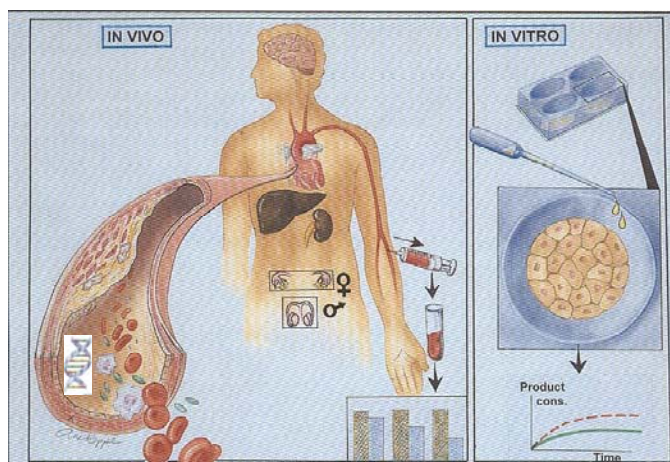


Center for Clinical Heart Research (CCHR)

Department of Cardiology
Medical Division
Oslo University Hospital, Ullevål

“Team building for individual excellence”



Annual Report 2013



<http://ous-research.no/clinicalheartresearch/>

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1. 1 Preface

Center for Clinical Heart Research (CCHR) was grounded in 1991 and is now organized as a part of the Department of Cardiology, Medical Division, OUH Ullevål.

The trademark of CCHR is researcher-initiated clinical, randomized intervention trials including studies on basic mechanisms in pathophysiology in cardiovascular disease states

The Center is one of 4 research groups within Department of Cardiology, playing an important role by being a core laboratory for other groups in the department as well as for other groups in the division.

CCHR is located within the department, close to the patients, which is crucial for the scientific activity.

The Center has from an early stage close collaboration with Vestre Viken Trust, Asker & Bærum Hospital and Akershus University Hospital by having common PhD-projects and students. This has continued also after the new group structure given by OUH and the University of Oslo.

New "geographical" facilities in 2013 have resulted in an improved milieu both for research and socially, by connecting phd-students, technologists and supervisors closer together.



1.2 Finances

Budgets for the single projects as well as for the running laboratory expenses are based on external funding.

The economical support from Stein Erik Hagens Foundation for Clinical Heart Research has been of fundamental importance for the activity also in 2013.

1.3 Strategy

The milieu continuously perform systematically researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUH and Health South-East. Projects related to acute myocardial infarction as well as chronic heart disease states like heart failure, atrial fibrillation and also diabetes, are central.

Studies on mechanisms/translational studies, on biochemical, cellular and genetic aspects especially related to inflammation, thrombotic processes and endothelial dysfunction, are focused. Biobanking, including sampling, processing, according to quality criteria and procedures are therefore a major part of the activity. To satisfy the high quality demands we have running costs for qualified technical support and large routine expenses. About 90% of all publications is based on biobanks.

Many PhD students are allocated to and supervised by the milieu, and several post-doc researchers are closely associated.

All research projects are in line with the strategy for research in Department of Cardiology.

CCHR is a group within the network of Center for Heart Failure Research, OUH/UiO.

1.4 Main Goals are

- to increase understanding of disease mechanisms, pathogenetic factors, as well as effects of interventions in patients with cardiovascular disease states
- to design and carry out randomized clinical trials, and to further expand on translational research in light of new knowledge and by use of new technology in material from extended biobanking
- to constitute a dynamic research group with highly motivated participants where group adherence and common efforts lead to progression – for the research group as well as for the individual researcher (“Team building for individual excellence”)
- to exert research of high quality, aiming at publications in high rated international journals
- to create an arena for scientific discussions, and for structured research supervision and teaching
- to educate competent PhD candidates a.o. who contribute to academic skill in clinical medicine and research
- to contribute to extended research skill on a post doc level
- to strengthen collaboration with national and international research groups

April 2014

Ingebjørg Seljeflot (sign)
professor dr. philos

Harald Arnesen (sign)
professor em dr. med

Svein Solheim (sign)
MD post.doc

2. Organization

2. Organization and functioning

2.1 Administration and organization aspects are undertaken by the center leaders.

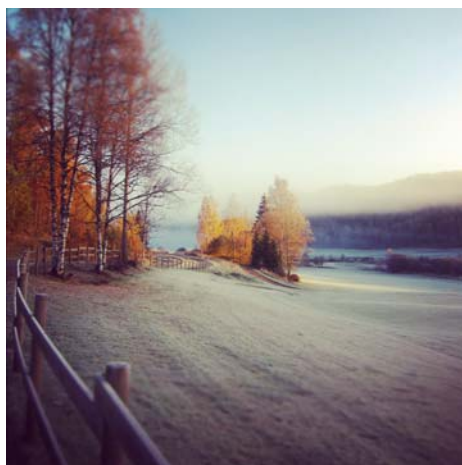
Our most important activity is the regular research 2-hour-meetings every 2-3 weeks. PhD students, post docs and laboratory personell participate together with the professors, and the main projects are reported with progress, results and relevant discussion. Furthermore, external experts on special relevant topics and co-workers from other groups and institutions, in addition to intramural experts in epidemiology and biostatistics are invited as lecturers.

Application issues for grants are discussed, and research-related scientific and administrative issues are reported. The PhD students are encouraged to prepare abstracts and participate on international congresses, primarily with presentation of own results. In 2013, 15 research meetings were arranged.

In addition, individual supervision of the single PhD student is undertaken, with an "open-door-policy", and specific projects are separately discussed in smaller groups. Decisions and "Contracts" for collaboration with other research groups are made by the leaders, all based on common scientific interests.

A **Scientific Symposium**, "Team building for individual excellence", was organized for all PhD-students and other participants of the group in October 2013 at Losby Gods, a very suitable location for our group size with about 20 persons. Two highly competent external guests were invited as discussants to the presentations which were given by all phd-students related to their individual research projects. The distinguished guests, professor Lina Badimon from Institut Català de Ciències Cardiovasculars Hospital de la Santa Creu, Barcelona and professor John-Bjarne Hansen from Hematological Research Group, University of North Norway, Tromsø also gave their special lectures.

With scientific work from Friday noon till Saturday afternoon, interrupted by physical activity by "touring" in the nice surroundings at the country-side, creating interesting new ideas, the symposium turned out very successful, scientifically and socially.



2. Organization

2.2 Personell

Leadership: The leader is also the head of the R&D Section at Department of Cardiology, 100% position, professor II at UiO. In addition, medical leaders are one previous post.doc and one professor emeritus, the latter is also the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, OUH Ullevål.

Employees: 2 medical technologists of which one has a Master of Science in biomedicine, the other is on the way to such, and 0.5 study nurse.

11 PhD students and 5 post.docs are participating in the milieu. In addition, the scientific milieu and the laboratory facilities are open for several other PhD-students, partially supervised at the Department of Cardiology and from other collaborating groups.

One of the PhD students is visiting Mt. Sinai Research Hospital in New York for 1 year in 2013/2014.

3. Scientific Activities Ongoing projects, mainly PhD-projects

3.1 Ongoing projects, mainly PhD-projects

EXCADI (Exercise training in patients with coronary artery disease and diabetes).

The primary aims of the EXCADI study are to investigate the effects of one year organized physical exercise in patients with both coronary artery disease (CAD) and type 2-diabetes on pathophysiological mechanisms related to i) atherothrombosis ii) glucometabolic state iii) risk factors for CVD iv) co-morbidity associated with type 2-diabetes.

Despite that physical activity has a well-established role in prevention of CAD *per se* and also for the progression and treatment of type 2-diabetes, few studies have described the effects of physical training in patients suffering from *both* diseases. There is also limited knowledge about the mechanisms involved in beneficial effects of physical exercise.

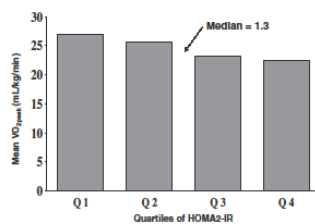
The project is a randomized, controlled, open study. 137 patients are included, based on power calculation. The exercise training is conducted in cooperation with the Norwegian School for Science in Sports.

A large biobank is founded for additional studies on the molecular level, including genetic expression in circulating leukocytes and in samples from adipose tissue.

Main Project: Cand.med. Rune Byrkjeland

Supervisors: Post doc. MD PhD Svein Solheim / Professor Ingebjørg Seljeflot / Professor em. Harald Arnesen

Baseline Results: *Significant inverse association between VO₂Max and Insulin resistance assessed by HOMA2-IR*



Peak oxygen uptake in quartiles of HOMA2-IR

Byrkjeland R, Edvardsen E, Njerve IU, Arnesen H, Seljeflot I, Solheim S. Diabetology & Metabolic Syndrome 2014, 6:36. DOI: 10.1186/1758-5996-6-36

Based on the biobank

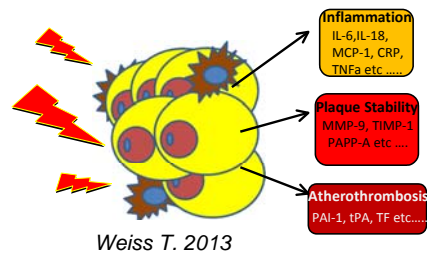
i) "The influence of glycemic control on genetic regulation of Interleukin-18"

Sub-study with special emphasis on the association between the degree of glycemic control and inflammation. Based on previous findings, extensive studies on the relationship between HbA1c, insulin resistance and Interleukin-18 are performed by genetic analyses in circulating cells and adipose tissue.

Master project: Sissel Åkra, Laboratory technologist

Supervisor: Professor Ingebjørg Seljeflot, MD PhD-student Rune Byrkjeland

3.1 Ongoing projects, mainly PhD-projects (cont.)



b) "The influence of glycemic control and effects of exercise training on genetic regulation of inflammation with special emphasis on fractalkine (CXC3CL) and its receptor CXC3CR"

Further explorative studies on the relationship between inflammation and glucose regulation by use of gene array in circulating leukocytes and adipose tissue.

Cand. med. Ida Unhammer Njerne

Supervisors: Professor Ingebjørg Seljeflot / Post doc. MD PhD Svein Solheim / Professor em. Harald Arnesen

SAXATH (Saxagliptin in atherosclerosis; effects beyond glucometabolic control)

The main aim of this study is to explore the effects of 3 months intervention with a dipeptidyl peptidase 4 (DPP-4) inhibitor on biomarkers related to atherosclerosis in patients with CAD and type 2 diabetes, both circulating and on tissue and cellular levels, with the hypothesis that the medication would improve a proinflammatory profile in these patients; thus any pleiotropic effect of saxagliptin is explored.

Patients with stable CAD and type 2 diabetes (n=12) treated with either metformin or glimepirid are recruited at OUH, Ullevaal and randomized to either saxagliptin 5 mg per day or placebo and followed for 3 months. Blood samples, PAX-gene tubes (for RNA analysis), subcutaneous fat tissue sample are collected, and polymorphonuclear cells (PBMS) are isolated at inclusion and the end of study.

Main Project: Cand.med. Ida Unhammer Njerne.

Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim / Post doc Thomas Weiss, Vienna.

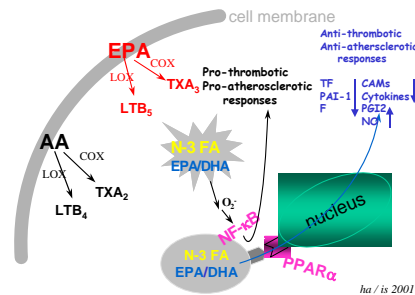
OMega-3 fatty acids in Elderly patients with Myocardial Infarction

Knowledge about elderly with CAD is limited. The aim of this study is to investigate the possible effects of supplementation with 2 g/day of n-3 PUFAs on cardiovascular morbidity and mortality during a follow-up period of 2 years in an elderly population after having experienced an acute MI.

The hypothesis is that this supplementation on top of modern therapy will reduce the combined cardiovascular end-point of death, non-fatal MI, stroke and

3.1 Ongoing projects, mainly PhD-projects (cont.)

revascularizations with at least 30%. Patients with acute MI discharged from hospital alive being ≥ 70 -82 years of age, both gender will be included. In addition, the study will generate important new knowledge about such an elderly population. The study is a randomized, placebo-controlled, double blind multicenter study with study center at CCHR.



A large biobank will be established and several sub-studies are planned related both to the intervention principles and to CAD in this elderly population.

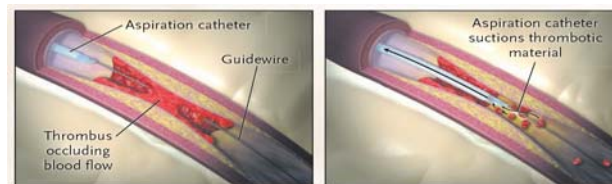
Participating centers are OUH Ullevål, Aalborg university hospital (AaUH), Denmark, Akershus university hospital (AHUH), Asker and Baerum Hospital (ABH)

Twin PhD students, Cand. med Kristian Laake at OUHU and Cand. med Peder Myhre at AUH.

Responsible/supervisors: Professor em. Harald Arnesen, post. doc Svein Solheim, professor Pål Smith, MD PhD Tone Nerdrum, Research Head Arnljot Tveit, professor Ingebjørg Seljeflot

Gene expression in coronary thrombus

This project aims to explore regulation of genes that are expressed in the coronary thrombus in an acute MI - related to atherothrombosis. Markers or mediators of fibrous cap rupture causing the acute myocardial infarction are focused. The levels of gene expression in the coronary thrombus as related to different clinical disease entities (sub groups), and also any associations with circulating levels of corresponding or related markers are investigated. Special attention will also be drawn to neutrophil leukocyte activation which lately has been given attention.



Coronary thrombus from approximately 80 patients with acute MI undergoing percutaneous coronary intervention (PCI) will be included, with blood samples from the same individuals. Collaboration with Department of Cardiology, Wilhelminenhospital, Vienna, Austria.

PhD project: Cand.med. Ragnhild Helseth

Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim / Post doc Thomas Weiss, Vienna.

3.1 Ongoing projects, mainly PhD-projects (cont.)

Inflammatory biomarkers in patients with ST-elevation myocardial infarction. Atherosclerotic mechanisms and implication for clinical outcome.

This project is based on "Biobanking of Acute Myocardial Infarction (BAMI)" (vide infra) in which patients admitted to the coronary care unit with an ST-elevation myocardial infarction at OUH, Ullevål, are included.

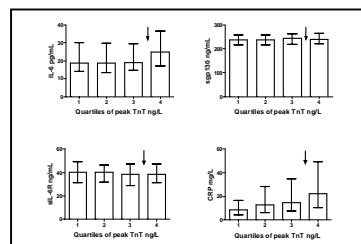
This project is a prospective cohort study on 1200 of these patients. A standardized biobank and a complete database with relevant clinical data are established. The patients will be followed for clinical events after 4-5 years (will be available during 2014).

In this specific project inflammatory signalling pathways are explored, especially related to 1) the interleukin-6 axis (IL-6, IL-6Receptor, Gp130, cardiotropin-1 and leukemia inhibitory factor), circulating levels as well as gene expression in leukocytes, and 2) the insulin growth factor (IGF)-1 axis (IGF-1, IGF-1BP3, growth hormone). The goal is to extend our understanding of these novel signalling pathways along with the present acute myocardial infarction and the remodelling process, and their role as risk markers for future cardiovascular events.

PhD project: Cand.med. Vibeke Ritschel

Supervisors: MD PhD Post.doc Geir Ø. Andersen, Professor Ingebjørg Seljeflot, MD PhD Jan Eritsland

Initial results: *IL-6 signalling in patients with acute ST-elevation myocardial infarction.*



IL-6 signalling and myocardial injury

Ritschel V, Seljeflot I, Eritsland J, Halvorsen S, Arnesen H, Andersen GØ. Results in Immunology 2013; doi.org/10.1016/j.rinim.2013.11.002

Metalloproteinases (MMP's) in different states in atherothrombosis.

This is a continuum of a Medical Student Research Program, Faculty of Medicine, UoO, "Studies on matrix metalloproteinases in atherosclerosis and coronary heart disease" finished in 2011.

In this finalizing study, the effect of autologous bone marrow stem cells (BMSC) in acute STEMI (based on the ASTAMI trial (Autologous Stem cell Transplantation in Acute Myocardial Infarction)) on MMP-9 is explored.

3.1 Ongoing projects, mainly PhD-projects (cont.)

The role of different metalloproteinases in acute myocardial infarction is still debatable, and there is limited knowledge on any influence of BMSC therapy on these proteinases.

In addition different regulatory pathways of MMP-9 are studied, by investigating both inhibitors and stimulators of MMP-9. The main hypothesis is that treatment with BMC's will reduce levels of MMP-9, and on the regulatory level, this is explained by reduction in EMMPRIN, an inducer of MMP-9.

PhD project: Cand.med. Eline Bredal Furenes

Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim / Professor em. Harald Arnesen, Senior scientist PhD Trine Baur Opstad.

CADENCE (Markers of Coronary Artery Disease During Exercise Testing)

The aim of this study, is to examine whether measuring changes in N-terminal fragment of pro-BNP (NT-pro-BNP) and troponin T during exercise may improve the accuracy of exercise ECG in the diagnosis of CAD. All subjects (n=600) will be examined with coronary angiography, which is regarded as the gold standard for diagnosing CAD. Moreover, we aim to clarify mechanisms related to sudden cardiac death related to exercise by studying whether there is an increase in biomarkers associated with haemostasis and inflammation during exercise, and examine whether ischemia may potentiate this increase. Furthermore, the relationship between exercise-induced changes in biomarkers and echocardiographic measures of systolic and diastolic function at rest will be performed. In a subsequent follow-up study, we aim to examine the predictive power of these markers on future cardiovascular mortality and morbidity.

The results may have important clinical implications for non-invasively diagnosing CAD, especially in women. Furthermore, the study may provide important insights into mechanisms responsible for exercise-related myocardial infarction.



Project for the PhD degree: Cand.med. Hilde Ulsaker

Supervisors: MD PhD Arnljot Flaa, MD PhD Eivind Berge, Professor Ingebjørg Seljeflot

3.1 Ongoing projects, mainly PhD-projects (cont.)

RATAF (RaTe control in Atrial Fibrillation)

So-called "rate control" has in recent years been claimed to be more important than "rhythm control" for patients with Atrial fibrillation. This randomized cross-over project (n=80) studies the effect of different drugs used in rhythm control to evaluate which drug gives optimal ventricular rate and at the same time improved quality-of-life. A biobank is mounted for relevant biochemical analyses. Joint project with Asker & Bærum Hospital, Vestre Viken HF.

Project for the PhD degree: Cand.med. Sara Ulimoen

Supervisors: Dr.med. Arnljot Tveit/Professor em. Harald Arnesen/Professor Knut Gjesdal

Atrial fibrillation - long-term risk predictors and importance for morbidity and mortality

The project comprises risk factors for atrial fibrillation, mainly epidemiological studies on a large database residing in Medical Research Laboratory, OUH Ullevål. Focus is on the predictive effects of upper normal systolic blood pressure, BMI, weight gain and physical fitness, as well as pulse rate at rest and during physical activity on atrial fibrillation after up to 35 years.

Project for the PhD degree: Cand.med. Irene Grundvold

Supervisors: Professor em. Harald Arnesen/Professor Sverre Erik Kjeldsen/Dr.med. Johan Bodegard

Biomarkers for diagnosis of deep venous thrombosis (DVT) in unselected patients

Patients with clinically suspect DVT and Pulmonary embolism (PE) are usually hospitalized. The clinical diagnosis is unspecific and radiological confirmation is necessary. In this study we want to evaluate the accuracy of the spot urine stix test in patients with clinically suspect DVT or PE. Our hypothesis is that the urine stix has a high negative predictive value and thus will exclude a number of patients from unnecessary radiological examinations.

We further want to follow those patients that do not have any confirmatory thrombotic findings on our radiological examinations, to observe if they develop some thrombin driven clinical events like stroke, myocardial infarction or venous events. Finally, we want to analyse stored blood samples from a biobank on markers on activation of coagulation and fibrinolysis, proteomics and other biomarkers for comparison with clinical outcome.

The study is a collaboration with Vestre Viken HF, Drammen.

Project for the PhD degree: Cand.med. Fredrik Wexels

Supervisors: MD PhD Ola Dahl, PhD Are Hugo Pripp, Professor Ingebjørg Seljeflot

3.1 Ongoing projects, mainly PhD-projects (cont.)

LEAF (Safety and efficacy of Levosimendan in patients with Acute myocardial infarction complicated with symptomatic left ventricular Failure).

A randomized, placebo-controlled study to investigate the effect and safety of the relatively new drug Simdax (levosimendan) in patients with PCI-treated STEMI with complicating heart failure. Infusion of levosimendan for 24 hours is compared to placebo, and a broad specter of biochemical analyses are performed in addition to tests of cardiac function, repeatedly during the 6 weeks follow-up. Sampling, processing, biobanking and the biochemical analyses are undertaken at CCHR. Biochemical analyses will be part of the main project.

Project for the PhD degree: Cand.med.Trygve Huseby

Supervisors: MD PhD Geir Ø. Andersen, MD PhD Jan Eritsland, Professor Ingebjørg Seljeflot

3.2 Post doc projects

"Glycoprotein 130 (Gp130) – interleukin-6 signalling pathway

GP130 is a transmembrane signaling protein, a part of the interleukin-6 signalling pathway, with important regulatory functions in several inflammatory reactions. Polymorphisms (SNP's) in the gene coding for Gp130 and their influence on phenotype (circulating proteins), for clinical end-points and for a possible effect of intervention with diet and/or omega-3 fatty acids are further studied in a norwegian population of 560 men with high risk for coronary heart disease The SNP's were studied in joint with a population from Vienna, Austria for the importance for clinical outcome.

Post doc project: Thomas Weiss MD PhD

Professor Ingebjørg Seljeflot/Professor em. Harald Arnesen

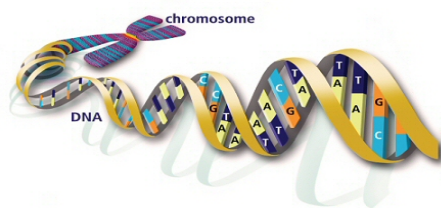
"Post ASTAMI"

In this projects the main goal was to study "Haemostatic factors in the ASTAMI study, with special reference to left ventricular thrombus", by which a 50% post doc. scholarship from Helse Sør-Øst was received. This was based on the observation of 15% mural left ventricular thrombus in the ASTAMI (Autologous Stem cell Transplantation in Acute Myocardial Infarction) trial during dual antiplatelet therapy. Thus, studies spesific on the coagulation system, as well as furter studies on the inflammatory aspects are undertaken, both systemic and at a regulatory level. The importance of GDF-15 and CTGF are especially further focused.

Post doc. Project: MD PhD Svein Solheim

"Genetic regulation of Interleukin-18 and MMP-9. Type 2 diabetes, Mets, clinical outcome"

In this project we want to further explore the regulatory mechanisms of IL-18 and MMP-9 with special reference to the metabolic syndrome (MetS) and type 2 diabetes. We have previously shown circulating levels of IL-18 to be predictive of cardiovascular events, and also a close relationship to the presence of MetS and hyperglycemia. We have also shown that IL-18 gene expression in adipose tissue in MetS patients is elevated compared to non-MetS individuals. Furthermore, we have shown that genetic polymorphisms (SNPs) in the IL-18 gene, especially the +187 A/G induces lower levels of IL-18 compared to wild type. We further want to explore the importance of the co-existence of the IL-18 +183 A/G and the MMP-9 -1562C/T polymorphisms which has been associated with elevated levels of MMP-9, on clinical prognosis.

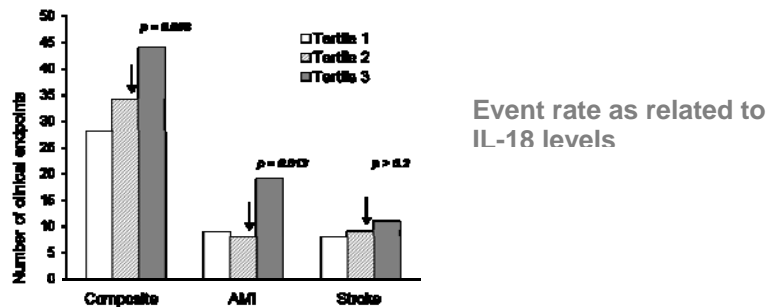


3.2 Post doc projects (cont.)

Any particular importance of these SNP's and proteins in patients with diabetes type-2 and MetS is investigated as well as the regulation of MMP-9 by further studying both inhibitors and stimulators in addition to the SNP's per se.

The pro-inflammatory properties of IL-18 might be in synergism with IL-12, and this will be investigated by measuring circulating levels of IL-12 as well as genetic expression. We also intend to explore any association between circulating microRNAs (i.e. miR-146) and gene expression/circulating protein levels of IL-18 to elucidate other regulatory pathways of IL-18.

Initial results:



Post doc project: MSc PhD Trine B. Opstad

Professor Ingebjørg Seljeflot, MD PhD Alf-Åge Pettersen

The ASCET study (ASpirin non-responsiveness and clopidogrel Clinical Endpoint Trial)

This main study which was to investigate the clinical importance of non-responsiveness to aspirin, was finalized in 2012. However, several questions with regard to response to both aspirin and clopidogrel are still not fully answered. Thus, different sub-studies based on the biobank obtained – on the stability of the response-phenomenon as well as further studies on the mechanisms behind, are ongoing and additionally planned. Special focus has been related to possible influence of relevant genetic differences in the response to aspirin and clopidogrel, and also on polymorphisms in the genes for other risk factors. (vide infra).

Post doc project: MD PhD Alf-Åge Pettersen

Professor em. Harald Arnesen/Professor Ingebjørg Seljeflot

GLUMIK (Glucometabolic status in patients with acute myocardial infarction).

MD PhD Eva Cecilie Knudsen who defended her thesis on this project 2011 are continuing in 50% post.doc position with supplementary investigations in this population. Special interests are paid to new markers in acute MI, antibodies to phosphorylcholine (PC), an important epitope on oxidized low-density lipoprotein (oxLDL). This is investigated in 220 patients with acute ST-elevation myocardial infarction (STEMI) related to clinical outcome after 3 years and to the presence of "abnormal glucose regulation". In addition, the cohort was re-investigated during 2013 for their glucometabolic status as well as for clinical outcome after 5.5 years.

Post.doc project: MD PhD Eva Cecilie Knudsen

Post.doc MD PhD Geir Øystein Andersen, Professor Ingebjørg Seljeflot

3.2 Post doc projects (Cont.)

NORDISTEMI (NORwegian Distance ST-Elevation Myocardial Infarction study).

This regional study in Helse Sør-Øst where 240 patients with acute ST-elevation myocardial infarction, all receiving thrombolytic therapy because of long distance(>90 minutes) to the PCI center, randomized to direct transport to OUH-Ullevål for primary coronary angiography ± PCI or to clinical stabilization at the local hospital for later referral to coronary angiography ± PCI when indicated (according to previous routine), was finished and defended in 2011. Additional studies on mechanisms related to Haemostasin and inflammation are ongoing.

Post doc project: MD PhD Sigrun Halvorsen, in collaboration with
Professor Ingebjørg Seljeflot, professor em. Harald Arnesen

Inflammation in Atrial Fibrillation

In two different studies, the **CAPRAF (Candesartan in the Prevention of Relapsing Atrial Fibrillation)** trial in patients with atrial fibrillation and the **ABAF (Asker and Bærum Atrial Fibrillation study)** - a population study to map the prevalence of atrial fibrillation (AF) in individuals above 75 years, large biobanks were established. Supplementary substudies are still ongoing. Studies especially related to the importance of inflammation are performed to increase the understanding of trigger mechanisms and potentially new therapeutic principles for the disease.

Post doc. Project: MD PhD Arnljot Tveit

3.3 Other projects

3.3 Other projects with supervision and support from CCHR

POSTEMI (Post-conditioning in STEMI treated with primary PCI).

A prospective, randomized trial undertaken at the coronary care unit to investigate the effect of 2 different regimes for PCI treatment in patients with acute ST-elevation myocardial infarction (n=260): traditional opening of the occluded artery or a "step-wise" opening/occlusion procedure, inducing so-called post-conditioning which is thought to contribute to diminished reperfusion injury after the PCI. The primary aim is infarct size measured with MRI. The mechanisms of post-conditioning are not fully understood, and a series of blood samples along the PCI procedure are gathered to elucidate the biochemical processes related to reperfusion injury (inflammatory, oxidative, apoptotic). Processing of samples, biobanking and biochemical analyses are undertaken at CCHR.

Project for the PhD degree. (Cand.med. Limalanathan Shanmuganath)

Supervisors: MD PhD Jan Eritsland, MD PhD Post.doc Geir Ø. Andersen

NORCAST (Norwegian Cardiac Arrest Survival Trial)

Combined clinical-neurological, neurophysiological, neuroradiological and biochemical markers in prognostication after cardiac and/or respiratory arrest. A prospective observation study at Oslo University Hospital, Ullevål.

In this multidisciplinary study performed in acute seriously ill patients, 250 patients are planned to be included. Blood samples are taken and processed at CCHR for analysis of a series of biomarkers especially related to neuro-inflammation and thrombotic risk markers in the very acute phase and also after 3 days in those staying alive. The patients are followed for one year.

A Steering Committee representing the different disciplines are involved, with *professor Kjetil Sunde, Department of Surgical Intensive Care Unit* as the leader of the project in close collaboration with the Acute Coronary Care Unit by Geir Ø. Andersen *ao.* The project is daily taken care of by *PhD-student Henrik Stær-Jensen, also supervised by MD Espen Rostrup Nakstad.*

Diabetes in children and atherosclerosis development.

Patients with type-1 diabetes from childhood have 20-30 times increased risk for premature death from cardiovascular diseases compared to non-diabetics. In the present study, initiated from Department of Pediatrics/Oslo Diabetes Center, 330 children/youth with type-1 diabetes are compared with 120 healthy controls matched for age and gender to investigate early signs of atherosclerosis as measured with various methods (anatomical, physiological, biochemical). Both groups will be followed for 5 and 10 years. All blood sampling/processing and facilities for biochemical translational research (biobanking, analyses) are undertaken at CCHR. The first "5 year follow-up" was completed during 2013.

PhD project (Cand.med. Martin Høyer)

Supervisor: Professor Knut Dahl-Jørgensen

3.3 Other projects with supervision and support from CCHR (Cont.)

Deleterious cardiac effects of long-time use of anabolic steroids evaluated with different cardiological methods.

The study is based on the assumption that doping with anabolic steroids increase the risk for and prevalence of ischemic heart disease. Body-builders with confessed use of anabolic steroids are compared to weight-lifting athletes not using stimulants. A multitude of cardiological methods (E-ECG, echocardiography, coloured tissue-Doppler, coronary CT) are used, and a series of biomarkers, including variables in coagulation and platelet activation (in detail by flowcytometry and aggregation) are studied. The project is initiated from OUH Aker with all biochemical investigations being performed at CCHR.

PhD project (Cand.med. Paul Vanberg)

Supervisor: Professor Dan Atar

Pulmonal arterial hypertension and right ventricle function in patients with chronic obstructive lung disease (COLD).

This study is aimed to evaluate non-invasive 3-D echo cardiography and Doppler method and ergospirometry, to diagnose pulmonal arterial hypertension (PAH) and systolic function of right ventricle in patient with COLD, and compare with magnetic resonance imaging (MR) and right ventricle catheterization. Biomarkers both venous and mixed arterial/venous, as related to the diagnosis and also to the severity of COLD (GOLD-classification), are collected. The laboratory analyses and biochemical supervision have been undertaken at CCHR. The study was performed at OUS Aker.

PhD project (Cand.med. Janne Mykland Hilde)

Supervisor: Amanuensis MD Kjetil Steine

BAMI ("Biobanking in patients with Acute Myocardial Infarction").

In this joint project between the the Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, an extended biobank is mounted along with prospectively registered clinical data and will be the basis for studies on predictive markers for later clinical events. Consecutive patients with STEMI are included after consent. At the end of 2013 about 1500 patients have been included and a PhD project on baseline biochemical variables is started (vide supra). In addition, studies on the response to clopidogrel, which initially is used by all patients are undertaken. Furthermore, when about 2000 patients are included, genetic analyses are planned. All logistics for processing of blood samples in the acute phase and the biochemical translational research are undertaken by CCHR.

A Steering committee for BAMI is established (*Professor em. Harald Arnesen, MD PhD Geir Øystein Andersen, MD PhD Sigrun Halvorsen, MD PhD Jan Eritsland, MD PhD Reidar Bjørnerheim, MD PhD Arild Mangschau, Professor Ingebjørg Seljeflot*)

3.3 Other projects with supervision and support from CCHR (Cont.)

Biomarkers of inflammation and haemostasis: welders under exposure to high-grade pollution

Increased mortality due to pulmonary and cardiovascular diseases by increasing pollution in the external environment has been documented. The mechanisms behind the cardiovascular and pulmonary systems vulnerability to such pollution, are not known. Welders are especially exposed to particulate and gaseous components during work, and this study address the hypothesis that particles inhaled during work can result in a low-grade chronic pulmonary inflammation inducing a low-grade systemic inflammation. The main focus is to study if such low-grade systemic inflammation may activate endothelial cells and platelets and simultaneously a hyper-coagulable state. If this is the case, it may constitute a work-related risk factor for the development of certain cardiovascular diseases. A total of 160 russian welders are investigated before and after a 3-year periode of daily/weakly work for inflammatory and haemostatic variables. Blood sampling is undertaken in Russia and brought to our laboratory. The degree of pollution is examined throughout the study period.

In collaboration with National Institute of Occupational Health (professor Dag Ellingsen).

A comparison between two types of anesthesia for open abdominal aortic surgery (ABSENT-study)

The primary aim in this study is to test if the volatile anesthetic agent sevoflurane is cardioprotective in open aortic aneurism surgery (AAA) as measured by troponines, time to extubation, inotropic medication, occurrence of atrial fibrillation, and the biochemical aspects like cytokine and chemokine production and degree of hypercoagulability. A total of 200 patients will be included and randomized to sevoflurane or TIVA (propofol/remifentanil) anesthesia. Blood samples are investigated before randomization, and after 8 hours, 1st and 2nd postoperative days. Cardiovascular events after 30 days are recorded. Biochemical analyses are undertaken at CCHR.

A study in collaboration with Vestfold HF, Tønsberg (MD Espen Lindholm, PhD-student, MD PhD Jan Erik Otterstad) and Department of Anesthesia, OUH, Ullevål (professor Knut Arvid Kirkebøen)

Markers of inflammation in cerebrospinal fluid (CSF) in delirium associated with hip-fracture

Potential biomarkers that may shed light on possible mechanisms related to delirium; association with exaggerated neuroinflammatory response, increased macrophage and neutrophil chemotaxis into CNS, damage of myelin along with low-grade ischemia and blood–brain barrier dysfunction. Inflammatory biomarkers that might be present also in CSF are investigated, as little knowledge exists on this issue. We try to sort out any presence of CRP and components of the interleukin-6 transsignalling pathway, in serum and CSF. About 100 patients are included.

A collaboration with Department of Geriatrics, OUH Ullevål (professor Torgeir Bruun Wyller and MD Leiv Otto Watne, PhD-student)

3.3 Other projects with supervision and support from CCHR (Cont.)

Endothelial dysfunction in relation to microbial translocation

Microbial translocation has been suggested as a driving force of immune activation in several disease states.

In chronic HIV-infected individuals the gastrointestinal mucosal barrier is distorted. Markers of microbial translocation have been shown to be independent predictors of future hypertension in HIV-infected patients. We hypothesize that markers of microbial translocation would be associated with asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction, and its structural isomer, symmetric dimethylarginine (SDMA) in HIV patients. We further want to explore the impact of microbial translocation in treated vs non-treated HIV-patients.

Any association between endothelial dysfunction/microbial translocation and obesity are explored in a study on obese individuals, who undergo weight reduction and additional gastric bypass surgery. Ongoing studies.

Main investigator post doc Marius Trøseid, in collaboration with Bodø Hospital Trust, Rikshospitalet København and Department of Infectious disease OUH.

4. Laboratory Methods

4.1 Locally

- Facilities for blood sampling and processing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and -80°C))
- Platelet function testing with aggregometry and flow-cytometry in addition to "bedside" screening tests (PFA100, VerifyNow)
- ELISA's
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied biosystems)
Studies on gene expression
Studies on genetic polymorphisms

4.2 Located at Institute of Experimental Medical Research

- HPLC, specially used for elucidation of endothelial function and peroxidation

5. Collaborators

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6. Publications 2013

6.1 Articles

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6. Publications 2013 Abstracts

6.2 Published Congress Abstracts

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Mykland Hilde J, Hisdal J, Hansteen V, Seljeflot I, Arnesen H, Nissen Melsom H, Steine K. Reduced systemic arterial compliance and subclinical LV systolic dysfunction in COPD. Congress of the European Society of Cardiology 2013, Amsterdam. Abstract P1525

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