Curriculum Vitea – Urban Alehagen

Name: Urban Alehagen

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Working address: Inst of Medicine and Health Sciences, University of Linköping, Sweden

Education: Exam as Dentist, University of Umeå 1975

Medical exam, University of Umeå 1983

Medical education:

Specialist in General Internal Medicine 1992

Specialist in Cardiology 1995

PhD in Cardiology 2003

Title of dissertation: " Heart Failure in Primary Care, Special emphasis on Natriuretic Peptides in the Elderly"

Associated Professor in Cardiology 2009

Professor in Cardiology 2016

Description of research:

F**our main areas**;

1. Implications of new biomarkers in the handling of patients with cardiovascular disease
2. Further research on the mechanisms of intervention with selenium and coenzyme Q10 combined
3. Consequences of specific genetic polymorphisms on cardiovascular risk
4. Basal mechanisms and differences between three different types of heart failure

Ad 1: Biomarkers

Survey of the field

The use of biomarkers both in the diagnosis and the handling of patients with heart failure have increased during the last 10 years. Today, the biomarker regarded as Golden Standard in handling of heart failure patients, NT-proBNP was developed by Roche Diagnostics, Mannheim based on blood samples from patients drawn by our research group. However, it has been shown that different biomarkers could give different prognostic information, e.g. copeptin in comparison with NT-proBNP, as shown by our group (Alehagen U, Dahlstrom U, Rehfeld JF, Goetze JP. Association of copeptin and N-terminal proBNP concentrations with risk of cardiovascular death in older patients with symptoms of heart failure. *JAMA.* May 25 2011;305(20):2088-

2095, Alehagen U, Dahlstrom U, Rehfeld JF, Goetze JP. Prognostic assessment of elderly patients with symptoms of heart failure by combining high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide measurements. *Clin Chem.* Nov 2010;56(11):1718-1724.)

In the effort to find different combinations of biomarkers, different biomarkers have been evaluated in comparison with NT-proBNP (Alehagen U, Dahlstrom U, Rehfeld JF, Goetze JP. Pro-A-type natriuretic peptide, proadrenomedullin, and N-terminal pro-B-type natriuretic peptide used in a multimarker strategy in primary health care in risk assessment of patients with symptoms of heart failure. *J Card Fail.* Jan 2013;19(1):31-39).

Recently, more interest have been focused on biomarkers with extra-cardial origin as copeptin, MR-proADM demonstrated above, but also chromogranin A and these new biomarkers have given an increasing research interest (Making sense of chromogranin A in heart disease. Goetze JP, Alehagen U, Flyvberg A, Rehfeld JF.The Lancet Diabetes & Endocrinology Vol 1 No.1 pp7-8). The focus of the coming research is therefore to evaluate new biomarkers in order to find a possible combination of three to four biomarkers to be evaluated in one "assay", and to be used both in the emergency room, but also by the primary health physician.

Main scientific achievements

The most interesting achievements in this area are the demonstration by our group of an extra-cardial biomarker, copeptin, as a useful prognostic biomarker in patients with heart failure resulting in a publication in JAMA.

Current and future research

The focus of the current and future research is to evaluate new biomarkers for the identification of, and response to treatment of heart failure. We also have an intention to try to identify three or four candidates biomarkers to be used in the process, and both at the ER, as well as by the primary health care physician.

Significance

By the research collaboration both with BRAHMS AG, Berlin and the Rigshosptialet, Copenhagen, and University Hospital of Århus, Denmark, we have been able to apply biomarkers early in the development of new assays, as copeptin (BRAHMS), but also recently chromogranin A (Rigshospitalet).

Research environment and collaboration

Professor Jens Peter Götze, Professor Jens F Rehfeld
Department of Clinical Biochemistry, Rigshospitalet, Denmark
BRAHMS- Themo Fisher, Hennigsdorf, Germany
Professor Allan Flyvberg, University Hospital of Århus, Denmark

Independent line of research

My own research line in the above is the presence of a unique population database that has been followed since 1995-96. What we also have done is that we have applied new biomarkers directly from those who have developed the biomarker assays – often after discussions with our group here in Linköping, into the database, and thus obtained new information.

Clinical applications

The main clinical application of our biomarker assays are the spread of NT-proBNP, originally from our population, from our blood samples, into an industrial standard used all over the world, through our work at the Lab of Experimental Surgery at the Rikshospitalet, Oslo, Norway.

Ad 2: Selenium and coenzyme Q10

Survey of the field

All living cells need both selenium and coenzyme Q10 in the production of energy, but also as antioxidants. In order to reduce ubiquinon to ubiquinol, the cell needs presence of selenium. There is well-documented lack selenium in the Northern Europe. This is even more pronounced in persons with heart failure. For the first time our group have performed an intervention trial using selenium and coenzyme Q10 combined for 4 years in an elderly population living in a rural community(Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. Alehagen U, Johansson P, Björnstedt M, Rosén A, Dahlström U. Int J Cardiol. 2013 Sep 1;167(5):1860-6). It could be shown that in the intervention group a significant reduction of cardiovascular mortality, a better cardiac function and a lower plasma concentration of NT-proBNP could be found. The further research of these results is to explore the mechanisms behind these extraordinary results. We are now evaluating quality-of-life measurements of the same population, as well as specific blood sample analyses of other biomarkers of cardiac stress, and also of inflammation/atherosclerosis. Also we have started an evaluation using metabolomics methodology where GC-MS analyses are applied into a database where other clinical variables are loaded. From this a discriminant analysis method is applied giving a possibility to identify both specific metabolic effects of the intervention, but also the size the effect. From a pilot study we have been able to identify 95 different metabolites, and seen at least 27 different effects by the intervention. We are now extending the analyses to be applied into the complete group, and to for the first time has the possibility to apply specific metabolic effects on a population where we have all information regarding mortality during a follow-up period of more than five years.

Main scientific achievements

In this area, the project represents the first population intervention trial using selenium and coenzyme Q10 combined in the world. The results are therefore unique, and have been discussed both in the research community as well as in BBC, and other media like Times of India.

Current research and future directions

The intervention trial has demonstrated surprising results in terms of reduced cardiovascular mortality, increased cardiac function and less production of the biomarker NT-proBNP. We are now trying to evaluate the mechanisms behind these results by analyzing some of the more than 54000 blood samples from the trial. Beside specific analyses of inflammation, cardiac stress that we perform in Linköping, we are also applying metabolomics methodology by use of GC-MS analyses and apply these results into a multivariate discriminant analysis system. Through this we will be able to identify metabolites that are affected by the intervention of selenium and coenzyme Q10. This methodology performed by our cooperation partner has been evaluated by EU and they have therefore received EU grants for the methodology. We are also validating some of the results by analyses performed by Imperial College of London. The future research will therefore be focused on to see different important metabolic profiles in those given selenium and Q10. There is also a planning phase for a new European multicenter trial that we have initiated.

Significance

The presented intervention trial using selenium and coenzyme Q10 combined based on new knowledge is the first in the literature. Even if we are the first group to

present these data we now have to focus on a mechanistic explanation. This will also be a unique presentation as we have a population where we both have blood samples from each consecutive 6th month but also mortality data from all individuals.

Research environment and collaboration

Professor Anders Rosén, IKE, University of Linköping
Professor Mikael Björnstedt.Dept of Pathology, Karolinska Institutet
Professor Peter Johansson,Dept of Cardiology, University of LinköpingProfessor Torbjörn Lundstedt, Acureomics AB, Umeå

Independent line of research

I have personally been responsible for the intervention project from the design phase, and have personally initiated all contacts with the present collaboration partners. I am also the main force in the planning a new European multicenter study.

Clinical application/relevance

For the first time we have been able to show effects of intervention with substances that both have effects within the mitochondrium, but also on more general effects in the body, like oxidative stress. The presented study is relatively small and therefore needs to be repeated before a more general application could be recommended. However, the obtained results are so far very promising.

Ad 3: Genetic polymorphism and cardiovascular risk

Survey of the field

Cardiovascular diseases are one of the major causes of death worldwide. Therefore, it is important to identify risk patients early in order to optimize treatment and reduce costs. However, little is known about the relation between genetic polymorphisms and cardiovascular risk. Studies have shown a genetic association between single nucleotide polymorphisms (SNP) and cardiovascular diseases. Special interest has recently been focused on the low density lipoprotein receptor-related protein 1 (LRP1), adiponectin and platelet derived growth factor D (PDGF-D). In particular, the SNP, rs1799986, in LRP1 is associated with increased rates of premature cardiovascular disease in familial hypercholesterolemia. The adipocytokine adiponectin has also been suggested to be a risk factor for cardiovascular disease. Therefore, we have evaluated if the above genetic markers could be used to identify patients at risk using long-term mortality data and evaluating the impact of gender difference (Manuscript submitted). From the evaluations we could demonstrate more than 6 fold increased risk of cardiovascular mortality in one the three genotypes of adiponectin. Also, we could demonstrate specific gender differences. This has stimulated us to further evaluate if other candidate genes could give important prognostic information.

Main scientific achievements For the first time we could apply long-time population data on evaluations of some candidate genes and present significant differences in risk, and also gender differences.

Current research and future directions

The presented project has for the first time been able to demonstrate highly significant differences in cardiovascular risk profiles for different genotypes of three candidate genes. We are now extending this research into three new candidate genes. Further, recent research has also shown that chemokine CXC ligand 12 has a correlation to ischemic heart disease. We are now planning to evaluate CXCL12 in an elderly population in order to see possible gender differences, but also as an instrument to risk stratify patients with ischemic heart disease.

Significance

In the process of identifying patients at risk for cardiovascular mortality we have for the first time applied genetic markers into an elderly population, and have been able to shown significant differences between different genotypes of the evaluated candidate genes. Also, specific and significant gender differences have been demonstrated.

Research environment and collaboration

Professor Dick Wågsäter, IMH, University of Linköping

Independent line of research

My own part of this project has been to initiate the different collaborations, and to apply the obtained genotype results into our population, perform the statistics and to produce the main draft of the now submitted manuscript. My own part in the future research will be the same as until now.

Clinical application/relevance

The expected importance of this project is a clinical result based on collaboration between preclinical and clinical researchers that could give an instrument to the clinician in the daily routine handling patients with potential cardiovascular risk.

Ad 4: Basal mechanisms behind the development of heart failure. Description of three types of heart failure

Survey of the field

Heart failure is a common and disabling condition, that has a serious prognosis and is increasing, and the expenses because of it are estimated to be 2% of total health care expenditure. The systolic heart failure is the type most investigated, although the underlying mechanisms are not sufficiently explored. This could also be applied for the diastolic heart failure where a preserved systolic function could be found. The third type of heart failure to be explored is the dilated cardiomyopathy. Even if the specific type of heart failure is diagnosed, the underlying mechanisms are often unclear. It has been shown earlier that as part of the heart failure syndrome, there is an activation of immunological mechanisms, and also activation of different biomarkers as part of the syndrome. It has also been shown the oxidative stress is increased in patients with heart failure, even if the potential differences between the three different conditions are not evaluated. Also, the effects of these mechanisms on impaired cardiac function are also unclear. The project therfore has a design to evaluate both effects on the major vessels in the body, the effects on blood flow as evaluated by MR, and tissue Doppler of the heart, but also through cytological evaluations, and evaluation of biomarkers.

Main scientific achievement

This project is a new project where we are in the inclusion of patients. The first results will be presented from the MR evaluations shortly.

Current research

This project is in the phase where inclusion of patients is ongoing. This inclusion will be completed during 2014, and then all planned analyses will be started for the 75 patients with ischemic heart failure, 75 patients with dilated cardiomyopathy, 75 patients with isolated diastolic heart failure, and 75 healthy controls.

Research environment and collaboration

Professor Lena Jonasson, IMH, University of Linköping
Professor, Jan Engvall, IMH, University of Linköping
Ass professor Carl Johan Carlhäll, IMH, University of Linköping
Professor Tomas Lindahl, IKE, University of Linköping

Independent line of research

My personal role in this project is the inclusion of each of the patients, and all clinical contacts with the patients, to coordinate the different subprojects (MR-examination, Doppler echocardiography, cytological evaluations, ultrasound examinations of the great vessels). My own research line in this project is to evaluate three different new biomarkers against the golden standard in heart failure handling – NT-proBNP. These biomarkers will be analysed in Linköping.

Clinical applications/relevance

As this project is an attempt to investigate the potential differences between different types of heart failure, the research results could extend our knowledge on the pathophysiological development of the different types of heart failure. This could give important knowledge that potentially could influence the handling of patients with specific types of heart failure. As this knowledge is presently not known, we could not state the implications of the coming results of the project.