rpm (at 37°) for 30 seconds whereupon the supernatant was gently removed and new buffer added. This was repeated two times to remove dead cells and to subsequently increase the Ca^{2+} concentration in the HEPES solution stepwise to 1.2 or 1.8 mM. In paper I the infarcted area was removed when the heart was cut down from the aorta cannula. Cardiomyocytes in paper I was isolated at least 24 hours after the VO_{2max} test, and in paper II and III, cardiomyocytes were isolated 24 hours after the last exercise training session to measure the chronic adaptation to exercise training. Our research group has over several years developed extensive experience in cardiomyocyte isolation. However, we had fewer viable cells before centrifugation from mice hearts in paper III than expected. This is a limitation to the cardiomyocyte measurements in paper III. In paper I and

II we had up to 75% viable cells before centrifugation in line with previous cardiomyocyte isolation experiments in our laboratory, and an average of 10 cells from each animal were studied. Viable, rod-shaped cells without visible morphological alterations who responded adequately to electrical stimulation were used for experiments, and analyses were based on these cells.

Cardiomyocyte contractile function and Ca^{2+} handling

Cells attached to coverslips rested for 1 hour in HEPES buffer before loading. Cardiomyocytes were loaded with 2 μM Fura-2/AM (Molecular Probes, Eugene, OR, USA) in order to measure contractile function and Ca^{2+} cycling simultaneously. The membrane-permeable derivative of the ratiometric Ca^{2+} indicator Fura-2/AM has acetoxymethyl (AM) ester attached to it (204). Therefore, cardiomyocytes were left in HEPES buffer for 20 minutes of de-esterfication after the 30 minutes of Fura-2/AM loading in room temperature before experiments were started. During de-esterfication nonspecific cellular esterases hydrolyze AM which liberates the Ca^{2+} sensitive indicator and ensures adequate Fura-2 loading. To avoid incorrect differences between cells a strict loading procedure was used for all experiments. This is especially important for fractional shortening, due to the depressive effect of Fura-2/AM on cardiomyocyte shortening. In all three papers rod-shaped cells without obvious morphological alterations, responding to electrical stimulation were included for cardiomyocyte experiments. During the experimental protocol cardiomyocytes in paper I were superfused in 1.8 mM Ca^{2+} HEPES-based solution, in paper II superfused with 1.2 mM Ca^{2+} HEPES-based solution, whereas cardiomyocytes in paper III were field stimulated in 1.8 mM Ca^{2+} HEPES-based solution without perfusion. Higher Ca^{2+} contents in solutions (1.8 mM vs. 1.2 mM) increase the electrical stimulated Ca^{2+} transients. To clarify differences in cardiomyocyte function between groups in paper I and III we used experimental solutions with higher Ca^{2+} content, since mice cardiomyocytes and failing cardiomyocytes have basically lower Ca^{2+} transients than healthy rats. All perfusion solution was kept at 37˚C during experiments.

Electrical field stimulation of isolated cardiomyocytes is a standard and widely used method for studies on contractile function and Ca^{2+} cycling (39,78-80,129). Cardiomyocytes were stimulated with increasing frequencies (1-5 Hertz (Hz) in paper I and III and 1-7 Hz in paper II) on an inverted epifluorecence microscope (Nikon TE-2000E, Tokyo, Japan). Attached to

the side port of the inverted microscope was a video camera, and velocity of shortening and relaxation as well as the magnitude of shortening were analyzed during transients (SarcLen™, Ionoptix, Milton, USA), using a special designed software (SarcLen Sarcomere Length Acqusition Module). Exercise-induced changes in cardiomyocyte function have previously been shown to be most marked at physiological frequencies (69,77). However, most experiments, including ours, have been performed at stimulation frequencies ranging from 1-5 Hz (paper II 1-7 Hz) which is below the physiological range in rats (5-10 Hz) and mice (7-12 Hz). Furthermore, the reliance on CaMKII activity also increases with increasing stimulation frequencies (152). Thus, the effects of CaMKII inhibition on i.e. RyR2 Ca^{2+} release rate (205) and cardiac contractility (165) are greater at higher stimulation frequencies compared to lower. This reflects a limitation to our studies that may have underestimated the effect of MI, exercise training and CaMKII inhibition on cardiomyocyte contractile function and Ca^{2+} handling.

Intracellular Ca^{2+} transients was collected by rationing the fluorescence intensities detected at 510 nm emission wavelength using excitation alternating between 340 and 380 nm wavelengths (Optoscan, Cairn Research, Kent, UK), which is the largest dynamic range for Ca^{2+} dependent fluorescence signals. Excitation at 340 nm causes fluorescence emission at 510 nm to increase with increasing Ca^{2+} concentrations, whereas excitation at 380 nm decreases fluorescence emission by increasing Ca^{2+} concentrations. Collecting excitation through band pass filters of 340 and 380 nm by a 500 Hz rotating optical chopper and using the ratio of the fluorescence intensities provide more stable Ca^{2+} measurements and minimize factors such as uneven dye distribution, leakage, photo bleaching, different room light, or compartments of Fura-2/AM in the cell (204). In addition to measuring systolic and diastolic intracellular Ca^{2+} levels, we examined the time course of the Ca^{2+} transient by measuring peak systolic Ca^{2+}, time to peak Ca^{2+}, time to 50% of peak Ca^{2+}, and time to 50% Ca^{2+} decay. Diastolic Ca^{2+} cycling was quantified with the use of rate constants of Ca^{2+} removal during twitch-induced stimulation, sustained caffeine stimulation in physiological solution and sustained caffeine stimulation in $0Na^{+}/0Ca^{2+}$. In paper I we used these measurements to quantify SERCA-2a, NCX and PMCA contribution to Ca^{2+} removal as previously described (206). Total SR Ca^{2+} content was measured by peak caffeine-induced Ca^{2+} release. Caffeine opens RyR2 completely and totally empties SR Ca^{2+} content. However, since RyR2 sensitivity to Ca^{2+} might increase after caffeine exposure, we stimulated the cardiomyocytes until normal

Ca^{2+} transients were obtained after each caffeine exposure before proceeding the cell experiments (164).

When using animal models as in the papers that constitute this thesis, it is important to note that the contribution to cellular Ca^{2+} removal is different in rats and mice compared to humans. In humans SERCA-2a removes 70% of the Ca^{2+} from cytosol into the SR lumen, whereas 92% is removed by SERCA-2a in rats and mice. NCX contributes with 28% Ca^{2+} removal out of the cell in human, and 7% in rats and mice, leaving about 1% for PMCA and mitochondrial Ca^{2+} uniporter in human, rats and mice (110).

SR Ca^{2+} leak

To determine whether diastolic SR Ca^{2+} leak was increased after MI in paper I we used the Ca^{2+} leak protocol established by Shannon et al (207). After measuring contractile function and Ca^{2+} handling during twitch-induced transients in HEPES 1.8 mM buffer, stimulation was ceased and quiescent cardiomyocytes were perfused with $0Na^{+}/0Ca^{2+}$ while measuring diastolic Ca^{2+} level for 40 seconds immediately followed by a $0Na^{+}/0Ca^{2+}$ diluted caffeine-induced transient. When Ca^{2+} levels were close to baseline caffeine perfusion was replaced by HEPES perfusion and cardiomyocytes were stimulated at 1 Hz until stable Ca^{2+} transients was restored (approximately 20 seconds). Subsequently, perfusion was switched to tetracaine solution, whereupon diastolic Ca^{2+} level were measured for another 40 seconds. This was also followed by a $0Na^{+}/0Ca^{2+}$ diluted caffeine-induced transient. The quantitative difference in diastolic Ca^{2+} level between the $0Na^{+}/0Ca^{2+}$ and tetracaine solution represents the absolute SR Ca^{2+} leak, since $0Na^{+}/0Ca^{2+}$ block the NCX Ca^{2+} influx and efflux and tetracaine blocks Ca^{2+} movement across RyR2 (Figure 6). Diastolic SR Ca^{2+} leak was presented in relation to total SR Ca^{2+} content.

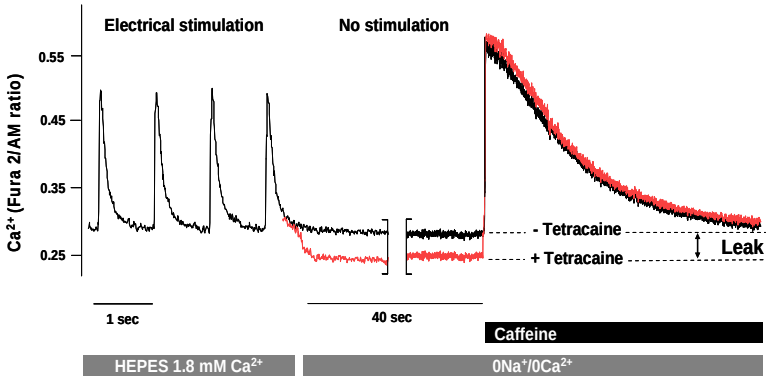

Figure 6. Illustration of Ca^{2+} transients and the diastolic SR Ca^{2+} leak protocol.

To examine the impact of PKA and CaMKII on RyR2 diastolic Ca^{2+} leakage, acute PKA and CaMKII inhibition were induced in paper I by pre-incubation of PKA inhibitor (H-89; 3 µM, Sigma Aldrich, MO, USA) and the potent and selective CaMKII inhibitor AIP (1 µM, Sigma Aldrich, MO, USA) (208). Pre-incubation of cardiomyocytes with either H-89 or AIP was started 1 hour prior to experiments. Experiments were conducted within 30 minutes after the incubation period, to avoid potential washout of AIP/H-89 by the perfusion system. Like most chemical compounds H-89 and AIP have non-specific side effects, which need consideration. Murray (209) have observed effects of H-89 on MAPK and Ca^{2+} signalling, however, we used a lower concentration of H-89 to avoid similar off target reactions. A former study has also shown effects of H-89 on PLB phosphorylation and SERCA-2a activity, but this cannot be attributed simply as a side effect (104). AIP, on the other hand, has been shown to effect RyR2 phosphorylation and therefore SR Ca^{2+} leak (104), however this is in regard with its inhibitory effect. Although caution should be made when interpreting data from these inhibitors, they provide us with valuable information about the effect of PKA and CaMKII.

T-tubule density and synchrony of Ca^{2+} release

Dense and intact T-tubule network throughout the cardiomyocyte is essential for rapid and synchronous Ca^{2+} release. In paper I and II T-tubule density and Ca^{2+} release synchrony were measured on a Pascal (510 LSM, Zeiss, Jena, Germany) confocal microscope with a pinhole of 1 airy unit giving a z-resolution < 1 µm. The membrane specific Di-8-ANEPPS (10 µM, Molecular Probes, Eugene, OR, USA) was used for T-tubule visualization and Fluo-3/AM (10 µM, Molecular Probes, Eugene, OR, USA) for Ca^{2+} release synchrony measurements. Fluo-3/AM is in comparison to Fura-2/AM more suitable for measuring quick changes of Ca^{2+}, due

to faster binding/ dissociation from Ca^{2+}, but is more sensitive to bleaching and compartmentalization. Similar to Fura-2/AM, Fluo-3/AM also contains acetoxymethyl ester, and likewise requires a 20 minutes de-esterfication after loading prior to experiments.

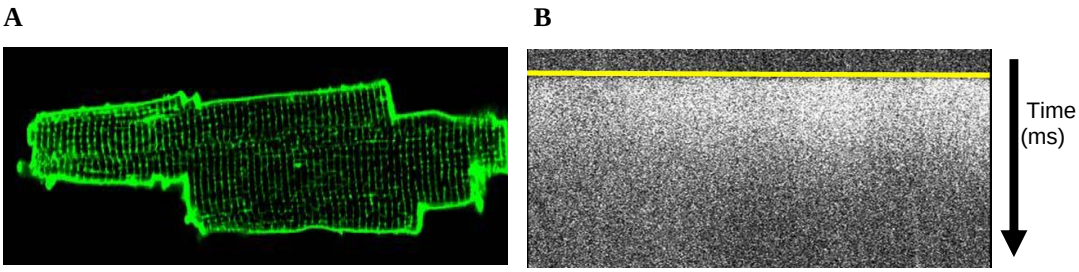

Figure 7. Confocal image of T-tubule structure, membrane specific stained with di-8-ANEPPS (**A**), and line scan image of Ca^{2+} release, where the yellow line indicate electrical stimuli (**B**) in ventricular cardiomyocytes.

T-tubules were stained and visualized in LV cardiomyocytes in paper I and II (Figure 7A). T-tubules density normalized to cell size, captured from the middle of the cell, was obtained from 5 images per cell. During analysis the pixels stained with the dye were counted relative to the total number of pixels, when pixels associated with the non-T-tubular sarcolemma were removed. Analysis of Ca^{2+} release synchrony in paper I was based on 1-3 Ca^{2+} transients per cell, where line scan of each Ca^{2+} transient was divided into ~25 equal strips (~4µm) and time from stimulation to 50% Ca^{2+} release was measured for each strip (Figure 7B). Standard deviation of these measurements was considered Ca^{2+} release synchrony across the cell.

Cell dimension

Measuring cardiomyocyte dimension in isolated cells has been proven sensitive enough to establish differences in cellular morphology after exercise training (69). In paper I, II and III we measured cardiomyocyte dimension on a Nikon Eclipse E400 Microscope with a DSFil camera (Nikon NIS- Elements Basic Research Version 3.00 software, Nikon Instruments Inc., New York, USA). Cell length and width were detected by photographing a large number of cells, whereupon approximately 100- 150 random cells per rat or mice were included for measurements. Cell volume was calculated by cell length · cell width · 0.00759 (210). Only viable undamaged rod-shaped cells were selected for measurements of cell dimensions.

Molecular analysis

Immunohistology

Apoptosis and fibrosis were assessed in paraffin-embedded LV tissue sections in paper II to investigate possible pathological alterations affecting Ca^{2+} handling and intrinsic exercise responsiveness. Apoptosis was assessed using the CardioTACS™ *In Situ* Apoptosis Detection Kit (Trevigen, Gaithersburg, MD, USA) which detects DNA fragmentation. Evaluation and quantification are often prone to error, thus to avoid false results we generated positive controls for both LRT and HRT. To enable evaluation of fibrosis we used hematoxylin-erythrosin-saffron (HES) staining, as saffron stains the connective tissue. In both cases thin slices of tissue (4 μm) were cut and mounted on a glass microscope slide to be examined with light microscopy. Staining provides contrast to the tissue in addition to highlighting specific parts of interest.

Assessment of apoptosis in myocardial tissue by detection of nuclear DNA fragmentation is a semi-quantitative and widely accepted method. In contrast to necrosis, apoptosis regulates cell death in a controlled process without inflammatory response (70,84). Thus, apoptosis generates no or little histological trace making it harder to detect (84). A disadvantage of this method is that some necrotic cells might appear as apoptosis positive (211), however this has not affected our study as the results were undoubtedly negative.

Western immunoblotting

To determine expression of selected proteins related to Ca^{2+} handling in LV tissue homogenate we used immunoblotting (Western analysis) in paper I and II. Western immunoblotting is a semi-quantitative method that allows detection of specific proteins within a tissue homogenate, only limited by availability of the specific antibody (212). We used western blot for detection of total and phosphorylated CaMKII (Pierce, Rockford, USA) and SERCA-2a expression (Badrilla, Leeds, UK), performed according to previously described methodology (213). In brief, gel electrophoresis was applied to separate proteins by their molecular weight. The sodium dodecyl sulphate (SDS) – polyacrylamide gel electrophoresis (PAGE) disc was loaded with molecular samples and submerged into a buffer where the electrical current was provided. The electrical current causes the molecules to migrate through the acrylamide mesh of the gel towards the positively charged electrode. Proteins are

separated according to size because smaller proteins migrate faster than the larger proteins through the mesh. After the electrophoresis separation, proteins were moved from within the gel to a nitrocellulose membrane by electro transfer. Ponceau S dye was used to monitor the effectiveness and uniformity of the protein transfer. Before probing, the membrane was subjected to blocking to avoid interaction between the membrane and the specific antibody. This procedure reduces "noise" and provides a more clear result. The membrane was then probed with a specific antibody of the desired proteins, washed and exposed to another antibody. Several perioxidase-conjugated secondary antibodies bound to one primary antibody and enhance the signal detected by autoradiography. ImageJ software (National Institutes of Health; USA) performed the quantification analysis of blots. Thus, the protocol contains many steps, and good reliable results depend on flawless performance of all steps. Limitations of the method include the time consumption in addition to being a mainly qualitative assay.

Statistics

Data are presented as mean ± SD. SPSS version 16 (SPSS Inc., Chicago, Illinois, USA) was employed for statistical analysis. Before the analysis all data were checked for normal distribution. Data was analysed by one-way ANOVA with LSD or Bonferroni post hoc test, independent samples T-test or Mann-Whitney U when appropriate. Determination of absolute effect of MI between HCR and LCR in paper I was analysed using mean differences with standard errors in a t-test. Pre to post test values in paper II were analysed by repeated measures ANOVA. In paper III, we used Paired Samples T-test to identify statistical differences from pre to post tests. $P<0.05$ was considered statistically significant.

SUMMARY OF RESULTS

Paper I High inborn aerobic capacity does not counteract deterioration of cardiac function and calcium handling after myocardial infarction

1. There were no significant difference in the deterioration of VO_{2max} between HCR and LCR after MI (20% and 36%, respectively). VO_{2max} was similar in HCR-MI and LCR sham.
2. MI depressed *in vivo* LV fractional shortening by 49% ($P<0.01$) in HCR and 62% ($P<0.01$) in LCR and ejection fraction measured by echocardiography by 46% ($P<0.01$) and 50% ($P<0.01$), respectively. Group differences were not statistically significant.
3. MI induced pathological hypertrophy to the same extent in both HCR and LCR rats.
4. The effect of MI was greater in HCR compared to LCR rats on cardiomyocyte fractional shortening (39% vs. 34%, $P<0.01$), Ca^{2+} transient amplitude (37% vs. 20%, $P<0.05$) and time to 50% re-lengthening (83% vs. 24%, $P<0.05$). SR Ca^{2+} content decreased by 20% ($P<0.01$) in both MI groups (group difference, $P<0.01$).
5. Diastolic Ca^{2+} handling was impaired after MI, reflected by decreased SERCA-2a Ca^{2+} removal (group difference, $P<0.05$) and increased NCX Ca^{2+} removal (group difference, $P<0.05$) from cytosol.
6. HCR-MI was closer to a healthy profile (i.e. HCR sham) than LCR-MI on cardiomyocyte contractile measurements, and not significantly different from LCR sham.
7. SR Ca^{2+} leak increased by 177% ($P<0.01$) in HCR and 67% ($P<0.01$) in LCR after MI (group difference, $P<0.05$). Acute CaMKII inhibition abolished the SR Ca^{2+} leak in both MI groups.
8. Phosphorylated CaMKII relative to total CaMKII assessed by western blot protein analysis showed no significant difference between groups.

Paper II Aerobic exercise response is dependent of cardiac plasticity

1. VO_{2max} was similar in HRT and LRT rats at baseline.
2. High intensity interval training increased VO_{2max} with 39% (P<0.001) in HRT rats whereas VO_{2max} was unaltered in LRT rats.
3. LV weight was 8% (P<0.01) lower and cardiomyocytes 32% (P<0.05) wider and 6% (P<0.05) shorter in LRT compared to HRT at baseline, indicating a pathology-like cell dimension probably caused by concentric hypertrophy. The morphological difference between HRT and LRT at baseline was not reflected by apoptosis or fibrosis detection.
4. High intensity interval training reduced LV weight (4%, P<0.05), and cell length (5%, P<0.05) and cell volume (10%, P<0.05) in LRT, whereas it induced physiological hypertrophy associated with increased LV weight (9%, P<0.01), cell length (7%, P<0.01), cell width (9%, P<0.05) and cell volume (15%, P<0.001) in HRT.
5. Before the exercise training intervention there was no difference between HRT and LRT rats on cardiomyocyte contractility and Ca^{2+} handling parameters.
6. LRT did not improve on any of the measured parameters for cardiomyocyte contractility or Ca^{2+} handling after exercise training. In contrast, exercise training induced improvements on all measured parameters for cardiomyocyte contractility and Ca^{2+} handling in HRT.
7. T-tubule density was lower in LRT compared to HRT (P<0.01) at baseline and after exercise training. Exercise training tended to increase T-tubule density in HRT (P=0.07).
8. Total CaMKII and ratio phosphorylated CaMKII in relation to total expression of CaMKII was not different between HRT and LRT at baseline.

Paper III **Chronic CaMKII inhibition blunts the cardiac contractile response to exercise training**

1. Chronic CaMKII inhibition with KN-93 treatment did not affect VO_{2max}, cardiac function measured with echocardiography or cardiomyocyte size in untrained KN-93 treated mice.
2. High intensity interval training increased VO_{2max} with 8% ($P<0.05$) in sham treated mice, whereas KN-93 treated mice increased VO_{2max} with 22% ($P<0.01$, group difference, $P<0.01$).
3. *In vivo* fractional shortening improved by 28% ($P=0.02$) with exercise training in sham mice, whereas no change was observed in KN-93 treated mice.
4. Exercise training induced physiological hypertrophy that increased cardiomyocyte length and width by 13% ($P<0.05$) and 30% ($P<0.05$) in sham, and by 8% ($P<0.05$) and 14% ($P<0.05$) in KN-93 mice, respectively. The physiological hypertrophy in cardiomyocyte length and width was significantly greater in sham compared to KN-93 mice (group difference, $P<0.05$).
5. Chronic CaMKII inhibition increased cardiomyocyte time to 50% re-lengthening with 25% ($P<0.05$), increased Ca^{2+} transient decay time with 16% ($P<0.05$) and reduced Ca^{2+} transient amplitude with 20% ($P<0.05$) in sedentary mice. These reductions in cardiomyocyte function were normalized by exercise training in KN-93 treated mice.
6. Cardiomyocyte fractional shortening was increased by 63% ($P<0.01$) in sham mice whereas it was increased by 18% ($P<0.05$) in KN-93 mice.

DISCUSSION

The present thesis shows that 1) inborn VO_{2max} do not provide cardioprotection from the deteriorating effects of MI on VO_{2max} and cardiomyocyte function, 2) low training response measured as VO_{2max} was associated with lack of cardiomyocyte adaptation to exercise training and 3) CaMKII was not required for exercise-induced increase in VO_{2max} in healthy mice but seems to be important to obtain optimal exercise response on cardiomyocyte function.

Inborn VO_{2max} and cardiac remodelling after MI (paper I)

Inborn VO_{2max} and cardioprotection

Several studies report that hearts from exercise-trained individuals are partly protected against cardiac injuries such as ischemia-reperfusion and acute MI (214-219). However, the effect of inborn exercise capacity on cardiac remodelling after MI has not been investigated. LCR rats have an increased risk of ventricular arrhythmias (220) and are predisposed for CVD with accumulation of cardiovascular risk factors including hypertension, endothelial dysfunction, insulin resistance, impaired glucose tolerance, visceral adiposity, hyperglycemia, hypertriglyceridemia, and elevated plasma free fatty acids (39,181). 1 540 cardiac genes are differentially expressed between HCR and LCR rats for pathways in cardiac energy substrate, growth signalling, contractility and cellular stress potentially triggered by hypoxic conditions in LCR rats (221). The LCR rats have decreased expression of inward K^+ channels, lower energy metabolism and ATP production compared to that observed in the HCR rats, all factors associated with failing hearts and CVD (221). It has also been demonstrated that higher sensitivity to nitric oxide inhibition in LCR rats is affecting cardiomyocyte function (181). Recent reviews indicate that mechanisms for cardioprotection are related to exercise-dependent induction of heat shock proteins, increase in cardiac antioxidant capacity, expression of endoplasmic reticulum stress proteins, anatomical and physiological changes in coronary arteries, changes in nitric oxide production, adaptational changes in cardiac mitochondria, increased autophagy, and improved function of sarcolemmal and/or mitochondrial ATP-sensitive K^+ channels (222-224). Based on these previous findings, we hypothesized that LCR rats would suffer a greater depression in VO_{2max} after MI than HRT rats. However, MI reduced VO_{2max} to the same extent in both HCR and LCR rats. The reduced VO_{2max} caused by MI corresponded with changes in cardiac function, cardiomyocyte

contractility and Ca^{2+} handling, in line with other studies demonstrating a relation between cardiomyocyte function and VO_{2max} (32,69,77,80,225).

Although VO_{2max} level is provided to be closely related to health outcome (3,16,26,42,226) and aerobic fitness level is considered more important for survival than physical activity level (17,19,25) this study (paper I) suggests that high inherited VO_{2max} per se is not sufficient to provide cardioprotection against cardiac remodelling and loss of cardiac function in HCR compared to LCR rats after MI. This is in consensus with previous studies demonstrating an absence of exercise-induced cardioprotection after cessation of exercise training (227,228). However, high inborn VO_{2max} appears to serve as a buffer capacity reducing the loss in absolute VO_{2max} level after MI (paper I). We did not intend to investigate longevity and prognosis, however, previous reports indicate that maintaining a high VO_{2max} after MI improves prognosis (3,5,7,226,229), as health risks are highest at low VO_{2max} levels and decrease with higher VO_{2max} levels (6,7,40,42). Indeed, a recent paper demonstrated that the LCR rats had a 28- 45% shorter lifespan compared to the HCR rats (40).

Echocardiography of cardiac function and dimension

MI reduced fractional shortening in HCR and LCR rats compared to their sham littermates. This is in line with previous MI studies in rats (79,89,192,230,231) and indicates that the current MI-model induces systolic dysfunction. Systolic dysfunction caused by the MI was confirmed by reduced positive dP/dt and ejection fraction in HCR and LCR rats. The similar decline in ejection fraction in HCR and LCR after MI might be explained by similar MI size. Decreased ejection fraction after MI can be caused by reduced contractile function due to myocardial damage or sustained ischemia and/or be a result of LV dilation due to infarct expansion or stretching of the scar (232). MI significantly increased both LV end-systolic diameter (LVESD) and LV end-diastolic diameter (LVEDD) in HCR-MI and LVESD in LCR-MI, indicating increased chamber dilatation and reduced myocardial contraction both consistent with the observed decrease in ejection fraction. LVEDD tended to increase also in LCR-MI but did not reach the statistical cut-off (P=0.06).

Despite equal relative effect of MI on cardiac function, the healthier inborn cardiac phenotype in HCR rats resulted in better absolute LV function after the MI compared to LCR rats. Although the HCR are not protected against pathological remodelling after the MI compared

to the LCR, their higher initial cardiac function serve as a buffer capacity reducing the loss in cardiac function. Studies with prior exercise training demonstrate smaller MI-induced pathological remodelling in exercise-trained individuals (214,215,227,233). Thus, exercise training appears to be necessary to obtain cardioprotection from pathological remodelling after MI.

Cardiomyocyte pathological hypertrophy

Cardiomyocyte dimensions were similar in HCR and LCR sham rats at baseline. This is in contrast to previous studies in the HCR/LCR model, demonstrating a mild pathological concentric hypertrophy in LCR rats compared to HCR rats (39,160,221,234). Following MI, HCR and LCR rats underwent similar pathological hypertrophy, shown by increased cardiomyocyte length and width. This is in line with the ventricular remodelling previously reported to follow MI (89,231).

Echocardiography measurements in HCR-MI and LCR-MI indicated chamber dilatation which is normally caused by volume overload due to impaired cardiac pump capacity after MI, leading to eccentric hypertrophy (elongation of cardiomyocytes) (235). Moreover, both HCR and LCR rats decreased length/width ratio after MI ($P<0.05$ and $P<0.01$, respectively, Figure 8), indicating that pressure overload may also have occurred. Concentric hypertrophy is often associated with pressure overload (74), and is characterized by assembly of contractile protein units in parallel (84,93,235,236).

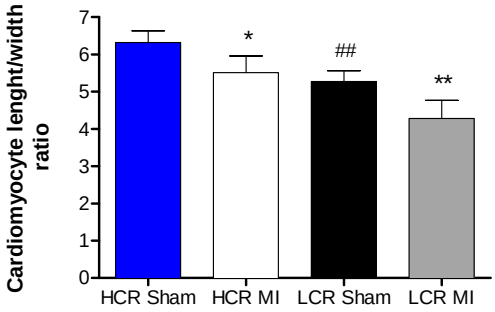

Figure 8. Cardiomyocyte length/width ratio (paper I), presented as mean ± SD. * $P<0.05$, different from HCR sham; ** $P<0.01$ different from HCR sham and LCR sham; ## $P<0.01$ different from HCR sham.

Ventricular remodelling after MI has been described as a mix of volume and pressure overload where stretched and dilated infarcted tissue increases LV volume with a combined

volume and pressure load on non-infarcted areas (237). Concentric hypertrophy has also been found to progress into eccentric hypertrophy and to promote dilation after long-term pressure overload (93). However, experiments in paper I was performed within 3 months after the MI and therefore future studies are needed to examine the development of hypertrophy over an extended period of time in the HCR and LCR rats. Of the potential mechanisms involved in the hypertrophic response, extracellular signal-regulated kinase (ERK1/2) signalling was recently found to promote concentric growth and prevent eccentric growth (235), which may contribute to explain the decrease in length/width ratio after MI in HCR and LCR rats. Moreover, calcineurin and CaMKII is also activated by pressure overload (156) and appears to be strictly cardiomyopathic (92,95,98). Inhibition of either calcineurin or CaMKII is suggested to reduce pathological hypertrophy and secondary pathological effects after pressure overload (92,95,139). However, western blot analysis showed no difference in total CaMKII expression or phosphorylation level at baseline or after MI between HCR and LCR.

Cardiomyocyte contractile function

We found depressed cardiomyocyte fractional shortening and slowed re-lengthening in HCR and LCR rats after MI, in line with other MI rat models (75,78,79,217,238). The relative effect of MI on contraction and re-lengthening was greater in HCR compared to LCR. However, cardiomyocyte contractile function in HCR-MI was not different from LCR sham, supporting the beneficial effect of high inborn VO_{2max} as a buffer capacity to reduce the deteriorating effects of MI. Similar to our observations in rats, reduced contraction and relaxation have been observed in isolated cardiomyocytes from human heart failure (239). Whether a high initial VO_{2max} may help preserve the cardiomyocyte function after MI in humans as in HCR rats is currently unknown.

A slightly more pronounced concentric than eccentric growth, indicated by the reduced length/width ratio, were observed in HCR and LCR cardiomyocytes after MI. This may have contributed to reduce the cardiomyocyte function, as concentric growth is known to produce a greater depression of cell contractile function than eccentric growth (240). However, the cellular basis for these changes in cardiomyocyte contractile function in our study needs further investigation, but may be partly linked to changes in intracellular Ca^{2+} handling as discussed below.

Cardiomyocyte Ca^{2+} handling

The reduction we observed in cardiomyocyte contractile function after MI was associated with impaired Ca^{2+} handling in both HCR and LCR MI rats compared to respective shams. However, Ca^{2+} handling was similar in HCR-MI and LCR sham and better compared to LCR-MI, indicating a beneficial buffer effect of high initial VO_{2max} also on deterioration of Ca^{2+} handling after MI. The well-known MI-induced defects in Ca^{2+} handling are attributed to alterations in SERCA-2a function, NCX function and PLB expression among other factors (93,132,238,241). We observed a reduction in SR Ca^{2+} content in HCR and LCR after MI (paper I), in consensus with previous MI studies (132,238), which was caused by decreased SERCA-2a function, reducing Ca^{2+} reuptake into the SR [108,230]. In line with previous studies (157,241-243), we also found that NCX activity increased after MI, compensating for the reduced SERCA-2a function and contributing to maintain diastolic Ca^{2+} levels by facilitating Ca^{2+} extrusion over the sarcolemma. These alterations caused an unfavourable situation where Ca^{2+} available for release from SR was reduced resulting in significantly decreased Ca^{2+} transient amplitude in HCR-MI. Such abnormalities in Ca^{2+} cycling lead to reduction in Ca^{2+} amplitude (150), which we observed in HCR-MI but not in LCR-MI (paper I). Previous reports on Ca^{2+} amplitude after MI have been inconsistent varying from unchanged (244,245), increased (79,246) to decreased (78,129,243,247), although the latter is most common. This is most likely due to differences in MI-induction methods, MI size, animal model and time after MI. The reason for the discrepancy between MI groups in our study is unclear, but may be explained by the significantly larger decrease in SERCA-2a function and Ca^{2+} transient amplitude in HCR compared to LCR. However, it is also possible that the pre-existing low systolic Ca^{2+} level in LCR rats blunt further deterioration after MI. The severe reduction in fractional cardiomyocyte shortening despite a modest decrease (HCR-MI), or unchanged (LCR-MI) systolic Ca^{2+} level indicate a depression in myofilament Ca^{2+} sensitivity. This hypothesis is supported by other studies showing that depressed myofilament Ca^{2+} sensitivity lead to reduction in contractile function after MI (79,248,249). However, the cellular basis for these changes in our study needs further investigation.

Diastolic SR Ca^{2+} leak

We observed increased diastolic SR Ca^{2+} leak in MI rats and LCR sham compared to HCR sham (paper I). Acute CaMKII inhibition with AIP in cardiomyocytes reduced the SR Ca^{2+} leak via RyR2 in MI rats and LCR sham towards levels observed in HCR sham (3% SR Ca^{2+}

leak). In contrast, acute PKA inhibition with H-89 did not affect the SR Ca^{2+} leak in either MI rats or LCR sham at all. These data suggest that CaMKII activity, and not PKA, was responsible for the increased diastolic SR Ca^{2+} leak in MI rats and LCR sham in our study. Although PKA has been suggested as a therapeutic target to reduce SR Ca^{2+} leak (250,251), it is controversial and most studies have observed CaMKII-dependent SR Ca^{2+} leak in failing cardiomyocytes (94,95,143,148,152,164,252). Cellular evidence that CaMKII is involved in SR Ca^{2+} leak is based on observations of enhanced SR Ca^{2+} leak in CaMKII over-expressing myocytes (155,253), enhanced SR Ca^{2+} leak by CaMKII-dependent phosphorylation of RyR2 in heart failure (143) and reduced SR Ca^{2+} leak with CaMKII inhibition (96,97,140,165). About 50% of heart failure patients die of sudden cardiac death caused by ventricular arrhythmias (254,255) and a large fraction of these arrhythmias are attributed to spontaneous Ca^{2+} release (96,110,157,172). Therefore, prevention of diastolic SR Ca^{2+} leak with CaMKII inhibition is a potentially life-saving treatment hindering Ca^{2+} waves and lethal arrhythmias as well as facilitating SR Ca^{2+} load to maintain force of contractions (155,165,175,256).

Adaptations to exercise training in high and low responder rats and chronic CaMKII inhibited mice

Exercise training is a useful and important tool to prevent and mend CVD and other life-style related diseases (6,7,11,22,60). However, inborn characteristics, environmental factors and pharmacological treatment may influence the nature of exercise response and must therefore be considered. We found that inborn exercise response determined VO_{2max} after exercise training in paper II and that chronic CaMKII inhibition with KN-93 treatment in paper III surprisingly improved VO_{2max} exercise response compared to sham mice that performed the same training regimen. The difference in VO_{2max} did not occur until after the exercise training period in either the HRT/LRT rat model or the CaMKII inhibited/sham mice model. Hence, baseline VO_{2max} was not associated with VO_{2max} exercise response in paper II and III, as supported by others (43,46,54). The potential mechanisms for differences in VO_{2max} exercise response in our studies are discussed below.

High intensity interval training did not improve VO_{2max} in LRT rats

Despite being proven effective in providing robust cardiovascular adaptations by numerous studies (22,58,59,63,69,257), high intensity interval training did not increase VO_{2max} in LRT

rats (paper II). In contrast, HRT rats increased VO_{2max} significantly by 39% (paper II). Thus, the HRT/LRT model reflects the higher and lower ends in the reported range of VO_{2max} exercise response (-5% to +50%) observed in humans (43,45-47,52,53,258), although comparing exercise load in rats and humans are complicated. The exercise-induced VO_{2max} improvements in HRT rats in paper II were explained by physiological hypertrophy and improved cardiomyocyte contractility and Ca^{2+} handling, as described in previous studies (67,77,80,181). In addition, peripheral factors, not measured in the present study, may further have contributed to the discrepancy in VO_{2max} exercise response between HRT and LRT rats. However, the lack of VO_{2max} exercise response in LRT rats was at least partly explained by the lack of cardiac adaptations to exercise training.

Although LRT rats did not improve VO_{2max} in response to exercise training we cannot exclude that they improved other physiological parameters. However, this was beyond the scope of the current study, as there are thousands of biochemical adaptations to exercise training (259). Indeed, low responders to VO_{2max} have been reported to improve other health related variables (47) and to increase VO_{2max} by use of other methods than endurance training, e.g. resistance training (260), supporting the idea that complete "non-responders" to exercise training do not exist. Therefore, exercise training for health purposes should be encouraged also in low responders to VO_{2max}.

Chronic CaMKII inhibition enhanced VO_{2max} exercise response

KN-93 treated mice increased VO_{2max} significantly more than sham mice (22% vs. 8%, respectively) after high intensity interval training (paper III). This finding was in contrast to our hypothesis based on previous reports of exercise-induced up-regulation of CaMKII activity in healthy individuals (103,127). The greater VO_{2max} improvement in KN-93 treated mice compared to sham mice was reflected by similar results on maximal running speed. There is a lack of studies investigating the effects of CaMKII on continued exercise training. However, acute studies of CaMKII inhibition on skeletal muscles have reported that KN-93 or KN-62 (another specific CaMKII inhibitor) injections do not impair exercise performance or decrease skeletal muscle contractile force (261,262). However, further investigation is needed to determine the effects of chronic CaMKII inhibition on peripheral factors such as skeletal muscles and their contribution to alterations in VO_{2max} after exercise training. The observed VO_{2max} level in our study is slightly lower than previous studies on female mice (85,186). The

reason for this is unclear, although it might be due to mice strain or possible abdominal discomfort from daily injections of KN-93 and DMSO.

Echocardiography of cardiac function in CaMKII inhibited mice

CaMKII inhibition with KN-93 did not alter cardiac function compared to sham littermates, which is in line with a study on genetic CaMKII inhibition (97). However, exercise training increased fractional shortening in sham mice, but not in KN-93 treated mice. Stroke volume was not significantly increased in either exercise group, but the absolute improvement after exercise was greater in KN-93 treated mice. This may presumably be due to a slightly higher LVEDD and LV mass. However, these indications were not supported by cardiomyocyte size or function measurements.

We found no echocardiography indices of physiological hypertrophy in contrast to measurements of isolated cardiomyocyte size. However, absolute change in size associated with physiological hypertrophy in rodents are rather small, and echocardiography is considered less sensitive in measuring physiological hypertrophy compared to measuring cardiomyocyte size or LV weight (69,79,85).

Pathological-like hypertrophy in LRT cardiomyocytes

Characterization of cardiac function in untrained HRT and LRT (paper II) revealed a pathological-like hypertrophy of cardiomyocytes in LRT, paradoxically with reduced LV weight. Interestingly, cardiomyocytes were shorter (6%) but wider (32%) in the LRT compared to HRT, as previously observed in the LCR and HCR (160), respectively, which is typical for concentric hypertrophy (93). Concentric hypertrophy is usually accompanied by apoptosis and increased fibrosis (84,93), which is mostly prominent at the detrimental late-phase remodelling associated with pathological hypertrophy (131,236). Although apoptosis would be suitable to explain the reduced LV weight in LRT, neither apoptosis nor fibrosis were present in LRT LV tissue at the time of sacrificing, suggesting a congenital nature of the hypertrophy possibly without other signs of pathology.

Although the underlying molecular mechanisms responsible for pathological hypertrophy are not completely clear, several signalling pathways have been suggested to influence on the

continuum of states in cardiac plasticity (70,263). Consistent with our observations in LRT rats, ERK1/2 activation may occur without signs of pathology and favour concentric hypertrophy (263). Moreover, we observed a trend for higher ratio of phosphorylated CaMKII in untrained LRT compared to HRT. Increased CaMKII phosphorylation affects calcineurin (264), activates hypertrophic pathways including MEF2 and NFAT (139,140) and is considered a central molecule in the pathological response mechanisms of the heart (156). CaMKII over-expression contribute to development of cardiac hypertrophy (156) whereas CaMKII inhibition reduces pathological hypertrophy (97,156,265). However, whether the CaMKII phosphorylation level contributed to the observed hypertrophy in LRT rats warrants further investigation.

Cardiomyocyte hypertrophy with exercise training

Exercise training increased LV cardiomyocyte dimensions in HRT rats (paper II) and sham mice (paper III) which corresponds with previous exercise studies in female rats (67,69,80) and mice (85), respectively. The increased dimensions are most likely a result of the hypertrophic stimuli induced by high intensity interval training (67,69,77,80,85). In contrast, LRT rats (paper II) experienced a further decrease in LV weight, probably due to the reduction in cell length. Distinct signalling pathways mediate physiological and pathological hypertrophy (266), and whether the response to exercise training in LRT is compensatory or a result of negative response to exercise is currently unknown. CaMKII inhibition with KN-93 (paper III) blunted the exercise-induced physiological hypertrophy, and exercise-trained KN-93 treated mice gained only half the increase in cardiomyocyte size compared to exercise-trained sham mice. This is quite paradoxical considering the close association between cardiomyocyte dimension and VO_{2max} reported in previous studies (77,181). Thus, our results indicate that CaMKII is necessary to yield optimal exercise response on physiological hypertrophy even though its exact role in physiological hypertrophy is still unknown.

Although not studied in the current thesis, IGF-1 is involved in most biological processes promoting physiological hypertrophy (267), and the IGF-1/Akt1 pathway is considered the main signalling pathway for physiological hypertrophy (86,87,268,269). The necessity of IGF-1/Akt1 activation in physiological hypertrophy is evidenced in experimental models where disruption of the IGF-1/Akt1 pathway leads to virtually no sign of physiological hypertrophy in response to exercise training (86,87). Disruption or deficiency in the IGF-

1/Akt1 pathway is a potential mechanism sufficient to explain the lack of cardiac exercise response in the LRT rats. Moreover, CaMKII inhibition with KN-93 has been shown to cause withdrawal of Akt (270), making it a potential mechanism to explain the blunted exercise response on physiological hypertrophy in KN-93 treated cardiomyocytes.

Cardiomyocyte contractile function

Cardiomyocyte contraction and relaxation was similar in sedentary HRT and LRT rats (paper II), and cardiomyocyte relaxation was reduced in mice receiving daily KN-93 injections (paper III). Exercise training is known to increase cardiomyocyte contractility measured as fractional shortening in both rats (77,79,80) and mice (33,69,80,85,103,106) as we observed in exercise-trained HRT rats, sham mice and KN-93 treated mice. However, KN-93 administration in mice during the exercise intervention blunted the improvement on fractional shortening compared to sham treated mice (18% vs. 63% improvement, respectively). This is in consensus with a previous study by Kemi et al (103), which reported that acute CaMKII inhibition substantially blunted the exercise-induced improvements in cardiomyocyte contractility. These results and ours (paper III) indicate that CaMKII activity is important in maintaining normal cardiomyocyte function and achieving full benefits of exercise training. However, the more the merrier does not apply to CaMKII activity level as mice with elevated CaMKII activity may possess heart failure (104).

Exercise-induced improvement on relaxation rates is a consistent finding following high intensity interval training (33,69,79,80). We observed that high intensity interval training shortened time to re-lengthening in HRT rats, sham mice and KN-93 treated mice. The prolonged time to re-lengthening in mice treated with KN-93 was normalized by exercise training. The relative effect of exercise training on time to re-lengthening was similar in both exercise-trained sham and KN-93 treated mice. Previous reports on contraction rates are not as consistent as relaxation rates and faster contraction rates have been reported in some (69,77) but not all studies (79,80). In paper II we observed faster contraction rates in HRT after exercise training. Cardiomyocyte contractile function is largely dependent on Ca^{2+} handling properties, and exercise training is known to increase speed of Ca^{2+} cycling, leading to a more rapid contraction and relaxation of the cardiomyocyte (80). This will be discussed in detail in the section below.

LRT rats did not improve on either of the contractile properties after exercise training. The underlying molecular mechanisms for lack of cardiac exercise response in LRT rats are currently unknown. However, Akt1 deficient mice also lack exercise response on cardiac function (86,271), as seen in LRT cardiomyocytes. Furthermore, Akt is found to enhance contractile function and modulate protein levels of several major Ca^{2+} regulatory proteins including SERCA-2a, PLB, NCX and RyR2 (268), making Akt an intriguing target for future studies of cardiac exercise response in the HRT/LRT model.

Cardiomyocyte Ca^{2+} handling

High intensity exercise training is known to improve cardiomyocyte Ca^{2+} handling (67,79,103,122), which is consistent with observations in HRT rats in paper II and mice in paper III. In contrast, LRT rats (paper II) did not improve any of the measured parameters of Ca^{2+} handling after exercise training.

There is a discrepancy among studies on alterations in Ca^{2+} transient amplitude after exercise training in healthy individuals (79,80,225). However, exercise-trained HRT rats, sham and KN-93 treated mice increased Ca^{2+} transient amplitude significantly. This has been observed in studies with exercise training in cardiomyocytes with pre-existing low Ca^{2+} transient amplitude due to CaMKII over-expression (unpublished work), heart failure (unpublished work) or diabetic cardiomyopathy (104). The increased Ca^{2+} transient amplitude in HRT rats may be explained by the increased SR Ca^{2+} load, providing more Ca^{2+} available for Ca^{2+} release, and in part provide the increased fractional shortening of the cardiomyocyte. In paper III sham treated mice improved Ca^{2+} transient amplitude significantly more than KN-93 treated mice. The difference in exercise-induced improvements in Ca^{2+} transient amplitude between sham and KN-93 treated mice may in part be explained by the pre-elevated systolic and diastolic Ca^{2+} levels in KN-93 treated mice. This increased systolic and diastolic Ca^{2+} levels caused by KN-93 administration suggest increased Ca^{2+} influx and/or decreased Ca^{2+} efflux, that may explain the blunted improvement in Ca^{2+} transient amplitude and fractional shortening in KN-93 treated mice (70).

For cardiomyocyte relaxation, Ca^{2+} must be removed from the cytosol. In line with other studies (79,80), exercise training decreased time to 50% Ca^{2+} decay in HRT rats and both sham and KN-93 treated mice. KN-93 treatment prolonged Ca^{2+} decay time in sedentary

mice, but as with cardiomyocyte re-lengthening, this was normalized with exercise training. The faster Ca^{2+} decay in exercise-trained HRT rats, KN-93 treated and sham treated mice might at least partly be explained by increased levels of SERCA-2a and NCX. This would facilitate diastolic Ca^{2+} reuptake into SR and Ca^{2+} removal over the sarcolemma, respectively, which has previously been shown in exercise studies (33,79,80,103). This is supported by the increased SR Ca^{2+} load in HRT rats and decreased diastolic Ca^{2+} level in sham treated mice. In KN-93 treated mice diastolic Ca^{2+} level was unaltered. However, the faster Ca^{2+} decay in exercise-trained KN-93 treated mice did not increase the Ca^{2+} amplitude as much as in the sham treated mice, indicating that SERCA-2a activity is blunted by CaMKII inhibition, as shown by others (205,272).

Changes in Ca^{2+} handling, but unaltered fractional shortening, in the sedentary KN-93 might indicate altered myofilament Ca^{2+} sensitivity through reduced myosin binding protein C, which may lead to decreased rate of force development regardless of intracellular Ca^{2+} levels (273). Ca^{2+} sensitivity is known to adapt to exercise training with a leftward shift in the tension-pCa^{2+} relationship, indicating faster shortening, greater contraction and higher force output at every contraction (102). In fact, improvement in Ca^{2+} sensitivity is considered a major cause of exercise-induced improvements in cardiomyocyte contractility (33,79,162).

The observed reduction in Ca^{2+} handling caused by CaMKII inhibition in our study were probably due to the combined actions of several CaMKII phosphorylated targets of the ECC (111). Whether these negative alterations in Ca^{2+} handling after chronic CaMKII inhibition would have developed into dysfunctional Ca^{2+} handling over an extended period of time is currently unknown and needs further investigation. Depressed cardiac function that may lead to pathological hypertrophy and heart failure due to sustained CaMKII inhibition have been shown by others (272,274), whereas some report stable cardiac phenotypes in transgenic CaMKII inhibited mice (97). Why there is a discrepancy between studies with sustained CaMKII inhibition is not known, but it may in part be explained by differences in CaMKII inhibition methods, sites and specificity.

CONCLUSIONS

1. High intrinsic (inborn) VO_{2max} do not provide cardioprotection from the detrimental effects of MI as relative cardiac remodelling and reduction in cardiomyocyte function was similar among HCR and LCR rats.
2. High inborn VO_{2max} may serve as a buffer capacity, maintaining higher absolute values on VO_{2max} and cardiac function measurements after ischemic remodelling when compared to rats with low intrinsic VO_{2max}.
3. Baseline VO_{2max} and cardiomyocyte function was not associated with inborn exercise response in the HRT/LRT rats.
4. High intensity interval training increased VO_{2max} in HRT rats, sham and KN-93 treated mice, but not in LRT rats.
5. Cardiomyocyte function failed to adapt to exercise training in LRT rats, indicating that the lack of cardiac plasticity attenuates VO_{2max} exercise response.
6. CaMKII seems important for maintenance of Ca^{2+} homeostasis as KN-93 treatment negatively affected Ca^{2+} removal evidenced by elevated intracellular Ca^{2+} levels and prolonged time to re-lengthening and time to Ca^{2+} decay.
7. Exercise-trained KN-93 treated mice increased VO_{2max} more than twice as much as sham mice, indicating that CaMKII is not necessary for VO_{2max} improvement with exercise training.
8. Exercise-induced improvements on cardiomyocyte size and contractile function were blunted by KN-93 treatment, suggesting that CaMKII is essential for optimal exercise adaptations in cardiomyocytes.

REFERENCES

1 Kentala, E. Physical fitness and feasibility of physical rehabilitation after myocardial infarction in men of working age. *Ann Clin Res* **4**, Suppl 9:1-84 (1972).

2 Sandvik, L. *et al.* Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med* **328**, 533-537 (1993).

3 Mora, S. *et al.* Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA* **290**, 1600-1607 (2003).

4 Mark, D. B. & Lauer, M. S. Exercise capacity: the prognostic variable that doesn't get enough respect. *Circulation* **108**, 1534-1536 (2003).

5 Hsich, E. *et al.* Importance of treadmill exercise time as an initial prognostic screening tool in patients with systolic left ventricular dysfunction. *Circulation* **119**, 3189-3197 (2009).

6 Myers, J. *et al.* Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* **346**, 793-801 (2002).

7 Kavanagh, T., Mertens, DJ, Hamm, LF, Beyene, J, Kennedy, J, Corey, P, Shepard, RJ. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* **106**, 666-671 (2002).

8 Kokkinos, P. *et al.* Exercise capacity and mortality in black and white men. *Circulation* **117**, 614-622 (2008).

9 Wei, M. *et al.* Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* **282**, 1547-1553 (1999).

10 Mora, S., Cook, N., Buring, J. E., Ridker, P. M. & Lee, I. M. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* **116**, 2110-2118 (2007).

11 Kavanagh, T. Exercise in the primary prevention of coronary artery disease. *Can J Cardiol* **17**, 155-161 (2001).

12 Belardinelli, R., Georgiou, D., Cianci, G. & Purcaro, A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* **99**, 1173-1182 (1999).

13 Church, T. S., Kampert, J. B., Gibbons, L. W., Barlow, C. E. & Blair, S. N. Usefulness of cardiorespiratory fitness as a predictor of all-cause and cardiovascular disease mortality in men with systemic hypertension. *Am J Cardiol* **88**, 651-656 (2001).

14 Shephard, R. J. & Balady, G. J. Exercise as cardiovascular therapy. *Circulation* **99**, 963-972 (1999).

15 Lakka, T. A. *et al.* Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med* **330**, 1549-1554 (1994).

16 Kodama, S. *et al.* Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* **301**, 2024-2035 (2009).

17 Lee, D. C. *et al.* Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med* **45**, 504-510 (2010).

18 Laukkanen, J. A. *et al.* Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med* **161**, 825-831 (2001).

19 Myers, J. *et al.* Fitness versus physical activity patterns in predicting mortality in men. *Am J Med* **117**, 912-918 (2004).

20 Kokkinos, P. *et al.* A graded association of exercise capacity and all-cause mortality in males with high-normal blood pressure. *Blood Press*, 1-7 (2009).
21 Kokkinos, P. *et al.* Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation* **122**, 790-797 (2010).
22 Wisloff, U. *et al.* Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* **115**, 3086-3094 (2007).
23 Schjerve, I. E. *et al.* Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. *Clin Sci (Lond)* **115**, 283-293 (2008).
24 Thompson, P. D. *et al.* Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* **107**, 3109-3116 (2003).
25 McMurray, R. G., Ainsworth, B. E., Harrell, J. S., Griggs, T. R. & Williams, O. D. Is physical activity or aerobic power more influential on reducing cardiovascular disease risk factors? *Med Sci Sports Exerc* **30**, 1521-1529 (1998).
26 Hoyos, I., Irazusta, A., Gravina, L., Gil, S.M., Gil, J., Irazusta, J. Reduced cardiovascular risk is associated with aerobic fitness in university students. *Eur J Sport Sci* **11**, 87- 94 (2011).
27 Hill, A. V., Lupton, H. Muscular exercise, lactic acid, and the supply and utilization of oxygen *Quart J Med* **16**, 135-171 (1923).
28 Aastrand, P., Rodahl, K. *Textbook of Work Physiology; Physiological Bases of Exercise*. (McGraw- Hill Book Co, 1986).
29 Hawkins, M. N., Raven, P. B., Snell, P. G., Stray-Gundersen, J. & Levine, B. D. Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. *Med Sci Sports Exerc* **39**, 103-107 (2007).
30 Levine, B. D. .VO2max: what do we know, and what do we still need to know? *J Physiol* **586**, 25-34 (2008).
31 Froelicher, V., Myers, J. *Exercise and the heart*. 5th edn, (Saunders Elsevier Inc., 2006).
32 Gledhill, N., Cox, D. & Jamnik, R. Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc* **26**, 1116-1121 (1994).
33 Kemi, O. J., Ellingsen, O., Smith, G. L. & Wisloff, U. Exercise-induced changes in calcium handling in left ventricular cardiomyocytes. *Front Biosci* **13**, 356-368 (2008).
34 Andersen, P. & Saltin, B. Maximal perfusion of skeletal muscle in man. *J Physiol* **366**, 233-249 (1985).
35 Bassett, D. R., Jr. & Howley, E. T. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc* **32**, 70-84 (2000).
36 Henderson, K. K. *et al.* Determinants of maximal O(2) uptake in rats selectively bred for endurance running capacity. *J Appl Physiol* **93**, 1265-1274 (2002).
37 Wagner, P. D. New ideas on limitations to VO2max. *Exerc Sport Sci Rev* **28**, 10-14 (2000).
38 Laukkanen, J. A. *et al.* Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men. *Eur J Cancer* **46**, 355-363 (2010).
39 Wisloff, U. *et al.* Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science* **307**, 418-420 (2005).
40 Koch, L. G. *et al.* Intrinsic Aerobic Capacity Sets a Divide for Aging and Longevity. *Circ Res* (2011).

41 Carnethon, M. R. *et al.* Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA* **290**, 3092-3100 (2003).
42 Aspenes, S. T. *et al.* Peak oxygen uptake and cardiovascular risk factors in 4,631 healthy women and men. *Med Sci Sports Exerc* (2011).
43 Lortie, G. *et al.* Responses of maximal aerobic power and capacity to aerobic training. *Int J Sports Med* **5**, 232-236 (1984).
44 Bouchard, C. *et al.* Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc* **30**, 252-258 (1998).
45 Bouchard, C. *et al.* Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol* **87**, 1003-1008 (1999).
46 Bouchard, C. & Rankinen, T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc* **33**, S446-451; discussion S452-443 (2001).
47 Vollaard, N. B. *et al.* Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance. *J Appl Physiol* **106**, 1479-1486 (2009).
48 Bouchard, C. *et al.* Aerobic performance in brothers, dizygotic and monozygotic twins. *Med Sci Sports Exerc* **18**, 639-646 (1986).
49 Bouchard, C. *et al.* Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE Family Study. *J Appl Physiol* **88**, 551-559 (2000).
50 Klissouras, V. Heritability of adaptive variation. *J Appl Physiol* **31**, 338-344 (1971).
51 Troxell, M. L., Britton, S. L. & Koch, L. G. Selected contribution: Variation and heritability for the adaptational response to exercise in genetically heterogeneous rats. *J Appl Physiol* **94**, 1674-1681 (2003).
52 Kohrt, W. M. *et al.* Effects of gender, age, and fitness level on response of VO2max to training in 60-71 yr olds. *J Appl Physiol* **71**, 2004-2011 (1991).
53 Sisson, S. B. *et al.* Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. *Med Sci Sports Exerc* **41**, 539-545 (2009).
54 Timmons, J. A. *et al.* Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol* **108**, 1487-1496 (2010).
55 Koch, L. G., Meredith, T. A., Fraker, T. D., Metting, P. J. & Britton, S. L. Heritability of treadmill running endurance in rats. *Am J Physiol* **275**, R1455-1460 (1998).
56 Bouchard, C. *et al.* Genomic Predictors of Maximal Oxygen Uptake Response to Standardized Exercise Training Programs. *J Appl Physiol* (2010).
57 Stolen, T., Chamari, K., Castagna, C. & Wisloff, U. Physiology of soccer: an update. *Sports Med* **35**, 501-536 (2005).
58 Kemi, O. J. & Wisloff, U. High-intensity aerobic exercise training improves the heart in health and disease. *J Cardiopulm Rehabil Prev* **30**, 2-11 (2010).
59 Amundsen, B. H., Rognmo, O., Hatlen-Rebhan, G. & Slordahl, S. A. High-intensity aerobic exercise improves diastolic function in coronary artery disease. *Scand Cardiovasc J* **42**, 110-117 (2008).
60 Tjonna, A. E. *et al.* Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* **118**, 346-354 (2008).
61 Rognmo, O., Hetland, E., Helgerud, J., Hoff, J. & Slordahl, S. A. 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* **11**, 216-222 (2004).
62 Fletcher, G. F. *et al.* Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* **104**, 1694-1740 (2001).

63 Davies, C. T. & Knibbs, A. V. The training stimulus. The effects of intensity, duration and frequency of effort on maximum aerobic power output. *Int Z Angew Physiol* **29**, 299-305 (1971).
64 Knuttgen, H. G., Nordesjo, L. O., Ollander, B. & Saltin, B. Physical conditioning through interval training with young male adults. *Med Sci Sports* **5**, 220-226 (1973).
65 Faria, I. E. Cardiovascular response to exercise as influenced by training of various intensities. *Res Q* **41**, 44-50 (1970).
66 Zhou, B. *et al.* Stroke volume does not plateau during graded exercise in elite male distance runners. *Med Sci Sports Exerc* **33**, 1849-1854 (2001).
67 Wisloff, U., Helgerud, J., Kemi, O. J. & Ellingsen, O. Intensity-controlled treadmill running in rats: VO(2 max) and cardiac hypertrophy. *Am J Physiol Heart Circ Physiol* **280**, H1301-1310 (2001).
68 Baldari, C., Videira, M., Madeira, F., Sergio, J. & Guidetti, L. Lactate removal during active recovery related to the individual anaerobic and ventilatory thresholds in soccer players. *Eur J Appl Physiol* **93**, 224-230 (2004).
69 Kemi, O. J. *et al.* Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. *Cardiovasc Res* **67**, 161-172 (2005).
70 Katz, A. M. *Physiology of the Heart*. Fourth edn, (Lippincott Williams & Wilkins, 2006).
71 Fishbein, M. C., Maclean, D. & Maroko, P. R. Experimental myocardial infarction in the rat: qualitative and quantitative changes during pathologic evolution. *Am J Pathol* **90**, 57-70 (1978).
72 McMurray, J. J. & Pfeffer, M. A. Heart failure. *Lancet* **365**, 1877-1889 (2005).
73 Chien, K. R. *Molecular basis of Cardiovascular Disease: a companion to Braunwald's heart disease*. Second edn, (Elsevier Inc., 2004).
74 McKay, R. G. *et al.* Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation* **74**, 693-702 (1986).
75 Holt, E. *et al.* Mechanisms of cardiomyocyte dysfunction in heart failure following myocardial infarction in rats. *J Mol Cell Cardiol* **30**, 1581-1593 (1998).
76 Bergmann, O. *et al.* Evidence for cardiomyocyte renewal in humans. *Science* **324**, 98-102 (2009).
77 Kemi, O. J., Haram, P. M., Wisloff, U. & Ellingsen, O. Aerobic fitness is associated with cardiomyocyte contractile capacity and endothelial function in exercise training and detraining. *Circulation* **109**, 2897-2904 (2004).
78 Loennechen, J. P., Wisloff, U., Falck, G. & Ellingsen, O. Cardiomyocyte contractility and calcium handling partially recover after early deterioration during post-infarction failure in rat. *Acta Physiol Scand* **176**, 17-26 (2002).
79 Wisloff, U., Loennechen, J. P., Currie, S., Smith, G. L. & Ellingsen, O. Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca2+ sensitivity and SERCA-2 in rat after myocardial infarction. *Cardiovasc Res* **54**, 162-174 (2002).
80 Wisloff, U. *et al.* Increased contractility and calcium sensitivity in cardiac myocytes isolated from endurance trained rats. *Cardiovasc Res* **50**, 495-508 (2001).
81 Buttrick, P. M. & Scheuer, J. Physiologic, biochemical, and coronary adaptation to exercise conditioning. *Cardiol Clin* **5**, 259-270 (1987).
82 Richey, P. A. & Brown, S. P. Pathological versus physiological left ventricular hypertrophy: a review. *J Sports Sci* **16**, 129-141 (1998).

83 Pluim, B. M., Zwinderman, A. H., van der Laarse, A. & van der Wall, E. E. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation* **101**, 336-344 (2000).
84 Hunter, J. J. & Chien, K. R. Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med* **341**, 1276-1283 (1999).
85 Kemi, O. J., Loennechen, J. P., Wisloff, U. & Ellingsen, O. Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. *J Appl Physiol* **93**, 1301-1309 (2002).
86 DeBosch, B. *et al.* Akt1 is required for physiological cardiac growth. *Circulation* **113**, 2097-2104 (2006).
87 Kim, J. *et al.* Insulin-like growth factor I receptor signaling is required for exercise-induced cardiac hypertrophy. *Mol Endocrinol* **22**, 2531-2543 (2008).
88 Bernardo, B. C., Weeks, K. L., Pretorius, L. & McMullen, J. R. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol Ther* **128**, 191-227 (2010).
89 Pfeffer, M. A. & Braunwald, E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* **81**, 1161-1172 (1990).
90 Serneri, G. G. *et al.* Cardiac angiotensin II formation in the clinical course of heart failure and its relationship with left ventricular function. *Circ Res* **88**, 961-968 (2001).
91 Levy, D., Garrison, R. J., Savage, D. D., Kannel, W. B. & Castelli, W. P. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* **322**, 1561-1566 (1990).
92 Wilkins, B. J. *et al.* Calcineurin/NFAT coupling participates in pathological, but not physiological, cardiac hypertrophy. *Circ Res* **94**, 110-118 (2004).
93 Kehat, I. & Molkentin, J. D. Molecular pathways underlying cardiac remodeling during pathophysiological stimulation. *Circulation* **122**, 2727-2735 (2010).
94 Anderson, M. E. Calmodulin kinase signaling in heart: an intriguing candidate target for therapy of myocardial dysfunction and arrhythmias. *Pharmacol Ther* **106**, 39-55 (2005).
95 Ling, H., Zhang, T., Pereira, L., Means, C.K., Cheng, H., Gu, Y., Dalton, N.D., Peteron, K.L., Chen, J., Bers, D., Brown, J.H. Requirement for Ca2+/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. *J Clin Invest* **119**, 1230-1240 (2009).
96 van Oort, R. J. *et al.* Ryanodine receptor phosphorylation by calcium/calmodulin-dependent protein kinase II promotes life-threatening ventricular arrhythmias in mice with heart failure. *Circulation* **122**, 2669-2679 (2010).
97 Zhang, R. *et al.* Calmodulin kinase II inhibition protects against structural heart disease. *Nat Med* **11**, 409-417 (2005).
98 Anderson, M. E. CaMKII and a failing strategy for growth in heart. *J Clin Invest* **119**, 1082-1085 (2009).
99 Zhang, T. *et al.* CaMKIIdelta isoforms differentially affect calcium handling but similarly regulate HDAC/MEF2 transcriptional responses. *J Biol Chem* **282**, 35078-35087 (2007).
100 Passier, R. *et al.* CaM kinase signaling induces cardiac hypertrophy and activates the MEF2 transcription factor in vivo. *J Clin Invest* **105**, 1395-1406 (2000).
101 Zhang, X. Q. *et al.* Sprint training attenuates myocyte hypertrophy and improves Ca2+ homeostasis in postinfarction myocytes. *J Appl Physiol* **84**, 544-552 (1998).
102 Diffee, G. M., Seversen, E.A., Titus, M.M. Exercise training increases the Ca2+ sensitivity of tension in rat cardiac myocytes. *J Appl Physiol* **91**, 309-315 (2001).

103 Kemi, O. J. *et al.* Aerobic interval training enhances cardiomyocyte contractility and Ca2+ cycling by phosphorylation of CaMKII and Thr-17 of phospholamban. *J Mol Cell Cardiol* **43**, 354-361 (2007).
104 Stolen, T. O. *et al.* Interval training normalizes cardiomyocyte function, diastolic Ca2+ control, and SR Ca2+ release synchronicity in a mouse model of diabetic cardiomyopathy. *Circ Res* **105**, 527-536 (2009).
105 Natali, A. J., Turner, D. L., Harrison, S. M. & White, E. Regional effects of voluntary exercise on cell size and contraction-frequency responses in rat cardiac myocytes. *J Exp Biol* **204**, 1191-1199 (2001).
106 Palmer, B. M., Thayer, A. M., Snyder, S. M. & Moore, R. L. Shortening and [Ca2+] dynamics of left ventricular myocytes isolated from exercise-trained rats. *J Appl Physiol* **85**, 2159-2168 (1998).
107 Rademakers, F., Van de Werf, F., Mortelmans, L., Marchal, G. & Bogaert, J. Evolution of regional performance after an acute anterior myocardial infarction in humans using magnetic resonance tagging. *J Physiol* **546**, 777-787 (2003).
108 Lehnart, S. E., Maier, L. S. & Hasenfuss, G. Abnormalities of calcium metabolism and myocardial contractility depression in the failing heart. *Heart Fail Rev* **14**, 213-224 (2009).
109 Zhang, L. Q., Zhang, X. Q., Musch, T. I., Moore, R. L. & Cheung, J. Y. Sprint training restores normal contractility in postinfarction rat myocytes. *J Appl Physiol* **89**, 1099-1105 (2000).
110 Bers, D. M. Cardiac excitation-contraction coupling. *Nature* **415**, 198-205 (2002).
111 Maier, L. S., Bers, D.M. Role of Ca2+/calmodulin-dependent protein kinase (CaMK) in excitation-contraction coupling in the heart. *Cardiovasc Res* **73**, 631-640 (2007).
112 Bers, D. M. & Weber, C. R. Na/Ca exchange function in intact ventricular myocytes. *Ann N Y Acad Sci* **976**, 500-512 (2002).
113 Cannell, M. B., Berlin, J. R. & Lederer, W. J. Effect of membrane potential changes on the calcium transient in single rat cardiac muscle cells. *Science* **238**, 1419-1423 (1987).
114 Fabiato, A. Simulated calcium current can both cause calcium loading in and trigger calcium release from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J Gen Physiol* **85**, 291-320 (1985).
115 Braun, A. P. & Schulman, H. The multifunctional calcium/calmodulin-dependent protein kinase: from form to function. *Annu Rev Physiol* **57**, 417-445 (1995).
116 Jett, M. F., Schworer, C. M., Bass, M. & Soderling, T. R. Identification of membrane-bound calcium, calmodulin-dependent protein kinase II in canine heart. *Arch Biochem Biophys* **255**, 354-360 (1987).
117 Couchonnal, L. F. & Anderson, M. E. The role of calmodulin kinase II in myocardial physiology and disease. *Physiology (Bethesda)* **23**, 151-159 (2008).
118 Maier, L. S. & Bers, D. M. Calcium, calmodulin, and calcium-calmodulin kinase II: heartbeat to heartbeat and beyond. *J Mol Cell Cardiol* **34**, 919-939 (2002).
119 Zhang, T. & Brown, J. H. Role of Ca2+/calmodulin-dependent protein kinase II in cardiac hypertrophy and heart failure. *Cardiovasc Res* **63**, 476-486 (2004).
120 Swaminathan, P. D. & Anderson, M. E. CaMKII Inhibition: Breaking the Cycle of Electrical Storm? *Circulation* (2011).
121 Tibbits, G. F., Barnard, R. J., Baldwin, K. M., Cugalj, N. & Roberts, N. K. Influence of exercise on excitation-contraction coupling in rat myocardium. *Am J Physiol* **240**, H472-480 (1981).

122 Kemi, O. J., Ceci, M., Condorelli, G., Smith, G. L. & Wisloff, U. Myocardial sarcoplasmic reticulum Ca2+ ATPase function is increased by aerobic interval training. *Eur J Cardiovasc Prev Rehabil* **15**, 145-148 (2008).
123 Voss, J., Jones, L. R. & Thomas, D. D. The physical mechanism of calcium pump regulation in the heart. *Biophys J* **67**, 190-196 (1994).
124 Brittsan, A. G. & Kranias, E. G. Phospholamban and cardiac contractile function. *J Mol Cell Cardiol* **32**, 2131-2139 (2000).
125 MacLennan, D. H. & Kranias, E. G. Phospholamban: a crucial regulator of cardiac contractility. *Nat Rev Mol Cell Biol* **4**, 566-577 (2003).
126 Simmerman, H. K., Collins, J. H., Theibert, J. L., Wegener, A. D. & Jones, L. R. Sequence analysis of phospholamban. Identification of phosphorylation sites and two major structural domains. *J Biol Chem* **261**, 13333-13341 (1986).
127 Shao, C. H. *et al.* Exercise training during diabetes attenuates cardiac ryanodine receptor dysregulation. *J Appl Physiol* **106**, 1280-1292 (2009).
128 Beuckelmann, D. J., Nabauer, M. & Erdmann, E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation* **85**, 1046-1055 (1992).
129 Gwathmey, J. K. *et al.* Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. *Circ Res* **61**, 70-76 (1987).
130 Chelu, M. G. & Wehrens, X. H. Sarcoplasmic reticulum calcium leak and cardiac arrhythmias. *Biochem Soc Trans* **35**, 952-956 (2007).
131 Gomez, A. M. *et al.* Defective excitation-contraction coupling in experimental cardiac hypertrophy and heart failure. *Science* **276**, 800-806 (1997).
132 Hobai, I. A. & O'Rourke, B. Decreased sarcoplasmic reticulum calcium content is responsible for defective excitation-contraction coupling in canine heart failure. *Circulation* **103**, 1577-1584 (2001).
133 Bers, D. M. Calcium and cardiac rhythms: physiological and pathophysiological. *Circ Res* **90**, 14-17 (2002).
134 Ferrier, G. R., Saunders, J. H. & Mendez, C. A cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin. *Circ Res* **32**, 600-609 (1973).
135 van der Velden, J. *et al.* Alterations in myofilament function contribute to left ventricular dysfunction in pigs early after myocardial infarction. *Circ Res* **95**, e85-95 (2004).
136 Pogwizd, S. M., Schlotthauer, K., Li, L., Yuan, W. & Bers, D. M. Arrhythmogenesis and contractile dysfunction in heart failure: Roles of sodium-calcium exchange, inward rectifier potassium current, and residual beta-adrenergic responsiveness. *Circ Res* **88**, 1159-1167 (2001).
137 Pieske, B. *et al.* Diminished post-rest potentiation of contractile force in human dilated cardiomyopathy. Functional evidence for alterations in intracellular Ca2+ handling. *J Clin Invest* **98**, 764-776 (1996).
138 Kass, R. S., Lederer, W. J., Tsien, R. W. & Weingart, R. Role of calcium ions in transient inward currents and aftercontractions induced by strophanthidin in cardiac Purkinje fibres. *J Physiol* **281**, 187-208 (1978).
139 Backs, J. *et al.* The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. *Proc Natl Acad Sci U S A* **106**, 2342-2347 (2009).
140 Ling, H. *et al.* Requirement for Ca2+/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. *J Clin Invest* **119**, 1230-1240 (2009).

141 Toko, H. *et al.* Ca2+/calmodulin-dependent kinase IIdelta causes heart failure by accumulation of p53 in dilated cardiomyopathy. *Circulation* **122**, 891-899 (2010).
142 Sipido, K. R. CaM or cAMP: linking beta-adrenergic stimulation to 'leaky' RyRs. *Circ Res* **100**, 296-298 (2007).
143 Ai, X., Curran, J. W., Shannon, T. R., Bers, D. M. & Pogwizd, S. M. Ca2+/calmodulin-dependent protein kinase modulates cardiac ryanodine receptor phosphorylation and sarcoplasmic reticulum Ca2+ leak in heart failure. *Circ Res* **97**, 1314-1322 (2005).
144 Anderson, M. E. Multiple downstream proarrhythmic targets for calmodulin kinase II: moving beyond an ion channel-centric focus. *Cardiovasc Res* **73**, 657-666 (2007).
145 Hoch, B., Meyer, R., Hetzer, R., Krause, E. G. & Karczewski, P. Identification and expression of delta-isoforms of the multifunctional Ca2+/calmodulin-dependent protein kinase in failing and nonfailing human myocardium. *Circ Res* **84**, 713-721 (1999).
146 Kirchhefer, U., Schmitz, W., Scholz, H. & Neumann, J. Activity of cAMP-dependent protein kinase and Ca2+/calmodulin-dependent protein kinase in failing and nonfailing human hearts. *Cardiovasc Res* **42**, 254-261 (1999).
147 Khoo, M. S. *et al.* Death, cardiac dysfunction, and arrhythmias are increased by calmodulin kinase II in calcineurin cardiomyopathy. *Circulation* **114**, 1352-1359 (2006).
148 Curran, J., Hinton, M. J., Rios, E., Bers, D. M. & Shannon, T. R. Beta-adrenergic enhancement of sarcoplasmic reticulum calcium leak in cardiac myocytes is mediated by calcium/calmodulin-dependent protein kinase. *Circ Res* **100**, 391-398 (2007).
149 Marx, S. O. *et al.* PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell* **101**, 365-376 (2000).
150 Smith, G. Matters of the heart: the physiology of cardiac function and failure. *Exp Physiol* **92**, 973-986 (2007).
151 Maier, L. S., Bers, D. M. & Brown, J. H. Calmodulin and Ca2+/calmodulin kinases in the heart - physiology and pathophysiology. *Cardiovasc Res* **73**, 629-630 (2007).
152 Wehrens, X. H., Lehnart, S. E., Reiken, S. R. & Marks, A. R. Ca2+/calmodulin-dependent protein kinase II phosphorylation regulates the cardiac ryanodine receptor. *Circ Res* **94**, e61-70 (2004).
153 Bers, D. M. & Grandi, E. Calcium/calmodulin-dependent kinase II regulation of cardiac ion channels. *J Cardiovasc Pharmacol* **54**, 180-187 (2009).
154 Kushnir, A. & Marks, A. R. The ryanodine receptor in cardiac physiology and disease. *Adv Pharmacol* **59**, 1-30 (2010).
155 Maier, L. S. *et al.* Transgenic CaMKIIdeltaC overexpression uniquely alters cardiac myocyte Ca2+ handling: reduced SR Ca2+ load and activated SR Ca2+ release. *Circ Res* **92**, 904-911 (2003).
156 Zhang, T. *et al.* The deltaC isoform of CaMKII is activated in cardiac hypertrophy and induces dilated cardiomyopathy and heart failure. *Circ Res* **92**, 912-919 (2003).
157 Pogwizd, S. M. & Bers, D. M. Na/Ca exchange in heart failure: contractile dysfunction and arrhythmogenesis. *Ann N Y Acad Sci* **976**, 454-465 (2002).
158 Weber, C. R., Piacentino, V., 3rd, Margulies, K. B., Bers, D. M. & Houser, S. R. Calcium influx via I(NCX) is favored in failing human ventricular myocytes. *Ann N Y Acad Sci* **976**, 478-479 (2002).
159 Kemi, O. J. *et al.* Exercise training restores aerobic capacity and energy transfer systems in heart failure treated with losartan. *Cardiovasc Res* **76**, 91-99 (2007).

160 Kemi, O. J. *et al.* The effect of exercise training on transverse tubules in normal, remodeled, and reverse remodeled hearts. *J Cell Physiol* (2010).
161 Medeiros, A. *et al.* Exercise training delays cardiac dysfunction and prevents calcium handling abnormalities in sympathetic hyperactivity-induced heart failure mice. *J Appl Physiol* **104**, 103-109 (2008).
162 de Waard, M. C. *et al.* Early exercise training normalizes myofilament function and attenuates left ventricular pump dysfunction in mice with a large myocardial infarction. *Circ Res* **100**, 1079-1088 (2007).
163 Bito, V. *et al.* Early exercise training after myocardial infarction prevents contractile but not electrical remodelling or hypertrophy. *Cardiovasc Res* **86**, 72-81 (2010).
164 Hashambhoy, Y. L., Greenstein, J.L., Winslow, R.L. Role of CaMKII in RyR leak, EC coupling and action potential duration: A computational model. *J Mol Cell Cardiol*, doi:10.1016/j.yjmcc.2010.1007.1011 (2010).
165 Sossalla, S. *et al.* Inhibition of elevated Ca2+/calmodulin-dependent protein kinase II improves contractility in human failing myocardium. *Circ Res* **107**, 1150-1161 (2010).
166 Vila-Petroff, M. *et al.* CaMKII inhibition protects against necrosis and apoptosis in irreversible ischemia-reperfusion injury. *Cardiovasc Res* **73**, 689-698 (2007).
167 Anderson, M. E. *et al.* KN-93, an inhibitor of multifunctional Ca++/calmodulin-dependent protein kinase, decreases early afterdepolarizations in rabbit heart. *J Pharmacol Exp Ther* **287**, 996-1006 (1998).
168 Erickson, J. R. & Anderson, M. E. CaMKII and its role in cardiac arrhythmia. *J Cardiovasc Electrophysiol* **19**, 1332-1336 (2008).
169 Yang, Y. *et al.* Calmodulin kinase II inhibition protects against myocardial cell apoptosis in vivo. *Am J Physiol Heart Circ Physiol* **291**, H3065-3075 (2006).
170 Anderson, M. E., Brown, J. H. & Bers, D. M. CaMKII in myocardial hypertrophy and heart failure. *J Mol Cell Cardiol* (2011).
171 Li, J. *et al.* Calmodulin kinase II inhibition shortens action potential duration by upregulation of K+ currents. *Circ Res* **99**, 1092-1099 (2006).
172 Sag, C. M. *et al.* Calcium/calmodulin-dependent protein kinase II contributes to cardiac arrhythmogenesis in heart failure. *Circ Heart Fail* **2**, 664-675 (2009).
173 Page, E. Quantitative ultrastructural analysis in cardiac membrane physiology. *Am J Physiol* **235**, C147-158 (1978).
174 Brette, F. & Orchard, C. T-tubule function in mammalian cardiac myocytes. *Circ Res* **92**, 1182-1192 (2003).
175 Bers, D. M. Calcium cycling and signaling in cardiac myocytes. *Annu Rev Physiol* **70**, 23-49 (2008).
176 Wei, S. *et al.* T-tubule remodeling during transition from hypertrophy to heart failure. *Circ Res* **107**, 520-531 (2010).
177 Heinzel, F. R. *et al.* Remodeling of T-tubules and reduced synchrony of Ca2+ release in myocytes from chronically ischemic myocardium. *Circ Res* **102**, 338-346 (2008).
178 Koch, L. G. & Britton, S. L. Artificial selection for intrinsic aerobic endurance running capacity in rats. *Physiol Genomics* **5**, 45-52 (2001).
179 Carlborg, O., Jacobsson, L., Ahgren, P., Siegel, P. & Andersson, L. Epistasis and the release of genetic variation during long-term selection. *Nat Genet* **38**, 418-420 (2006).
180 Gonzalez, N. C. *et al.* Continued divergence in VO2max of rats artificially selected for running endurance is mediated by greater convective blood O2 delivery. *J Appl Physiol* **101**, 1288-1296 (2006).
181 Høydahl, M. A., Wisløff U., Kemi, O.J., Britton S.L., Koch L.G., Smith, G.L., Ellingsen, Ø. Nitric oxide synthase type- 1 modulates cardiomyocyte contractility and

calcium handling: association with low instrinsic aerobic capacity. *Eur J Cardiovasc Prev Rehabil* **14**, 319- 325 (2007).
182 Sumi M, K. K., Ishikawa T, Ishii A, Hagiwara M, Nagatsu T, Hidaka H. The newly synthesized selective Ca2+/calmodulin dependent protein kinase II inhibitor KN-93 reduces dopamine contents in PC12h cells. *Biochem Biophy Res Comm* **181**, 968-975 (1991).
183 Gao, L., Blair, L.A.C., Marshall, J. CaMKII-independent effects of KN93 and its inactive analog KN92: Reversible inhibition of L-type calcium channels. *Biochem Biophy Res Comm* **345**, 1606-1610 (2006).
184 Lee, T. S. *et al.* Calmodulin kinase II is involved in voltage-dependent facilitation of the L-type Cav1.2 calcium channel: Identification of the phosphorylation sites. *J Biol Chem* **281**, 25560-25567 (2006).
185 Swanson, B. N. Medical use of dimethyl sulfoxide (DMSO). *Rev Clin Basic Pharm* **5**, 1-33 (1985).
186 Hoydal, M. A., Wisloff, U., Kemi, O. J. & Ellingsen, O. Running speed and maximal oxygen uptake in rats and mice: practical implications for exercise training. *Eur J Cardiovasc Prev Rehabil* **14**, 753-760 (2007).
187 Moholdt, T. T. *et al.* Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J* **158**, 1031-1037 (2009).
188 Johns, T. N. & Olson, B. J. Experimental myocardial infarction. I. A method of coronary occlusion in small animals. *Ann Surg* **140**, 675-682 (1954).
189 Muders, F. & Elsner, D. Animal models of chronic heart failure. *Pharmacol Res* **41**, 605-612 (2000).
190 Pfeffer, M. A. *et al.* Myocardial infarct size and ventricular function in rats. *Circ Res* **44**, 503-512 (1979).
191 Hasenfuss, G. Animal models of human cardiovascular disease, heart failure and hypertrophy. *Cardiovasc Res* **39**, 60-76 (1998).
192 Litwin, S. E., Katz, S. E., Morgan, J. P. & Douglas, P. S. Serial echocardiographic assessment of left ventricular geometry and function after large myocardial infarction in the rat. *Circulation* **89**, 345-354 (1994).
193 Taylor, C. R. *et al.* Design of the mammalian respiratory system. III Scaling maximum aerobic capacity to body mass: wild and domestic mammals. *Respir Physiol* **44**, 25-37 (1981).
194 Gardin, J. M., Siri, F. M., Kitsis, R. N., Edwards, J. G. & Leinwand, L. A. Echocardiographic assessment of left ventricular mass and systolic function in mice. *Circ Res* **76**, 907-914 (1995).
195 Stein, A. B. *et al.* Effects of anesthesia on echocardiographic assessment of left ventricular structure and function in rats. *Basic Res Cardiol* **102**, 28-41 (2007).
196 Yang, X. P. *et al.* Echocardiographic assessment of cardiac function in conscious and anesthetized mice. *Am J Physiol* **277**, H1967-1974 (1999).
197 Wu, J. *et al.* Effects of heart rate and anesthetic timing on high-resolution echocardiographic assessment under isoflurane anesthesia in mice. *J Ultrasound Med* **29**, 1771-1778 (2010).
198 Sjaastad, I., Sejersted, O. M., Ilebekk, A. & Bjornerheim, R. Echocardiographic criteria for detection of postinfarction congestive heart failure in rats. *J Appl Physiol* **89**, 1445-1454 (2000).
199 Semeniuk, L. M., Kryski, A. J. & Severson, D. L. Echocardiographic assessment of cardiac function in diabetic db/db and transgenic db/db-hGLUT4 mice. *Am J Physiol Heart Circ Physiol* **283**, H976-982 (2002).

200 Kober, F., Iltis, I., Cozzone, P. J. & Bernard, M. Cine-MRI assessment of cardiac function in mice anesthetized with ketamine/xylazine and isoflurane. *MAGMA* **17**, 157-161 (2004).
201 Holt, E. & Christensen, G. Transient Ca2+ overload alters Ca2+ handling in rat cardiomyocytes: effects on shortening and relaxation. *Am J Physiol* **273**, H573-582 (1997).
202 Guatimosim, S., Sobie, E. A., Cruz, J.D.S., Martin, L. A., Lederer, W.J. Molecular identification of a TTX-sensitive Ca2+ current. *Am J Physiol Cell Physiol* **280**, 1327-1339 (2001).
203 Mitra, R., Morad, M. A uniform enzymatic method for dissociation of myocytes from hearts and stomachs of vertebrates. *Pfluegers Arch* **391**, 85-100 (1981).
204 Grynkiewicz, G., Poenie, M. & Tsien, R. Y. A new generation of Ca2+ indicators with greatly improved fluorescence properties. *J Biol Chem* **260**, 3440-3450 (1985).
205 Werdich, A. A. ***et al.*** Differential effects of phospholamban and Ca2+/calmodulin-dependent kinase II on [Ca2+]i transients in cardiac myocytes at physiological stimulation frequencies. *Am J Physiol Heart Circ Physiol* **294**, H2352-2362 (2008).
206 Seidler, T. ***et al.*** Effects of adenovirus-mediated sorcin overexpression on excitation-contraction coupling in isolated rabbit cardiomyocytes. *Circ Res* **93**, 132-139 (2003).
207 Shannon, T., Ginsburg, KS, Bers, DM. Quantative assessment of the SR Ca2+ leak-load relationship. *Circ Res* **7**, 594-600 (2002).
208 Ishida, A., Kameshita, I., Okuno, S., Kitani, T. & Fujisawa, H. A novel highly specific and potent inhibitor of calmodulin-dependent protein kinase II. *Biochem Biophys Res Commun* **212**, 806-812 (1995).
209 Murray, A. J. Pharmacological PKA inhibition: all may not be what it seems. *Sci Signal* **1**, re4 (2008).
210 Satoh, H., Delbridge, L. M., Blatter, L. A. & Bers, D. M. Surface:volume relationship in cardiac myocytes studied with confocal microscopy and membrane capacitance measurements: species-dependence and developmental effects. *Biophys J* **70**, 1494-1504 (1996).
211 Yaoita, H., Ogawa, K., Maehara, K. & Maruyama, Y. Apoptosis in relevant clinical situations: contribution of apoptosis in myocardial infarction. *Cardiovasc Res* **45**, 630-641 (2000).
212 Aldridge, G. M., Podrebarac, D. M., Greenough, W. T. & Weiler, I. J. The use of total protein stains as loading controls: an alternative to high-abundance single-protein controls in semi-quantitative immunoblotting. *J Neurosci Methods* **172**, 250-254 (2008).
213 Towbin, H., Staehelin, T. & Gordon, J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. *Proc Natl Acad Sci U S A* **76**, 4350-4354 (1979).
214 de Waard, M. C. & Duncker, D. J. Prior exercise improves survival, infarct healing, and left ventricular function after myocardial infarction. *J Appl Physiol* **107**, 928-936 (2009).
215 Freimann, S. ***et al.*** Prior exercise training improves the outcome of acute myocardial infarction in the rat. Heart structure, function, and gene expression. *J Am Coll Cardiol* **45**, 931-938 (2005).
216 Brown, D. A. ***et al.*** Cardioprotection afforded by chronic exercise is mediated by the sarcolemmal, and not the mitochondrial, isoform of the KATP channel in the rat. *J Physiol* **569**, 913-924 (2005).

217 Brown, D. A., Jew, K. N., Sparagna, G. C., Musch, T. I. & Moore, R. L. Exercise training preserves coronary flow and reduces infarct size after ischemia-reperfusion in rat heart. *J Appl Physiol* **95**, 2510-2518 (2003).
218 Dayan, A., Feinberg, M. S., Holbova, R., Deshet, N. & Scheinowitz, M. Swimming exercise training prior to acute myocardial infarction attenuates left ventricular remodeling and improves left ventricular function in rats. *Ann Clin Lab Sci* **35**, 73-78 (2005).
219 McElroy, C. L., Gissen, S. A. & Fishbein, M. C. Exercise-induced reduction in myocardial infarct size after coronary artery occlusion in the rat. *Circulation* **57**, 958-962 (1978).
220 Lujan, H. L., Britton, S. L., Koch, L. G. & DiCarlo, S. E. Reduced susceptibility to ventricular tachyarrhythmias in rats selectively bred for high aerobic capacity. *Am J Physiol Heart Circ Physiol* **291**, H2933-2941 (2006).
221 Bye, A. *et al.* Aerobic capacity-dependent differences in cardiac gene expression. *Physiol Genomics* **33**, 100-109 (2008).
222 Frasier, C. R., Moore, R. L. & Brown, D. A. Exercise-induced cardiac preconditioning: How exercise protects your achy-breaky heart. *J Appl Physiol* (2011).
223 Kavazis, A. N. Exercise preconditioning of the myocardium. *Sports Med* **39**, 923-935 (2009).
224 Golbidi, S. & Laher, I. Molecular mechanisms in exercise-induced cardioprotection. *Cardiol Res Pract* **2011**, 972807 (2011).
225 Kemi, O. J. & Wisloff, U. Mechanisms of exercise-induced improvements in the contractile apparatus of the mammalian myocardium. *Acta Physiol (Oxf)* **199**, 425-439 (2010).
226 Myers, J. Exercise capacity and prognosis in chronic heart failure. *Circulation* **119**, 3165-3167 (2009).
227 Lennon, S. L. *et al.* Loss of exercise-induced cardioprotection after cessation of exercise. *J Appl Physiol* **96**, 1299-1305 (2004).
228 Calvert, J. W. *et al.* Exercise protects against myocardial ischemia-reperfusion injury via stimulation of beta(3)-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosothiols. *Circ Res* **108**, 1448-1458 (2011).
229 Gulati, M. *et al.* Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation* **108**, 1554-1559 (2003).
230 Loennechen, J. P., Stoylen, A., Beisvag, V., Wisloff, U. & Ellingsen, O. Regional expression of endothelin-1, ANP, IGF-1, and LV wall stress in the infarcted rat heart. *Am J Physiol Heart Circ Physiol* **280**, H2902-2910 (2001).
231 Pfeffer, J. M., Pfeffer, M. A., Fletcher, P. J. & Braunwald, E. Progressive ventricular remodeling in rat with myocardial infarction. *Am J Physiol* **260**, H1406-1414 (1991).
232 Mollema, S. A., Nucifora, G. & Bax, J. J. Prognostic value of echocardiography after acute myocardial infarction. *Heart* **95**, 1732-1745 (2009).
233 Morris, J. N., Everitt, M. G., Pollard, R., Chave, S. P. & Semmence, A. M. Vigorous exercise in leisure-time: protection against coronary heart disease. *Lancet* **2**, 1207-1210 (1980).
234 Britton, S. L. & Koch, L. G. Animal models of complex diseases: an initial strategy. *IUBMB Life* **57**, 631-638 (2005).
235 Kehat, I. *et al.* Extracellular Signal-Regulated Kinases 1 and 2 Regulate the Balance Between Eccentric and Concentric Cardiac Growth. *Circ Res* (2010).
236 Hill, J. A. & Olson, E. N. Cardiac plasticity. *N Engl J Med* **358**, 1370-1380 (2008).
237 Opie, L. H., Commerford, P. J., Gersh, B. J. & Pfeffer, M. A. Controversies in ventricular remodelling. *Lancet* **367**, 356-367 (2006).

238 Zhang, X. Q., Musch, T. I., Zelis, R. & Cheung, J. Y. Effects of impaired Ca2+ homeostasis on contraction in postinfarction myocytes. *J Appl Physiol* **86**, 943-950 (1999).
239 Davies, C. H. *et al.* Reduced contraction and altered frequency response of isolated ventricular myocytes from patients with heart failure. *Circulation* **92**, 2540-2549 (1995).
240 Capasso, J. M. & Anversa, P. Mechanical performance of spared myocytes after myocardial infarction in rats: effects of captopril treatment. *Am J Physiol* **263**, H841-849 (1992).
241 Hasenfuss, G. *et al.* Calcium handling proteins in the failing human heart. *Basic Res Cardiol* **92 Suppl 1**, 87-93 (1997).
242 Litwin, S. E. & Bridge, J. H. Enhanced Na(+)-Ca2+ exchange in the infarcted heart. Implications for excitation-contraction coupling. *Circ Res* **81**, 1083-1093 (1997).
243 Bers, D. M., Pogwizd, S. M. & Schlotthauer, K. Upregulated Na/Ca exchange is involved in both contractile dysfunction and arrhythmogenesis in heart failure. *Basic Res Cardiol* **97 Suppl 1**, I36-42 (2002).
244 Kaprielian, R. *et al.* Relationship between K+ channel down-regulation and [Ca2+]i in rat ventricular myocytes following myocardial infarction. *J Physiol* **517 (Pt 1)**, 229-245 (1999).
245 Brooksby, P., Levi, A. J. & Jones, J. V. Investigation of the mechanisms underlying the increased contraction of hypertrophied ventricular myocytes isolated from the spontaneously hypertensive rat. *Cardiovasc Res* **27**, 1268-1277 (1993).
246 Bing, O. H. *et al.* Intracellular calcium transients in myocardium from spontaneously hypertensive rats during the transition to heart failure. *Circ Res* **68**, 1390-1400 (1991).
247 Zhang, X. Q., Moore, R. L., Tenhave, T. & Cheung, J. Y. [Ca2+]i transients in hypertensive and postinfarction myocytes. *Am J Physiol* **269**, C632-640 (1995).
248 Li, P. *et al.* Myocyte performance during evolution of myocardial infarction in rats: effects of propionyl-L-carnitine. *Am J Physiol* **268**, H1702-1713 (1995).
249 Li, P. *et al.* Myocardial infarction alters myofilament calcium sensitivity and mechanical behavior of myocytes. *Am J Physiol* **272**, H360-370 (1997).
250 Wehrens, X. H. *et al.* Ryanodine receptor/calcium release channel PKA phosphorylation: a critical mediator of heart failure progression. *Proc Natl Acad Sci U S A* **103**, 511-518 (2006).
251 Shan, J. *et al.* Role of chronic ryanodine receptor phosphorylation in heart failure and beta-adrenergic receptor blockade in mice. *J Clin Invest* **120**, 4375-4387 (2010).
252 Neef, S. *et al.* CaMKII-dependent diastolic SR Ca2+ leak and elevated diastolic Ca2+ levels in right atrial myocardium of patients with atrial fibrillation. *Circ Res* **106**, 1134-1144 (2010).
253 Kohlhaas, M. *et al.* Increased sarcoplasmic reticulum calcium leak but unaltered contractility by acute CaMKII overexpression in isolated rabbit cardiac myocytes. *Circ Res* **98**, 235-244 (2006).
254 Noseworthy, P. A. & Newton-Cheh, C. Genetic determinants of sudden cardiac death. *Circulation* **118**, 1854-1863 (2008).
255 Farr, M. A. & Basson, C. T. Sparking the failing heart. *N Engl J Med* **351**, 185-187 (2004).
256 Said, M. *et al.* Calcium-calmodulin dependent protein kinase II (CaMKII): A main signal responsible for early reperfusion arrhythmias. *J Mol Cell Cardiol* **51**, 936-944 (2011).

257 Haram, P. M. *et al.* Aerobic interval training vs. continuous moderate exercise in the metabolic syndrome of rats artificially selected for low aerobic capacity. *Cardiovasc Res* **81**, 723-732 (2009).
258 Prud'homme, D., Bouchard, C., Leblanc, C., Landry, F. & Fontaine, E. Sensitivity of maximal aerobic power to training is genotype-dependent. *Med Sci Sports Exerc* **16**, 489-493 (1984).
259 Booth, F. W. & Laye, M. J. The future: genes, physical activity and health. *Acta Physiol (Oxf)* **199**, 549-556 (2010).
260 Hautala, A. J. *et al.* Individual differences in the responses to endurance and resistance training. *Eur J Appl Physiol* **96**, 535-542 (2006).
261 Smith JAH, K. T., Chetty AK, Ojuka EO. CaMK activation during exercise is required for histone hyperacetylation and MEF2A binding at the MEF2 site on the Glut4 gene. *Am J Physiol Endocrinol Metab* **295**, 698-704 (2008).
262 Witczak, C. A. *et al.* CaMKII regulates contraction- but not insulin-induced glucose uptake in mouse skeletal muscle. *Am J Physiol Endocrinol Metab* **298**, E1150-1160 (2010).
263 Kehat, I. *et al.* Extracellular signal-regulated kinases 1 and 2 regulate the balance between eccentric and concentric cardiac growth. *Circ Res* **108**, 176-183 (2011).
264 MacDonnell, S. M. *et al.* CaMKII negatively regulates calcineurin-NFAT signaling in cardiac myocytes. *Circ Res* **105**, 316-325 (2009).
265 Ramirez, M. T., Zhao, X. L., Schulman, H. & Brown, J. H. The nuclear deltaB isoform of Ca2+/calmodulin-dependent protein kinase II regulates atrial natriuretic factor gene expression in ventricular myocytes. *J Biol Chem* **272**, 31203-31208 (1997).
266 Beisvag, V. *et al.* Pathological and physiological hypertrophies are regulated by distinct gene programs. *Eur J Cardiovasc Prev Rehabil* **16**, 690-697 (2009).
267 Elia, L. *et al.* Reciprocal regulation of microRNA-1 and insulin-like growth factor-1 signal transduction cascade in cardiac and skeletal muscle in physiological and pathological conditions. *Circulation* **120**, 2377-2385 (2009).
268 Condorelli, G. *et al.* Akt induces enhanced myocardial contractility and cell size in vivo in transgenic mice. *Proc Natl Acad Sci U S A* **99**, 12333-12338 (2002).
269 Kemi, O. J. *et al.* Activation or inactivation of cardiac Akt/mTOR signaling diverges physiological from pathological hypertrophy. *J Cell Physiol* **214**, 316-321 (2008).
270 Rokhlin, O. W., Guseva, N. V., Taghiyev, A. F., Glover, R. A. & Cohen, M. B. KN-93 inhibits androgen receptor activity and induces cell death irrespective of p53 and Akt status in prostate cancer. *Cancer Biol Ther* **9**, 224-235 (2010).
271 Chang, Z. *et al.* Deletion of Akt1 causes heart defects and abnormal cardiomyocyte proliferation. *Dev Biol* **347**, 384-391 (2010).
272 Ji, Y. *et al.* Targeted inhibition of sarcoplasmic reticulum CaMKII activity results in alterations of Ca2+ homeostasis and cardiac contractility. *Am J Physiol Heart Circ Physiol* **290**, H599-606 (2006).
273 Tong, C. W., Gaffin, R. D., Zawieja, D. C. & Muthuchamy, M. Roles of phosphorylation of myosin binding protein-C and troponin I in mouse cardiac muscle twitch dynamics. *J Physiol* **558**, 927-941 (2004).
274 Rokolya, A. & Singer, H. A. Inhibition of CaM kinase II activation and force maintenance by KN-93 in arterial smooth muscle. *Am J Physiol Cell Physiol* **278**, C537-545 (2000).

Paper I

Is not included due to copyright

Paper II

Is not included due to copyright

Paper III

Eur J Appl Physiol (2012) 112:579–588
DOI 10.1007/s00421-011-1994-0

ORIGINAL ARTICLE

Chronic CaMKII inhibition blunts the cardiac contractile response to exercise training

Guri Kaurstad · Marcia N. Alves · Ole J. Kemi · Natale Rolim · Morten A. Høydal · Helene Wisløff · Tomas O. Stølen · Ulrik Wisløff

Received: 23 November 2010 / Accepted: 30 April 2011 / Published online: 26 May 2011

Abstract Activation of the multifunctional Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) plays a critical role modulating cardiac function in both health and disease. Here, we determined the effect of chronic CaMKII inhibition during an exercise training program in healthy mice. CaMKII was inhibited by KN-93 injections. Mice were randomized to the following groups: sham sedentary, sham exercise, KN-93 sedentary, and KN-93 exercise. Cardiorespiratory function was evaluated by ergospirometry during treadmill running, echocardiography, and cardiomyocyte fractional shortening and calcium handling. The results revealed that KN-93 alone had no effect on exercise capacity or fractional shortening. In sham animals, exercise training increased maximal oxygen uptake by 8% ($p < 0.05$) compared to a 22% ($p < 0.05$) increase after exercise in KN-93 treated mice (group difference $p < 0.01$). In contrast, in vivo fractional shortening evaluated by echocardiography improved after exercise in sham animals only: from 25 to 32% ($p < 0.02$). In inactive mice, KN-93 reduced rates of diastolic cardiomyocyte relengthening (by 25%, $p < 0.05$) as well as Ca^{2+} transient decay (by 16%, $p < 0.05$), whereas no such effect was observed after exercise training. KN-93 blunted exercise training response on cardiomyocyte fractional shortening (63% sham vs. 18% KN-93; $p < 0.01$ and $p < 0.05$, respectively). These effects could not be solely explained by the Ca^{2+} transient amplitude, as KN-93 reduced it by 20% ($p < 0.05$) and response to exercise training was equal (64% sham and 47% KN-93; both $p < 0.01$). We concluded that chronic CaMKII inhibition increased time to 50% re-lengthening which were recovered by exercise training, but paradoxically led to a greater increase in maximal oxygen uptake compared to sham mice. Thus, the effect of chronic CaMKII inhibition is multifaceted and of a complex nature.

Keywords Aerobic interval training · KN-93 · Exercise training and cardiac function · CaMKII inhibition in healthy mice

Communicated by Keith Phillip George.

G. Kaurstad · M. N. Alves · N. Rolim · M. A. Høydal · T. O. Stølen · U. Wisløff
K.G. Jebsen Center of Exercise in Medicine,
Norwegian University of Science and Technology (NTNU),
Trondheim, Norway

G. Kaurstad · M. N. Alves · N. Rolim · M. A. Høydal · T. O. Stølen · U. Wisløff (✉)
Department of Circulation and Medical Imaging,
Norwegian University of Science and Technology (NTNU),
Olav Kyrresgate 9, Postboks 8905, 7491 Trondheim, Norway
e-mail: ulrik.wisloff@ntnu.no

O. J. Kemi
Institute of Cardiovascular and Medical Sciences,
University of Glasgow, Glasgow, UK

H. Wisløff
Department of Pathology, National Veterinary Institute,
Oslo, Norway

U. Wisløff
Centre for Sports and Physical Activity Research,
Norwegian University of Science and Technology (NTNU),
Trondheim, Norway

Introduction

The ubiquitous and multifunctional Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) regulates a number of intracellular processes related to cellular contractility

and nuclear gene expression, thereby controlling the pump function and growth of the heart. Some of the specific targets include the L-type Ca^{2+} channel, the sarcoplasmic reticulum (SR) Ca^{2+} release channel (ryanodine receptor 2, RyR2), phospholamban (PLB), Na^{+} and K^{+} channels making CaMKII a prominent regulator of excitation–contraction coupling (Couchonnal and Anderson 2008; Hashambhoy et al. 2010; Maier et al. 2007; Maier and Bers 2002). Furthermore, CaMKII can regulate nuclear gene expression on class II histone deacetylase (HDAC), which increases myocyte-enhanced factor 2 (Mef2)-regulated transcription (Erickson and Anderson 2008; Maier and Bers 2002, 2007; Maier et al. 2007; Sag et al. 2009). However, the functional consequences of CaMKII activation are still unclear, since heart failure is associated with increased CaMKII (Anderson 2005; Anderson et al. 1998; Couchonnal and Anderson 2008; Khoo et al. 2006; Vila-Petroff et al. 2007; Zhang et al. 2005); in fact, CaMKII may constitute a molecular switch between cardiac hypertrophy and failure (Zhang et al. 2005), and CaMKII activation may also precede arrhythmic events and contractile dysfunction, mainly because of its effect on the RyR2 (Anderson 2005; Ling et al. 2009; van Oort et al. 2010). On the other hand, improved contractile function after aerobic interval exercise training also associates with activated CaMKII, but in this scenario, the main effect is on the SR Ca^{2+} uptake due to phosphorylation of PLB. Interestingly, in mice with type-2 diabetes with chronically increased cardiac CaMKII and reduced cardiomyocyte contractile function and Ca^{2+} handling, aerobic interval exercise training resulted in reduced levels of CaMKII and improved cardiomyocyte contractile function and Ca^{2+} handling (Stolen et al. 2009). Recent studies have shown that CaMKII negatively regulates calcineurin activity (Khoo et al. 2006; MacDonnell et al. 2009), which in turn regulates mitochondrial respiration, and further complicates the role of CaMKII (Jiang et al. 2010; Wang et al. 2011).

The exact role of CaMKII activation in the heart remains unclear, as it associates with dysfunction, failure, and propensity for arrhythmias, but also with increased function under different circumstances such as exercise training. Based on the potential clinical value of chronic CaMKII inhibition (Khoo et al. 2006; Sag et al. 2009; Zhang et al. 2005) and the beneficial effect of exercise training on delaying cardiac dysfunction and correcting function after onset of heart disease (Stolen et al. 2009; Wisloff et al. 2002, 2007; Adams et al. 2005; Erbs et al. 2010; Mezzani et al. 2008; Hambrecht et al. 2000; Anderson et al. 1998; Kemi et al. 2007; Zhang et al. 2005) two scenarios that may mutually oppose each other, determining the effect of chronic CaMKII inhibition on the response to exercise training would be of considerable interest. Therefore, we aimed to study the effect of chronic CaMKII inhibition during the course of an exercise training program in healthy mice. We hypothesized that chronic CaMKII inhibition would abolish the normal exercise training response in the hearts.

Materials and methods

Mice and CaMKII inhibition

Eighteen female C57 BL/6J mice (Møllegaard Breeding Center, Lille Skensved, Denmark) 18–20 g, 8 weeks of age at inclusion were randomized into four groups: (1) sham control sedentary, (2) sham control exercise training, (3) KN-93 sedentary, and (4) KN-93 exercise training. KN-93 (2-[*N*-(2-hydroxyethyl)-*N*-(4 methoxybenzenesulfonyl)] amino-*N*-(4-chlorocinnamyl)-*N*-methylbenzylamine; Alexis-Biochemical, Enzo Life Science, PA, USA) diluted in dimethyl sulfoxide (DMSO, Sigma-Aldrich, St. Louis, MO, USA, 2 mg KN-93/1 mL DMSO, 10 μmol/kg (Zhang et al. 2005)) was intraperitoneally injected daily after the exercise training session (for those that exercise trained), throughout the experimental period. In a previous study, Zhang et al. (2005) observed dose-dependent CaMKII inhibition by KN-93, in which daily injections of 10 μmol/kg KN-93 produced similar effect on left ventricular contraction measurements as the genetically CaMKII-inhibited AC3:I mice (Zhang et al. 2005; Khoo et al. 2006). Sham control mice received similar amounts of DMSO daily. The Norwegian council for Animal Research approved the study, which was in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health Publications No. 85–23, revised 1996).

Exercise training

Exercise training was performed as aerobic interval training for 6 weeks, 5 days/week, on an inclined (25°) treadmill, each session starting with a 10-min warm-up at 50–60% of maximal oxygen uptake (VO_{2max}), whereupon exercise then alternated between 4- and 2-min intervals at 85–90 and 50–60% of VO_{2max}, respectively for 60 min. VO_{2max} was assessed during a treadmill running test to exhaustion in a metabolic chamber. After a warm-up period of about 10 min, treadmill band velocity was increased by 0.03 m/s for every second minute until mice were not able to maintain the treadmill velocity (Hoydal et al. 2007; Kemi et al. 2002). To maintain the exercise intensity throughout the experimental period, VO_{2max} was tested at the beginning of each week in addition to pre- and post-tests. This exercise protocol has previously been proven efficient for inducing exercise and cardiovascular

adaptations in both the clinical and experimental studies (Tjonna et al. 2008; Hoydal et al. 2007; Kemi et al. 2002, 2005; Wisloff et al. 2001; Stolen et al. 2009).

Echocardiography

High-resolution echocardiography (Vevo 770, VisualSonics, Toronto, Canada) using a single-element mechanical transducer with a center frequency of 30 MHz was performed on self-breathing mice exposed to a mixture of 2% isoflurane and 98% oxygen. A two-dimensional long-axis view was used to visualize both ventricles, the ascending aorta, and the right ventricular outflow tract by placing the ultrasound transducer on the left parasternal position, whereas a short-axis view was used to visualize systolic and diastolic movement of both ventricles by placing the transducer horizontally above the heart. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum (IVST) and posterior wall thickness (PWT) were recorded with M-mode echocardiography, which allowed calculation of the fractional shortening (% = [(LVEDD − LVESD)/LVEDD] × [100]) as an index of systolic left ventricular function. The following equation was used to calculate LV mass (mg) = [(LVEDD + IVST + PWT)^3 − LVEDD^3] × 1.055, where 1.055 (mg/mm^3) is the density of myocardium. IVST and PWT were measured at end diastole.

Cardiomyocyte isolation, contractile function, Ca^{2+} measurements and cell size

Left ventricular cardiomyocytes were isolated as previously described using a Hepes-based solution (Mitra and Morad 1981; Guatimosim et al. 2001). Exercised hearts were excised 24 h after the last exercise session. A mixture of 3–4% isoflurane and 96–97% oxygen were used to anesthetize the mice, whereupon the heart was heparinized and removed. Until it was connected to the aortic cannula on a standard Langendorff retrograde perfusion system, the hearts were kept on ice cold Hepes solution. The hearts were cleaned with a Hepes solution containing EGTA (Sigma-Aldrich Corp., Missouri, USA) before the perfusion was switched to Hepes solution with collagenase (Worthington, Lakewood, USA), and perfusion was continued for approximately 10 min (3.5 ml/min). After the hearts were taken down, left ventricles were carefully cut off and gently shaken for 2 min before the non-digested tissue was filtered out (nylon mesh, 250 μm). Further, cells were stepwise exposed to increasing Ca^{2+} levels (initially 0.05 mM). The isolated cells were centrifuged (30 s, 600 rpm) before solution was switched to 1.2 mM Hepes-based solution. Fura-2/AM-loaded (2 μmol/l, Molecular Probes, Eugene, OR, USA) cardiomyocytes were field stimulated by bipolar electrical pulse at 1 Hz, on an inverted epifluorescence microscope (Nikon TE-2000E, Tokyo, Japan), whereupon cell shortening was recorded by video-based myocyte sarcomere spacing (SarcLen^{TM}, IonOptix, Milton, MA, USA) and intracellular Ca^{2+} concentration was measured by fluorescence after excitation by alternating 340 and 380 nm wavelengths ($F^{340/380}$ ratio) (Optoscan, Cairn Research, Kent, UK). Cells with a clear visual intracellular structure that were able to follow stimulation frequency were included for the experiment. The total number of cardiomyocytes included for all analysis in the different groups was: sham sedentary 8, sham exercise 20, KN-93 sedentary 5, and in KN-93 exercise 9. During the stimulation protocol, cells were kept in 1.2 mM Ca^{2+} HEPES-based solution at 37°C. Cell size was measured with Nikon Eclipse E400 Microscope with a DSFil camera (Nikon NIS-Elements Basic Research Version 3.00 software, Nikon Instruments Inc., Melville, NY, USA). Cardiomyocyte size was measured on 80–120 cardiomyocytes per group.

Statistics

A one-way ANOVA with LSD post hoc test was used to detect significant differences between groups. For within-group differences from pre- to post-test, a paired sample T test was used. Statistical significance level was set to $p < 0.05$.

Results

VO_{2max} and exercise capacity

In sedentary mice, daily intraperitoneal injections of the CaMKII-selective inhibitor KN-93 did not affect VO_{2max}, running speed at VO_{2max}, or body mass (Fig. 1). However, while chronic CaMKII inhibition had no effect in sedentary mice, it did affect the response to exercise training. Whereas exercise training increased VO_{2max} by 8% ($p < 0.05$) in sham, the effect was 22% ($p < 0.01$) in KN-93 mice after the exercise training period (magnitude of response difference $p < 0.01$, Fig. 1a). KN-93 tended to suppress the growth in body mass (Fig. 1c), which made it necessary to normalize VO_{2max} according to correct scaling procedures, which involves the correct normalization of a physiological variable (here VO_{2max}) to a body dimension (here body mass). It is well established that cardiorespiratory capacity in lighter individuals will be overestimated compared to heavier ones when VO_{2max} is expressed in direct relation to body mass (i.e., ml/kg/min) and that VO_{2max} should be expressed with body mass raised to the power of 0.75 (i.e., ml/kg$^{0.75}$/min) when comparing individuals that differ in

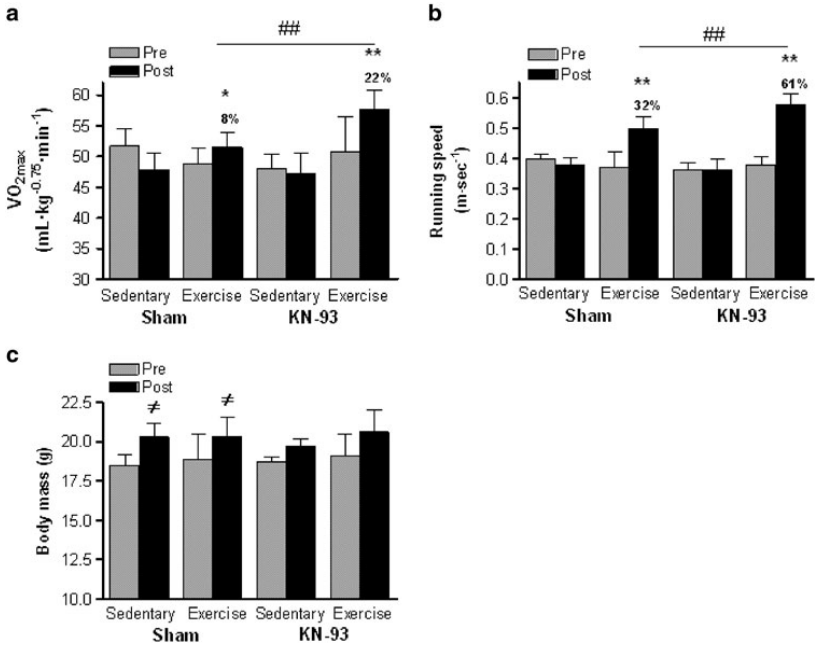

Fig. 1 Values of VO_{2max} (**a**), maximal aerobic running speed (**b**), and body mass (**c**), before and after the exercise training intervention (pre- and post-tests), presented as mean values ± SD. $^{*}p < 0.05$ versus sedentary; $^{**}p < 0.01$ versus sedentary; $^{\#\#}p < 0.01$ versus sham exercise; $^{\S}p < 0.05$ versus pre-test

body mass (Taylor et al. 1981). Hence, VO_{2max} was divided by body mass raised to the power of 0.75 as an exponent in the present study in order not to overestimate the effect of KN-93 on VO_{2max}. In line with a larger increase in VO_{2max} after exercise training in KN-93 mice, we observed that running speed at VO_{2max} also increased twice as much compared to that observed in sham mice 32% ($p < 0.01$), and 61% ($p < 0.01$) in KN-93 mice.

Cardiac remodeling

KN-93 injections did not significantly change LVEDD, LVESD, PWT, or IVST (Table 1). However, there was a trend for decreased LV mass, and LVEDD in sedentary KN-93 treated mice compared to sham sedentary.

Also, CaMKII inhibition by KN-93 injections did not affect cardiomyocyte size in sedentary mice, measured as cell length and width in isolated cardiomyocytes, but it did blunt the exercise training-induced hypertrophy of the cardiomyocytes. Exercise-induced cardiomyocyte hypertrophy was observed in both sham and KN-93 mice, but the effect was larger in sham mice. Exercise training increased cardiomyocyte length and width by 13% ($p < 0.05$) and 30% ($p < 0.05$) in sham mice, and by 8% ($p < 0.05$) and 14% ($p < 0.05$) in KN-93 mice, respectively (group differences $p < 0.05$, Fig. 2a, b). Thus, the cardiomyocyte hypertrophy response to exercise in KN-93 mice was approximately half of that in sham mice.

Table 1 Two-dimensional echocardiography measurements

	Sham		KN-93	
	Sedentary	Exercise	Sedentary	Exercise
n	6	4	4	4
Echocardiography				
HR (beats/min)	441 ± 21.3	450 ± 36.2	478 ± 18.0	447 ± 36.4
SV (μl/min)	23.7 ± 4.0	25.2 ± 1.4	20.2 ± 5.7	25.4 ± 6.0
CO (ml/min)	10.4 ± 1.8	11.3 ± 1.4	9.7 ± 2.7	11.3 ± 2.3
LVEDD (mm)	3.7 ± 0.2	3.7 ± 0.2	3.5 ± 0.3	3.8 ± 0.2
LVESD (mm)	2.8 ± 0.3	2.5 ± 0.3	2.6 ± 0.2	2.7 ± 0.1
LV mass (mg)	96 ± 11.7	94 ± 8.7	85 ± 23.5	99 ± 23.0
FS (%)	25 ± 4.5	32 ± 5.2*	28 ± 3.2	30 ± 1.6
PWT (mm)	0.69 ± 0.07	0.7 ± 0.09	0.75 ± 0.09	0.7 ± 0.11
IVST (mm)	0.74 ± 0.06	0.66 ± 0.14	0.7 ± 0.12	0.68 ± 0.06

Data are presented as mean values ± SD

HR heart rate, *SV* stroke volume, *CO* cardiac output, *LVEDD* left ventricular end-diastolic dimension, *LVESD* left ventricular end-systolic dimension, *FS* fractional shortening, *PWT* posterior wall thickness, *IVST* intraventricular septal thickness

* $p < 0.05$ versus sedentary

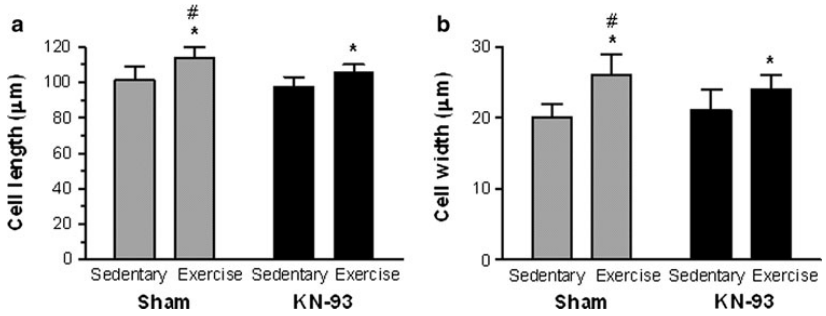

Fig. 2 Isolated cardiomyocyte dimension; cell length (**a**), and cell width (**b**), presented as mean values ± SD. $^{*}p < 0.05$ versus sedentary; $^{\#}p < 0.05$ versus KN-93 exercise

Cardiac contractile function

According to the measurements of in vivo cardiac function with echocardiography, KN-93 injections did not significantly affect heart rate, stroke volume (SV), cardiac output or fractional shortening (Table 1; Fig. 3). In contrast to VO_{2max} and exercise capacity, left ventricular fractional shortening improved from 25 to 32% after exercise training in sham mice (28% training response, $p < 0.02$). Cardiac contractile function is largely dependent on Ca^{2+} handling properties. Systolic Ca^{2+} and diastolic Ca^{2+} level were significantly increased by KN-93 injections (Fig. 4a, b, $p < 0.01$). Only sham exercise increased systolic Ca^{2+} levels (Fig. 4a, $p < 0.05$), and decreased diastolic Ca^{2+} level (Fig. 4b, $p < 0.01$).

Chronic CaMKII inhibition by KN-93 injections induced a reduction of the cardiomyocyte ability to re-lengthen (25% increased time to 50% re-lengthening; Fig. 4c, $p < 0.05$) after twitch contractions. This was at least partly explained by the 16% increase in the Ca^{2+} transient decay time (Fig. 4d, $p < 0.05$). Exercise training normalized cardiomyocyte re-lengthening and Ca^{2+} transient decay times to levels comparable to sedentary sham mice, and the response to exercise training was not different between sham and KN-93 mice. In particular, exercise training decreased the re-lengthening time by 12% ($p < 0.05$) and 16% ($p < 0.05$) in sham and KN-93 mice, respectively, which was linked to comparable exercise training-induced changes in the Ca^{2+} transient decay times (Fig. 4c, d).

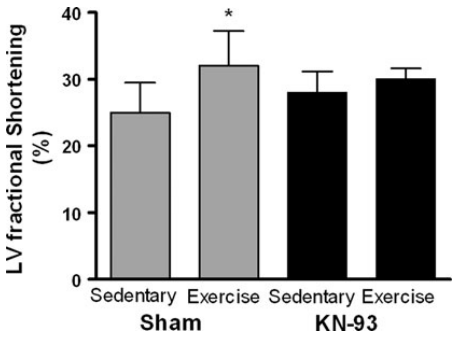

Fig. 3 In vivo LV fractional shortening, presented as mean values ± SD. $^{*}p < 0.05$ versus sedentary

In contrast to the above, the observed effects of KN-93 and exercise training on cardiomyocyte fractional shortening (amplitude of the contraction) and the associated Ca^{2+} transient amplitude showed a more complex nature. First, KN-93 reduced the Ca^{2+} transient amplitude by 20% (Fig. 4e, $p < 0.05$), but this did not translate into a comparable reduction in the fractional shortening, as no effect was observed. Second, fractional shortening improved by exercise training, but the response was blunted in KN-93 mice compared to sham mice. Exercise training in sham mice increased fractional shortening by 63% ($p < 0.01$), but only by 18% ($p < 0.05$) in KN-93 mice (magnitude of response difference $p < 0.05$, Fig. 4f). This could not be solely explained by changes to the Ca^{2+} transient amplitude, as the exercise training response did not differ between sham and KN-93 mice; sham increased by 64% ($p < 0.01$), and KN-93 by 47% ($p < 0.01$) in response to exercise training (Fig. 4e). Table 2 provides an overview of the effects of CaMKII inhibition on whole-body and cardiac, and cardiomyocyte exercise training response.

Discussion

Given that (1) experimental trials (Anderson 2005; Zhang et al. 2005; Grimm and Brown 2010) have raised the possibility that systemic CaMKII inhibition may be a viable and effective strategy for the treatment of heart disease, and (2) exercise training in both experimental (Rose et al. 2007; Wisloff et al. 2002; Stolen et al. 2009) and clinical

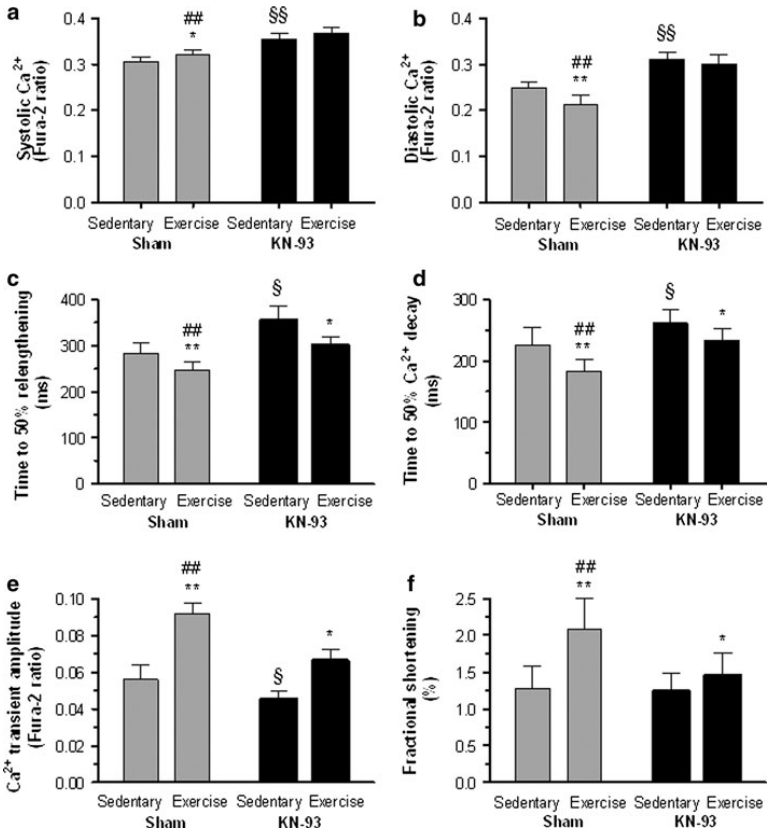

Fig. 4 Cardiomyocyte systolic Ca^{2+} level (**a**), diastolic Ca^{2+} level (**b**), time to 50% diastolic re-lengthening (**c**), Ca^{2+} transient decay time (**d**), intracellular Ca^{2+} transient amplitude (**e**), and fractional shortening (**f**), presented as mean values ± SD. $^{*}p < 0.05$ versus sedentary; $^{**}p < 0.01$ versus sedentary; $^{\#}p < 0.05$ versus KN-93 exercise; $^{\#\#}p < 0.01$ versus KN-93 exercise; $^{\S}p < 0.05$ versus sham sedentary; $^{\S\S}p < 0.01$ versus sham sedentary

Table 2 Comparison of effects of CaMKII inhibition on exercise training response

Variable	Sham exercise	KN-93 exercise
Aerobic exercise capacity		
VO_{2max}	↑	↑↑
Echocardiography		
LV fractional shortening	↑	↔
Cardiomyocyte Ca^{2+} handling		
Systolic Ca^{2+}	↑	↑
Diastolic Ca^{2+}	↓	↔
Fractional shortening	↑↑	↑
Ca^{2+} transient amplitude	↑	↑
Time to 50% re-lengthening	↓	↓
Time to 50% Ca^{2+} decay	↓	↓
Cardiomyocyte dimension		
Cell length	↑↑	↑
Cell width	↑↑	↑

↑, indicates value increase; ↓, value decrease; ↔, value remain unchanged; 1 or 2 arrows, indicate size of exercise-induced response

(Adams et al. 2005; Erbs et al. 2010; Hambrecht et al. 2000; Mezzani et al. 2008; Wisloff et al. 2007) trials show improved heart function in similar scenarios of heart disease, we aimed to test the potential value of combining those strategies; first in normal healthy mice. The reasoning for the latter is that exercise training and CaMKII also interact in the heart, as the inotropic effects of exercise training are at least partly modulated by an exercise training-induced increase in CaMKII activity (Kemi et al. 2007). This complicates the combination scenario as CaMKII seems to act as a two edged sword. In fact, CaMKII contributes to decompensate pathologic hypertrophy to heart failure, mainly by its action on the RyR2 to increase SR Ca^{2+} leak (Sag et al. 2009; Ling et al. 2009). Thus, the possibility arises that chronic CaMKII inhibition and exercise training may oppose each other, though it remains to be studied.

As such, this is the first study to introduce the combination of chronic CaMKII inhibition by daily KN-93 injections and aerobic interval exercise training. The main finding was that chronic CaMKII inhibition blunted several

aspects of the response patterns of cardiomyocyte contractility, and intracellular Ca^{2+} handling to exercise training, but it did not fully prevent such adaptations. Moreover, CaMKII inhibition also enhanced exercise training-induced improvements on VO_{2max} and aerobic exercise capacity, whereas it did not affect either of them in sedentary mice.

Mechanisms of exercise training-induced adaptation

The present study provides several mechanistic clues as to the response to exercise training. First, it shows that while CaMKII activation contributes to the cardiac improvements after exercise training (Kemi et al. 2007), other mechanisms must also contribute, as CaMKII inhibition only partly blunted the exercise response. Whether those mechanisms naturally co-exist or occur to compensate for the loss of CaMKII activation remains unknown.

Second, the finding that VO_{2max} and exercise capacity responded more to exercise training in the presence of the chronic CaMKII inhibition compared to the absence thereof indicates that CaMKII also may negatively regulate exercise adaptation in peripheral organs. While this requires further investigation, it is plausible all the while it is ubiquitous and exists in most, if not all, cellular systems (Hudmon and Schulman 2002; Chin 2004).

Third, the opposite effects of exercise training on VO_{2max} and exercise capacity on the one side, and cardiac inotropy and hypertrophy on the other side in the face of CaMKII inhibition highlights that other organs are important in determining VO_{2max} (Bassett and Howley 2000; Coffey and Hawley 2007). In particular, chronic exercise training elicits resistance to muscle fatigue through metabolic responses including mitochondrial biogenesis, increased oxidative capacity, and alterations in gene and protein expression that ultimately leads to phenotype changes that support endurance-type activity (Rose et al. 2007; Benziane et al. 2008; Chin 2004; Coffey and Hawley 2007; Bassett and Howley 2000). The exact mechanism of this rather surprising observation is not known; however, the interaction between CaMKII and calcineurin is a possible candidate. CaMKII modulation of calcineurin signaling is released by CaMKII inhibition. Calcineruin modulates exercise-induced skeletal muscle phenotypes and enhances exercise capacity through increase in mitochondrial oxidative function and energy substrate storage in skeletal muscles (Wang et al. 2011; Jiang et al. 2010). This should be elucidated in future studies.

Cardiac contractile capacity, Ca^{2+} handling, and CaMKII

Both in vivo and cellular fractional shortening were unaffected by KN-93-induced inhibition of CaMKII in sedentary mice, whereas the expected training-induced increase in both whole-heart and cellular fractional shortening was blunted by the chronic KN-93 treatment. However, chronic CaMKII inhibition did reduce the rate of diastolic cellular relaxation in sedentary mice, which was explained by slower intracellular Ca^{2+} removal (longer time to 50% Ca^{2+} transient decay) and higher systolic Ca^{2+} levels. Exercise training normalized Ca^{2+} removal times, and in contrast to fractional shortening, the effect was not blunted by CaMKII inhibition. These results are in accordance with Kemi et al. (2007), who found that acute pre-incubation, with AIP (comparable CaMKII inhibitor) in isolated cardiomyocytes also blunted the exercise training-induced improvements in cellular contractility. Together, these results suggest that CaMKII at least partly modulates the exercise training-induced improvements in cardiac contractility, excitation–contraction coupling, and intracellular Ca^{2+} handling (Kemi et al. 2007; Stolen et al. 2009). The accumulated evidence also suggests that this modulation occurs via targeting of several loci of excitation–contraction coupling and Ca^{2+} handling (Stolen et al. 2009). Indeed, fractional shortening is dependent on both SR Ca^{2+} release and myofilaments Ca^{2+} sensitivity, where the latter may explain the dissociation between fractional shortening and the intracellular Ca^{2+} transient amplitude in the present study, as shown directly by others after exercise training (de Waard et al. 2007; Diffee et al. 2001). However, in our experiments we used unloaded myocytes where tension development and basal sarcomere length were not considered.

Current results together with the previous studies (Anderson 2005; Anderson et al. 1998; Couchonnal and Anderson 2008; Erickson and Anderson 2008; Kemi et al. 2007; Khoo et al. 2006; Maier and Bers 2002; Maier et al. 2007; Sag et al. 2009; Vila-Petroff et al. 2007; Zhang et al. 2005) suggest that CaMKII is a versatile kinase that may shift cardiac function into different and also opposite phenotypes. In healthy mice, it appears that a controlled increase in the CaMKII activity increases cardiac contraction (Kemi et al. 2007); that CaMKII inhibition reduces cardiac contraction, and that these effects mainly occur because CaMKII inhibition reduces SR Ca^{2+} uptake via SERCA2a. Therefore, it is also possible that the depression of cardiomyocyte contractile parameters by chronic CaMKII inhibition observed here might have progressed to a global dysfunction and a failure if CaMKII inhibition was continued. As such, maintained CaMKII seems to be important for normal cardiomyocyte function in healthy mice. In contrast, the cardiac dysfunction that also has been linked to increased CaMKII activity (Ai et al. 2005; Couchonnal and Anderson 2008; Maier et al. 2007; Zhang and Brown 2004) has mainly been attributed to hypersensitization of the RyR2 to luminal Ca^{2+} with subsequent

diastolic SR Ca^{2+} leak and a shift of Ca^{2+} out of the cell; a scenario that may lead to contractile dysfunction and increased propensity for arrhythmic events (Sag et al. 2009; Ai et al. 2005; Grimm and Brown 2010; Khoo et al. 2006; Ling et al. 2009; Stolen et al. 2009; Wu et al. 2002), in which CaMKII inhibition or reduction would become particularly beneficial (Kemi et al. 2007; Laurita and Rosenbaum 2008; Li et al. 2006; Vila-Petroff et al. 2007; Yang et al. 2006; Zhang et al. 2005). In a recent modulation study, Hashambhoy et al. (2010) report that inhibition of CaMKII phosphorylation of the L-type Ca^{2+} channel rather than the RyR2 is more effective in modulating diastolic RyR2 flux. Thus, a pharmacological approach of CaMKII inhibition in the heart should also target the L-type Ca^{2+} channel in order to prevent or treat cardiac dysfunction and disease. Whether this will be feasible remains to be investigated. KN-93 inhibits CaMKII by competing for the calmodulin binding site, and has been widely used to implicate roles of CaMKII in Ca^{2+} handling (Sumi et al. 1991). KN-93 is not heart-specific and is known to have other actions than CaMKII inhibition (Anderson et al. 1998; Gao et al. 2006). Previous studies have observed that KN-93 might inhibit L-type Ca^{2+} current independent of CaMKII (Anderson et al. 1998; Gao et al. 2006). This negative effect of KN-93 on intracellular Ca^{2+} levels are balanced by inhibition of voltage-dependent potassium currents which enhance Ca^{2+} entry via L-type Ca^{2+} channel (Anderson et al. 1998; Rezazadeh et al. 2006; Ledoux et al. 1999). The lack of organ specificity of KN-93 is a limitation of this study, and interpretations should be considered with caution. We did, however, control for non-cardiac side effects of chronic KN-93 injections by the pathological examinations of the vital organs after euthanasia in mice.

Physiological hypertrophy

Echocardiography measurements observed a trend for decreased LV mass in sedentary KN-93 treated mice, which was normalized by exercise-induced hypertrophy, and cardiomyocyte length and width increased significantly less in KN-93-treated mice compared to sham-treated mice. These results are somewhat similar to the observations of Zhang et al. (2005), with myocardial infarction as the physiological stressor, who reported that cardiomyocyte transverse cross-sectional area and heart weight were comparably smaller after genetic inhibition of CaMKII than in control cardiomyocytes. Furthermore, Ramirez et al. (1997) reported that pre-treatment with KN-93 blocked hypertrophic responses to the hypertrophy developed by pressure overload or endothelin-1 (Zhang et al. 2004; Zhu et al. 2000). Our observation suggests that CaMKII may also modulate cardiomyocyte growth in response to exercise training (physiological hypertrophy) and not only in response to the pathologic conditions.

Conclusion

This study indicates the importance of maintaining normal CaMKII activity in cardiomyocytes of healthy individuals, also because it positively modulates inotropic/lusitropic responses to exercise training. However, targeting CaMKII by selective inhibitors has recently been suggested to correct cardiac dysfunction and prevent decompensation and progression of heart disease; a clinical scenario that also is targeted by exercise training. This study indicates that a combination strategy of CaMKII inhibition and exercise training may be feasible for the purpose of attenuating heart disease, although this does present a complex scenario that may also reduce some of the beneficial effects of exercise training, especially if CaMKII inhibitors cannot be closely tuned into localized subcellular targets that mainly cause the cardiac dysfunction.

Limitations

The small molecule inhibitor KN-93 has potential non-specific effects other than CaMKII inhibition which were not controlled for; this is a limitation of the present study. The pathological examinations were done to rule out effects on the results from any of the other vital organs due to KN-93 or DMSO injections.

Acknowledgments We thank Trine Skoglund for excellent laboratory assistance. The study was supported by grants from the K.G. Jebsen Foundation; the Blix Foundation for the Promotion of Medical Science (GK), and the Norwegian Research Council Funding for Outstanding Young Investigators (UW), and the British Heart Foundation (OJK).

Conflict of interest None.

References

Adams V, Linke A, Krankel N, Erbs S, Gielen S, Mobius-Winkler S, Gummert JF, Mohr FW, Schuler G, Hambrecht R (2005) Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. Circulation 111(5):555–562. doi:10.1161/01.CIR.0000154560.88933.7E

Ai X, Curran JW, Shannon TR, Bers DM, Pogwizd SM (2005) Ca2+/calmodulin-dependent protein kinase modulates cardiac ryanodine receptor phosphorylation and sarcoplasmic reticulum Ca2+

leak in heart failure. Circ Res 97(12):1314–1322. doi:10.1161/01.RES.0000194329.41863.89

Anderson ME (2005) Calmodulin kinase signaling in heart: an intriguing candidate target for therapy of myocardial dysfunction and arrhythmias. Pharmacol Ther 106(1):39–55. doi:10.1016/j.pharmthera.2004.11.002

Anderson ME, Braun AP, Wu Y, Lu T, Schulman H, Sung RJ (1998) KN-93, an inhibitor of multifunctional Ca++/calmodulin-dependent protein kinase, decreases early after depolarizations in rabbit heart. J Pharmacol Exp Ther 287(3):996–1006

Bassett DR Jr, Howley ET (2000) Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc 32(1):70–84

Benziane B, Burton TJ, Scanlan B, Galuska D, Canny BJ, Chibalin AV, Zierath JR, Stepto NK (2008) Divergent cell signaling after short-term intensified endurance training in human skeletal muscle. Am J Physiol Endocrinol Metab 295(6):E1427–E1438. doi:10.1152/ajpendo.90428.2008

Chin ER (2004) The role of calcium and calcium/calmodulin-dependent kinases in skeletal muscle plasticity and mitochondrial biogenesis. Proc Nutr Soc 63(2):279–286. pii:10.1079/PNS2004335S0029665104000370

Coffey VG, Hawley JA (2007) The molecular bases of training adaptation. Sports Med 37(9):737–763

Couchonnal LF, Anderson ME (2008) The role of calmodulin kinase II in myocardial physiology and disease. Physiology 23:151–159. doi:10.1152/physiol.00043.2007

de Waard MC, van der Velden J, Bito V, Ozdemir S, Biesmans L, Boontje NM, Dekkers DHW, Schoonderwoerd K, Schuurbiers HCH, de Crom R, Stienen GJM, Sipido KR, Lamers JMJ, Duncker DJ (2007) Early exercise training normalizes myofilament function and attenuates left ventricular pump dysfunction in mice with a large myocardial infarction. Circ Res 100(7):1079–1088. doi:10.1161/01.Res.0000262655.16373.37

Diffee GM, Seversen EA, Titus MM (2001) Exercise training increases the Ca2+ sensitivity of tension in rat cardiac myocytes. J Appl Physiol 91:309–315

Erbs S, Hollriegel R, Linke A, Beck EB, Adams V, Gielen S, Mobius-Winkler S, Sandri M, Krankel N, Hambrecht R, Schuler G (2010) Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. Circ Heart Fail 3(4):486–494. doi:10.1161/CIRCHEARTFAILURE.109.868992

Erickson JR, Anderson ME (2008) CaMKII and its role in cardiac arrhythmia. J Cardiovasc Electrophysiol 19(12):1332–1336. doi:10.1111/j.1540-8167.2008.01295.x

Gao L, Blair LAC, Marshall J (2006) CaMKII-independent effects of KN93 and its inactive analog KN92: reversible inhibition of L-type calcium channels. Biochem Biophys Res Commun 345:1606–1610

Grimm M, Brown JH (2010) Beta-adrenergic receptor signaling in the heart: role of CaMKII. J Mol Cell Cardiol 48(2):322–330. doi:10.1016/j.yjmcc.2009.10.016

Guatimosim S, Sobie EA, Cruz JDS, Martin LA, Lederer WJ (2001) Molecular identification of a TTX-sensitive Ca2+ current. Am J Physiol Cell Physiol 280:1327–1339

Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, Schoene N, Schuler G (2000) Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 342(7):454–460. doi:10.1056/NEJM200002173420702

Hashambhoy YL, Greenstein JL, Winslow RL (2010) Role of CaMKII in RyR leak, EC coupling and action potential duration: a computational model. J Mol Cell Cardiol. doi:10.1016/j.yjmcc.2010.1007.1011

Hoydal MA, Wisloff U, Kemi OJ, Ellingsen O (2007) Running speed and maximal oxygen uptake in rats and mice: practical implications for exercise training. Eur J Cardiovasc Prev Rehabil 14(6):753–760. doi:10.1097/HJR.0b013e3281eacef1

Hudmon A, Schulman H (2002) Structure-function of the multifunctional Ca2+/calmodulin-dependent protein kinase II. Biochem J 364:593–611

Jiang LQ, Garcia-Roves PM, de Castro Barbosa T, Zierath JR (2010) Constitutively active calcineurin in skeletal muscle increases endurance performance and mitochondrial respiratory capacity. Am J Physiol Endocrinol Metab 298(1):E8–E16. doi:10.1152/ajpendo.00403.2009

Kemi OJ, Loennechen JP, Wisloff U, Ellingsen O (2002) Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. J Appl Physiol 93(4):1301–1309. doi:10.1152/japplphysiol.00231.2002

Kemi OJ, Haram PM, Loennechen JP, Osnes JB, Skomedal T, Wisloff U, Ellingsen O (2005) Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. Cardiovasc Res 67 (1):161–172. doi:10.1016/j.cardiores.2005.03.010

Kemi OJ, Ellingsen O, Ceci M, Grimaldi S, Smith GL, Condorelli G, Wisloff U (2007) Aerobic interval training enhances cardiomyocyte contractility and Ca2+ cycling by phosphorylation of CaMKII and Thr-17 of phospholamban. J Mol Cell Cardiol 43(3):354–361. doi:10.1016/j.yjmcc.2007.06.013

Khoo MS, Li J, Singh MV, Yang Y, Kannankeril P, Wu Y, Grueter CE, Guan X, Oddis CV, Zhang R, Mendes L, Ni G, Madu EC, Yang J, Bass M, Gomez RJ, Wadzinski BE, Olson EN, Colbran RJ, Anderson ME (2006) Death, cardiac dysfunction, and arrhythmias are increased by calmodulin kinase II in calcineurin cardiomyopathy. Circulation 114(13):1352–1359. doi:10.1161/CIRCULATIONAHA.106.644583

Laurita KR, Rosenbaum DS (2008) Mechanisms and potential therapeutic targets for ventricular arrhythmias associated with impaired cardiac calcium cycling. J Mol Cell Cardiol 44(1):31–43. doi:10.1016/j.yjmcc.2007.10.012

Ledoux J, Chartier D, Leblanc N (1999) Inhibitors of calmodulin-dependent protein kinase are nonspecific blockers of voltage-dependent K+ channels in vascular myocytes. J Pharmacol Exp Ther 290(3):1165–1174

Li J, Marionneau C, Zhang R, Shah V, Hell JW, Nerbonne JM, Anderson ME (2006) Calmodulin kinase II inhibition shortens action potential duration by upregulation of K+ currents. Circ Res 99(10):1092–1099. doi:10.1161/01.RES.0000249369.71709.5c

Ling H, Zhang T, Pereira L, Means CK, Cheng H, Gu Y, Dalton ND, Peteron KL, Chen J, Bers D, Brown JH (2009) Requirement for Ca2+/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. J Clin Invest 119:1230–1240

MacDonnell SM, Weisser-Thomas J, Kubo H, Hanscome M, Liu Q, Jaleel N, Berretta R, Chen X, Brown JH, Sabri AK, Molkentin JD, Houser SR (2009) CaMKII negatively regulates calcineurin-NFAT signaling in cardiac myocytes. Circ Res 105(4):316–325. doi:10.1161/CIRCRESAHA.109.194035

Maier LS, Bers DM (2002) Calcium, calmodulin, and calcium-calmodulin kinase II: heartbeat to heartbeat and beyond. J Mol Cell Cardiol 34(8):919–939. pii:S0022282802920389

Maier LS, Bers DM (2007) Role of Ca2+/calmodulin-dependent protein kinase (CaMK) in excitation–contraction coupling in the heart. Cardiovasc Res 73:631–640

Maier LS, Bers DM, Brown JH (2007) Calmodulin and Ca2+/calmodulin kinases in the heart—physiology and pathophysiology. Cardiovasc Res 73(4):629–630. doi:10.1016/j.cardiores.2007.01.005

Mezzani A, Corra U, Giannuzzi P (2008) Central adaptations to exercise training in patients with chronic heart failure. Heart Fail Rev 13(1):13–20. doi:10.1007/s10741-007-9053-y

Mitra R, Morad M (1981) A uniform enzymatic method for dissociation of myocytes from hearts and stomachs of vertebrates. Pflugers Arch 391:85–100

Ramirez MT, Zhao X, Schulman H, Brown JH (1997) The nuclear deltaB isoform of Ca2+/Calmodulin-dependent protein kinase II regulated atrial natriuretic factor gene expression in ventricular myocytes. J Biol Chem 272:31203–31208

Rezazadeh S, Claydon TW, Fedida D (2006) KN-93 (2-[*N*-(2-hydroxyethyl)]-*N*-(4-methoxybenzenesulfonyl)]amino-*N*-(4-chlorocinnamyl)-*N*-methylbenzylamine), a calcium/calmodulin-dependent protein kinase II inhibitor, is a direct extracellular blocker of voltage-gated potassium channels. J Pharmacol Exp Ther 317(1):292–299. doi:10.1124/jpet.105.097618

Rose AJ, Frosig C, Kiens B, Wojtaszewski JF, Richter EA (2007) Effect of endurance exercise training on Ca2+ calmodulin-dependent protein kinase II expression and signalling in skeletal muscle of humans. J Physiol 583(Pt 2):785–795. doi:10.1113/jphysiol.2007.138529

Sag CM, Wadsack DP, Khabbazzadeh S, Abesser M, Grefe C, Neumann K, Opiela MK, Backs J, Olson EN, Brown JH, Neef S, Maier SK, Maier LS (2009) Calcium/calmodulin-dependent protein kinase II contributes to cardiac arrhythmogenesis in heart failure. Circ Heart Fail 2(6):664–675. doi:10.1161/CIRCHEARTFAILURE.109.865279

Stolen TO, Hoydal MA, Kemi OJ, Catalucci D, Ceci M, Aasum E, Larsen T, Rolim N, Condorelli G, Smith GL, Wisloff U (2009) Interval training normalizes cardiomyocyte function, diastolic Ca2+ control, and SR Ca2+ release synchronicity in a mouse model of diabetic cardiomyopathy. Circ Res 105(6):527–536. doi:10.1161/CIRCRESAHA.109.199810

Sumi MKK, Ishikawa T, Ishii A, Hagiwara M, Nagatsu T, Hidaka H (1991) The newly synthesized selective Ca2+/calmodulin dependent protein kinase II inhibitor KN-93 reduces dopamine contents in PC12h cells. Biochem Biophys Res Commun 181:968–975

Taylor CR, Maloiy GM, Weibel ER, Langman VA, Kamau JM, Seeherman HJ, Heglund NC (1981) Design of the mammalian respiratory system. III Scaling maximum aerobic capacity to body mass: wild and domestic mammals. Respir Physiol 44 (1):25–37

Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E, Slordahl SA, Kemi OJ, Najjar SM, Wisloff U (2008) Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation 118(4):346–354. doi:10.1161/CIRCULATIONAHA.108.772822

van Oort RJ, McCauley MD, Dixit SS, Pereira L, Yang Y, Respress JL, Wang Q, De Almeida AC, Skapura DG, Anderson ME, Bers DM, Wehrens XH (2010) Ryanodine receptor phosphorylation by calcium/calmodulin-dependent protein kinase II promotes life-threatening ventricular arrhythmias in mice with heart failure. Circulation 122(25):2669–2679. doi:10.1161/CIRCULATIONAHA.110.982298

Vila-Petroff M, Salas MA, Said M, Valverde CA, Sapia L, Portiansky E, Hajjar RJ, Kranias EG, Mundina-Weilenmann C, Mattiazzi A (2007) CaMKII inhibition protects against necrosis and apoptosis in irreversible ischemia-reperfusion injury. Cardiovasc Res 73(4):689–698. doi:10.1016/j.cardiores.2006.12.003

Wang JX, Jiao JQ, Li Q, Long B, Wang K, Liu JP, Li YR, Li PF (2011) miR-499 regulates mitochondrial dynamics by targeting calcineurin and dynamin-related protein-1. Nat Med 17(1):71–78. doi:10.1038/nm.2282

Wisloff U, Helgerud J, Kemi OJ, Ellingsen O (2001) Intensity-controlled treadmill running in rats: VO(2 max) and cardiac hypertrophy. Am J Physiol Heart Circ Physiol 280(3):H1301–H1310

Wisloff U, Loennechen JP, Currie S, Smith GL, Ellingsen O (2002) Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca2+ sensitivity and SERCA-2 in rat after myocardial infarction. Cardiovasc Res 54(1):162–174. pii: S000863630100565X

Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O, Skjaerpe T (2007) Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 115(24):3086–3094. doi:10.1161/CIRCULATIONAHA.106.675041

Wu Y, Temple J, Zhang R, Dzhura I, Zhang W, Trimble R, Roden DM, Passier R, Olson EN, Colbran RJ, Anderson ME (2002) Calmodulin kinase II and arrhythmias in a mouse model of cardiac hypertrophy. Circulation 106(10):1288–1293

Yang Y, Zhu WZ, Joiner ML, Zhang R, Oddis CV, Hou Y, Yang J, Price EE, Gleaves L, Eren M, Ni G, Vaughan DE, Xiao RP, Anderson ME (2006) Calmodulin kinase II inhibition protects against myocardial cell apoptosis in vivo. Am J Physiol Heart Circ Physiol 291(6):H3065–H3075. doi:10.1152/ajpheart.00353.2006

Zhang T, Brown JH (2004) Role of Ca2+/calmodulin-dependent protein kinase II in cardiac hypertrophy and heart failure. Cardiovasc Res 63(3):476–486. doi:10.1016/j.cardiores.2004.04.026

Zhang T, Miyamoto S, Brown JH (2004) Cardiomyocyte calcium and calcium/calmodulin-dependent protein kinase II: friends or foes? Recent Prog Horm Res 59:141–168

Zhang R, Khoo MS, Wu Y, Yang Y, Grueter CE, Ni G, Price EE Jr, Thiel W, Guatimosim S, Song LS, Madu EC, Shah AN, Vishnivetskaya TA, Atkinson JB, Gurevich VV, Salama G, Lederer WJ, Colbran RJ, Anderson ME (2005) Calmodulin kinase II inhibition protects against structural heart disease. Nat Med 11(4):409–417. doi:10.1038/nm1215

Zhu WZ, Zou Y, Shiojima I, Kudoh S, Aikawa R, Hayashi D, Mizukami M, Toko H, Shibasaki F, Yazaki Y, Nagai R, Komuro I (2000) Ca2+/Calmodulin-dependent Kinase II and Calcineurin play critical roles in endothelin-1-induced cardiomyocyte hypertrophy. J Biol Chem 275(19):15239–15245

Dissertations at the Faculty of Medicine, NTNU

1977

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

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

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

1985

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

1986

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

1987

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

1988

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

1989

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

1990

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

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

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

1993

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

1994

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

1995

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

1996

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

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
544. Sasha Gulati: SURGICAL RESECTION OF HIGH-GRADE GLIOMAS
545. John Chr. Fløvig: FREQUENCY AND EFFECT OF SUBSTANCES AND PSYCHOACTIVE MEDICATIONS THE WEEK BEFORE ADMISSION TO AN ACUTE PSYCHIATRIC DEPARTMENT
546. Kristin Moksnes Husby: OPTIMIZING OPIOID TREATMENT FOR CANCER PAIN – CLINICAL AND PHARMACOLOGICAL ASPECTS
547. Audun Hanssen-Bauer: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 ASSOCIATED MULTIPROTEIN COMPLEXES IN BASE EXCISION REPAIR
548. Marit Saunes: ECZEMA IN CHILDREN AND ADOLESCENTS – EPIDEMIOLOGY, COURSE AND IMPACT. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY, YOUNG-HUNT 1995-97
549. Guri Kaurstad: CARDIOMYOCYTE FUNCTION AND CALCIUM HANDLING IN ANIMAL MODELS OF INBORN AND ACQUIRED MAXIMAL OXYGEN UPTAKE