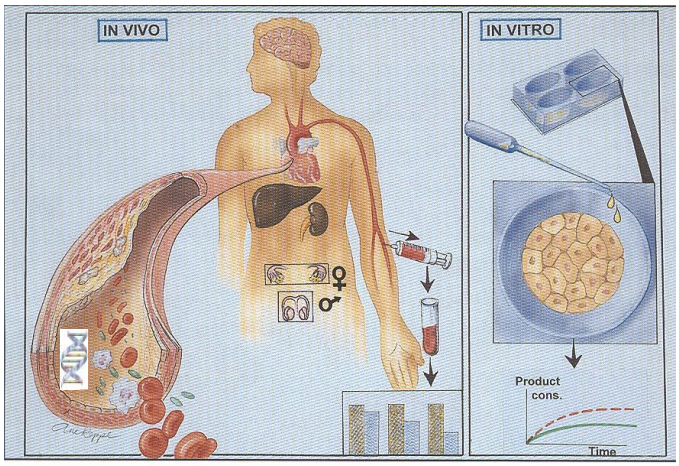
Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital, Ullevål

"Team building for individual excellence"



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

Annual Report 2015

Content

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 is researcher-initiated clinical, randomized intervention trials including studies on basic mechanisms in pathophysiology in cardiovascular disease states.

The Center is one of the research groups within Department of Cardiology. In addition, the Center plays an important role as a core laboratory for other research groups in the Department as well as for other in the Division and other collaborators.
CCHR is located within the Department, close to the patients, which is crucial for the scientific activity.
The Center has from an early stage fruitful collaboration with Vestre Viken Trust, Asker & Bærum Hospital and Akershus University Hospital by having common PhD-projects and students.

In 2015 the activity has been scientifically high with 2 defended PhD theses supervised from the Center, deeply involved in 2 other PhD theses, 20 internationally published papers and 27 published congress abstracts.

We are very satisfied to have hosted post.doc Gemma Chiva-Blanch from ICIC in Barcelona, a prestigious lab, for 6 months, which has been a very fruitful period, with introduction of new laboratory methods.
Laboratory work has increased and the methodology extended in general during 2015.

The 5th Scientific CCHR Symposium was arranged in October, this year again at Noreheim, Norefjell with invited distinguished discussants. It was very successful, scientifically and socially - for building bridges.

We are very pleased to give this annual report for 2015.

April 2016

Ingebjørg Seljeflot (sign)
professor dr. philos

Harald Arnesen (sign)
professor em dr. med

Svein Solheim (sign)
MD post.doc

Finances

The leader is financed from the Department of Cardiology, OUH, Ullevål by a combined position for the Center and for being Head of the Research and Development Section in the Department.
Budgets for the single projects, including salary for PhD-students, technical personal and running laboratory expenses are based on external funding from different sources. In 2015 we were happy to receive fundings for one PhD-project related to elderly patients with acute myocardial infarction from Olav Thon Stiftelsen.

The major economical support from Stein Erik Hagens Foundation for Clinical Heart Research has been of crucial importance for the activity also in 2015.

Strategy

The strategies are unchanged

- Systematic researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUH
- Projects related to acute myocardial infarction, chronic heart diseases like heart failure, atrial fibrillation and diabetes
- Focus on ischemic heart disease in the elderly
- Biobanking, standardized sampling and processing of blood and tissue
  About 90 % of all publications are based on biobanks
- Main issue: Studies on mechanisms/translational studies, on biochemical, cellular and genetic aspects especially related to inflammation, thrombotic processes and endothelial dysfunction
- All 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
- To be an interdisciplinary composed group, including researchers at post.doc level

Main Goals

The main goals are still

- to increase the understanding of disease mechanisms, pathogenetic factors, as well as effects of interventions in patients with cardiovascular disease

- 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 materials 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

Organization

Administration and organizational aspects are undertaken by the Center leaders.

Our most important activity is the regular research 2-hour-meetings every 2-3 weeks. PhD candidates, 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. In 2015 we have also introduced more topic-related smaller meetings for more deep discussions into fields of relevance.
Application issues for grants are discussed, and research-related scientific and administrative issues are reported. The PhD candidates are encouraged to give presentations at the meetings and to prepare abstracts for international congresses. In 2015, 12 research meetings were arranged.
In addition, individual supervision of the single PhD candidate 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 all based on common scientific interests.

Scientific Symposium, ”Team building for individual excellence”, was organized for the 5th time in October 2015 at Noreheim, Norefjell.

Organization (cont.)

Personell

Leadership: The leader is also the head of the R&D Section at Department of Cardiology, 100% position, and 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, both with a Master of Science in Biomedicine, 1 post.doc researcher (PhD) and 0.5 study nurse.

10 PhD students, 4 post.docs participate in the milieu. A biostatistician /epidemiologist participate occationally. In addition, the scientific milieu and the laboratory facilities are open for several other PhD-students, partially supervised at the Department of Cardiology, but also from other collaborating groups.

In 2015, thanks to the economic possibilites from Stein Erik Hagens Foundation for Clinical Heart Research, **post doc Gemma Chiva Blanch from Cardiovascular Research Center (CSIC-ICCC), Hospital de la Santa Creu i Sant Pau, Barcelona,** has been working at CCHR for 6 months, resulting in increased scientific and methodological knowledge and created important international collaboration.

Scientific Activities

Defended PhD-thesis 2015

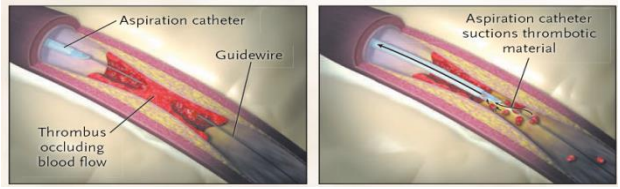
Ragnhild Helseth, Cand. Med.

Coronary thrombus genes and neutrophil cell activation in acute myocardial infarction

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

In collaboration with Department of Cardiology, Wilhelminenhospital, Vienna, Austria.

This project aims to explore regulation of genes that are expressed in the coronary thrombus in an acute MI in association to circulating levels of the corresponding protein levels - related to atherothrombosis. Special attention was given to neutrophile leukocyte activation which lately has been given much attention.



Her work concluded that aspirated coronary thrombi from patients with AMI were highly genetic active, expressing a diversity of genes related to plaque rupture, platelet and neutrophil cell activation, coagulation, fibrinolysis and inflammation, and were highly influenced by ischemic time. The gene profile also changed according to the presence of traditional cardiovascular risk factors like T2DM and hypertension.
The dynamic changes in the genes were not reflected in the circulating levels, indicating a highly local genetic milieu at the site of atherothrombosis.

The neutrophil cell mediators pentraxin-3 (PTX3) and myeloperoxidase (MPO) were elevated in peripheral blood in the acute and subacute phase of AMI and correlated partly with indices of infarct size and left ventricular function.
PTX3 levels were to some degree reflected in the genetic regulation in circulating leukocytes. Otherwise, the genetic regulation of these mediators are still relatively unclear.
Intracoronary stem cell treatment in STEMI patients seems not to affect PTX3 or MPO, neither circulating levels nor the gene expression levels in leukocytes.

The work on neutrophil cell activation is continued as a post.doc project.

Scientific Activities

Defended PhD-thesis 2015

Sara Ulimoen, Cand. Med.

RATAF (RaTe control in Atrial Fibrillation)

Supervisors:
Dr.med. Arnljot Tveit
Professor em. Harald Arnesen
Professor Knut Gjesdal
Joint project with Asker & Bærum Hospital,
Vestre Viken HF.

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=60) studied the effect of 4 different drugs (2 Calcium channel blockers and 2 beta-blockers) used in rhythm control to evaluate which drug gives optimal ventricular rate and at the same time improved quality-of-life. In addition the influence on exercise capacity was investigated. Furthermore, a biobank is mounted for relevant biochemical analyses, and initial focus has been on NT-proBNP at rest and at peak exercise, as well as on Cardiac Troponin T at rest and after maximal exercise test. The observation period on each drug before re-testing was 3 weeks.
The main results were that the Calcium channel blockers reduced the ventricular rate more than the beta-blockers, and that the arrhythmia-related symptoms also were reduced with the Calcium channel blockers, but not with the beta-blockers.
In the biochemical substudies it was found that the Calcium channel blockers preserved exercise capacity and reduced the levels of NT-proBNP, whereas the beta-blockers reduced exercise capacity and increased NT-proBNP levels.
Regarding the circulating levels of Cardiac Troponin T as a measure of myocardial damage, all drugs reduced the levels significantly without significant differences between the drugs. The levels of Cardiac Troponin T increased significantly in response to exercise.
The main conclusion from this randomized cross-over project is that Calcium channel blockers should be considered more often for rate control in patients with atrial fibrillation without co-morbidities that mandate the use of beta blockers.

Scientific Activities
Defended PhD-thesis 2015

CCHR have been deeply involved in 2 other defended theses in 2015

Martin Heier, Cand. Med.

Early atherosclerosis in childhood onset diabetes - The impact of inflammation and advanced glycation

Initiated from Department of Pediatrics/Oslo Diabetes Center
Supervisor: Professor Knut Dahl-Jørgensen

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 of ~330 children/youth with type-1 diabetes (T1D) 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 were followed for 5 years. Blood sampling/processing and facilities for biochemical translational analyses were undertaken and scientifically discussed at CCHR.
The work concluded that children and adolescents with T1D have increased levels of several markers of inflammation in which CRP was the most pronunced, compared to healthy control subjects. In addition, levels of AGE MG-H1 were increased in T1D and associated with inflammation, indicating a role for AGEs in early atherogenesis in T1D. It was also shown that atherosclerosis development assessed by cIMT is accelerated in T1D, already at the age of 13 and with only 5 years of diabetes duration.
More aggressive preventive action against atherosclerosis seems warranted from shortly after the onset of T1D.

Espen Lindholm, Cand. Med.

Perioperative aspects of abdominal aortic surgery; focus on choice of anesthetics

Initiated from Department of Anesthesiology, Vestfold Hospital Trust, Tønsberg.
Supervisor: Professor Knut Arvid Kirkebøen

Main purpose of the study was to compare two different types of anesthesia in abdominal surgery with the hypothesis that sevofluvane-based type would be cardioprotective and reduce inflammatory responses during surgery compared to total intravenous anesthesia.
Outcomes were judged by troponins, inflammatory variables during surgery, as well as echocardiographic measures. The hypotheses were not obviously verified with regard to abdominal surgery.

Scientific Activities

PhD projects

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

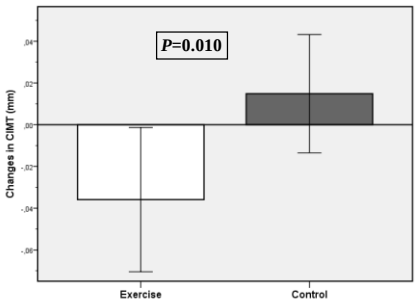
Main Project: Cand. Med. Rune Byrkjeland

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

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 collaboration with the Norwegian School for Science in Sports.

Changes in carotid intima media thickness (IMT) after one year exercise intervention



Byrkjeland R et al. Cardiovasc Diabetol 2015

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

Scientific Activities

PhD projects

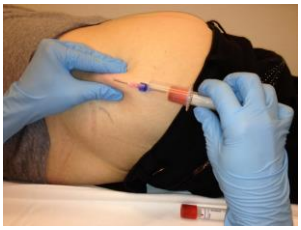
Based on the EXCADI biobank

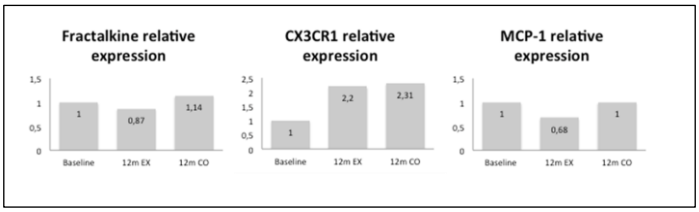
The influence of glycemic control and effects of exercise training on genetic regulation of fractalkine (CXC3CL) and its receptor CXC3CR

Cand. Med. Ida Unhammer Njerve

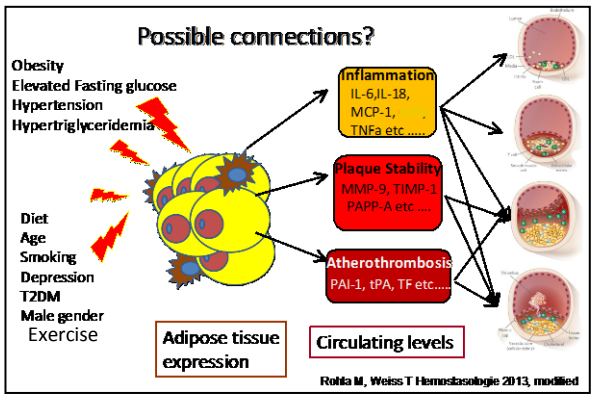
Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim, Professor em. Harald Arnesen

The chemokine fractalkine and it´s receptor CX3CR1, associated with inflammation and atherosclerosis, are expressed in endothelial cells, macrophages and adipocytes amongst others. Conflicting results regarding associations between fractalkine levels and coronary artery disease (CAD) and glucometabolic state exist.
We specifically aimed to investigate whether there are any associations between glucometabolic control (HbA1c), insulin resistance (HOMA2-IR), BMI and fractalkine in patients with both CAD and type 2 diabetes, and further the effects of exercise training. Gene expression of fractalkine in adipose tissue was specially focused.





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



Modified with permission

Scientific Activities

PhD projects

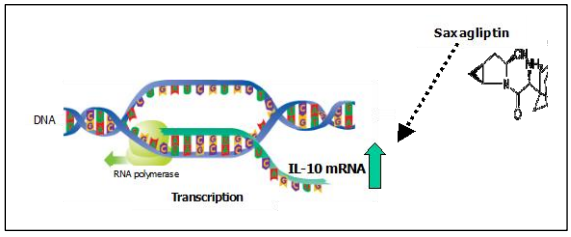
SAXATH (Saxagliptin in atherosclerosis; effects beyond glucometabolic control)

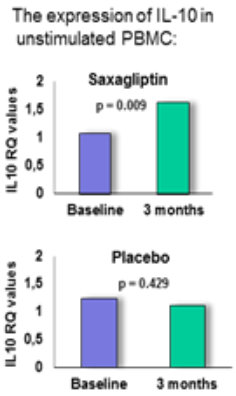
Main Project: Cand. Med. Ida Unhammer Njerve

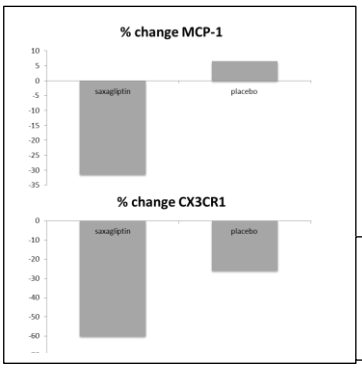
Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim

The main aim of this study is to explore the effects of 3 months intervention with a dipeptidyl peptidase 4 (DPP-4) inhibitor on inflammation on a cellular level in patients with CAD and type 2 diabetes. Circulating and tissue levels of selected markers are investigated. As atheroscleris is an inflammatory disease, we hypothesise that the medication would improve a proinflammatory profile in these patients; thus any pleiotrophic effect of saxagliptin is explored.

Patients with stable CAD and type 2 diabetes (n=12) treated with either metformin or glimepirid were 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) were isolated at inclusion and the end of study.







Change in MCP-1 and CX3CR1 in adipose tissue gene expression after 3 months; Saxagliptin vs placebo

Scientific Activities

PhD projects

Based on the EXCADI biobank

Adipose tissue inflammation in patients with coronary artery disease and type 2 diabetes; effects of exercise training

Cand. Med. Hani Zaidi

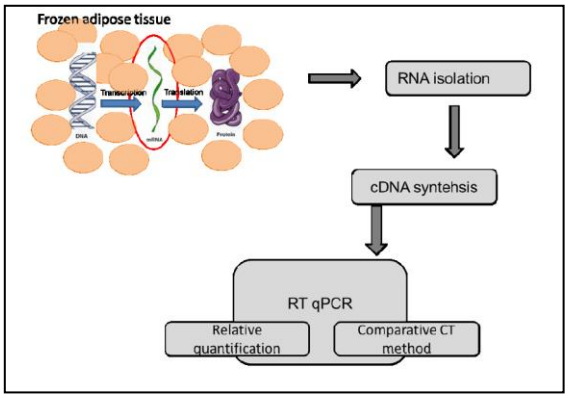
Supervisors: Professor Ingebjørg Seljeflot, Post.doc Trine B. Opstad
Phd-student Rune Byrkjeland, Post doc Svein Solheim

In this project the regulatory mechanisms of

i) the IL-18/IL-12/miR-21/NLRP3/Caspase-1 axis
ii) the MMP-9/TIMP-1/EMMPRIN/miR-21 axis
iii) the adiponectin/visfatin/PAI-1 axis

as related to Glucometabolic variables, and effects of exercise training from the EXCADI biobank (i.e. patients with CAD and Type-2 diabetes) will be further explored.

Initial phase in 2015



Scientific Activities

PhD projects

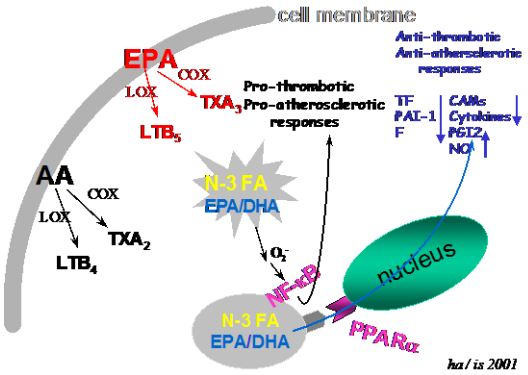
OMEMI (OMega-3 fatty acids in Elderly patients with Myocardial Infarction)

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 Arnljot Tveit, Professor Ingebjørg Seljeflot

Knowledge about elderly with CAD is limited. The aim of this study is to investigate the possible effects of supplementation with 1.8 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, revascularizations and re-hospitalization for heart failure with at least 30%. Patients with acute MI discharged from hospital alive being ≥70-82 years of age, both gender will be included. Special emphasis will be paid on the incidence of atrial fibrillation and heart failure in this elderly population.
In addition, the study will generate important new knowledge about such an elderly population with CAD.

The study is a randomized, placebo-controlled, double blind multicenter study with study center at CCHR. Participating centers are OUH Ullevål, Aalborg University Hospital, Denmark, Akershus University Hospital, Asker and Baerum Hospital and Stavanger University Hospital.

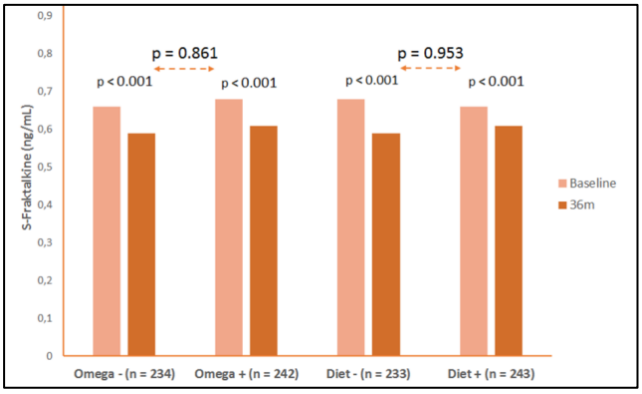


Suggested effects of n-3 PUFA

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

In one substudy including the first 299 patients no association between individual serum fatty acids and estimated myocardial infarct size could be demonstrated. However, a history of hyperlipidemia and the presence of CVD were associated with lower peak TnT levels.
In the same cohort of 299 patients, relations between omega-3 fatty acids and markers of left ventricular remodeling are explored.

The impact of omega-3 fatty acids and Mediterranean diet on inflammation in an elderly population has also been focused.

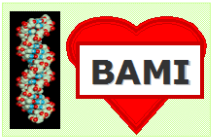


Laake et al. Mediators of Inflammation 2015.

Scientific Activities

PhD projects

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

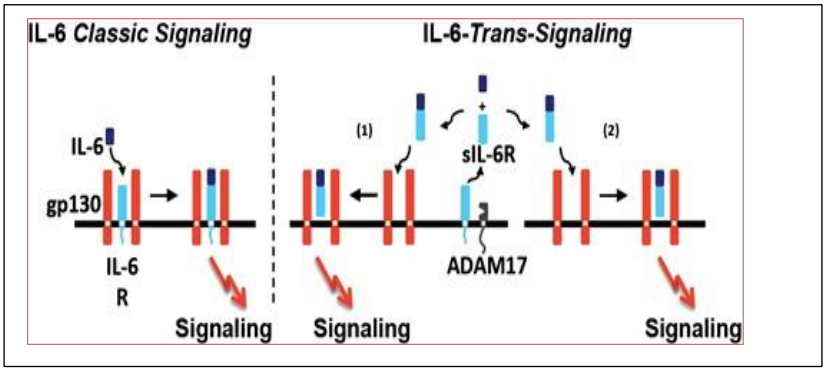


Cand. Med. Vibeke Ritschel

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

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 1000 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 (available during 2015).
In this specific project inflammatory signalling pathways are explored, especially related to 1) the interleukin-6 axis (IL-6, IL-6 Receptor and Gp130). Association studies at inclusion and prospective studies on the predictive role of these markers on clinical endpoints are undertaken.

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.



Scientific Activities

PhD-projects

CADENCE (Markers of Coronary Artery Disease During Exercise Testing)

Cand. Med. Joanna Cwikiel

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

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=500) 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.

In a substudy, patients treated with PCI will repeat the exercise ECG after 4 months in order to explore any difference in their secretion of NT-proBNP and troponin T.

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.

Scientific Activities

PhD-projects

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

Cand. Med. Fredrik Wexels

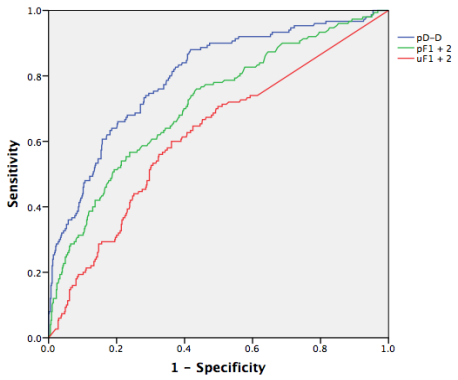
Supervisors: MD PhD Ola Dahl, PhD Are Hugo Pripp, Professor Ingebjørg Seljeflot

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 in collaboaration with and initiated at Vestre Viken HF, Drammen.

Receiver Operator Characteristic curves for plasma D-dimer, F1 + 2 in plasma and urine in the diagnosis of venous thromboembolism (n=720).



Wexels F et al. Blood Coag Fibrinolysis 2015; 26

Scientific Activities

PhD-projects

LEAF (Safety and efficacy of Levosimendan in patients with Acute myocardial infarction complicated with symptomatic left ventricular Failure).
Initiated at CCU, Dept of Cardiology, OUH

Cand. Med.Trygve Huseby

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

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 have been undertaken at CCHR, and results presented during 2015. The main study is close to be finalized.

PhD-projects

Inflammation and ischemia/reperfusion injury in STEMI patients treated by PCI and ischemic postconditioning

Cand. Med. Christian Shetelig

Supervisors: MD PhD Geir Ø. Andersen, MD PhD Jan Eritsland, professor Ingebjørg Seljeflot
From the POSTEMI study (vide infra) , the purpose of the present investigation is to identify novel inflammatory pathways involved in acute MI, reperfusion injury and cardiac remodelling. The main objectives are to specifically explore 3 potential chemokines/growth factors, which, based on previous research may be involved in both reperfusion damage but also potential salvage of the vulnerable reperfused myocardium.
The study is also a cross-modality imaging study, which may enable us to explore and compare the use of CMR and novel echocardiographic methods to assess myocardial function during the development of an acute MI.
Study on osteoprotegerin (OPG), a member of the TNF receptor superfamily acting as a soluble decoy receptor of the receptor activator of NFkappa B ligand (RANKL), is the first factor to be explored.

Scientific Activities

PhD-projects

Cardiac and prothrombotic markers in Atrial Fibrillation

Initiated at Vestre Viken HF, Askler & Bærum Hospital

Project for the PhD degree: Cand. Med. Anja Wiedswang Horjen

Supervisors MD PhD Arnljot Tveit, Professor Ingebjørg Seljeflot

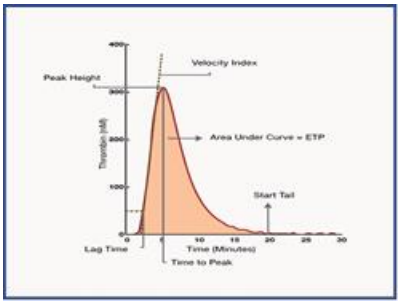
In the **CAPRAF** (Candesartan in the Prevention of Relapsing Atrial Fibrillation) trial and the **RATAF-**study *(vide supra*) on patients with atrial fibrillation, the importance of cardiac biomarkers (troponins) is explored, as related to AF per se, but also to electrical cardioversion, exercise ECG and use of anti-hypertensive medications, like angiotensin receptor blockers, Calcium channel blockers and beta-blockers. In addition, procoagulant activity, assessed by *in vivo* and *ex vivo* thrombin generation *(vide infra*), in AF patients, related to cardioversion is investigated.

Scientific Activities; Other

Based on the EXCADI biobank: Study on pro-thrombotic activity

MSc Vibeke Bratseth

Patients with combined type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) represent a high risk population regarding athero-thrombotic events.
In this sub-study the effects of 12-months exercise training on markers of coagulation, in patients with combined T2DM and CAD are explored. The hypothesis is that exercise has a beneficial effect on the hypercoagulable state in these patients.
The Calibrated Automated Thrombogram (CAT- assay) for *ex vivo* thrombin generation, in addition to *in vivo* thrombin generation measurements (prothrombin fragment 1+2 and D-dimer) and TFPI are undertaken.



Calibrated Automated Thrombogram (CAT- assay)

A significant association between poor glycaemic control and levels of TFPI was demonstrated, potentially due to endothelial activation.

We could, however, not demonstrate any effects of exercise training on markers of pro-coagulant activity in our population. Both groups experienced increased coagulation potential after 12 months, which might be discussed along with progression of diseases.

Scientific Activities; Other

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

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, Professor Ingebjørg Seljeflot)

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 2015 about 1800 patients have been included and a PhD project on selected biomarkers are underway (vide supra).
Further projects are planned, including genetic studies. All logistics for processing of blood samples in the acute phase and the biochemical translational research are undertaken by CCHR.

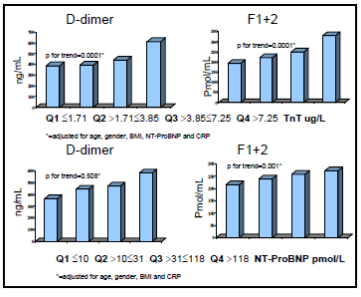
Based on the BAMI Cohort: Study on pro-thrombotic activity

Study nurse Charlotte Holst Hansen

Pro-coagulant activity has been studied for its influence on infarct size and development of heart failure.
The Calibrated Automated Thrombogram (CAT- assay) was used for *ex vivo* thrombin generation, in addition to *in vivo* thrombin generation measurements
(prothrombin fragment 1+2 and D-dimer) and TFPI. 990 patients were included. Patients on anticoagulant treatment were excluded,

Highlights

- Procoagulant activity is associated with myocardial necrosis in STEMI patients
- STEMI patients with reduced myocardial function present with a hypercoagulable state
- BMI correlated inversely with both D-dimer and F1+2 in the acute phase of STEMI



Hansen CH et al. Thrombosis Journal 2015; 13

Scientific Activities; Other

Thrombus Aspiration in acute ST-elevation myocardial Infarction (TASTI)

Cand. Med. Jostein Nordeng

Based on results from the "Coronary thrombus genes in acute myocardial infarction", in this study we aim to further explore the cell types and content, in addition to the genetic profile in the aspirated coronary thrombus. Both cellular and non cellular content of the thrombus will be examined with morphological and immunhistochemical methods and related to time from onset of symptoms to PCI, as well as to the degree of myocardial necrosis. Furthermore, mRNA expression of selected signal molecules will be performed. In addition, peripheral venous blood samples will be analysed for signalling molecules and corresponding mRNA expression in circulating leukocytes.

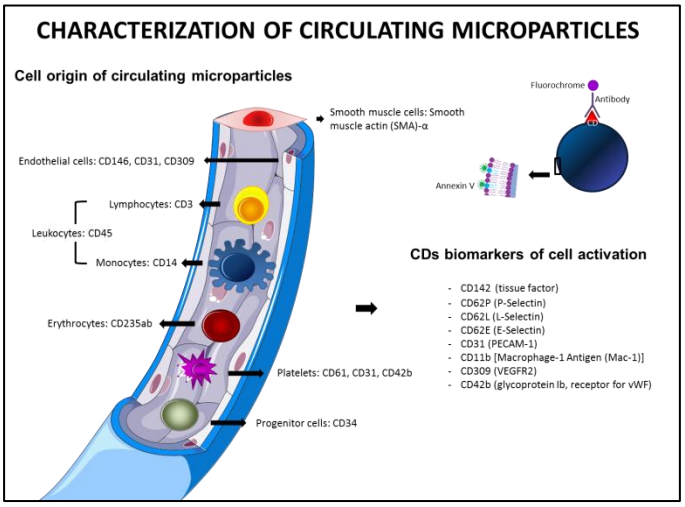
Scientific Activities

Post.doc-projects

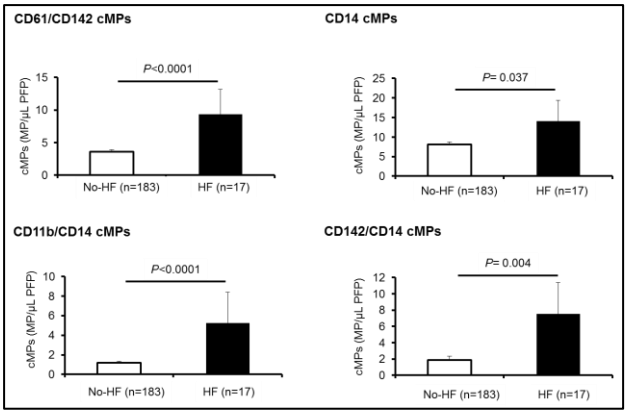
Quantification of circulating microparticles in patients with cardiovascular disease

Post doc Gemma Chiva Blanch, Cardiovascular Research Center (CSIC-ICCC), Hospital de la Santa Creu i Sant Pau, Barcelona

Cell membrane microparticles (MPs) are phospholipid blebs of 0.2–1.0 µm in size shed from the plasma membrane of eukaryotic cells when injured, activated, or undergoing apoptosis. MPs are shed from several cell types, including platelets, endothelial cells, erythrocytes and leukocytes, and have been shown to reflect cellular activation and/or tissue degeneration occurring in vivo.
Increased MP levels have been strongly associated with cardiovascular disease states, and MPs are suggested to be of relevance in clinical applications, including their potential both as biomarkers of disease for improving cardiovascular risk prediction and as novel therapeutic targets.



From the OMEMI study, MPs have been investigated with regard to their relation to myocardial injury, heart failure as well as the circulating levels of omega-3 fatty acids.



Scientific Activities

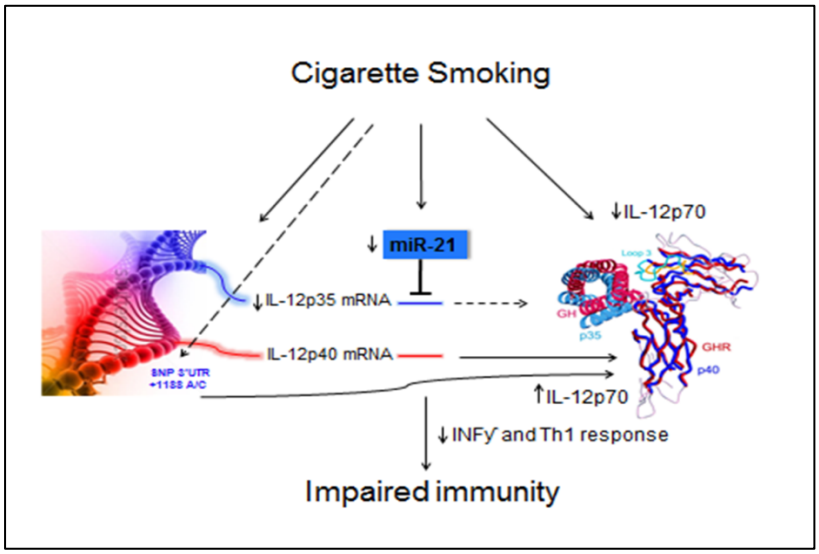
Post.doc-projects

Genetic regulation of Interleukin-12 in patients with CAD

MSc PhD Trine B. Opstad

The pro-inflammatory properties of IL-18 which has been claimed to be changed with hyperglycemia, might act in synergy with IL-12, and this has been investigated by measuring circulating levels of IL-12 additionally to IL-18 in relation hyperglycemia and clinical events in patients with stable coronary artery disease.
Hyperglycemia seemed not to influence the synergy between IL-18 and IL-12, however, their interaction associated with worse clinical outcome.
We could also show that circulating levels of IL-12 were markedly lower in smokers.

In the following project, we are further exploring the regulatory mechanisms of IL-12 in patients with CAD , by measuring genetic expression of the heterodimer IL-12s two subunits; IL-12p35 and IL-12p40, and further IFNy, as well as circulating levels of micro-RNA (miR)-21, as IL-12p35mRNA is one of miR-21s main targets. Additionally, a genetic polymorphism in the IL-12p40 gene (3'UTR 1188 A/C), previously shown to modify circulating IL-12 levels, is investigated. An increase in the expression of miR-21 in smokers could potentially be an explanation for the 50% lower IL-12 levels observed in smokers.
The hypothesis could, however, not be confirmed, as smoking associated with reduced miR-21 expression and attenuated the IL-12 pro-inflammatory axis, by down-regulation of the IL-12p35 and INFy genes. The IL-12p40 genetic variant seems also to have different clinical impact in smokers versus non-smokers.



Scientific Activities

Post.doc-projects

Glycoprotein 130 (Gp130) – interleukin-6 signalling pathway

Thomas Weiss MD PhD, Ass.professor

GP130 is a transmembrane signaling protein, a part of the interleukin-6 signalling pathway, with important regulatory functions in several inflammatory reactions.
The circulating protein sGP130 has been claimed to be protective in this setting. The influence of intervention with a Mediterranean like diet and/or omega-3 fatty acids on the actors in the transsignalling system were studied in a Norwegian population of 560 men with high risk for coronary heart disease.
Our data point out that there was no effect of either the diet or n-3 PUFA supplementation on the IL-6 trans-signalling system in elderly men.

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

MD PhD Eva Cecilie Knudsen

MD PhD Eva Cecilie Knudsen who defended her thesis on this project 2011 are continuing 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.

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

MD PhD Alf-Åge Pettersen / Ellen Warlo, Medical Student Research program
Professor IngebjørgSeljeflot

This main study which was to investigate the clinical importance of non-responsiveness to aspirin in 1000 CAD-patients, 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 mechanisms behind, are ongoing. Special focus has been related to the impact of von Willebrand factor and ADAMTS-13 on the responsiveness to aspirin. Possible influence of relevant genetic differences in this regard is further explored.

Scientific Activities

Post.doc-projects

NORDISTEMI (NORwegian DIstance ST-Elevation Myocardial Infarction Study).

MD PhD Professor Sigrun Halvorsen

Professor Ingebjørg Seljeflot, professor em. Harald Arnesen, post doc Trine B. Opstad

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, were 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 PhD thesis defended (Ellen Bøhmer, MD).
Additional studies, based on an established biobank, on mechanisms related to metalloproteinases, their inhibitors and inducers are ongoing, with special emphasis on infarct injury and the development of heart failure.

Other projects

with supervision and/or support from CCHR

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

Project for the PhD degree: Cand. Med. Limalanathan Shanmuganath
Supervisors: MD PhD Jan Eritsland, MD PhD Post.doc Geir Ø. Andersen

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, with main focus on inflammation.

NORCAST (Norwegian Cardiac Arrest Survival Trial)

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*.

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 have been 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.

Diabetes in children and atherosclerosis development

Post.doc project (MD PhD Hanna Dis Margeirsdottir
Supervisor: Professor Knut Dahl-Jørgensen

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.

DIALONG (Diabetes type-1: long-term survivors with a new syndrome of late complications?)

PhD project (Cand. Med. Kristine Holte)

Supervisor: Professor Tore Julsrud Berg, Professor Kristian Hanssen, MD PhD Svein Solheim

With the hypothesis that in patients with diabetes type-1 there exists a diabetic late complication syndrome consisting of cheiropathy and fatigue, in addition to the traditional micro-and microvascular complications. Markers of glycaemic burden, HbA1c and AGE's, as well as markers of inflammation and endothelial dysfunction are associated with this syndrome. The main aims are to study 150 patients with a duration of diabetes type-1 for 40 years in comparison with age-matched controls without any signs of related disease - for the presence of cheiropathy, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors. All subjects are also investigated for their prevalence of coronary artery disease (by CT coronary angiography).
The inclusion of subjects started in 2014 and is assumed to continue until primo 2016. All blood sampling/biobanking and analyses of biomarkers for inflammation and endothelial activation are performed at CCHR.

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

Cand. Med. Paul Vanberg

Supervisor: Professor Dan Atar

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 used 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 flow cytometry and aggregation) are

studied. The project is initiated from OUH Aker with all biochemical investigations being performed at CCHR.

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

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

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 period 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.

Lifestyle intervention: Effects on cardiovascular disease risk factors in high risk individuals.

PhD project (Cand. Med. Eli Heggen)

Supervisor: Serena Tonstad MD PhD

In young adults with a familiy history of premature coronary heart disease, the risk for developing atherosclerosis and coronary artery disease is high. In this project the effect of lifestyle intervention (diet and smoking cessetion) is investigated, especially with regard to so-called novel biomarkers, i.e. biomarkers of inflammation, endothelial activation and haemostasis. About 150 individuals are randomized to the intervention or not for 6 months. The laboratory analyses are performed at CCHR.

Microbial translocation as related to endothelial dysfunction, HIV, Hypertension, Diabetes and Obesity

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

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

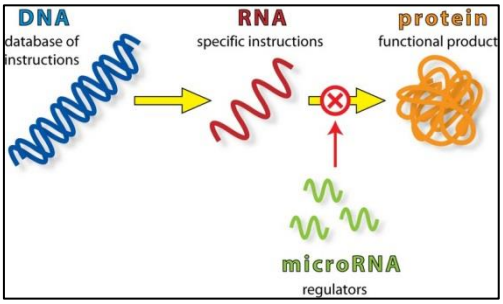
In chronic HIV-infected individuals the gastrointestinal mucosal barrier is distorted. Markers of microbial translocation have been shown to be independent predictors of future hypertension in HIV-infected patients. We hypothesize that markers of microbial translocation would be associated with asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction, and its structural isomer, symmetric dimethylarginine (SDMA) in HIV patients, treated and non-treated. We further want to explore the impact of microbial translocation in HIV-infectred patients with and without diabetes and also in obese people undergoing weight reduction and additional gastric bypass surgery.

Further ongoing studies on the microbial translocation topic are under planning.

Laboratory Methods

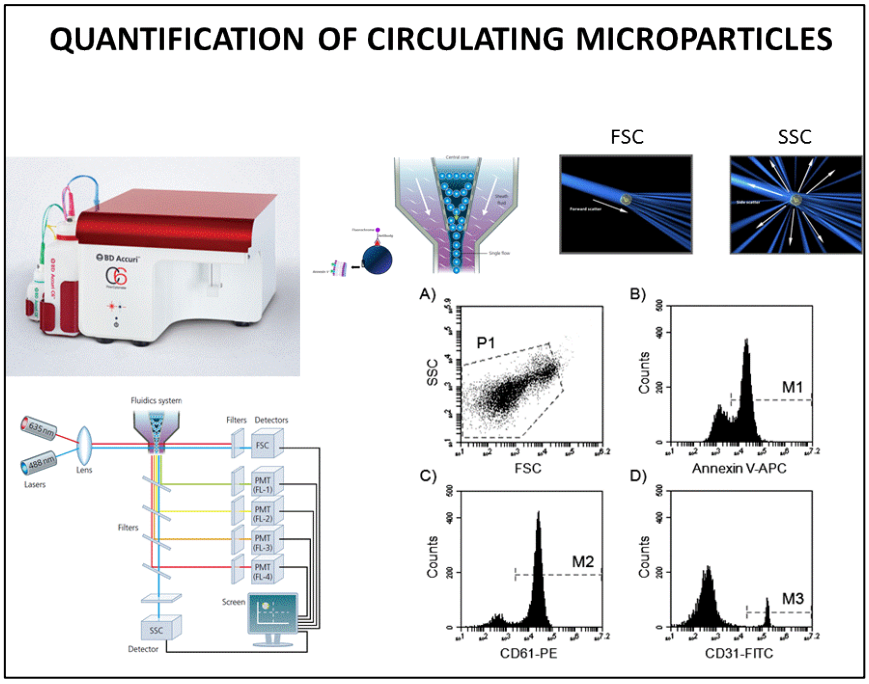
has been further developed, according to recent knowledge and available equipments.

- Method for micro RNA, used as a tool for gene regulation of proteins as well as use as biomarkers



- Arrays for gene regulation
- Use of Luminex for protein measures
- Use of Proseek, the OLINK platform (Uppsala)

- Flow cytometry



Methods, equipments

- Facilities for blood sampling and processing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and –80°C))
- Platelet function testing (aggregometry and ”bedside” screening tests (PFA100, VerifyNow)
- Flowcytomtry (BD Accuri C6)
- ELISA’s
- Fluoroscan
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied Biosystems)
- HPLC (Located at Institute for Experimental Medical Research, OUH Ullevål)

Cell-culture studies and Luminex analyses

- In collaboration with Department of Medical Biochemistry, R&D Unit OUS Ullevål

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  Uppsala University Hospital, Uppsala, Sweden

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Articles

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Abstracts

1. Santos-Gallego CG, Picatoste B, Njerve IU, Vahl TP, Ishikawa K, Hajjar RJ, Fuster V, Badimon J.The Sphingosine-1-Phosphate Receptor Agonist Fingolimod Reduces Ischemia-Reperfusion Injury by Decreasing Cardiomyocyte Apoptosis Mediated by activation of the RISK pathway. ACC San Diego 2014, Abstract
2. Santos-Gallego CG, Picatoste B, Njerve IU, Vahl TP, Ishikawa K, Hajjar RJ, Fuster V, Badimon J. The Sphingosine 1-Phosphate Receptor Agonist Fingolimod Reduces Myocardial Ischemia-Reperfusion Injury mediated by Activation of Autophagy: an in vitro and in vivo study. ACC San Diego 2014, Abstract
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