Danish Cardiovascular Academy

ABSTRACTS

DCACADEMY SUMMER MEETING 2025

22-24 June 2025
Storebælt Sinatur Hotel & Konference
Nyborg

DCAcademy is supported by
novo nordisk fonden
Hjerte foreningen

TABLE OF CONTENTS

Poster session

P1: Vascular - clinical & preclinical
Chairs: Joanna Kalucka & Lasse Steffensen
P1_1 Andrietta Grentzmann
P1_2 Anton Mariager
P1_3 Beijia Zhang
P1_4 Helen Hemmling
P1_5 Michelle Due Nilsson
P1_6 Stephanie Pham
P1_7 Stine Lindegaard
P1_8 Tarannum Ara

P2: Cardiac – clinical
Chairs: Rikke Buhl & Dominik Linz
P2_1 Anne Bjerg Nielsen
P2_2 Emil Anton Frandsen
P2_3 Emilie Kongebro
P2_4 Jakob Solgaard
P2_5 Jasmin Dam
P2_6 Kristine Avetisyan
P2_7 Leonardo Graever
P2_8 Lucas Westergaard
P2_9 Rasmus Lindhardt
P2_10 Signe Hasler
P2_11 Sophie Sander

P3: Cardiac – preclinical
Chairs: Michael Davies & Anke Fender
P3_1 Alisha Niskala
P3_2 Benedikt Kuhs
P3_3 Charles Ye
P3_4 Claudia Cozzolino
P3_5 Jacob Hald
P3_6 Jiaqi Xu
P3_7 Johannes Jedrzejczyk
P3_8 Johs Dannesboe
P3_9 Josephine Kanta
P3_10 Marlene Bentestuen

P4: Data Science + Cardiac – preclinical
Chairs: Sarah Nissen & Johannes Castelein
P4_1 Katrine Rasmussen
P4_2 Kezia Jerltorp
P4_3 Malene Nørregaard
P4_4 Malene Wind
P4_5 María José Romero Lado
P4_6 Mélodie Schneider
P4_7 Milad Hasani
P4_8 Natalia Łopuszyńska
P4_9 Vignesh Gnanaskandan
P4_10 Zhongyan Zhou

P5: Epidemiology
Chairs: Britt Borregaard & Helena Dominguez
P5_1 Dar Nerst
P5_2 Filip Gnesin
P5_3 Ida Taraldsen
P5_4 Karen Hvid
P5_5 Laís Santos
P5_6 Malene Højgaard
P5_7 Mathilde Løk
P5_8 Peter Thomas
P5_9 Tobias Skjelbred
P5_10 Tummas Ternhamar

P6: Early projects presentations
Chairs: Arnela Saljic & Bjørn Larsen
P6_1 Amalie Frederiksen
P6_2 Ara Media
P6_3 Daniel Tchemerinsky Konieczny P6_4 Deepthi Rajan
P6_5 Dung Riis
P6_6 Emily Meyer
P6_7 Katharina Friederichs
P6_8 Kathrine Friis
P6_9 Laura Rytoft
P6_10 Louise Sørensen
P6_11 Nicoline Thorsen
P6_12 Rasmus Haahr
P6_13 Shermaine Tay
P6_14 Sie Fensman
P6_15 Stine Søndergaard
P6_16 Thomas Ehlig-Jensen
P6_17 Trine Obel

Investigating the role of S100A8/A9 proteins as a therapeutic target in atrial fibrillation

Alisha Niskala[1], Charles Ye[1], Johs Dannesboe[1], Joakim Bastrup[1], Florian Bruns[2], Thomas A. Jepps[1], Arnela Saljic[1], Dobromir Dobrev[2,3,4], Thomas Jespersen[1]

[1]Department of Biomedical Science, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [2]Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany; [3]Department of Molecular Physiology & Biophysics, Baylor College of Medicine, Houston, USA; [4]Montréal Heart Institute and University de Montréal, Medicine and Research Center, Montréal, QC, Canada

Background and aim: Enhanced inflammation and cardiac fibrosis are common features of atrial fibrillation (AF). Recent studies have shown that S100A8/A9, calcium-binding proteins, are significantly upregulated in atrial tissue from AF patients. These proteins are released by macrophages and are endogenous ligands to toll like receptor 4 (TLR4), which potentially may downstream activate the NLRP3 inflammasome, a key player in AF pathogenesis. However, ***the specific mechanisms by which S100A8/A9 proteins activate the NLRP3 inflammasome and their involvement in AF-related structural remodeling remains unclear***.

Methods: Fifteen chronic AF patients were selected with age, sex and comorbidity matched sinus rhythm controls were evaluated for S100A8/A9 expression and levels of fibrosis. Isolated human monocyte derived macrophages (hMDM) and atrial fibroblasts were stimulated with *E. coli* lipopolysaccharide (LPS) and Nigericin for inflammasome activation with blocking of inflammasome activation by compound ABR238901. Inflammasome component and product gene expression and secretion were evaluated through qPCR and ELISA.

Results: S100A8/A9 proteins were found to be expressed in both AF and sinus rhythm patients and co-localize with CD45+ CCR2+ macrophages. Atrial fibroblast stimulation for 24 hours significantly increased NLRP3 (p=0.0107), IL-1β (p=0.0118), and IL-6 (p=0.0054) gene expression, with elevated IL-1β secretion (p=0.1517). Similar trends were observed in monocyte derived macrophage stimulation. Upon co-culture of activated macrophage secretome and atrial fibroblasts for 24 hours, NLRP3 (p=0.0020), IL-1β (p=0.0052), and IL-6 (p=0.0035) gene expression increased significantly, alongside increased S100A8/A9 (p=0.1497) and IL-1β (p=0.0010) secretion. This increase was significantly attenuated following blocking of S100A8/A9 – TLR4 interaction with ABR238901. However, IL-18 expression and secretion remained unchanged, suggesting LPS and Nigericin selectively activate NLRP3 specific IL-1β pathways.

Conclusion: Blocking the interaction between S100A8/A9 and TLR4 using ABR238901 reduced gene expression and secretion of the NLRP3 inflammasome components to unstimulated levels. These initial results suggest that S100A8/A9-TLR4 signaling could be a promising therapeutic target for AF related inflammation.

Vascular and Metabolic Effects of Acute Short-Chain Fatty Acid Intake

Amalie S. Frederiksen[1], Amalie London[1], Andreas M. Fritzen[1]

[1]*Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen*

Background: Metabolic impairment has been identified as a contributing factor in the pathophysiology of heart failure. While infusion or ingestion of ketone bodies are shown to increase cardiac function in heart failure patients, recent rodent studies propose that short-chain fatty acids (SCFAs, containing 2-6 carbon atoms) outpace ketone body oxidation in the failing heart. SCFAs are naturally occurring accounting for up to 4% of dairy lipids and are also key metabolic products of microbial fermentation in the large intestine. SCFAs are absorbed directly into the portal vein and undergo extensive first-pass metabolism in the liver, where they are assumed to be primarily oxidized. Metabolic effects differ between the individual fatty acids depending on chain-length despite structural similarity. Ingestion of propionate (C3:0) have been found to increase gluconeogenesis and elevate blood glucose levels, whereas butyrate (C4:0) markedly increases circulating ketone body levels. In animal models and isolated vessels, both propionate and butyrate induced vasorelaxation, while butyrate also increased cardiac contractility. However, it remains unclear whether these vasorelaxant effects of SCFAs translate to humans, and whether they reflect a direct vascular action of SCFAs or are indirectly mediated through SCFA-induced ketogenesis. The aim of this study is to investigate the vascular and metabolic effects of both propionate and butyrate in humans, and to what extent these effects may be mediated through ketone bodies.

Hypothesis: We hypothesize that acute intake of both propionate and butyrate will improve peripheral vascular dilator function, and further we hypothesis that butyrate, but not propionate, will increase circulating ketone body levels.

Method: In a randomized, controlled, crossover study, 10 heathy participants will undergo two test days separated by a two to four week wash-out period. Prior to each test day, a standardized dinner will be consumed by the participants. Following an overnight fast, body weight and composition will be assessed, and a venous catheter will be inserted for repeated blood sampling throughout the test day. Then, the participants will consume 3g of either sodium propionate or sodium butyrate together with water. Blood samples will be collected at multiple time points pre and post ingestion to evaluate metabolic and hormonal responses. Metabolic rate and substrate oxidation will be measured using indirect calorimetry, and vascular function will be assessed via blood pressure monitoring and flow-mediated dilation (FMD) at selected intervals post consumption of the SCFAs.

Perspective: Should propionate and butyrate induce acute vasodilation in humans, this may indicate a cardiovascular effect of these SCFAs. Reduced systemic vascular resistance would lower afterload, potentially easing cardiac workload. Investigating these effects further may provide new insights into how SCFA supplementation could support cardiac function and overall cardiovascular health.

Evidence that myeloid pyruvate dehydrogenase kinase-1 regulates glucose homeostasis and obesity in a sex-dependent manner

Grentzmann A[1], Savvoulidou O[1], Tripodi GL[1], Nilsson MD[1], Møller PM[2,3], Peleli M[1], Stubbe J[1], Steffensen LB[1], Ketelhuth DFJ[1]

[1]Cardiovascular and Renal Research Unit, Department of Molecular Medicine, University of Southern Denmark (SDU), Odense, Denmark

[2]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark

[3]Department of Clinical Research, SDU, Odense, Denmark

Background and aims. Obesity, expected to affect one in eight individuals globally, is tightly linked to chronic low-grade inflammation and insulin resistance. Macrophage polarization toward a pro-inflammatory (M1-like) or anti-inflammatory (M2-like) phenotype has been suggested to play a central role in shaping these immunometabolic disturbances. The pyruvate dehydrogenase kinase/pyruvate dehydrogenase (PDK/PDH) axis—particularly PDK1—has been identified as a master regulator of macrophage metabolic reprogramming and polarization towards the M1-like phenotype. In this project, we investigated whether macrophage-specific deletion of Pdk1 modulates the immunometabolic phenotype in male and female mice with diet-induced obesity.

Methods and results. Eight-week-old male and female mice with a myeloid-specific deletion of Pdk1 (LysM-Pdk1$^{-/-}$) and wild-type littermates (Pdk1$^{+/+}$) were placed on a high-fat diet (HFD; 60% kcal from fat) and monitored weekly for weight gain over a 16-week period. Body composition analysis (Minispec) and glucose tolerance tests (GTT) were performed during the two weeks prior to sacrifice. At the end of the study, mice were sacrificed for blood and organ collection, and tissues were individually weighed and saved for further analysis. Over the 16-week high-fat diet, although overall weight gain was comparable across genotypes and sexes, male LysM-Pdk1$^{-/-}$ mice showed a trend toward higher final body weight compared to Pdk1$^{+/+}$ mice ($p = 0.088$). No differences in plasma cholesterol or triglycerides were observed between groups. Analysis of body composition and organ weights revealed no detectable effects of Pdk1 deletion in female mice. However, male LysM-Pdk1$^{-/-}$ mice presented a significantly greater percentage of lean mass ($p = 0.005$) and increased brown adipose tissue weight ($p = 0.046$) compared to Pdk1$^{+/+}$ males. Surprisingly, despite these favorable changes, glucose tolerance was significantly impaired in LysM-Pdk1$^{-/-}$ males relative to controls ($p = 0.036$).

Conclusion. Our study revealed that myeloid-specific deletion of Pdk1 in mice subjected to a HFD results in a sex-specific metabolic phenotype. While female mice seemed unaffected, male LysM-Pdk1$^{-/-}$ mice developed impaired glucose tolerance despite increased lean mass and brown adipose tissue. This unexpected dissociation suggests a critical role for macrophage PDK1 in maintaining metabolic homeostasis in males in the context of obesity. Further studies are needed to clarify tissue-specific mechanisms and sex-dependent roles of macrophage PDK1 in immunometabolic regulation.

Left Atrial Strain and Risk of Heart Failure in the General Population: The Copenhagen City Heart Study

Anne Bjerg Nielsen, MD; Kristoffer Grundtvig Skaarup, MD; Raphael Hauser, MD; Niklas Dyrby Johansen, MD; Mats Christian Højbjerg Lassen, MD; Riccardo M. Inciardi, MD, PhD; Gorm Boje Jensen, MD, DMSc; Peter Schnohr, MD, DMSc; Rasmus Møgelvang, MD, PhD; Tor Biering-Sørensen MD, MSc, PhD, MPH.

Background:

Left atrial (LA) function has shown to be a significant predictor of cardiovascular outcomes. We sought to determine the prognostic value of LA strain in relation to incident heart failure (HF) in the general population.

Methods:

The present study includes 3,540 participants without prevalent atrial fibrillation or HF from the 5th Copenhagen City Heart Study. All participants underwent health examinations and echocardiography, including measures of LA function by means of peak atrial longitudinal strain (PALS), peak atrial contraction strain (PACS), and LA strain during the conduit phase (LACS).

Results:

Median age of the study population was 57 years (interquartile range: 40, 69) and 2,015 (57%) were female. During follow-up (median 5.4 years), 66 (2%) participants were diagnosed with HF. Participants who developed HF had lower PALS (26.4% vs. 36.6%, $p < 0.001$), PACS (15.6% vs. 16.5%, $p = 0.016$), and LACS (11.4% vs. 19.3%, $p < 0.001$) at baseline. Lower values of all three LA strain parameters were associated with a higher risk of developing HF in univariable analysis. After multivariable adjustments for Framingham Risk Score and global longitudinal strain, PALS (HR = 1.06, CI95% [1.03; 1.09], $p < 0.001$, per 1% decrease), PACS (HR = 1.07, CI95% [1.02; 1.12], $p = 0.003$, per 1% decrease), and LACS (HR = 1.05, CI95% [1.01; 1.10], $p = 0.016$, per 1% decrease) remained significantly associated with incident HF. However, in participants with normal-sized LA (LA volume index < 34 ml/m^2) and no ischemic heart disease (n = 3,046), only PALS and PACS remained independently associated with incident HF.

Conclusion:

LA strain provides independent prognostic value regarding the risk of incident HF in the general population.

Prevalence and Cardiac Impact of Patent Ductus Arteriosus in Term-Born Children: Insights from the Copenhagen Baby Heart Study

Anton Friis Mariagera,b,c, MD, Mikkel Malham, MD, PhDc,d, Alberte Hammeken, MDj, Raheel Altaf Raja MD, PhDf, Henning Bundgaard, Prof, MDa,i Kasper Iversen, Prof, MDa,h, Dorthe Lisbeth Jeppesen, Assoc. Prof, MD, PhDa,

Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark , Department of Cardiology, Copenhagen University Hospital – Herlev Hospital, Herlev, Denmark, Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark, Copenhagen Health Complexity Center, Department of Public Health, University of Copenhagen, Co-penhagen, Denmark. Department of Pediatrics and Adolescents, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
Department of Intensive Care Medicine, Copenhagen University Hospital – Rigshospitalet, Copenha-gen, Denmark
Department of Internal Medicine, Copenhagen University Hospital – Herlev Hospital, Herlev, Denmark. The Capital Region's Unit of Inherited Cardiac Diseases, Copenhagen University Hospital – Rigshospita-let, Copenhagen, Denmark, Department of Cardiology, Copenhagen University Hospital, Amager and Hvidovre Hospital

Background
Patent ductus arteriosus (PDA) is a common congenital heart defect most associated with premature birth. In term-born children, PDA can be asymptomatic and silent in stereoscopy, leaving uncertainty on its prevalence and impact on the developing heart. We used data from a large population-based cohort to estimate the prevalence of PDA in term-born children. Additionally, we investigate if the silent PDA influences cardiac morphology in term-born children and if we can find potential associated maternal and neonatal risk factors.

Method
This study analyzed echocardiography data from full-term neonates collected as part of the Copenhagen Baby Heart Study, a population-based cohort of over 25,000 participants. A review of the echocardiographic data identified 534 cases of open ductus arteriosus (DA). After a year, we subsequently contacted the parents, offering follow-up examinations. We used binomial logistic regression to assess associations between perinatal and neonatal factors and the presence of PDA. We matched a control group to compare echocardiographic parameters between neonates with and without PDA.

Results
Among the 534 cases of open DA in term-born infants, 383 (72%) participated in a follow-up examination. Of these, 27 infants (7%) had a PDA, representing approximately 0.1% of the total cohort or 1 in 750. Four cases required device occlusion. Compared to a matched control, a PDA was associated with increased left atrial volume (P=0.02), pulmonary artery diameter (P=<0.01), and left ventricular diameter (P=<0.01). Female sex and late gestational age were associated with an increased risk of PDA.

Conclusion

In a large Danish birth cohort, we estimated the prevalence of PDA in term-born neonates to be 0.2%. We found that silent PDA was generally associated with echocardiographic characteristics for increased left heart strain compared to a matched control. We identified female sex and late gestational age as risk factors.

(Poster) Physiological and Psychological Effects of Surgical Correction of Pectus Excavatum

AUTHORS

Ara Shwan Media, M.D., PhD-student [1,2]

Frank Vincenzo de Paoli, M.D., PhD, Ass. Prof. [1,2]

[1] Dept. of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark
[2] Dept. of Biomedicine, Aarhus University, Aarhus, Denmark

This project hypothesizes that surgical correction of pectus excavatum (PE) improves cardiorespiratory fitness, health related quality of life, and self-image. The PhD project consists of three randomized trials (RCT) to assess immediate and long-term effects of surgical correction on CRF and psychology.

Background PE is the most common chest wall deformity, affecting approx.1 in 400-500 individuals. Patients often experience reduced exercise tolerance and poor self-image compared to healthy individuals. The minimally invasive repair of PE (MIRPE) is the gold-standard surgical treatment and is typically performed on children and adolescents with considerable perioperative complication (10-20 %). The benefits and risks of MIRPE have yet to be evaluated by a RCT.

Aim The aims of this PhD are to determine if MIRPE improves CRF (measured by V̇O2max) and psychological outcomes in patients with PE, through high-quality randomized studies.

Methods/Design

Study 1: RCT (n~110 patients) comparing immediate (intervention group) versus delayed MIRPE (control group), measuring V̇O2max and patient-reported outcomes assessing quality of life and self-image. The outcomes will be assessed at two time points: preoperatively and 12 months postoperatively.

Study 2: RCT (n~18 patients) assessing immediate effects of the vacuum bell device on cardiac function evaluated with cardiac MRI.

Study 3: RCT (n~10 patients) examining perioperative cardiac output and dimension changes during MIRPE measured with a Swan-Ganz catheter under dobutamine stress.

Perspectives These studies will address the lack of high-quality evidence on the physiological and psychological benefits of PE surgery, which is crucial given the high surgical complication rates and the ongoing debate in the medical community.

Targeting Obesity-induced Vascular Dysfunction Using Adiponectin Collagenous Domain Glycoform peptides (GlyACD): an *ex vivo* pressure myography study

Beijia Zhang,[1] Yu Wang,[1] Lars Jørn Jensen[2]

[1]The State Key Laboratory of Pharmaceutical Biotechnology and Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China. [2]Department of Veterinary and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, DK-1870 Frederiksberg C, Denmark.

Background: Obesity is associated with hypertension and accelerated vascular ageing, which increase the risk of heart failure, renal failure, stroke and neurodegenerative diseases. The high-molecular weight form of the human polypeptide hormone adiponectin (hAdn) secreted from adipose tissue has insulin-sensitizing and anti-inflammatory actions, along with anticontractile effects and endothelium-dependent dilation in the vasculature. Recently, a chemically synthesized short form of the collagenous domain of hAdn (ACD) was shown to retain biological effects of native hAdn, but only when glycosylated (GlyACD). Resistance arteries (< 300 μm) are crucial determinants of blood pressure and organ blood flow. The present study investigated if the chemically synthesized GlyACD can normalize local microvascular control mechanisms altered by a diet rich in fat and fructose, which has previously been shown to induce obesity with hypertension and vascular dysfunction in rats.

Methods: Diameter changes (inner/outer) were measured by pressure myography using 2nd-3rd order mesenteric arteries from young female C57BL/6 mice (11-20 weeks old) fed either a standard diet (SD) or a high-fat, high-fructose diet (HF-HFrD) for 10 weeks. Smooth muscle vs. endothelial function and structural remodeling were evaluated by measuring phenylephrine (PE)-induced constriction, myogenic tone (MT), acetylcholine (ACh)-induced vasodilation, flow-mediated vasodilation (FMVD), passive lumen diameter (PLD), wall/lumen-ratio (W/L), cross-sectional area (CSA), and vessel stiffness. We tested the effects of intraluminal perfusion vs. abluminal exposure to 2 μg/mL GlyACD, non-glycosylated ACD (WM; 2 μg/mL), or vehicle.

Results: In SD mice, intraluminal perfusion with GlyACD resulted in a slight reduction of the constriction at higher concentration of PE, and a highly significant increase in the dilation to ACh (N=7). In HF-HFrD mice (N=4), there was no effect on PE-induced constriction, but a similar enhancing effect was observed for the ACh-induced dilation. In SD mice, MT was reduced by abluminal exposure to WM and to GlyACD (N=5), and FMVD was increased by abluminal GlyACD exposure (N=10). In HF-HFrD mice, there were no significant effects of abluminal peptide exposure in MT or FMVD experiments (N=4). Overall comparison of SD (N=16) and HF-HFrD mice (N=6) showed a significant reduction of MT, inward remodeling (no change in W/L), and increased vessel stiffness in the HF-HFrD mice.

Conclusions: Our data indicates the potential of GlyACD to enhance endothelial function along with an anticontractile effect. So far, none of the experiments indicated potential of GlyACD peptide to prevent vascular dysfunction in obesity/hypertension. Ongoing studies are testing the effects on vascular function of 4-week daily GlyACD dosing in HF-HFrD mice.

Abstract DCAcademy Summer Meeting 2025

Title: A Technical Evaluation- Towards an Automated Proteomic Analysis of FFPE Cardiac Tissue to Enable Mechanistic Insights into Cardiovascular Disease

Benedikt Lukas Kuhs*, Johan Rytved* Jonathan Samuel Achter, Alicia Lundby | Department of Biomedical Sciences

Background

Cardiovascular diseases (CVDs) remain a major global health burden, with complex molecular underpinnings that are not fully understood. Mass spectrometry-based proteomics has emerged as a powerful tool to outline protein profiles of tissues and to uncover protein remodeling involved in disease mechanisms. At hospitals, formalin-fixed, paraffin-embedded (FFPE) cardiac biopsies collected for diagnostic purposes constitute the majority of archived cardiac biospecimens. Our research group has recently demonstrated the feasibility to acquire proteomic profiles of cardiac FFPE-preserved biopsy samples, and the ability to outline cardiac protein remodeling characterizing the disease state from such samples. Building on this foundation, we set to streamline the experimental and analytical approach to pursue proteomic profiling of FFPE biopsies from a cohort of 400 patients spanning multiple cardiac disease states in an automized and standardized fashion.

Objective

Archived FFPE samples are a valuable resource but contain limited tissue amounts. Thus, we aim to optimize our workflow towards a minimal sample input while maintaining deep and comprehensive proteome measurements. Once established, the optimized workflow will be used for the large-scale analysis of FFPE cardiac biopsies collected from 400 heart disease patients using the automated processing of samples and quantitative mass spectrometry.

Methods

Archived FFPE preserved endomyocardial biopsies were processed using a robust sample processing workflow for cardiac FFPE tissue by combining suspension trapping (S-Trap) technology with direct solubilization of FFPE scrolls or dissected tissue in high concentrations of SDS, eliminating the need for prior deparaffinization. For the determination of minimal sample input the workflow is miniaturized. Label- free data independent acquisition with quantitative mass spectrometry was performed, followed by differential protein expression analysis and pathway enrichment to analyze proteins in a disease specific context.

Results

The feasibility of the workflow has been shown by the analysis of FFPE samples from 40 individuals We were able to routinely measure >5000 proteins with low technical variation from the FFPE samples using TIMS-TOF. Next to distinct proteomics phenotypes we showed that FFPE storage times of <10 years had no effect on the proteome depth independent of sex or age of the individuals. Building on this we aim on miniaturizing our workflow towards low FFPE sample input to increase technical precision in low input measurements.

Conclusions

The analysis of a large scale FFPE cohort in an automated fashion opens new avenues for the retrospective analysis of archived tissue collections. The perspective of this project is to build on a solid foundation and combine a robust, miniaturized and standardized FFPE processing workflow with the high throughput of automation to outline the proteome of heart samples from 400 patients to unravel the molecular profile that characterize the cardiac disease state.

Effect of chronic oral SK channel blocker on atrial fibrillation burden in Göttingen Minipigs

Charles Ye[1], Sofia Hammami Bomholtz[2], Lea Abildgaard Jensen[2], Kezia Jerltorp[1], Malene Nørregård Nielsen[1], Lucas Lindberg[1], Olivia Sadolin Jensen[1], Nienke van Rooij[1], Anna Paaske Bühring[1], Bo Hjorth Bentzen[2], Stefan Sattler[1], Jonas Goldin Diness[2], Arnela Saljic[1], Thomas Jespersen[1]

[1]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [2]Acesion Pharma, Copenhagen, Denmark

Aim

This study aims to evaluate the effects of an oral calcium-activated potassium (SK) channel blocker on atrial fibrillation (AF) burden in Göttingen Minipigs, as a translational large-animal model.

Hypothesis

Oral SK channel inhibition reduces AF burden by prolonging atrial refractoriness and suppressing AF duration in a chronic large-animal model of AF.

Background

AF is the most common sustained cardiac arrhythmia, contributing to significant morbidity and healthcare burden. SK channels are small-conductance calcium-activated potassium channels and have an atrial specific function with minimal function in the ventricles. They play a critical role in atrial repolarization and have been implicated in AF pathophysiology. Recent studies suggest that SK channel blockade may have antiarrhythmic effects by reducing atrial excitability and stabilizing electrical conduction. However, the efficacy of oral SK channel blockers in modifying AF burden has not been extensively investigated in preclinical large-animal models.

Methods

Göttingen Minipigs were used as a translational model due to their electrophysiological and anatomical similarities to humans. AF was induced using intermittent burst-pacing from an implanted ICD with custom made firmware which delivers 20 seconds of burst-pacing at 20 Hz and a wait period of 20 seconds. When mean AF duration reaches at least 20 minutes oral administration of a novel SK channel blocker will be administered twice daily. AF burden was assessed through interrogation of ICD which can monitor AF duration. To evaluate the drug's efficacy, AF burden before and after SK channel blocker administration was compared, assessing changes in AF duration and frequency following treatment.

Perspectives

If SK channel inhibition proves effective in reducing AF burden, it may represent a novel therapeutic strategy for AF management. These findings could provide a basis for further clinical development of SK channel blockers as antiarrhythmic agents, potentially offering an alternative to current AF therapies with fewer proarrhythmic risks.

Investigating the role of OPA1 and mitochondrial dynamics in modulating cardiac stromal cell phenotype

Claudia Cozzolino[1], Vittorio Picchio[2], Erica Floris[1], Luca D'Ambrosio[1], Giacomo Frati[1], Antonella Bordin[1], Francesca Pagano[3], Maurizio Forte[2], Sebastiano Sciarretta[1], Isotta Chimenti[1]

[1]Sapienza University of Rome, Department of Medical Surgical Sciences and Biotechnologies, Rome, Italy – [2]Irccs I.N.M. Neuromed,Pozzilli, Italy – [3]National Research Council, Rome, Italy

Background: Resident cardiac stromal cells (CSCs) contribute to heart fibrosis and remodeling by differentiating into myofibroblasts in response to pathological stimuli. Mitochondrial morphology and function, regulated by fission and fusion, are essential for tissue homeostasis. Optic Atrophy 1 (OPA1), a dynamin-related GTPase, supports inner mitochondrial membrane fusion and has cardioprotective roles. However, its function in CSCs remains unclear.

Purpose: To examine mitochondrial dynamics in CSCs and assess whether OPA1 modulation influences their phenotype and paracrine functions upon activation.

Methods: CSCs from 4-week-old C57Bl6J mice were cultured and exposed to TGFβ1 and ischemia-like (IL) conditions. OPA1 was silenced via siRNA. Mitochondrial analysis was performed using Mitotrackers, flow cytometry, MiNA batch analysis, and Western Blot techniques.

Results: CSCs exposed to TGFβ1 for 6h-48h display a shift toward mitochondrial fusion at 16h, followed by fragmentation at 24h, confirmed by MiNA analysis (16h: 1.29-fold vs CTR; 24h: 0.87-fold vs CTR, a.u). Fluorescence intensity per cell showed an increasing trend after 16, 24, and 48h, reflecting enhanced mitochondrial activity (16h: 3.63-fold vs CTR; 24h: 2.11-fold vs CTR; 48h: 2.02-fold vs CTR). OPA1 silencing via siRNA led to lower gene (log2FC=-2.43; N=2) and protein expression (log2FC=-6.3, $P<0.0001$), increased mitochondrial fission by MiNA (0.69-fold vs scramble a.u, $p<0.05$), and reduced TGFβ1-induced activation, as shown by αSMA expression in immunofluorescence (5.24-fold vs CTR scramble, $p<0.001$; 0.48-fold vs TGFβ scramble, $p<0.01$) and Western blot (2.37-fold vs CTR scramble, $p<0.01$; 0.57-fold vs TGFβ scramble, $p<0.05$). Western blot also confirmed reduced intracellular procollagen levels (4.34-fold vs CTR scramble, $p<0.001$; 0.36-fold vs TGFβ scramble, $p<0.01$). Under IL stress, CSCs showed mitochondrial fission at 6h, with reduced branch length (0.96-fold vs CTR a.u, $p<0.05$) and fewer branch numbers per network (0.82-fold a.u., N=3), followed by partial recovery at 16h, where branch length increased (1.24-fold vs CTR a.u, $p<0.01$) and branch numbers returned to control levels. However, mitochondrial activity remained lower (6h: 0.84-fold vs CTR, $p<0.05$; 16h: 0.83-fold vs CTR, $p<0.05$). Flow cytometry indicated increased mitochondrial mass at 16h (2.23-fold vs CTR), suggesting changes in number and/or volume. Western blot revealed increased OPA1 levels after 6h of IL stress (1.45-fold vs CTR, N=2), returning to control at 16h (1.03-fold, N=2).

Conclusion: CSCs undergo dynamic mitochondrial changes in response to TGFβ1 and IL stress. TGFβ1 initially induces fusion, followed by fragmentation and increased activity, while OPA1 silencing enhances fission and reduces fibroblast differentiation into myofibroblasts. IL stress triggers early fission, partial recovery, and persistent functional alterations, suggesting a role for mitochondrial fusion in CSC activation and differentiation.

Predicting Neurological Outcome in Post-Cardiac Arrest Patients Using Advanced DWI Metrics: Rationale and Design

Daniel Tchemerinsky Konieczny[1], John Bro-Jeppesen[2], Christian Juhl Terkelsen[2], Christian Lambert[3], Melanie Boly[4,5], Kristian Sandberg[1]

1. Center for Functionally Integrative Neuroscience, Aarhus University, Denmark
2. Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
3. Wellcome Centre for Human Neuroimaging, 12 Queen Square, London, WC1N, United Kingdom
4. Department of Neurology, University of Wisconsin, Madison, Wisconsin 53705.
5. Department of Psychiatry, University of Wisconsin, Madison, Wisconsin 53719,

Out-of-hospital cardiac arrest (OHCA) is a significant global health concern, reaching numbers of approximately 4500 cardiac arrests per year in Denmark alone, and frequently leads to hypoxic-ischemic brain injury (HIBI) and subsequent disorders of consciousness (DoC) in survivors. Predicting long-term outcomes for this patient group, ranging from recovery of consciousness to persistent vegetative states or death, remains a major clinical challenge. Current predictors, including age, anoxic episode duration, motor responses, and electroencephalography, provide limited precision, particularly for evaluating levels of consciousness. Magnetic resonance imaging (MRI) is underutilized, as the diffuse nature of HIBI damage complicates interpretation using conventional methods.

In this study, we seek to enhance outcome prediction for DoC by leveraging machine learning models trained on classical predictors in combination with advanced diffusion-weighted imaging (DWI)-derived features. Our approach aims to provide a more granular understanding of the relationship between structural brain changes and consciousness recovery as well as neurocognitive functioning after HIBI.

We present an experimental framework to solicit cross-sectional collegial feedback on our methods, including the multimodal integration of advanced MRI metrics and machine learning, to ensure their clinical relevance. Data collection is scheduled to commence in July. Our aim is to contribute to the development of approaches that ultimately improve outcome prediction and clinical decision-making for disorders of consciousness (DoC) following hypoxic-ischemic brain injury (HIBI) in post-cardiac arrest patients.

Repair of Tetralogy of Fallot using transannular patch and replacement with smaller bioprosthetic valves is associated with an increased risk of supraventricular tachycardia

Nerst D[1], Gröning M[1], Jørgensen TH[1], Jensen AS[1], Campens L[1], Schmidt M R[1], Jøns C[1]
1 Department of Cardiology, The Heart Centre, Rigshospitalet, Capital Region of Denmark

Background and aim

Residual lesions following repair of Tetralogy of Fallot (TOF) are common and typically related to the correction of pulmonary stenosis (PS). According to current guidelines, such lesions may warrant pulmonary valve replacement (PVR). However, there is limited evidence that PVR reduces arrhythmic burden or delays the onset of arrythmia in these patients. This study aims to evaluate the effect of PVR in TOF patients, particularly its role in delaying the onset of arrhythmias and reducing arrhythmic burden. The analysis also considers covariates such as the mode of initial repair, prosthetic valve size, and age of the prosthesis.

Method

This retrospective study included patients with TOF, categorized based on the surgical method used to correct PS. Patients were followed from birth until death or December 31, 2018. The primary outcomes were the onset of supraventricular tachycardia (SVT) and SVT-related hospital admissions lasting longer than 24 hours. PVR was treated as a time-varying covariate in all analyses.

Results

A total of 850 patients were included in the study. Patients repaired with TAP were the largest group and consisted of 368 (43,3%) patients. SVT developed in 67 patients, with 216 admissions. Repair with TAP was associated with risk of developing SVT (HR 2.58, 95% CI: 1.28–5.20, $p < 0.01$). Valve replacement had no statistical significant effect on the risk of arrythmia onset (HR 1.21, 95% CI 0,67- 2.3, $p=0.5$). Valve prosthetics smaller than 19 mm were associated with increased post-PVR SVT risk (HR 21.56, 95% CI: 2.08–224.0, $p < 0.01$). The risk of SVT increased with prosthesis sizes smaller than 15 mm (HR 45.28, 95% CI: 3.52 – 836.7, $p <0.01$). Arrhythmic burden increased significantly with bioprosthetic valves older than 8 years (HR 3.67, 95% CI 1.16 – 11.7, $p<0.05$).

Conclusion

Repair with the use of TAP was associated with increased risk of SVT. Valve Replacement did not decrease the risk of arrythmia onset or arrhythmic burden. Valvular prostheses smaller than 19 mm was associated with elevated risk of SVT following PVR and PVR-prosthesis older than eight years was associated with increased arrythmia burden. There is a need for randomised controlled studies evaluating the effect of PVR on risk of SVT.

Investigating the association between atrial fibrillation and sudden cardiac death: a nationwide cohort study

Deepthi Rajan[1], Peder Emil Warming[1], Bo Gregers Winkel[1], Rodrigue Garcia[2], Fredrik Folke[3], Jacob Tfelt-Hansen[1]

(1) Rigshospitalet - Copenhagen University Hospital, Copenhagen, Denmark (2) University Hospital of Poitiers, Cardiology, Poitiers, France (3) Herlev Hospital, Herlev, Denmark

Background: Atrial fibrillation (AF) is an impending epidemic and sudden cardiac death (SCD) remains accountable for a substantial proportion of overall mortality. While emerging evidence suggests an association between these two conditions, it is yet to be determined whether the relationship is causal or rather influenced by shared comorbidities.

Purpose: To investigate whether AF is associated with a higher risk of SCD, independent of frequently co-occurring conditions, such as ischaemic heart disease, heart failure, and diabetes.

Methods: This study was performed as a Danish, register-based, nationwide cohort study using the Sudden Cardiac Death in the Young Register from 1st January 2000 to 31st December 2019 in individuals aged 0-35 years. Follow-up began at the last of 1st January 2000, date of immigration, or date of birth. Exposure was defined as presence of an AF diagnosis. Outcomes of interest were SCD and all-cause mortality without SCD. Follow-up ended at the first date of SCD, all-cause mortality, emigration, 35th birthday, or 31st December 2019. Multivariable cox regression models using age as a time scale were used with results presented as hazard ratios (HR) of SCD and competing risk of all-cause mortality.

Results: The study included 4.42 million individuals, of which 4,346 had AF. Average ages were 14 years (51% male) in non-AF patients versus 29 years (68% male) in AF patients. Compared with non-AF patients, AF patients had a significantly higher HR of SCD: 16.32 (CI: 9.61-27.70) and all-cause mortality: 7.45 (5.95-9.32), respectively. After adjustments for ischaemic heart disease, heart failure, diabetes, and cancer, those with AF retained higher HR of SCD: 4.76 (CI: 2.53-8.96) and all-cause mortality: 5.01 (CI: 3.95-6.36).

Conclusion: AF remained a significant risk factor for SCD in the young population under 35 years, even after adjusting for ischaemic heart disease, heart failure, diabetes, and cancer. These findings highlight the need for further research to clarify precise mechanisms underlying this association in order to better identify high-risk AF patient subgroups who could benefit from enhanced SCD prevention strategies.

Implementation of Novel Cardiopulmonary Resuscitation Training Strategies to Improve In-hospital Cardiac Arrest Outcomes

Dung Nguyen Riis, MD[1,2]; Kristian Krogh, MD, PhD[2,4]; Adam Cheng, MD, PhD[3]; Bo Løfgren, MD[1,2], PhD; Kasper Glerup Lauridsen, MD, PhD[1,2,5]

[1]Department of Medicine, Randers Regional Hospital, [2]Research Center for Emergency Medicine, Aarhus University Hospital, [3]Departments of Pediatrics and Emergency Medicine, Alberta Children's Hospital, Canada, [4]Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, [5]Department of Anesthesiology and Critical Care Medicine, Children´s Hospital of Philadelphia, USA

Introduction: To improve survival outcomes for in-hospital cardiac arrest, the initial steps of basic life support are of utmost importance. The current basic life support (BLS) training strategy for ward staff is generally based on half-day courses every 2-3 years in simulation centers although research has suggested in-situ low-dose, high-frequency training to be more efficient. How to implement such a strategy is, however, unknown. This project investigates how to implement a novel BLS training strategy that utilizes low-dose, high-frequency training with in-situ simulations and skill stations.

Methods: Based on an effectiveness-implementation framework, we will study the implementation of a low-dose, high-frequency training with in-situ simulations and skill stations for ward staff in the Central Denmark Region. The included ward staff will switch from their current refresher training regime to the novel training regime using a stepped-wedge approach with one department serving as initial pilot testing. We will assess training needs through interviews with staff following clinical resuscitation attempts and identify perceived barriers and facilitators of the novel training strategy through interviews with department managers, ward staff, and CPR educators before and after the shift in training strategy. Data on CPR quality will be collected from the training manikins, and data on time to critical resuscitation performance metrics and teamwork competencies will be collected from video cameras during in-situ simulations.

Perspective: This project will provide new important knowledge on how to implement a comprehensive training strategy into the clinical setting and what the effectiveness of such a change in training strategy is. This may guide hospitals to implement guideline-recommended training strategies using low-dose, high-frequency training in the future, resulting in improved CPR skills and patient care.

His pacing versus Biventricular pacing in patients with heart failure and left bundle branch block: Long-term follow-up from the His-alternative study

Emil Anton Frandsen, MD[1*], Johanna Krøll, MD, PhD[1*], Berit Thornvig Philbert, MD, PhD[1], Jesper Hastrup Svendsen, MD, DMSc[1,2], Niels Risum, MD, PhD[1], Michael Vinther, MD, PhD[1]

[1] Department of Cardiology, The Heart Centre, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark

[2] Department of Clinical and Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

* These authors contributed equally to this work.

Background: Cardiac Resynchronization Therapy (CRT) is a well-established treatment for patients with drug refractory symptomatic heart failure and left bundle branch block. CRT is most commonly delivered through biventricular pacing (BiV-CRT). CRT delivered with His-bundle pacing (His-CRT) has emerged as an alternative approach, but comparative studies between these methods remain limited. This study aimed to evaluate the long-term outcomes of BiV-CRT versus His-CRT from the His-alternative study.

Methods: Fifty patients with standard indications for CRT (NYHA functional class II-IV, left ventricular ejection fraction ≤35% and left bundle branch block) were randomized in a 1:1 ratio to receive either BiV-CRT or His-CRT and were followed for five years. The outcomes were a composite endpoint of hospitalization for heart failure and all-cause mortality, the occurrence of reinterventions and echocardiographic response to CRT defined as a ≥15% reduction in left ventricular end-systolic volume at long-term follow-up compared to baseline.

Results: The median follow-up was 63 months (IQR: 55 to 68 months). At implantation, seven patients randomized to His-CRT crossed over to BiV-CRT and one patient randomized to BiV-CRT crossed over to His-CRT. During follow-up four patients crossed over from His-CRT to BiV-CRT and three patients crossed over from His-CRT to receive CRT through left bundle branch area pacing. Significantly more lead revisions (p = 0.003) and generator changes (p = 0.013) were observed in the His-CRT group compared to the BiV-CRT group. However, patients with His-CRT and a threshold of the His-lead ≤ 2.5 vols at implantation had similar rates of reinterventions when compared to the BiV-CRT group. The risk of the combined endpoint of all-cause mortality or hospitalization for heart failure was not significantly different, with nine events (29 %) in the BiV-CRT group and two events (11 %) in the His-CRT group (p = 0.147). At follow-up, echocardiographic response to CRT was observed in 90% of the patients in the BiV-CRT group and in 89% of the His-CRT group (p=1.00).

Conclusions: In the His-alternative study His-CRT was associated with a higher incidence of lead revisions and generator changes. However, when the His-lead implantation threshold was ≤ 2.5 vols, the rate of reinterventions was comparable to that observed with BiV-CRT. Both pacing strategies resulted in similar long-term improvements in left ventricular function.

Thromboelastography in women with overweight and obesity planning pregnancy: impact of BMI on thrombotic risk

Emilie Bahne[1], Emilie L. Grønlund[1], Per G. Hagelqvist[1], Emilie Grønlund[1], Signe Foghsgaard[2], Nina Kornerup[1], Julie Hagstrøm Danielsen[1], Ronni Sahl[1], Signe Torekov[3], Louise Groth Grunnet[1], Tina Vilsbøll[4]

[1]Clinical and Translational Research, Steno Diabetes Center Copenhagen, Herlev, Denmark

[2]Clinical and Translational Research, Steno Diabetes Center Copenhagen, Herlev, Denmark, Department of Obstetrics, Herlev Hospital, University of Copenhagen, Herlev, Denmark

[3]Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

[4]Clinical and Translational Research, Steno Diabetes Center Copenhagen, Herlev, Denmark, Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Introduction

Obesity and pregnancy are recognised as hypercoagulable conditions, contributing to an increased risk of thromboembolic events. The pathophysiological link between overweight and thrombogenesis remains poorly understood, and whether weight loss reduces prothrombotic risk in these high-risk individuals has yet to be studied. Our aim is to investigate the relationship between haemostasis, assessed using TEG, and body composition in women with overweight or obesity seeking pregnancy.

Method

The current study presents baseline data from the ongoing PRE-STORK trial. All women were seeking pregnancy within one year and were evaluated before inclusion in the main trial. In a total of 145 women aged 18-40 years with BMI: 25-44 kg/m^2 we measured TEG, BMI and body fat percentage. The TEG analysis includes the initiation process of clot formation (R-time), the rate of clot formation (K-time and α-angle), the clot´s maximum amplitude (MA), the contribution of fibrinogen to clot strength (MA-FF) and the fibrinolytic activity (LY-30).

Results

For each one-unit increase in BMI and body fat percentage, the clot strength, expressed by MA, increased with 0.30 mm (95% CI [0.18;0.42], R^2=0.14) and 0.31 mm (95% CI [0.19;0.43], R^2=0.16) respectively. The contribution of fibrinogen to the clot strength, MA-FF, increased similarly with 0.38 mm (95% CI [0.23;0.53], R^2=0.15) and 0.43 mm (95% CI [0.30;0.58], R^2=0.22). Accordingly, higher BMI and body fat percentage were associated with an increased rate of clot formation, expressed by a reduction in K-time (−0.021 min; 95% CI [−0.036; −0.007]; R^2 = 0.059 and 95% CI [−0.035; −0.007]; R^2 = 0.062, respectively) and an increase in α-angle (0.19°; 95% CI [0.064; 0.31]; R^2 = 0.059 and 95% CI [0.067; 0.30]; R^2 = 0.063, respectively). Clot strengths expressed by MA was significantly increased in women with class II and III obesity compared to overweight (3.5 mm; 95% CI [2.0;5.1] and 3.7 mm 95% CI [1.7;5.8]; p<0.001 respectively).

Conclusion

The present study demonstrates that increased BMI and body fat percentage are associated with hypercoagulable findings, as measured by TEG. This contributes to the understanding of the increased susceptibility to thrombotic events during a future pregnancy in women with overweight or obesity.

Quality Of Life After Atrial Fibrillation Diagnosed Through Population-Based Screening

Emilie Katrine Kongebro, Md[1], Christian Kronborg, Msc, Phd[2], Ketil Jørgen Haugan, Md, Phd[3], Claus Graff, Phd[4], Søren Højberg, Md, Phd[5], Derk Krieger, Md, Phd[6,], Axel Brandes, Md, Dmsc[7,8], Lars Køber, Md, Dmsc[1,9], Jesper Hastrup Svendsen, Md, Dmsc[1,9]*, Søren Zöga Diederichsen, Md, Phd[1]* (* Denotes Equal Contribution)

Background & Aim

Population screening for atrial fibrillation (AF) has not proven efficacious for stroke prevention. Nonetheless, screening is rising, and the adverse effects, including those on quality of life, are largely unknown. We investigated quality of life associated with screening-detected AF compared to conventionally diagnosed AF.

Methods

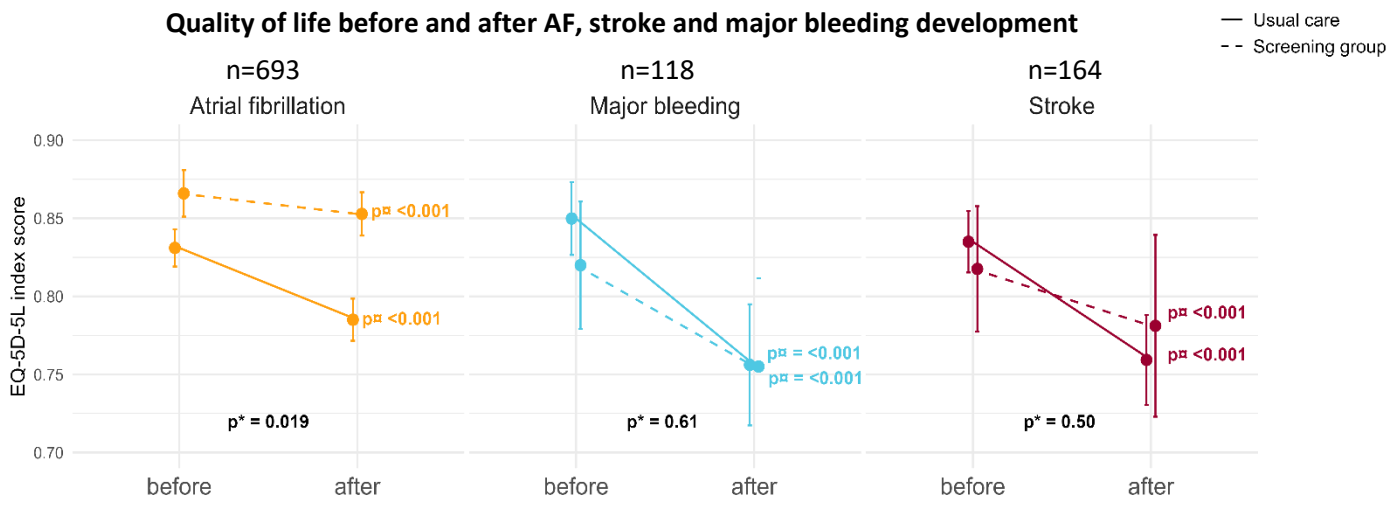
We assessed quality of life data in 6004 trial participants with stroke risk factors randomised to usual care (n=4503) or AF screening using implantable loop recorder with anticoagulation upon AF detection (n=1501). EQ-5D-5L assessments of five domains [mobility, selfcare, usual activities, pain/discomfort, anxiety/depression] yielded annual individual EQ-5D-5L index (worst=-0.76, best=1.00) and EQ-VAS scores (Visual Analogue Scale, 0=worst, 100=best). Changes were estimated with linear mixed models from before to after, and from baseline to end of follow-up for incident AF, stroke, and major bleeding.

Results

During three years of follow-up, 693 of 6004 (12%) participants were diagnosed with AF (Screening: 424 of 1501 (28%), usual care: 269 of 4503 (6.0%)), with 636 alive at year three. For participants developing AF, the EQ-5D-5L index score declined from 0.87 before to 0.85 after AF (p<0.001) in the screening group, and from 0.83 before to 0.79 after AF (p<0.001) in usual care, with less decline in the screening group than in usual care ($p_{interaction}$=0.019). For patients developing stroke and major bleeding, the EQ-5D-5L index scores in the screening group declined from 0.82 to 0.78 (p<0.001) and 0.82 to 0.76 (p<0.001) before and after diagnosis, and from 0.84 to 0.76 (p<0.001) and 0.85 to 0.76 (p<0.001) in usual care, without differences between the randomisation groups. All EQ-VAS analyses yielded very similar results.

Conclusion

AF detected by screening resulted in a smaller negative impact on HRQoL compared with AF detected by usual care. Stroke and major bleeding diagnoses were followed by large HRQoL reductions regardless of randomisation group.



These analyses compare the closest HRQoL before diagnosis with the closest HRQoL after; p* for the difference in decline between screening and usual care (interaction analysis); p¤ for difference in HRQoL from before to after event within randomisation group; For all events, chi squared tests showed no difference in time to event between the randomisation groups

[1] Dept. of Cardiology, Copenhagen University Hospital – Rigshospitalet;[2] Dept. of Economics, University of Southern Denmark;[3] Dept. of Cardiology, Zealand University Hospital Roskilde; [4] Dept. of Health Science and Technology, Aalborg University;[5] Dept. of Cardiology, Bispebjerg Hospital, Copenhagen University Hospital,[6] Mohammed Bin Rashid University of Medicine and Health Sciences;[7] Dept. of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark;[8] Dept. of Cardiology, Esbjerg Hospital – University Hospital of Southern Denmark;[9] Dept. of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen

Molecular Phenotyping of Arrhythmogenic Right Ventricular Cardiomyopathy by Spatial Proteomics

Emily L. Meyer[1], Alicia Lundby[1]
[1] Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiac disorder marked by progressive loss of myocardial tissue and a high risk of life-threatening arrhythmias. Fibro-fatty infiltration in the myocardium is a hallmark of ARVC and is hypothesized to be driven by molecular remodeling in multiple cell populations - including fibroblasts, adipocytes and cardiomyocytes. Bulk tissue analysis overlooks the specific molecular changes within individual cell populations.

To address this, my PhD project employs spatial proteomics to examine the proteomic profiles of cardiomyocytes neighboring infiltrating adipocytes and fibroblasts in ARVC biopsies. This approach provides valuable insights into localized interactions and mechanisms driving disease progression, emphasizing the importance of analyzing these cells both individually and within their spatial context. In spatial proteomics, single cells and cell areas can be collected from thin cardiac sections using laser microdissection (LMD) followed by ultra-high sensitive mass spectrometry, characterizing the cellular proteome. This method allows the characterization of different cell types while keeping spatial relationships intact, thus giving an insight into the interaction within the cellular environment.

I hypothesize that pathological remodeling in ARVC is driven by both intrinsic cardiomyocyte dysfunction and intercellular signaling, contributing to fibro-fatty infiltration. To test this, I will first establish a robust microdissection-based workflow on formalin-fixed paraffin-embedded (FFPE) human heart tissue and then compare the proteomes of infiltrating and resident cardiac cell populations in ARVC versus non-diseased control hearts.

Preliminary data demonstrate the feasibility of our approach: from pooled sections of just 10 laser-microdissected cardiomyocytes from FFPE tissue, we can quantify approximately 1,300 protein groups using ultra-sensitive mass spectrometry. This highlights the potential of spatial proteomics to capture deep proteomic signatures from minimal input material.

By characterizing cardiac cells at the molecular level within their natural tissue context, this work seeks to advance our knowledge of ARVC and identify opportunities for targeted treatment.

Amiodarone in Real Time: Immediate Effects on Left Ventricular Hemodynamics and Mechanics

Emma Illum, MD[1], Laura Svanekjær, Bsc[2], Peter Frederiksen MD, Ph.D.[1], Louise Linde, MD[1], Karoline Korsholm Jeppesen, MD[1], Anika Klein, MD[3], Ann Banke Ass. Professor, MD, Ph.D.[1], Lisette Okkels Jensen Professor, MD, DMsc.[1], Jens Flensted Lassen Professor, MD, DMsc[1]., Henrik Schmidt Ass. Professor, MD, DMsc.[2], Hanne Ravn Professor, MD, DMsc.[1], Jacob Eifer Møller Professor, MD, DMsc.[2,3]

[1]Department of Cardiology, Odense University Hospital, University of Southern Denmark, [2] Department of Thoracic Anesthesia, [3]Department of Cardiology, Rigshospitalet.

Background:
Intravenous amiodarone is widely used for the acute management of life-threatening arrhythmias and is known to cause hypotension. However, its direct hemodynamic and myocardial effects in rhythm-stable conditions remain poorly characterized. This study aimed to examine the immediate effects of 30-minutes amiodarone infusion on left ventricular hemodynamics and ventricular mechanics in anesthetized pigs with sinus rhythm.

Methods:
Twenty-five anesthetized pigs (75–80 kg) in sinus rhythm were instrumented with advanced hemodynamic monitoring, including left ventricular pressure-volume loop analysis, pulmonary artery catheterization, and measurement of carotid and renal perfusion. A 300 mg amiodarone bolus was infused over 30 minutes. Data were recorded at baseline, 15, and 30 minutes.

Results:
Amiodarone infusion significantly reduced systolic blood pressure, mean arterial pressure, and cardiac output, primarily due to reductions in heart rate and myocardial contractility. End-systolic elastance, dP/dt max, and stroke work decreased significantly. Carotid artery blood flow and renal perfusion pressure also declined, while systemic vascular resistance remained unchanged.

Discussion:
Even in the absence of arrhythmias, amiodarone acutely impairs cardiovascular performance by depressing contractility and reducing organ perfusion. These effects are particularly relevant in patients with hemodynamic compromise, such as those with cardiogenic shock, advanced heart failure, or during peri-arrest, where initial infusion may exacerbate instability. The observed reduction in ventriculo-arterial coupling suggests decreased cardiovascular efficiency. Clinicians should closely monitor hemodynamics and be prepared to initiate vasopressor or inotropic support during amiodarone loading, especially in ICU or emergency settings.

Conclusion:
A 30-minute infusion of amiodarone induced significant hemodynamic depression and impaired left ventricular contractility in pigs with sinus rhythm. These findings highlight the importance of close monitoring of hemodynamics and potential proactive management during amiodarone treatment in vulnerable patients.

Donor Atherosclerotic Cardiovascular Disease Risk, Coronary Angiography, and Allograft Survival in Heart Transplantation

Filip Gnesin[1], Mandeep R. Mehra[1], Jennifer Thomalla[1], Asya Lyass[2] , Akinobu Itoh[1], Michael M. Givertz[1], Charlotte Andersson[1]

[1]: Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA [2]: Department of Mathematics and Statistics, Boston University, Boston MA

Background

Guidelines recommend a coronary angiogram in potential heart donors at increased risk of coronary artery disease (age >45 years, diabetes, or tobacco or illicit drug use). Offers are often declined if an angiogram is unavailable.

Purpose

We investigated the short-to-mid-term survival free from graft failure among recipients of hearts from donors with versus without a pre-transplant coronary angiogram, stratified by the donor's estimated 10-year risk of atherosclerotic cardiovascular disease (ASCVD).

Methods

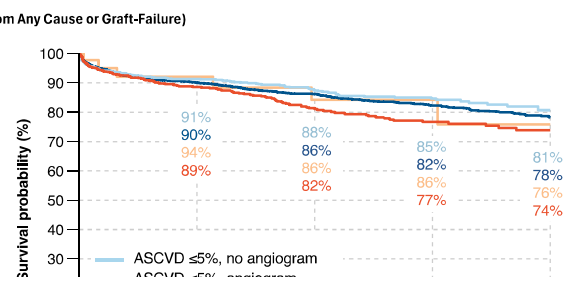
We evaluated heart transplant recipients in the contemporary allocation policy from the United Network for Organ Sharing (UNOS) database (October 2018-December 2023) and stratified donors based on their estimated 10-year ASCVD risk (≤5% versus >5%). A composite outcome of death from any cause or occurrence of allograft failure up to 4 years post-transplant was analyzed using multivariable-adjusted Cox regression models.

Results

Among 5,152 recipients, 4,438 (86.1%) received a heart from a donor with a calculated 10-year ASCVD risk ≤5%. Coronary angiograms were performed in 663 (92.9%) donors with estimated ASCVD risk >5% and in 3,378 (76.1%) donors with estimated ASCVD risk ≤5%. Compared to donors with ASCVD risk ≤5% with angiograms (N = 3,378, donor median age 42 years, 65.4% male donors, 26.8% smokers, referent group), hazard ratios were 0.91 (confidence interval 0.74-1.11) for ASCVD ≤5% without angiogram (N = 1,060, donor median age 36 years, 69.6% male donors, 22.2% smokers), 1.30 (1.05-1.60) for donors with ASCVD >5% with angiogram (N = 663
smokers), and 0.88 (0.36-2.13) f
46 years, 90.2% male donors, 5
who met guideline criteria for a

Conclusion

Our findings suggest that coronary angiograms could be deferred in a substantial proportion of donors at low ASCVD risk, and that donor ASCVD risk may be an independent risk factor for less favorable outcomes. More data are, however, needed to evaluate the longer-term outcomes of accepting a heart without coronary angiogram.



Postmenopausal hormone therapy and major adverse cardiac events in women with prior myocardial infarction

Authors: Hannah K. Wood-Kurland[1], Kathrine Kold Sørensen[1], Amani Meiadi[2], Christian Torp-Pedersen[1,3]

Affiliations:1: Department of Cardiology, Hillerød Hospital, Denmark; 2: Danish Cancer Institute, Denmark; 3: Department of Public Health, University of Copenhagen, Denmark

Background: Hormone therapy for postmenopausal symptoms is contraindicated in women with a prior cardiovascular event but is still used. Further investigation is needed regarding the risk of a subsequent cardiovascular event in these women.

Purpose: To investigate the rate of reinfarction, stroke, or cardiovascular death in women using hormone therapy following a myocardial infarction compared to those who did not.

Methods: All Danish women ≥ 50 years of age with a first-time acute myocardial infarction diagnosis during the study period from January 2000 to December 2021 were identified using the Danish nationwide registers. Time zero was defined as 90 days after their myocardial infarction, and women were followed for up to three years or until the occurrence of a major adverse cardiac event (MACE), all-cause mortality, emigration, or December 31, 2022. Hormone therapy use was defined as at least one prescription redemption of a hormone therapy drug in the 90 days following their myocardial infarction diagnosis. A Cox proportional hazards model, adjusted for age at infarction, calendar year of infarction, income level, diabetes, cancer, peripheral vascular disease, hypertension, kidney disease, heart failure, atrial fibrillation, and chronic obstructive pulmonary disease, was used to estimate the hazard ratio for MACE. MACE was defined as a composite outcome of reinfarction, stroke or cardiovascular death.

Results: Among 43,932 women who experienced acute myocardial infarction and survived at least 90 days the mean age at time zero was 76.8 (± 9.6) and 4,488 (10.2%) had redeemed a hormone therapy drug prescription. In total, 13,169 (30.0%) experienced MACE within 3 years. Among women using hormone therapy 1,125 (25.1%) experienced MACE while it was 12,044 (30.5%) of those who did not. Hormone therapy was not significantly associated with MACE within 3 years (hazard ratio: 0.95 (95% CI: 0.89-1.01)).

Conclusion: Hormone therapy use following acute myocardial infarction was not associated with increased or decreased rate of reinfarction, stroke or cardiovascular death. Knowledge about the benefits and possible harms of hormone therapy is important in decision making when treating women for postmenopausal symptoms and should be further investigated.

Characterisation of oxidative histone modification in neutrophil extracellular traps and their impact on macrophage reactivity – a contributing factor to atherosclerosis?

Helen Hemmling, Line A.E. Hallberg, Per M. Hägglund, Clare L. Hawkins
Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

Extracellular traps (NETs) are released by neutrophils during inflammation and play a role in the pathology of atherosclerosis, as well as their innate immune function of clearing infection. NETs are composed of a mesh of DNA and histones and contain anti-microbial granule proteins, including myeloperoxidase, which remains enzymatically active, and able to produce the oxidant hypochlorous acid (HOCl). Extracellular histones are toxic, and together with other NET components, they limit the spread of infection. However, histones also damage host tissues and are implicated in plaque formation and stability. In this study, we examined whether histones in NETs are a target for HOCl, and if these modifications effect the reactivity of histones with macrophages. NETs were collected from neutrophil-like PLB-985 cells and primary neutrophils stimulated with phorbol myristate acetate (PMA) or nigericin. Post-translational modifications resulting from HOCl exposure, including Tyr chlorination, on linker (H1) and core (H2A, H2B, H3, and H4) histones within NETs were analysed using mass spectrometry. Evidence was obtained for chlorination of Tyr on histones, particularly Tyr88 in histone H4, which was more abundant in NETs obtained from neutrophils exposed to PMA compared to nigericin. This is consistent with nigericin triggering NET release primarily via a non-oxidative pathway. Exposure of macrophages to native and HOCl-modified histones resulted in a decrease in metabolic activity due to loss of viability, with HOCl modulating the toxicity of the histones. Current studies are investigating how the modification of histones influences the expression of inflammatory markers in macrophages. These findings provide the first evidence that NETs contain histones modified by HOCl, which alters the reactivity of histones with macrophages, and provide new insights into how NETs contribute to the development of atherosclerosis.

Prevalence of acute heart failure among unselected non-traumatic emergency department patients admitted with and without oxygen supplementation

Ida Arentz Taraldsen[1]M.D., Aginsha Kandiah[1]M.D., Frederik Dencker Wisborg[1] M.D., Sandra Tonning[1] M.D., Mohammed El-Sheikh[1] M.D., Nora Olsen El Caidi[1] M.D., Ove Andersen[2] M.D., D.M.Sc., Jens Dahlgaard Hove[1] M.D., Ph.D., MS.c., Johannes Grand[1] M.D., MPH., Ph.D.

1) Department of Cardiology, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark

2) Department of Clinical Research, Copenhagen University Hospital Amager and Hvidovre, Hvidovre, Denmark.

Background: Supplemental oxygen therapy is a routine treatment in the emergency department (ED). In acute heart failure (AHF), oxygen treatment is recommended as part of initial treatment if peripheral oxygen saturation (SpO2) < 90% or PaO2<60 mmHg. However, the clinical evidence in this area is limited.

Purpose: The purpose of this study was to assess the prevalence of AHF among patients admitted to the ED with and without the need of oxygen. Furthermore, to assess association of oxygen-need with mortality.

Methods: In this prospective cohort study, all patients admitted at the medical ED at a large University hospital in Denmark between March 10th, 2020, to March 31st, 2022, were consecutively included. Patients were divided into four groups depending on the presence of AHF and oxygen-need. All patient records were screened by trained cardiologist, to identify patients admitted with AHF.

Results: The cohort consisted of a total of 6290 patients; 1311 (21%) patients in need of oxygen and 4979 (79%) patients without need of oxygen. In the group in need of oxygen, 224 (17%) patients had AHF and in the group without need of oxygen 184 (4%) patients had AHF. The patients with AHF were older and had more comorbidities compared with patients without AHF.

Oxygen-need was associated with higher mortality in both patients with and without AHF (*Figure 1*). In AHF-patients, higher oxygen-need was associated with higher mortality in a dose-response relationship ($HR_{adjusted}$ 1.04 per L/min oxygen (1.01-1.1), p=0.001), see Figure 2.

Patients with AHF had a higher readmission rate (2 (1-3) times, median (IQR) compared with patients without AHF (1 (0-2) times, p-value < 0.0001). The length of stay in the AHF group was 5 (3-10) days, compared with 1 (0-5, p-value < 0.0001) day in the group without AHF. In AHF-patients, the need of oxygen was associated with increased length of stay (7 (4-12) days, compared with 4 (2-8) days, p-value < 0.0001). Furthermore AHF-patients in need of oxygen were more admitted to the ICU (41(18.3%) versus 18 (9.8%), p-value = 0.02) than patients without need of oxygen. There was a non-significant increase in intubation rate for AHF-patients in need of oxygen compared to those without need of oxygen (26 (11.6%) vs. 14 (7.6%), p-value = 0.18).

Conclusion: AHF was significantly more prevalent in patients admitted with oxygen need compared to patients admitted without oxygen need. Almost 1 in 5 patients needing oxygen in the ED was admitted with AHF. The need of supplemental oxygen was significantly associated with increased mortality in patients with AHF, and strategies to improve outcome in this patient group should be investigated.

Figure 1. Kaplan-Meier mortality curve and adjusted cox regression models for mortality

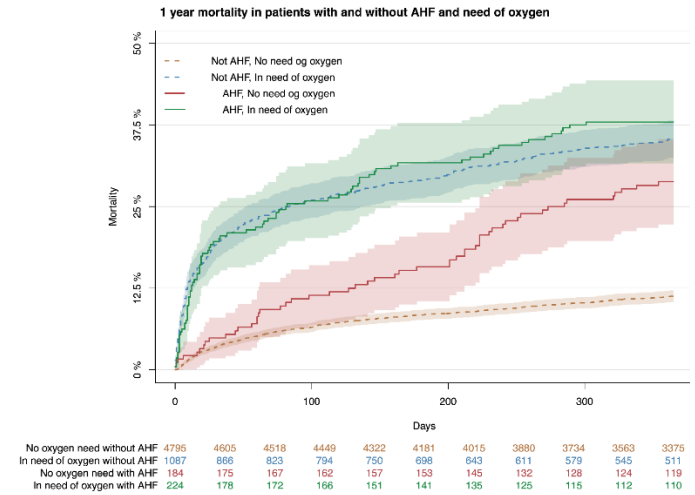
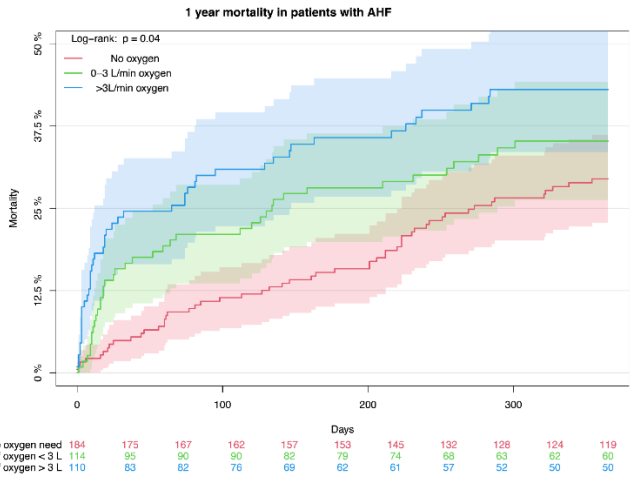


Figure 2. Mortality divided by different levels of oxygen demand



AHF, acute heart failure.

Whole-Heart Histological Workflow for Fibrosis Assessment in a Minipig Model of Myocardial Infarction using Picrosirius Red Staining and Digital Image Analysis

Authors: Jacob Hald. Mette Flethøj Madsen, Anne Hessellund Langhave, Natalia Łopuszyńska, Signe Winther Hasler

Affiliation: Minerva Imaging, Ølstykke, Denmark

Cardiac fibrosis is a hallmark of adverse remodeling following myocardial infarction and a key parameter for evaluating therapeutic effects. We established a comprehensive histological pipeline to visualize and enable quantification of fibrosis across the entire left ventricle in a minipig model of myocardial infarction.

Following excision, whole hearts were rinsed in PBS and fixed in neutral buffered formalin (NBF) for 7 days at room temperature. The tissue was embedded in agar and the whole heart cut into 5 mm thick slabs using a conventional meat slicer. To accommodate the full size of the heart, slabs were processed in standard cassettes, super mega cassettes, or, when too large, placed in a metal grid. Paraffin embedding was followed by sectioning at 6 µm using a microtome (with adapter for super mega blocks when needed) or a gigatome for oversized tissue. Sections were mounted on 1×3 inch or 3×4 inch slides and stained with picrosirius red (pSR) to visualize collagen. Slides were digitized using the VS200 scanner (Evident). All slabs will be stained with pSR to visualize the fibrosis. Total fibrosis in the heart will be quantified based on pSR stain using an AI-driven image analysis module in Visiopharm and be related to MRI-data.

By analyzing the entire left ventricle rather than focusing solely on the infarct region, this approach enables a more comprehensive assessment of both regional and global fibrosis. Importantly, the whole-heart workflow facilitates additional histological evaluations such as vascular density, angiogenesis, and inflammatory infiltration. This provides a better understanding of cardiac remodeling. Future correlation with MRI-derived fibrosis maps will support validation of non-invasive imaging modalities and enhance translational relevance.

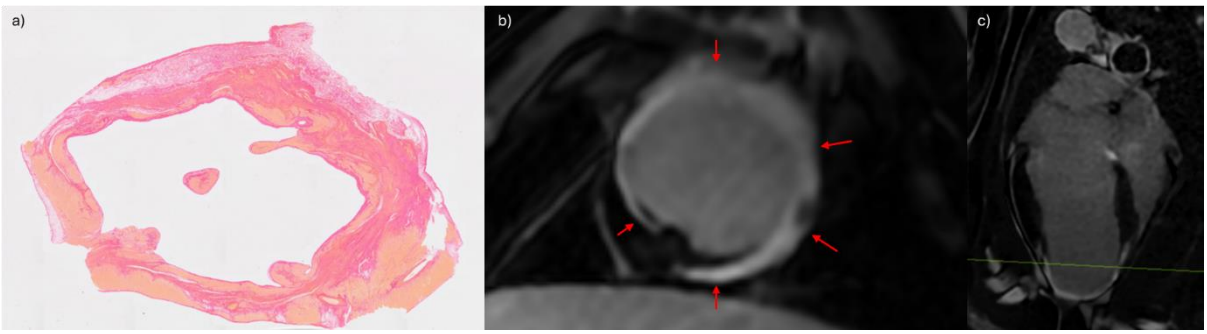


Figure 1 a) Picrosirius red stained section showing fibrotic areas (red) in the apical region of the heart (non-collagen tissue is seen in yellow). b) Late-gadolinium enhancement (LGE) magnetic resonance image (MRI) of same animal showing contrast enhancement in MRI in corresponding regions (red arrows). C) Long-axis LGE-MRI showing level of short-axis LGE-MRI and histology section (green line).

Elevated 24 hours and Exercise Blood Pressures in Adolescents Conceived Through Assisted Reproductive Technologies

Jensen JS.[1,3], Pinborg A.[1], Sejersen C.[3], Gliemann L.[3], Madsen PL.[2,3]
1) Fertility Dept., Copenhagen University Hospital Rigshospitalet. 2) Dept. of Cardiology, Herlev-Gentofte Hospital. 3) The August Krogh Section for Human Physiology, Copenhagen University.

Background Assisted reproductive technologies (ART) account for up to 9% of births in Europe and more than 10 million conceptions globally. Concerns have been raised about long-term cardiovascular health consequences for the offspring. ART primarily includes two procedures: fresh and frozen embryo transfer, which are associated with small-for-gestational-age births and large-for-gestational-age births, respectively. Both outcomes are associated with hypertension later in life. Therefore, we investigated the 24-hour blood pressure and exercise blood pressure in adolescents conceived by ART compared to naturally conceived adolescents to determine the risk of cardiovascular disease associated with conception by ART in the offspring.
Methods We included adolescents, 15-17 years at invitation, conceived by ART and natural conception (control group) in a cross-sectional cohort design. Participants' BP was measured during 24h and incremental exercise with BP determined at rest, light (25-39% of VO2-reserve), moderate (40-64%), vigorous (65-84%), and peak (85-100%) exercise intensities and compared between groups. Exercise hypertension was defined as a systolic BP ≥210 and 190 mmHg in males and females, respectively. Arterial Hypertension was defined as 24 h BP > 130/80; daytime BP > 135/85; nighttime BP > 120/70 mmHg.
Results A total of 279 adolescents were included: 113 in the fresh embryo transfer group (18±0.7 years (mean±SD), 60%F); 59 in the frozen embryo transfer group (17±1.1 years, 54%F); and 107 in the control group (17.3±0.9 years, 53%F).
The 24h systolic BP was 3 mmHg higher in the Fresh group compared to the control group (118±8.6 mmHg *vs*. 115±7.8 mmHg; p=0.03) with no difference between the frozen and control group. We observed no difference in the 24 h diastolic BP between groups. The prevalence of arterial hypertension was 17% in both the fresh and frozen group vs. 6% in the control group.
Without differences in maximal workload, VO2-max, BMI, or lean body mass, the systolic BPs were higher at every exercise intensity in the fresh group compared to the control group with no differences in the frozen group compared to the control group. We observed the highest intergroup differences at vigorous and peak relative exercise intensities with systolic BP and mean arterial BP differences of 7mmHg and 4mmHg ($p<0.01$), respectively. At absolute intensities the systolic BP and mean arterial BP was 12 and 8 mmHg higher ($p<0.01$), respectively, in the fresh group compared to the control group. The prevalence of exercise hypertension was 30% in the fresh group; 20% in the frozen group and 10% in the control group.
Conclusion Adolescents conceived by ART had significantly elevated systolic BP during both 24-hours and exercise with higher prevalence of both arterial hypertension and exercise hypertension. These findings suggest that adolescents conceived by ART have significantly increased risk of future cardiovascular disease. Screening for hypertension in individuals conceived through ART could be warranted.

Neutrophil-to-lymphocyte ratio and c-reactive protein and mortality in patients admitted with acute dyspnoea suspected of acute heart failure

Authors
Jasmin Dam Lukoschewitz[a] MD, Kristina C. Miger, MD,[b] Anne Sophie O. Olesen, MD,[b] Olav W. Nielsen, MD, PhD, DMSC,[b,] Johannes Grand, MD, PhD[a]

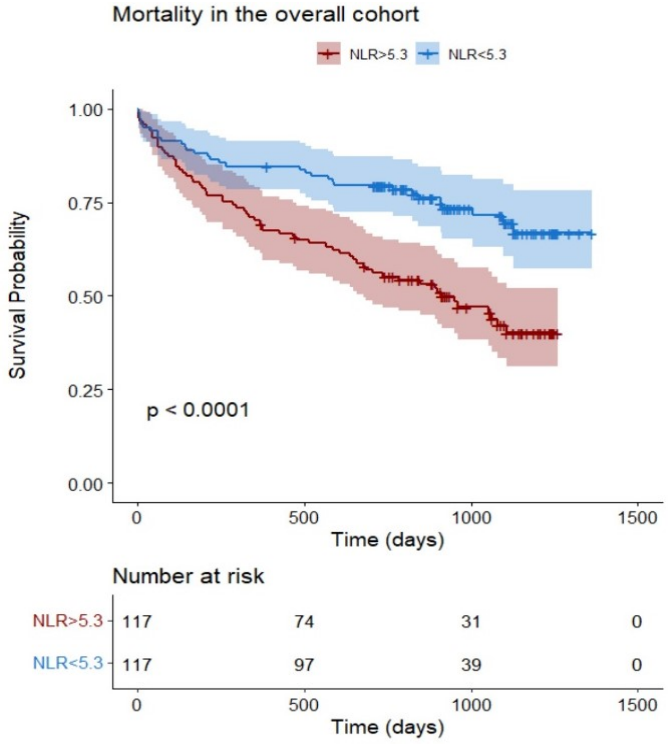
a: Department of Cardiology, Hvidovre Hospital. b: Department of Cardiology, Bispebjerg and Frederiksberg Hospital

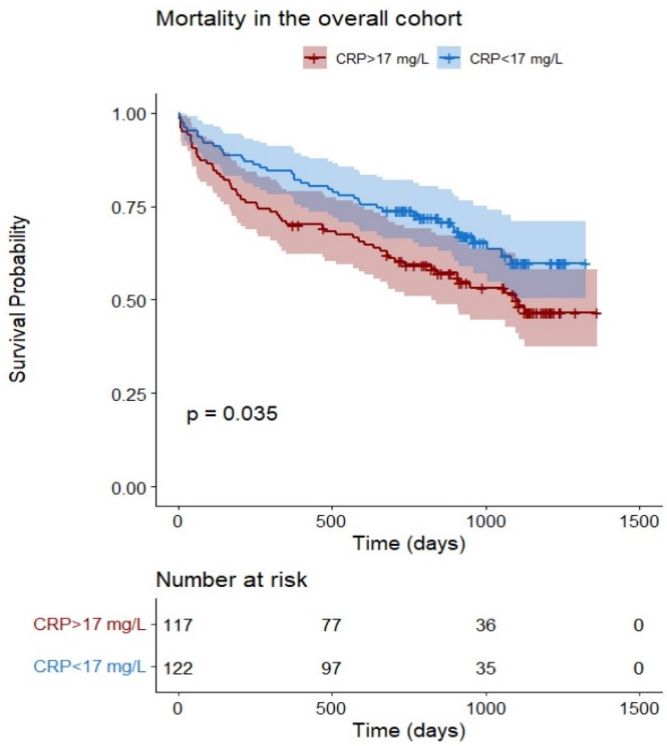
Background and aim: Neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) are inexpensive inflammatory biomarkers. This study aims to evaluate the prognostic relevance of NLR and CRP in patients presenting to the emergency department (ED) with acute dyspnoea, including those with acute heart failure (AHF).

Methods: This prospective study included patients presenting with acute dyspnoea in the ED between October 2018 and August 2019. Upon admission, NLR and CRP levels were measured. Diagnoses of AHF and other dyspnoea causes (non-AHF) were retrospectively and independently adjudicated by expert cardiologists and pulmonologists. The primary endpoint was all-cause mortality. NLR and CRP were dichotomised into categories based on median values. Log-rank tests were used to compare survival between the dichotomised groups. Hazard ratios (HRs) were calculated using univariable and multivariable cox regression for the dichotomised variables. Analyses were conducted in the total cohort and for AHF and non-AHF subgroups.

Results: The cohort included 239 patients; 60 (25%) with AHF and 179 (75%) without AHF. AHF patients were older (78 vs. 73 years) and had more comorbidities than non-AHF patients. Median NLR was 5.3 in the total cohort, 5.0 in AHF patients, and 5.5 in non-AHF patients. Median CRP was 17 mg/L in the total cohort, 11 mg/L in AHF patients, and 20 mg/L in non-AHF patients. Over a median follow-up of 969 days, 98 patients (41%) died. NLR>5.3 was significantly associated with mortality in the total cohort (HR: 2.3, 95% CI: 1.5–3.5, p<0.001), and this association remained significant in multivariable analysis. In AHF patients, NLR>5 was associated with increased mortality rates in univariable analysis (HR: 2.3, 95% CI: 1.05-5.13. p=0.04), but not in multivariable analysis. In non-AHF patients, NLR>5.5 was associated with increased risk of mortality in both univariable (HR: 2.5, 95% CI: 1.50–4.16, p<0.001) and multivariable analysis. CRP>17 mg/L was associated with increased mortality risk in univariable analysis (HR: 1.53, 95% CI: 1.03–2.29, p = 0.04), but this association was no longer significant in multivariable analysis. In AHF patients, CRP>11 mg/L was associated with higher mortality in both univariable (HR: 2.26, 95% CI: 1.04–4.90, p = 0.04) and multivariable models. No association was found in non-AHF patients.

Conclusion: NLR is a strong predictor of all-cause mortality in consecutive patients admitted to the ED with acute dyspnoea. Elevated CRP is associated with increased risk of all-cause mortality in patients with AHF, but no such association was observed in non-AHF patients.





The Role of Branched-Chain Amino Acids in Cardio-oncology: A review.

Jiaqi Xu[1#], Yu Wang[1,2#], Jing Zhang[3,4], Jingyi Tang[1], Zhongyan Zhou[1, 3,4*]

1. Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

2. Department of Cardiology, The First Hospital of Hebei Medical University, Hebei, China

3. State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong SAR, China

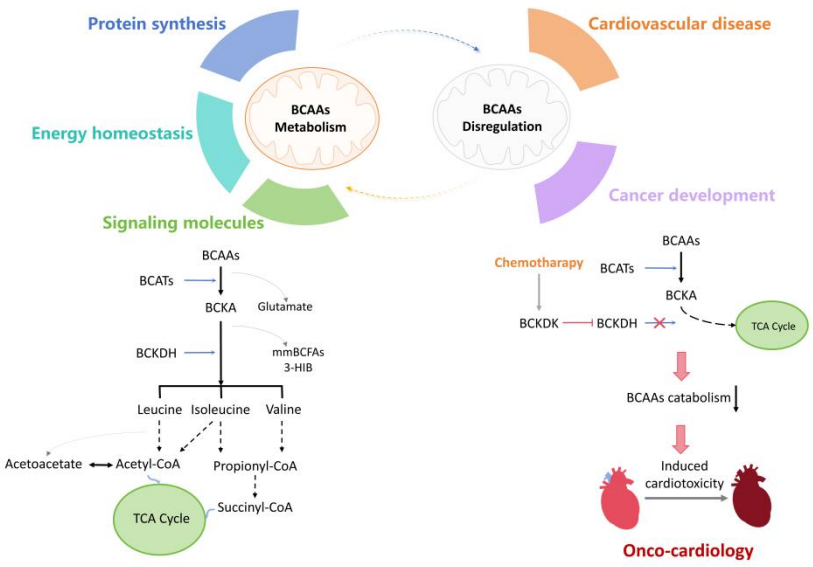
4. Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

# These authors contribute equally to this work.

* Corresponding author

Abstract

Cancer and cardiovascular diseases (CVDs) are global health challenges. In cancer patients, CVDs is the second leading cause of death following disease progression. There are few specialized services for cardio-oncology patients worldwide currently. Branched-chain amino acids (BCAAs) are essential amino acids and promote protein synthesis and energy homeostasis. The disruption of BCAAs metabolism facilitates the development of cancer and CVDs while the benefit of BCAAs supplement is full of controversy. In this review, we summarized BCAA-related studies in cardiometabolism, cancer and chemotherapy-induced cardiotoxicity, and provided our perspectives on the roles of BCAAs in cardio-oncology research. We find that supplementation of BCAAs presents protective effects in cardiometabolic diseases, while the influence on cancer is intricate and varies across different types. Large-scale clinical studies are needed to understand the long-term effects of BCAA intake and its impact on different disease stages. BCAAs have potential to mitigate chemotherapy-induced cardiotoxicity such as doxorubicin and 5-fluorouracil. Continued research is still essential to understand the precise mechanisms, determine optimal usage, and assess the effectiveness of BCAAs supplement.



Regenerative Heart Valve Surgery – A New Paradigm?

Johannes H. Jedrzejczyk, Frederik T. Andersen, Jacob Petersen, Alex E. Kaspersen, Søren N. Skov, Rasmus Kraghede, J. Michael Hasenkam, Marcell Tjørnild

1. Department of Clincial Medicine, Aarhus University, Aarhus, Denmark
2. Department of Cardiothoracic & Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark

Background: Heart valve disease incidence remains high in Denmark. However, treatment options are scarce and limited to surgical repair or replacement. Repair is the preferred treatment option, but it is infeasible for patients with severe valve pathology. Patients with severe valve pathology are confined to biological or mechanical valve replacement, both fraught with complications. Bio scaffolds, promoting host cell repopulation as the scaffold material naturally degrades, present a unique avenue for regenerative heart valve surgery. This regenerative approach may offer superior treatment for patients with severe valve pathology.

Methods: A bio scaffold material called small intestinal submucosa extracellular matrix (CorMatrix®) was investigated. Initial assessments were conducted using diverse in vitro models. Subsequently, acute porcine models were used for both partial and complete heart valve reconstructions. Valve competence was assessed through echocardiography and invasive pressure measurements.

Results: Valve competence was successfully attained in partial and complete heart valve reconstructions, with echocardiography and invasive pressure measurements showing consistent results before and after the procedure.

Conclusion: Heart valve reconstruction using small intestinal submucosa extracellular matrix proved viable in both in vitro and acute in vivo models. The next phase involves evaluating the recellularisation process and assessing the biomechanical characteristics of the reconstructed heart valves in a chronic porcine model.

Obesity drives hypertrophy in human cardiac adipose tissue

Johs Dannesboe[1], Thomas Jespersen[1], Helena Dominguez[1], Arnela Saljic[1]

1 Department of Biomedical Sciences, University of Copenhagen, Blegdamsvej 3, Copenhagen N 2200, Denmark

Background

Epicardial adipose tissue (EAT) and intramyocardial adipose tissue (inFAT) are both fat deposits located around the heart. These tissues have been linked to disease progression and the development of arrhythmias. Obesity, in particular, is known to increase EAT accumulation around the heart. However, the factors influencing inFAT accumulation are less understood. This study aims to characterize cardiac adipocytes and investigate how obesity affects cardiac adipose physiology.

Method

We analyzed 40 paired left and right atrial appendage tissue samples obtained from patients enrolled in the LAACS-2 clinical trial. These patients, undergoing open-heart surgery for valve replacement or bypass, provided consent for the removal of both appendages. The 4 mm thick sections of these appendages were stained with Sirius Red and imaged using an AxioscanZ1. Subsequently, collagen content was analyzed using either automated intelligent image segmentation or manual selection in Qupath software.

Results

Our analysis reveals significant structural differences between the left and right human atrial appendages. The left appendage contains a significantly greater proportion of EAT compared to the right (35% vs. 11%; $p<0.001$). Intramyocardial fat is also more prevalent in the left appendage, reaching up to 6%, while the right appendage showed a maximum of 2% ($p=0.02$). The body mass index (BMI) of the patients correlated with the size of the adipocytes in the left appendage in both EAT ($p=0.006$) and inFAT ($p=0.054$). A positive, but non-significant, correlation was found in the right appendage. A shift towards larger adipocyte size was observed in the normal distribution of adipocytes in both EAT and inFAT in both appendages. This indicates that the expansion of cardiac fat in obesity is at least partly driven by hypertrophy in both EAT and inFAT.

Perspective

This study provides fundamental knowledge about how cardiac adipose tissue expands in obesity through hypertrophy. Hypertrophic adipocytes are often associated with a pro-inflammatory profile and could partially explain the role of cardiac adipose tissue in cardiac disease progression. Understanding the mechanisms by which cardiac adipose tissue expands sheds light on the mechanism on how SGLT2 inhibitors and GLP1 decrease EAT volume in patients. The next step is to investigate how the signaling profile and secretome are altered in obese cardiac adipocytes.

Cardiometabolic effects of medium-chain triacylglycerol

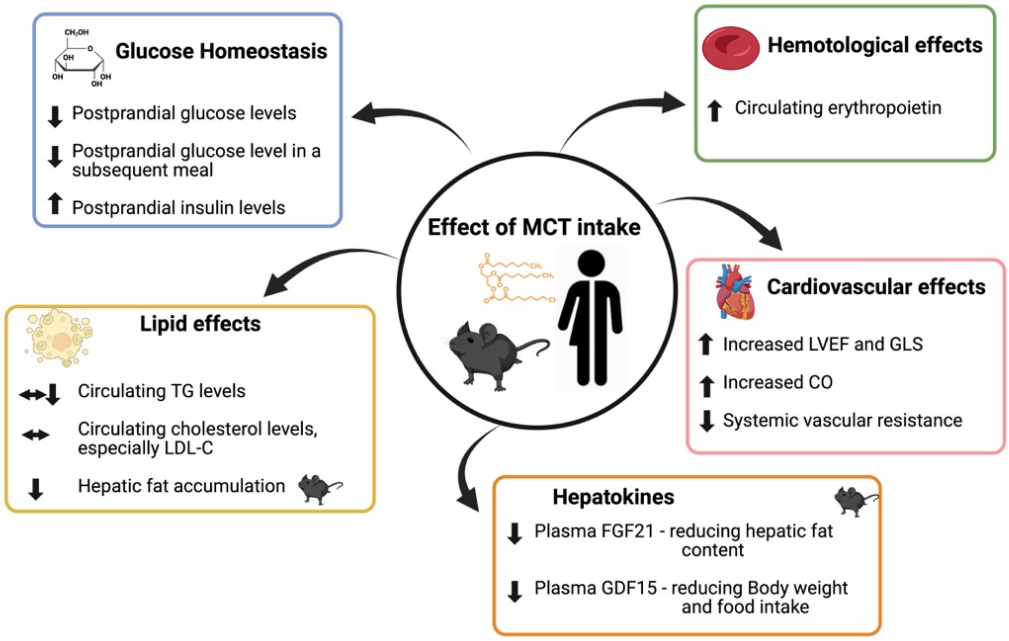
Josephine Maria Kanta[1], Amalie S. Frederiksen[2], Amalie London[2], Annemarie Lundsgaard1, Casper M. Sigvardsen[1], Amanda Schaufuss[2], Louisa Deisen[3], Jacob W. Christensen[1], Ye Cao[3], Jens-Peter Gøtze[4], Nils Færgeman[5], Erik A. Richter[1], Niels G. Vejlstrup[6], Maximillian Kleinert[4], Per L. Madsen[1,7], Bente Kiens[1], and Andreas M. Fritzen[2]

[1]Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark. [2]Department of Biomedical Sciences, University of Copenhagen, Denmark. [3]German Institute of Human Nutrition (DIfE) & German Center for Diabetes Research (DZD), Germany. [4]Department of Clinical Biochemistry, Copenhagen University Hospital - Rigshospitalet, Denmark. [5]Department of Biochemistry and Molecular Biology, University of Southern Denmark, Denmark. [6]Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Denmark. [7]Department of Cardiology, Copenhagen University Hospital Herlev, Denmark.

Background: Medium-chain triacylglycerol (MCTs, C8:0–C12:0) are a subclass of natural triacylglycerols with a distinct metabolic fate. They are readily oxidized in various tissues, especially the liver, and can induce rapid ketogenesis. Originally, dietary MCTs were promoted for therapeutic use in fat malabsorption syndromes and as treatment in intractable epilepsy. More recently, MCTs have gained attention for their potential anti-obesity properties, effects on metabolism, and possible cardiovascular benefits. However, much remains unknown, both related to effects and mechanisms, but MCTs may exert therapeutically relevant pleiotropic cardiometabolic effects in the human body.

Methods: Study 1: Metabolic and hematological effects of acute intake and 8-day supplementation of MCT vs. LCT in young lean men and young men with obesity. Study 2: Acute cardiovascular effects to MCT vs. LCT intake in healthy older adults and patients with heart failure with reduced ejection fraction. Study 3: Acute effects of prior MCT-enriched fat intake during a mixed meal in healthy young men. Study 4: Acute and chronic MCT intake investigated in mouse models with focus' on cardiometabolic outcomes, cardiac function, and hepatokine regulation.

Results:



Conclusion: MCT intake exerts pleiotropic cardiometabolic effects that are of interest not only from the context of basic cardiometabolic research, but also a therapeutic perspective.

Abstract ACR 2025

Biomarkers Associated with Left Atrial Structure and Function in Patients with Psoriasis

Julie Inge-Marie Helene Borchsenius, MD; Maria Dons, MD; Morten Sengeløv, MD; Flemming Javier Olsen, MD, Caroline Espersen, MD; Kristoffer Grundtvig Skaarup, MD; Mats Højbjerg Lassen, MD; Niklas Dyrby Johansen; PhD; Filip Søskov Davidovski MD, Manan Pareek, MD, PhD; MB; Brittany Weber MD, PhD; Claus Zachariae MD, PhD; Lone Skov, MD, PhD; Tor Biering-Sørensen, MD, MSc, MPH, PhD

Background
Patients with psoriasis are at increased risk of developing heart disease. Echocardiographic parameters of impaired left atrial (LA) strain (Peak atrial contraction and longitudinal strain (PACS and PALS)) and volume index (LAVi) are associated with increased risk of atrial fibrillation. Whether cardiac and inflammatory biomarkers are associated with left atrial impairment in patients with psoriasis is unknown.

Aim
The aim of this study was to assess whether plasma levels of hsCRP, troponin I (TnI) and pro-brain natriuretic peptide (proBNP) were associated with LA structure and function in patients with psoriasis.

Methods
A prospective cohort of 1,010 patients with psoriasis underwent echocardiographic examination and had blood samples analyzed from 2021-2024. Patients without available measurements of hsCRP (n=27), TnI (n=5) or proBNP (n=17), LA strain (n=23) or LAVi (n=11) were excluded. The population was stratified according to hsCRP, TnI and proBNP tertiles, respectively. We used ANOVA, Pearson's Chi^2-test, Kruskal-Wallis test, linear regression and cubic spline models as appropriate to assess the associations between biomarkers, cardiac risk factors and measures of LA structure and function. Biomarkers were logarithmically transformed for the linear regression analyses. In multivariable analyses, models were adjusted for sex, age, package years, BMI>30, hypertension, hypercholesterolemia, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, atrial fibrillation and psoriasis treatment.

Results
We included 927 patients with psoriasis (mean age 54.0 years, 46.5 % women). In the entire cohort, median hsCRP was 1.1 mg/l (IQR 0.5-2.7), median TnI was 3.0 n/l (IQR 1.2-6.0) and median proBNP was 7.6 ng/l (4.2-14.3). The patients in the highest tertile groups of these biomarkers were overall older, had more package years and a higher prevalence of hypertension. Furthermore, the hsCRP group >1.73 mg/l had more women, higher BMI's and were less physically active. The TnI group >5 ng/l had more men and a higher prevalence of severe psoriasis and cardiovascular disease. The proBNP-group >11.5 ng/l had more women and a higher prevalence of cardiovascular disease.

In univariable analyses, higher levels of hsCRP were associated with lower PALS, while higher levels of TnI and proBNP were associated with lower PACS and PALS and higher LAVi. In multivariable analyses, higher levels of TnI and proBNP remained significantly associated with lower PACS and PALS and higher LAVi. (Figure)

Conclusion
In a sample of patients with psoriasis, higher levels of TnI and proBNP were associated with impaired LA structure and function. Given the known association between LA dysfunction and atrial fibrillation, an implication of these findings could be better detection of patients with psoriasis at high risk of cardiac disease.

Elevated remnant cholesterol confers high risk of ASCVD without prompting lipid-lowering therapy: an unmet medical need.

Karen Hvid[a,b], MD, Mie Balling[a,b,c], MD, PhD, Børge G. Nordestgaard*[a,b,d], MD, DMSc, Shoaib Afzal*[a,b,d] , MD, PhD, DMSc

*Shared last authorship
a: Department of Clinical Biochemistry, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark.
b: The Copenhagen General Population Study, Herlev and Gentofte Hospital, Herlev, Denmark.
c: Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
d: Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

Abstract

Background

Initiation of lipid-lowering therapy may primarily be prompted by high low-density lipoprotein (LDL) cholesterol levels. If so, individuals with high risk of atherosclerotic cardiovascular disease (ASCVD) due to elevated remnant cholesterol may not be started on lipid-lowering therapy. We tested the hypothesis that elevated remnant cholesterol confers high risk of ASCVD but less initiation of lipid-lowering therapy compared to elevated LDL cholesterol.

Methods

From the Copenhagen General Population Study, 94 299 lipid-lowering therapy naïve adults without a history of ASCVD were included. Discordance groups were formed by median levels of remnant cholesterol, LDL cholesterol and apolipoprotein B (apoB). In the national Danish health registries, individuals were followed for a prescription of lipid-lowering therapy and for incident ASCVD or until December 2021.

Results

During a median follow-up of 12 years, 9 269 developed ASCVD. Compared to individuals with concordant low values of LDL and remnant cholesterol, those with high remnant cholesterol and apoB but low LDL cholesterol had a hazard ratio (HR) of 1.45 (95% confidence interval: 1.34-1.56) for ASCVD and an odds ratio (OR) of 3.0 (2.5-3.6) for starting lipid-lowering therapy within one year. Correspondingly, those with low remnant cholesterol but high apoB and high LDL cholesterol had a HR of 1.20 (1.11-1.30) for ASCVD and an OR of 5.1 (4.3-5.9) for starting lipid-lowering therapy.

Conclusions

In primary prevention elevated remnant cholesterol confers high risk of ASCVD but less initiation of lipid-lowering therapy compared to elevated LDL cholesterol, representing an unmet medical need.

Evaluation of AI-based chart review for acute myocardial infarction and cardiogenic shock: a registry-based study

Karoline Korsholm Jeppesen[1,3], Rasmus Bo Lindhardt[2,3], Anika Klein[4], Emma Illum[1], Rasmus Bank Lynggaard[5], Ann Banke[1,3], Jacob Eifer Møller[1,3,4], Hanne Berg Ravn[2,3], Pernille Just Vinholt[3,5]

1 Department of Cardiology, Odense University Hospital, Odense.

2 Department of Anesthesiology and Intensive Care, Odense University Hospital, Odense.

3 Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense.

4 Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

5 Department of Clinical Biochemistry, Odense University Hospital, Odense.

Introduction. The Danish RETROSHOCK registry has provided valuable insights into patients with acute myocardial infarction complicated by cardiogenic shock (AMICS) and their clinical trajectories. Continuously updating the registry through manual chart review is time-consuming.

Purpose. The aim of this study was to evaluate, whether artificial intelligence (AI)-assisted chart review could reduce patient screening time for identifying AMICS patients eligible for the RETROSHOCK registry as well as excluding non-eligible patients, while maintaining diagnostic accuracy.

Methods. Electronic medical records were retrieved from patients admitted to Odense University Hospital from Jan 2018 to Dec 2022, who were assigned an ICD-10-code suggestive of AMICS. From this cohort, a random sample of 100 consecutive patients were selected for testing the AI-assisted chart review. The tool used for the AI-assisted chart review was a natural language processing model identifying keywords related to the AMICS diagnosis. Thus, the tool highlighted and extracted information on relevant keywords such as “coronary angiography”, “ejection fraction”, “blood pressure” etc. Electronic medical records were initially screened using AI-assisted chart review with time recorded until confirmation of the AMICS diagnosis or exclusion due to an alternative diagnosis. One week later, the same charts were manually reviewed. The screening time for the AI-assisted and manual chart review was compared using Wilcoxon signed-rank test.

Results. AI-assisted chart review identified 26 AMICS patients among the 100 screened, matching the results of the manual chart review (Cohen’s kappa = 1). The median manual inclusion time was 2:20 minutes, compared to 1:16 minutes with AI-assisted chart review (median difference: 1:03 minutes, $p<0.001$). Median manual exclusion time was 2:45 minutes, whereas AI-assisted exclusion time was significantly faster at 0:59 minutes (median difference: 1:47 minutes, $p<0.001$).

Conclusion. AI-assisted chart review significantly reduced screening time for both inclusion of AMICS patients in the RETROSHOCK registry and exclusion of non-eligible patients, while maintaining diagnostic accuracy.

The impact of atrial preload on ventricular electrophysiology in left bundle branch block

Friederichs K[1], Meijborg VMF[2], Jespersen T[1], Gottlieb LA[1]

[1] Department of Biomedical Sciences, University of Copenhagen, Denmark
[2] Department of Cardiology, UMC Utrecht, the Netherlands

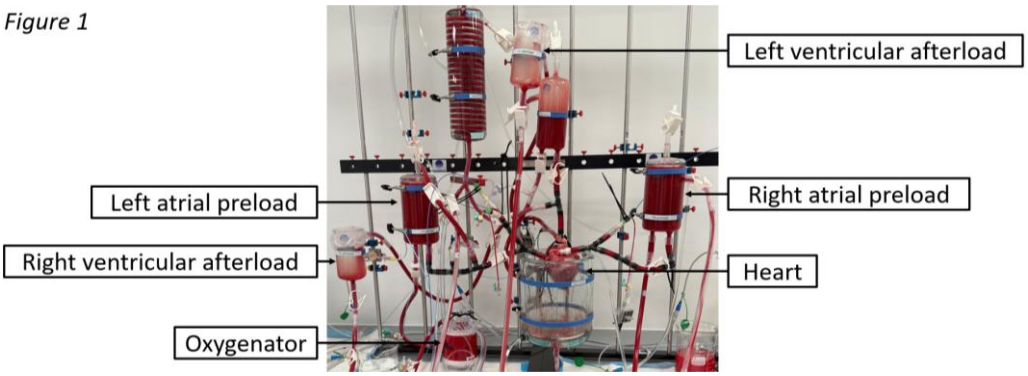
More than 64 million people worldwide suffer from heart failure, which has a 5-year mortality rate of >50%. One third of patients with heart failure additionally present with left bundle branch block (LBBB). With LBBB the electrical conduction through the left ventricle is impaired and cardiac resynchronization therapy (CRT) is performed as a standard treatment for heart failure with LBBB. However, it does not relieve the symptoms in a third of patients. Especially, a large left atrium before CRT predicts a nonresponse or a negative outcome to the treatment. This implies that the underlying disease mechanisms and especially the interplay between the hearts electrophysiology and mechanical functions are incompletely understood.

Therefore, we hypothesize, that an increased left or right atrial preload negatively impacts the left ventricle, by acting as a mechanical stimulus. Due to mechano-electric coupling this causes further disruption to the ventricular electrophysiology, ultimately reducing ventricular output in LBBB.

We will test this in a whole-organ setting using an ex-vivo porcine working-heart setup (Figure 1). Each pig heart is explanted during general anaesthesia with propofol (15mg/kg/h) and whole blood (1-2L) is collected. The heart is installed in a perfusion system with a 1:4 perfusate of whole blood:Tyrode´s solution, mimicking the physiological circulation and allowing all four heart chambers to function. Small-needle-electrodes inserted into the right and left ventricular myocardium, allow for epicardial, intramural and endocardial measurements, providing detailed depolarization and repolarization maps of both ventricles. Recordings are performed during left and right atrial preload pressure modulation as well as immediately before and after LBBB induction. LBBB is induced by delivery of ablative radiofrequency energy to the left conduction branch until a 30% increase in QRS interval, which is measured using a pseudo-ECG with electrodes in a tissue bath, is reached.

With this we intend to gain new insights into the underlying mechanism of heart failure with LBBB, ultimately improving the selection of patients who will receive CRT. By choosing patients dependent on their atrial preload, which can be determined prior to treatment, we hope to improve patient care by avoiding nonresponse and negative outcomes.

Figure 1



Heat shock protein 47: A novel biomarker of thrombosis risk

KA Friis[1,2], JB Larsen[2,3], T Pezold[4], O Frøbert[2,5], EL Grove[1,2]

1: Department of Cardiology, Aarhus University Hospital 2: Department of Clinical Medicine, Aarhus University 3: Department of Clinical Biochemistry, Aarhus Univsersity Hospital 4: Deutsches Herzzentrum der Charité, University Hospital Berlin 5: Steno Diabetes Center Aarhus; Department of Cardiology, Örebro University

Background: Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is the 3rd leading cause of vascular death. Immobilization is a strong and independent risk factor of VTE. Despite this, brown bears mitigate the risk of VTE during hibernation. This led to the identification of Heat Shock Protein 47 (HSP47) on platelets being down regulated 55-fold in hibernating bears. HSP47 is a part of collagen signalling and, thus, important for aggregation and adhesion of platelets. Therefore, by lowering platelet HSP47, clotting of blood is prevented.

Aim: To investigate whether platelet HSP47 levels can serve as a novel biomarker for thrombosis risk in patients with VTE.

Methods: We plan to include 120 patients with VTE and 120 healthy individuals. The patients will have their platelet HSP47 level measured at inclusion within 48 hours of diagnosis, and again at follow-up after 3 and 12 months. HSP47 levels will be analysed using proteomics. Further, patients will have their primary and secondary haemostasis and fibrinolysis assessed by impedance aggregometry (Multiplate(R)), thromboelastometry (ROTEM), flow cytometry, ex vivo thrombin generation and fibrin clot formation and lysis assay.

Perspective: This study will elucidate the role of HSP47 in VTE, establishing its potential as a novel biomarker for thrombosis risk. Additionally, the study could position HSP47 as a promising therapeutic target for next-generation antithrombotic drugs, leading to more effective and safer treatment.

The acute effect of docosahexaenoyl-taurine, an omega-3 fatty acid metabolite, on postprandial triglyceride metabolism following a high-fat mixed meal test – a randomised, crossover, double-blind, placebo-controlled trial

Katja T. Michler[1,2], Casper K. Nielsen[2,3], Samuel A. J. Trammell[1], Bolette Hartmann[1], Jens F. Rehfeld[4], Jens J. Holst[1,5], Filip K. Knop[2,3,6] *, Trisha J. Grevengoed[1] *

[1]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[2]Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

[3]Novo Nordisk A/S, Søborg, Denmark

[4]Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[5]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Background: One major risk factor of CVD is elevated plasma lipid concentrations. Plasma triglyceride (TG) concentration dose-dependently increases the risk of CVD. High doses of omega-3 fatty acids (n3-FA) are recommended for the treatment of hypertriglyceridaemia (plasma TG ≥ 2 mmol/l). The molecular mechanisms underlying the TG-reducing effects of n3-FA are not fully understood. A novel n3-FA metabolite, docosahexaenoyl-taurine (DHA-T), was recently found to acutely reduce TG absorption from an oil meal in mice, similarly to long-term dietary n3-FA supplementation.

Methods: In this randomised, double-blind, placebo-controlled, crossover study (ClinicalTrials.gov identifier: NCT05953064), we investigated how acute, oral administration of DHA-T affects postprandial serum triglyceride in 20 healthy men. On two separate days, participants underwent a high-fat mixed meal test (HF-MMT) with DHA-T (2 mg/kg) or placebo. During the 240-min. HF-MMT, blood samples were obtained, and gallbladder volume was assessed by ultrasonography.

Results: DHA-T indicatively reduced serum triglyceride incremental area under curve (iAUC) (15.4% compared to placebo (iAUC: placebo: 172 (95% CI 141–204) mmol/l × min vs. DHA-T: 145.8 (95% CI: 120–172) mmol/l × min, p = 0.13). DHA-T was absorbed and peaked at serum concentrations of 10,570 (95% CI 7,465–13,675) nmol/l. DHA-T significantly increased the serum concentration of taurine-conjugated bile acids (iAUC: placebo: 124 (95% CI 89–158) µmol/l × min vs. DHA-T: 161 (95% CI 114–207) µmol/l × min, p = 0.02), and a similar trend was observed for glycine-conjugated bile acids and total conjugated bile acids.

Conclusions: Acute administration of DHA-T tended to reduce serum TG during a HF-MMT in healthy, normotriglyceridaemic men, while also increasing serum concentration of conjugated bile acids. Our study provides new insight into the TG-lowering effects of n3-FA, through the endogenous n3-FA metabolite DHA-T. Further research is necessary to establish whether the potential TG-lowering effects of DHA-T influence plasma TG in people with hypertriglyceridaemia and at elevated risk of CVD.

Ischemia with No Obstructive Coronary Artery Disease (INOCA) in mice and exploring treatment options

Katrine Hegelund Rasmussen, Morten B Thomsen, Thomas AQ Jepps.
Department of Biomedical Sciences, University of Copenhagen, Denmark.

Introduction

INOCA is a condition where patients have cardiac ischemia without having epicardial coronary artery disease. A clinical presentation of INOCA with microvascular dysfunction is defined by a reduction in coronary flow reserve (CFR). The underlying mechanisms of INOCA remain unresolved affecting diagnosis, treatment and quality of life for symptomatic patients.

Aim

The project aims to investigate the underlying mechanisms of microvascular dysfunction and INOCA in mice and explore treatment potential with exercise or anti-inflammatory treatment.

Methods

A mouse model of heart failure with preserved ejection fraction and potentially INOCA is established by high-fat diet and L-NAME in the drinking water for 16 weeks. CFR is defined by the ratio of hyperaemic blood flow to baseline coronary blood flow and will be characterized in-vivo by ultrasound doppler echocardiography and ex-vivo by whole heart isolations using the Langendorff technique.

Acute atrial lesion stiffness assessment by multifrequency MR elastography after catheter ablation

Kezia Jerltorp[a†], Johannes Castelein[a,b†] Oliver Böhm[c], Sarah D Nissen[a], Arnela Saljic[a], Malene Nørregaard[a], Caroline Hansen[a], Lucas A Lindberg[a], Laura H Friderichsen[a], Bjørn S Larsen[a,d], Ben JM Hermans[e], Sevasti-Maria Chaldoupi[e], Uffe Gang[f], Jim Hansen[g], Niels Vejlstrup[h], Morten Asp Vonsild Lund[a,h], Thomas Jespersen[a+], Ingolf Sack[c+], Dominik Linz[a,e+].

[a]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[b]Department of Radiology, University Medical Center Groningen, Groningen, the Netherlands
[c]Department of Radiology, Charite – Universitätsmedizin Berlin, Berlin, Germany
[d]Department of Cardiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark
[e]Department of Cardiology, Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands
[f]Department of Cardiology, Zealand University Hospital Roskilde, Roskilde, Denmark
[g]Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark
[h]The Heart Centre, Copenhagen University Hospital, Rigshospitalet Copenhagen, Denmark

Background: Extensive catheter ablation beyond pulmonary vein isolation may acutely increase atrial tissue stiffness, however this may differ between energy sources used.
Objectives: This study aimed to compare acute (<4 hours) effects of focal radiofrequency ablation (F-RFA) and focal monopolar pulsed-field ablation (F-PFA) on atrial tissue stiffness in a porcine model using multifrequency magnetic resonance elastography (MMRE).
Methods: In 17 pigs, an intercaval line was ablated using F-RFA (25 W, 30 sec, n=12/17) or F-PFA (CENTAURI PFA generator, 25 A, 10 pulse trains, n=8/17). Post-ablation, in vitro MMRE data were acquired with a tabletop MRE scanner (n=8/17). In vivo, a novel MMRE protocol utilizing electrocardiography-triggered spin-echo, echo-planar-imaging was established (n=11/17). Shear wave speed (SWS) was reconstructed to quantify tissue stiffness.
Results: In vitro tabletop MRE results revealed significantly higher SWS for the F-RFA ablation zone compared to both the F-PFA ablation (p=0.008) and F-PFA border zone (p=0.003). This was confirmed in vivo with a novel MMRE protocol successfully assessing atrial tissue stiffness which found 37% higher SWS of the F-RFA ablation than its border zone (p=0.016) and 16% higher than the F-PFA ablation zone (p=0.033). Absolute in vivo SWS differences between ablation and border zones were significantly higher for F-RFA compared to F-PFA (p=0.019).
Conclusions: F-RFA produces stiffer acute atrial linear lesions compared to F-PFA in pigs.

Artificial intelligence-Based Detection of Acute Heart Failure in Acute Dyspneic Patients using Chest Computed Tomography

Kristina Miger (1)(2), Anne Sophie Overgaard Olesen (1)(2), Johannes Grand (3), Silas Nyboe Ørting (4), Jens Petersen (4), Marleen de Bruijne (4), Mikael Ploug Boesen (2)(5), Michael Brun Andersen (6), Jens Jakob Thune (1)(2), Olav W. Nielsen (2)

(1) Department of Cardiology, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Denmark
(2) Department of Clinical Medicine, University of Copenhagen, Denmark
(3) Department of Cardiology, Copenhagen University Hospital – Amager and Hvidovre, Denmark
(4) Department of Computer Science, University of Copenhagen, Denmark
(5) Department of Radiology, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Denmark
(6) Department of Radiology, Copenhagen University Hospital – Herlev Gentofte, Denmark

Background: Diagnosing acute heart failure (AHF) through radiology is challenging for non-radiologists. While chest CT is increasingly used in patients with undifferentiated dyspnea and accurately assesses pulmonary congestion, the shortage of radiologist limits its application. We hypothesized that artificial intelligence (AI) can detect radiological signs of AHF and aimed to develop and validate an AI-algorithm for this purpose.

Methods: We validated an in-house AI-algorithm for detecting AHF on acute chest CT scans. The model utilized twelve key radiological features and established optimal thresholds for the AHF diagnosis. We validated the AI-algorithm in a separate, prospective cohort of 236 acute dyspnoeic patients who underwent low-dose, non-contrast, chest CT and echocardiography. The primary outcome was radiological AHF, determined by on-call radiologists. Secondary outcomes included a range of clinically relevant AHF diagnoses.

Results: Of 236 patients, 62 (26%) were diagnosed with radiologic AHF. The AI-algorithm demonstrated high diagnostic accuracy for radiologic AHF (AUC 0.95 [95%-CI: 0.93-0.98]), with a sensitivity of 89% [95%-CI: 78-95%] and specificity of 89% [95%-CI: 83-93%]. At the rule-in threshold, the sensitivity was 97% [95%-CI: 86-100%], and at the rule-out threshold, the specificity was 96% [95%-CI: 92-98%]. For the secondary outcome diagnoses, the median AUC was 0.93 [range 0.91-0.96], with exceptional performance in cardiogenic AHF and pulmonary overlay (AUC 0.96).

Conclusion:
This novel AI-algorithm demonstrated high diagnostic accuracy for radiologic AHF on chest CT in patients presenting with acute dyspnea, matching the performance of current best clinical practice. These results underscore its potential to advance early, reliable identification of AHF.

“Non-Compaction Cardiomyopathy in an asymptomatic patient with Ischemic stroke. A multimodal imaging approach’’.

Kristine Avetisyan, Saint Gregory Illuminator Medical Center

Left Ventricular Non-Compaction (LVNC), also known as non-compaction cardiomyopathy, is characterized by prominent left ventricular (LV) trabeculations and deep intertrabecular recesses. The compacted epicardial and excessive non-compacted endocardial layers likely result from an arrest of myocardial compaction during intrauterine development. LVNC can be associated with other congenital conditions or may be isolated.
A 63-year-old male was admitted to the neurology department complaining of left-sided weakness, facial drooping, and speech difficulties. His medical history included arterial hypertension, for which he was taking Perindopril (10 mg), Indapamide (2.5 mg), and Amlodipine (10 mg). Upon admission, his blood pressure was 210/100 mm Hg. Brain MRI revealed right frontoparietal lobar ischemia with a 20 x 10 mm lesion in the delayed acute stage. The patient was diagnosed with an acute ischemic stroke in the territory of the terminal branches of the right middle cerebral artery and was treated accordingly in the neurology department. During cardiac evaluation the patient did not report symptoms characteristic of heart failure, palpitation or chest pain: The ECG showed sinus rhythm at 75 beats per minute with T-wave inversion in leads II, III, aVF, and V3-V5. Echocardiography revealed significant left ventricular hypertrophy, with an interventricular septum (IVS) measuring 17 mm and posterior wall (PW) measuring 15 mm. The ascending aorta was slightly dilated at 40 mm, with mild aortic and tricuspid regurgitation. Left ventricular ejection fraction (EF) was 40-45%, with no signs of hypokinesis. Significant trabeculations were noted in the LV apical region. Laboratory results included high-sensitivity troponin T
(hsTnT) at 19 pg/ml (normal <14 pg/ml) and LDL cholesterol at 3.31 mmol/L. After successful treatment for the ischemic stroke, the patient was discharged with prescriptions for Perindopril (10 mg OD), Indapamide (2.5 mg OD), Amlodipine (10 mg OD), Nebivolol (5 mg OD), Atorvastatin (40 mg OD), Acetylsalicylic acid (100 mg OD), Clopidogrel (75 mg OD) and Dapagliflozin (10 mg OD). Four weeks later, the patient was admitted to the cardiology department, where coronary angiography was performed. No hemodynamically significant coronary artery stenosis was detected. Dynamic ECG showed inverted T waves in leads
V2-V4, as well as biphasic T waves in leads II, III, and aVF. Cardiac MRI revealed significant LV trabeculation with a non-compacted myocardium-to-compacted myocardium ratio of 2.6:1, along with eccentric LV hypertrophy (108 g/m^2), LV end-diastolic diameter (LVEDD) of 58 mm, and an EF of 40%. The right ventricle was also significantly trabeculated, and both atria were dilated. No myocardial edema, perfusion defects, or late gadolinium enhancement
(LGE) were observed. Mild aortic and tricuspid regurgitation were noted. The MRI findings were consistent with non-compaction cardiomyopathy. 24-hour Holter monitoring revealed sinus rhythm with 160 premature atrial complexes, 2 atrial couplets, 2 episodes of atrial tachycardia, and 2,400 monomorphic premature ventricular complexes with 8 couplets. NT-proBNP level was 587.5 pg/ml., and Torasemide 10 mg was added to the patient’s regimen. Considering that the MRI image is not characteristic of cardiogenic embolism and ischemic stroke development, and that no episodes of atrial fibrillation were detected through Holter monitoring, oral anticoagulants were not prescribed to the patient. Conclusion: Non-compaction cardiomyopathy is a rare condition that primarily presents with heart failure, arrhythmias, and systemic embolism. In some cases, it may be asymptomatic and detected incidentally through imaging tests. Echocardiography is the primary diagnostic tool that raises suspicion of LVNC. Cardiac MRI is required for diagnostic confirmation. Even in asymptomatic patients with LV systolic dysfunction, guideline-directed medical therapy (GDMT) should be initiated. The necessity of anticoagulation should be carefully assessed on a case-by-case basis, and patients should be monitored dynamically to prevent disease-related complications.

Situational Diagnosis of Cardiovascular Mortality in Brazil and Denmark: A Comparative Perspective

Laís Santos [1]
Raphael Guimarães [1]
[1]National School of Public Health, Oswaldo Cruz Foundation, Brazil

Background: Cardiovascular disease remains the leading cause of death globally. However, high-income countries like Denmark experienced cancer overtake cardiovascular mortality in the 1970s due to the Cardiovascular Revolution —a marked decline in cardiovascular deaths. In upper-middle-income countries, such as Russia, early signs of this transition were observed at the beginning of the 21st century. Brazil, with its regional inequalities, may present varied epidemiological patterns. Identifying areas within Brazil that reflect this shift could help tailor health system responses. Comparing Brazil with a more equal country like Denmark may offer valuable insights to strengthen cardiovascular healthcare strategies across diverse socioeconomic settings. **Methods:** We used secondary data from the Brazilian Information System (DATASUS) and Denmark registries (Statistik), applying ICD-10 codes for cardiovascular diseases and six subgroups (myocardial infarction, stroke, heart failure, atrial fibrillation, peripheral disease, and valvular disease), as well as cancer, to analyse mortality trends in Brazil and Denmark from 1996 to 2022. We calculated age-adjusted rates for the analysed causes of death and conducted time-series analysis using the Joinpoint Regression method to identify significant changes in trends over time. **Results:** The burden of cardiovascular mortality is much higher in Brazil (141.6/100,000 inhabitants) compared to Denmark (46/100,000), whereas cancer mortality differs slightly (86.2/100,000 in Brazil vs 97.3/100,000 in Denmark). Over time, Denmark has shown convergence in mortality rates between males and females, indicating a narrowing gender mortality gap, while a significant gender difference remains in Brazil. Analysis of cardiovascular subgroups shows that Denmark experienced a gradual decrease in myocardial infarction mortality for both sexes over time, with a slight gender gap in 2022: 7.8/100,000 for males and 4.43/100,000 for females. In Brazil, male mortality remains 35% higher, reaching 43/100,000 in 2022. Stroke mortality in 2022 was 30% higher in Brazil, though trends show a decrease in both countries. In Denmark, significant changes occurred between 1996–2006 ($p = 0.004$) and 2005–2009 ($p < 0.001$) for males, and 2005–2009 ($p < 0.001$) for females. In Brazil, annual percentage changes were significant from 1996–2002 for both males ($p = 0.007$) and females ($p = 0.001$), and from 2008–2022 for males ($p = 0.016$) and females ($p = 0.005$). Rapid changes in heart failure mortality occurred in Denmark between 1996 and 2009 ($p < 0.001$), followed by stability in female mortality and an increase in male mortality after 2010. In Brazil, trends show a gradual decrease in heart failure mortality for both sexes (AAPC: $p < 0.001$). For atrial fibrillation, a notable difference in age-adjusted rates was observed between Denmark (18/100,000) and Brazil (2/100,000). Denmark already had higher rates in 1996, which increased significantly between 2009 and 2015 for males (APC 12.40; CI 8.88–21.80; $p < 0.001$) and females (APC 8.87; CI 5.20–19.01; $p = 0.007$). In Brazil, rates were below 1/100,000 in 1996, rising steadily from 2002 for both males (AAPC 4.56; CI 3.79–5.59; $p < 0.001$) and females (AAPC 3.74; CI 3.34–4.09; $p < 0.001$). **Discussion:** Results indicate a significant difference in cardiovascular mortality between Brazil and Denmark, with a much higher burden in Brazil, potentially linked to premature mortality. However, some cardiovascular subgroups, like cerebrovascular diseases, show similar patterns that may relate to improved control of risk factors such as diet, smoking, and blood pressure. In contrast, diseases like myocardial infarction (linked to access to treatment) or atrial fibrillation (associated with older age) show wider gaps, possibly reflecting differences in development and equity. **Conclusion:** In future steps, we aim to identify whether any Brazilian state exhibits cardiovascular mortality patterns similar to Denmark's and may have undergone a Cardiovascular Revolution. We will conduct the same analysis for Brazil's 27 Federal Units to detect potential trends and collect social indicators—such as life expectancy, average income per capita, poverty rate, Gini index, and HDI—to interpret the results.

The Natural History of Coronary Microvascular Dysfunction: Rationale and Design of the iPower 2 Longitudinal Follow-Up Study

Laura Amalie Rytoft MD[1]; Rasmus Ripa, Professor, MD, DMSc[2,3]; Lisbeth Marner, MD, DMSc[4]; Naja Mygind, MD, PhD[1]; Eva Prescott, Professor, MD, DMSc[1,2]

[1] Department of Cardiology, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
[2] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[3] Department of Clinical Physiology and Nuclear Medicine, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
[4] Department of Clinical Physiology and Nuclear Medicine, Herlev and Gentofte Hospital, Copenhagen, Denmark

Background
Coronary microvascular dysfunction (CMD) is increasingly recognized as a key contributor to angina in the absence of obstructive coronary artery disease and is associated with adverse cardiovascular outcomes. However, the natural history and systemic consequences of CMD remain poorly understood. The iPower 2 study aims to evaluate the evolution of CMD and its associations with inflammation, heart failure with preserved ejection fraction (HFpEF), cerebral hypoperfusion, and renal dysfunction.

Method and Analysis
iPower 2 is a Danish investigator-initiated, prospective, longitudinal cohort study and a 10-year follow-up of the original iPower cohort conducted between May 2012 and December 2017, where 1852 patients and 102 controls were enrolled. The baseline assessment included full echocardiography during rest and stress, including coronary flow velocity reserve, detailed clinical characteristics, medical history, risk factors, symptoms, quality of life and a panel of 184 cardiovascular biomarkers, including inflammation. These women will be followed using comprehensive data from Danish National Registries (*substudy 1*). A survey will be conducted of all living iPower participants to assess persistency of symptoms and quality of life (*substudy 2*).
A subset of randomly selected women (n=200) will undergo clinical reassessment (*substudy 3*). This includes repeated coronary flow velocity reserve by transthoracic Doppler echocardiography, cardiac CT, biomarker analysis and renal function testing. A group of 60 participants will undergo additional advanced imaging using brain [15O]H2O PET, vascular [18F]FDG-PET and cardiac MRI to assess cerebral perfusion, vascular inflammation and HFpEF.

Conclusion
iPower 2 will provide unique long-term insights into the systemic effects of CMD and identify potential mechanisms and risk markers for cardiovascular and microvascular disease progression in women with angina and no obstructive coronary artery disease.

With a little help from our friends: telemedicine support for caring of patients with heart failure in Rio de Janeiro, Brazil. The Brazilian Heart Insufficiency with Telemedicine project (BRAHIT)

Leonardo Graever[1], Helena Dominguez[1]
[1] Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen

BACKGROUND: Heart failure is a global public health challenge and a common cause of recurrent hospital admissions and reduced quality of life. The integration of healthcare sectors can improve outcomes for patients with heart failure. We hypothesise that telemedicine between cardiologists and primary care physicians (PCPs) is an efficient strategy to foster the integration of healthcare sectors. However, evidence regarding the effectiveness of telemedicine between providers on patient-relevant outcomes, such as hospital admission rates, mortality, and quality of life, is lacking. During the BRAHIT (Brazilian Heart Insufficiency with Telemedicine) project, a collaboration between academic institutions in Denmark and Brazil, we implemented telemedicine support from cardiologists to PCPs in Rio de Janeiro and evaluated the intervention. METHODS: Based on the UK Medical Research Council Framework for the Study of Complex Interventions, we have conducted three studies: 1 - a mixed-method feasibility study combining content analysis of focus groups and individual physicians' interviews with a before-and-after assessment of clinical data; 2 - a cross-sectional study where we analysed and compared the usage patterns and the content of the telemedicine interactions in two telemedicine services in Rio, one implemented within the BRAHIT project and other from the city's Health Department. We used the ICPC-3 to classify reasons for consultations and diagnoses, the Taxonomy of General Clinical Questions for clinical questions, and the Champlain eConsult BASE™ classification for answers; 3 - a cluster-randomised trial to assess the effectiveness of telemedicine between providers on patient readmission rates and mortality (currently in the follow-up phase). RESULTS: Feasibility Study: All groups considered telemedicine feasible and perceived it as a good strategy. However, patients expressed concerns regarding reduced direct access to cardiologists, some primary care physicians reported work overload and a lack of perceived advantage, and cardiologists voiced worries about the sustainability of the intervention. Quantitative analysis of 83 patients showed a poor baseline clinical status, with over 50% presenting low physical capacity (NYHA 3 or 4). Although much of the follow-up data was unavailable, the baseline compliance with drug prescriptions according to Guideline-Directed Medical Therapy principles for treating heart failure with reduced ejection fraction was 12/22 (55%), and did not change after telemedicine interaction. Individual drug prescription compliance improved for beta-blockers (10% rise), renin-angiotensin system inhibitors (9% rise), and SGLT-2 inhibitors, not prescribed before the teleconsultation interaction and prescribed to five patients after. However, the prescription of mineralocorticoid antagonists showed a 5% decline. Cross-sectional study: When comparing the usage frequency of both studies' services, the Health Department service use by the PCPs working in the city practices was higher (332/1093, 31%) compared to the BRAHIT project service (43/1331, 5%). The average answer time was much shorter in the Health Department service (50 min) than in the BRAHIT telemedicine service (two days). Most clinical questions (203/278, 73%) to the Health Department's service were about diagnosis, mainly regarding electrocardiography interpretation (190, 91%). The questions asked in the BRAHIT service were more frequently about treatment (30/68, 44.1%) or case management (29/68, 42.6%). The analysis of both models and their contribution to future implementation projects and continuing medical education opportunities were discussed. EXPECTED RESULTS: Cluster-randomised trial: The ongoing trial will help determine whether the intervention effectively affects patient-relevant outcomes. CONCLUSIONS: Telemedicine between cardiologists and primary care physicians was feasible in the study setting. Significant barriers include the high workload and a lack of perceived relative advantage in primary care. Factors associated with the telemedicine delivery model may also influence uptake and use patterns, and a balance between practicality and complexity is needed. Shared care through telemedicine may present a good strategy to integrate specialists and PCPs to care for patients with heart failure. The upcoming trial results will describe the effects on mortality, readmission rates, and quality of life.

Title: Investigating Left Ventricular Mass in Children with Obesity – a Cross-Sectional Study

Mathilde Løk Olsen[1,2,3], Benjamin M. Nerup[1,2], Niels Vejlstrup[3], Torben Hansen[4], Thomas Jespersen[1], Jens-Christian Holm[1,2,4], Per Lav Madsen[5,6], and Morten A. V. Lund[1,2,3].

1. The Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
2. The Children's Obesity Clinic, Accredited European Centre for Obesity Management, Department of Pediatrics, Copenhagen University Hospital Holbæk, Holbæk, Denmark
3. Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
4. Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen N, Denmark.
5. Department of Cardiology, Copenhagen University Hospital—Herlev, Denmark.
6. The August Krogh Institute, NEXS, University of Copenhagen, Copenhagen, Denmark.

Background: Elevated left ventricular (LV) mass (LVM) is an established complication to obesity and has also been reported in children with obesity. This is worrying, as childhood obesity is rising worldwide. We aimed to assess LVM and prevalence of hypertrophy in children with obesity compared to peers with normal weight. Secondly, we assessed the correlations between body composition and LVM.

Methods and Results: In this cross-sectional study, cardiac MRI (CMR), dual-energy x-ray absorptiometry and anthropometrics were obtained in 141 children between 10-15 years with obesity (n=92) and with normal weight (n=49). LVM were derived from CMR and indexed to height$^{2.7}$ and lean body mass. The obesity group exhibited elevated LVM and LV volumes compared to the control group ($p<0.001$). LVM indexed to height$^{2.7}$ was significantly higher in the obesity group (25.1 g/m$^{2.7}$ (IQR: 23.3, 28.2) vs. 20.5 g/m$^{2.7}$ (IQR: 18.7,22.3), $p<0.001$), while LVM indexed to lean body mass only tended to be higher (2.38 g/kg (IQR: 2.18, 2.56) vs. 2.29 g/kg (2.16, 2.45), $p=0.075$). We identified 31 (34%) cases of hypertrophy in the obesity group. Correlations between LVM and measures of body composition were modeled with simple and multiple linear regression. We found significant positive correlations with body mass index (BMI) standard deviation scores (SDS), weight SDS, lean body mass, fat percentage, waist-, and hip circumference, when adjusted for age, sex, and systolic blood pressure SDS.

Conclusion: LVM was significantly elevated in children with obesity compared to peers with normal weight. We identified hypertrophy in 34% of the obesity group. We found a positive correlation between LVM and BMI SDS, weight SDS, lean body mass, fat percentage, waist circumference, and hip circumference.

EMPagliflozin after Aortic Valve Replacement – the EMPAVR study

Louise Marqvard Sørensen, MD; Emil L. Fosbøl, MD PhD.

Introduction: Left ventricular (LV) dysfunction secondary to aortic stenosis (AS) is a key part of the underlying pathophysiology for patients with AS. Pre- and post-aortic valve replacement (AVR) related LV remodeling may be an important path to improve patient outcomes. Previous trials suggest that up to 1/3 of patients do not benefit symptomatically after AVR. This could be explained by delayed or laden LV remodeling. Sodium-glucose Cotransporter-2 (SGLT2) inhibitors are efficacious in heart failure and has been shown to positively influence LV function and size. In the EMPAVR trial we want to test whether SGLT2 inhibition after AVR is superior to placebo in reducing left ventricular mass and improve patients' symptoms.

Methods: The EMPAVR study is an investigator initiated randomized, placebo-controlled, and double-blinded trial comparing the effect of empagliflozin to placebo in patients with severe and symptomatic AS undergoing AVR. The aim is to investigate whether empagliflozin is superior to placebo in reducing left ventricular mass and improve patients' symptoms. At present 130 patients of 206 patients have been randomized in the EMPAVR trial program. Patients are randomized 1:1 to 180 days of treatment, during which they will attend follow-up visits.

Discussion: The EMPAVR study is the first placebo-controlled trial investigating the effects of SGLT2 inhibition in a AVR population. The EMPAVR study has the potential to pave the way for treatment of the left ventricle in valvular heart disease and may help patients worldwide and challenge our understanding of aortic stenosis disease. Study results are anticipated to be ready by the beginning of 2026.

Trial Registration The EMPAVR study have been registered on December 2024 (Clinical Trial Registration number: NCT06171802) before enrollment of the first patient. All patients will provide oral and written informed consent. The EMPAVR study is approved by the Regional Committee on Health Research Ethics and the Danish Medicines Agency.

Heart size on acute low-dose CT and risk of clinical outcomes among dyspnoeic patients admitted to the emergency department

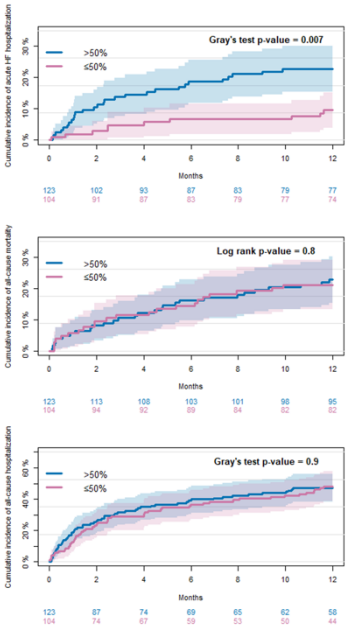
Lucas Malta Westergaard[a] MD; Emilie Meldgaard[a] MB; Anne Sophie Olesen[b] MD; Kristina Miger[b], MD; Olav Wendelboe[b,c] MD, Drmsch; Johannes Grand[a] MD, PhD
[a] Department of Cardiology, Copenhagen University Hospital Amager-Hvidovre, Denmark
[b] Department of Cardiology, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[c] Department of Clinical Medicine, Copenhagen University, Denmark

Background: Despite the growing number of chest computed tomography (CT) scans in recent years, there remains a lack of a validated, systematic approach for assessing signs of heart failure on CT. Traditionally, a heart occupying more than 50% of the thoracic cavity on a chest radiograph has been considered enlarged by radiologists, warranting cardiological assessment.

Purpose: To evaluate heart size on low-dose chest CT among dyspneic patients admitted to the emergency department and to assess the risk of acute heart failure (AHF) hospitalization, all-cause mortality, and all-cause hospitalization during 1-year follow-up.

Methods: This observational study included 230 patients consecutively admitted to the emergency department with acute dyspnea. All patients underwent low-dose chest CT, lung and cardiac ultrasound, and NT-proBNP testing. A diagnosis of AHF was adjudicated by two cardiologists. Heart size was defined as the ratio of heart size to lung size measured on low-dose chest CT (i.e., heart-to-lung ratio). Multivariate Cox proportional hazards regression models were used to assess the association between heart-to-lung ratio and the risk of AHF hospitalization, all-cause mortality, and all-cause hospitalization during a 1-year follow-up after discharge from the index hospitalization with acute dyspnea. Hazard ratios (HRs) were reported with 95% confidence intervals (CIs). Patients were stratified by heart-to-lung ratio (>50% vs. ≤50%).

Figure 1. Cumulative incidence of AHF hospitalization, all-cause mortality, and all-cause hospitalization during 1-year follow-up.



Results: We included 230 patients (median age 75 years [IQR=67,81], 57% male, median left ventricular ejection fraction 55% [IQR=45,60], median heart size on low-dose CT 122 mm [IQR=106,137], lung size on low-dose CT 237 mm [IQR=201,280]). Patients with heart-to-lung ratio >50% had a higher prevalence of heart failure, valvular heart disease, and atrial fibrillation, and were more likely to be treated with beta-blockers and loop diuretics. During hospitalization with acute dyspnoea, 3 patients died. During 1-year follow-up, 38 patients (17%) were AHF hospitalized, 50 patients died (22%), and 108 (48%) were all-cause hospitalized (Figure 1). A 1% increment in heart-to-lung ratio was associated with an increased risk of AHF hospitalization (HR=1.07, CI=1.01,1.13, p-value=0.02) during 1-year follow-up. Heart-to-lung ratio was not associated with all-cause mortality (HR=1.03, CI=0.99,1.08, p-value=0.2) or all-cause hospitalization (HR=1.00, CI=0.97,1.03, p-value=0.9).

Conclusion: An increase in heart-to-lung ratio measured on low-dose chest CT was associated with an increased risk of AHF hospitalization during 1-year follow-up among dyspneic patients admitted to the emergency department. This simple yet effective measure may help identify high-risk patients requiring cardiological assessment.

Detection of vascular risk factors in nocturnal photoplethysmograms using deep learning

Malene Nørregaard[1], Konstanze Betz[2], Astrid N L Hermans[2], Kevin Vernooy[2], Ulrich Schotten[4], Jørgen K. Kanters[1,3], Dominik Linz[1,2], Jonas L. Isaksen[1]

[1]Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

[2]Department of Cardiology, Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands

[3]Center for Biosignal Research, University of California San Francisco, San Francisco, USA

[4]Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands

Background:
Photoplethysmography (PPG) is a technology already widely available in e.g. smartwatches. It is currently used for live monitoring of e.g. heart rate and even detection of AF episodes. However, it is unknown if the patient's vascular risk factors, such as age, sex and hypertension, manifest in the PPG signals and whether these factors should be considered in algorithm development.
We aimed to assess whether vascular risk factors were detectable in PPG signals using deep neural networks.

Methods:
We included 389 patients (mean age 63 (9.1) years, 39 % females) with AF from the VIRTUAL-SAFARI study. The patients were scheduled for AF ablation and underwent a sleep disordered breathing management pathway, including an overnight home sleep test using a WatchPAT device (Zoll Itamar, Atlanta, GA). The PPG recordings were extracted and divided into one-minute segments and used as input to a convolutional neural network (CNN).
We trained convolutional neural networks to estimate selected vascular risk factors based on the individual components from the CHA_2DS_2-VASc score, using 5-fold cross-validation.

Results:
We were able to detect female sex with a sensitivity of 64% and a positive predictive value (PPV) 81%. Age was detectable with a root mean squared error (RMSE) of 7.3. The remaining vascular factors were not detectable in the PPG signal.

Conclusion:
Sex and age were detectable in nocturnal PPGs with high sensitivity and PPV. Further research is required to assess whether these factors need to be considered when developing algorithms using PPGs.

Abstract

Malene Højgaard Andersen[1], MD, Jesper Møller Jensen[1], MD PhD, Helle Kanstrup[1], MD PhD, Niels P. Rønnow Sand[4], MD PhD, Martin Busk[6], MD PhD, Malene Kærslund Hansen[1], MD, Pernille Gro Thrane[1], MD PhD, Kevin Kris Warnakula Olesen[1], MD PhD, Børge G. Nordestgaard[2,3], MD PhD, DMsc, Michael Maeng[1], MD PhD, Michael J. Blaha[5], MD, Bjarne Linde Nørgaard[1], MD PhD, DMsc, Martin Bødtker Mortensen[1,5], MD PhD.

[1]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Clinical Biochemistry, Copenhagen University Hospital - Herlev and Gentofte, Gentofte, Denmark
[3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[4]Department of Cardiology, University Hospital of Southern Denmark, Esbjerg and Institute of Regional Health Research, University of Southern Denmark, Denmark
[5]Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States
[6]Department of Cardiology, Lillebaelt Hospital, Vejle, Denmark

Background: The role of low-density lipoprotein cholesterol (LDL-C) in atherosclerotic cardiovascular disease in elderly individuals >75 years of age remains controversial.

Purpose: To assess whether LDL-C is associated with coronary atherosclerotic plaque burden and future myocardial infarctions (MI) in statin-naïve individuals across different ages with a primary focus on individuals aged >75 years.

Methods: This contemporary cohort study included individuals who underwent computed tomography angiography (CCTA) between 2008 and 2021 from the Western Denmark Heart Registry. Outcomes and measures included 1) adjusted risk ratio (aRR) for any plaque, 2) aRR for early revascularization (within 90 days of CCTA) indicating significant obstructive plaque, and 3) adjusted hazard ratio (aHR) for MI.

Results: The study included 37,910 statin-naïve symptomatic individuals, including 1,562 aged >75 years. During a median follow-up of 5.1 years, 433 individuals experienced MI. The prevalence of any plaque was 19,962 (53%) and was associated with LDL-C levels across all age-groups. Thus, the aRR for presence of any plaque and for early revascularization was 1.14 (95% CI 1.07-1.22) and 3.18 (1.94-5.23), respectively, in individuals aged >75 years with high versus low LDL-C (>4.4 versus <2.7 mmol/L) being comparable to the association in younger age-groups. The aHR for MI was 1.57 (95% CI 1.06-2.32) per 1 mmol/L higher LDL-C for individuals aged >75 years.

Conclusion: LDL-C was strongly associated with the presence of coronary plaque and elevated MI risk in individuals beyond 75 years of age. These findings suggest that LDL-C drives coronary artery disease throughout life.

Structure and functional studies of TRPV2 with the inhibitor valdecoxib

Malene L. Wind[1], Alexandra Ptáková[2], Viktorie Vlachová[2], Peter Zygmunt[3], Pontus Gourdon[1]. [1] Department of Biomedical Sciences, University of Copenhagen, Denmark, [2] Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic, [3] Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden.

The transient receptor potential vanilloid (TRPV) sub-family of proteins is known for their cation selectivity and is a well-studied group of ion channels. They respond to sensations of pain, heat and inflammation and have been targeted by multiple small molecules [1,2]. TRPV2 has been linked to pathogenesis of cardiomyopathy [3], cancer and atrial fibrillation in the context of pulmonary hypertension [4]. Despite this, TRPV2 has a poorly defined pharmacological profile with multiple non-selective agonists and antagonists and has been suggested to play a role as a redox- and or ligand-operated channel. Thus, there is potential and intent to deepen the knowledge of TRPV2.

In this study, we purified recombinant rTRPV2 from *Pichia Pastoris* and solubilized it in detergent. TRPV2 was briefly incubated with the recently reported selective antagonist, valdecoxib before freezing. We solved the structure bound to valdecoxib using cryo-EM at a 3.6 Å resolution. The structure reveals classic TRPV features, including the vanilloid pocket.

To support the structure, we explored the synergistic effects of probenecid and 2-APB with valdecoxib, by whole-cell patch clamp electrophysiology measurements. The experiments confirm the selective antagonistic effect of valdecoxib effectively inhibiting channel activity in a context-dependent manner. Overall, our study marks a significant step toward establishing TRPV2 as a viable, selective drug target, for treatment of atrial fibrillation and associated cardiovascular pathologies.

References

1) Seebohm, G. & Schreiber, J. A. Beyond hot and spicy: TRPV channels and their pharmacological modulation. Cell Physiol. Biochem. 55, 108–130 (2021).
2) Liu, B., & Qin, F. (2016). Use dependence of heat sensitivity of vanilloid receptor TRPV2. Biophysical journal, 110(7), 1523-1537.
3) Watanabe H, Murakami M, Ohba T, Ono K, Ito H. The pathological role of transient receptor potential channels in heart disease. Circ J. 2009 Mar;73(3):419-27. doi: 10.1253/circj.cj-08-1153
4) Tianxin Ye, Zhuonan Song, Yunping Zhou, Zhangchi Liu, Yi Yu, Fangcong Yu, Yanan Chu, Jiaran Shi, Longbo Wang, Cui Zhang, Xin Liu, Bo Yang, Jinxiu Yang, Xingxiang Wang. TRPV2 inhibitor tranilast prevents atrial fibrillation in rat models of pulmonary hypertension. Cell Calcium, 117, (2024)

Divergent genetic influences on BMI and BF%: Implications for musculoskeletal and cardiometabolic health

María José Romero-Lado[1], I. Khrystoforova[1], G.D. Carrasquilla[2], T.O. Kilpeläinen[1]

[1] Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

[2] Novo Nordisk A/S, Måløv, Denmark.

Body mass index (BMI) and body fat percentage (BF%) are key metrics for assessing adiposity. While BMI is simple to use, BF% offers a detailed view by distinguishing fat mass (FM) from fat-free mass (FFM). The genetic differences between BMI and BF% and their implications for body composition and cardiometabolic health remain unclear.

We conducted GWAS on 417,959 UK Biobank participants, identifying 814 and 697 significant loci for BMI and BF%, respectively. Despite high genetic correlation (0.85 in women, 0.81 in men) and many shared loci, tissue enrichment analyses revealed distinct biological pathways: BMI-related genes were enriched in the brain, while BF%-related genes were enriched in adipose tissue.

Weighted polygenic scores were created to explore the effects of these loci on body composition and fat distribution. Both scores were linked to increased FM, but the BMI score was also associated with increased FFM, bone mineral density, and hand-grip strength. In contrast, the BF% score was linked to a preference for subcutaneous over visceral fat.

We classified BMI and BF% loci into body composition clusters based on their effects on FM and FFM. Two clusters were shared between BMI and BF%, associated with increased FM alone or with increased FFM. A unique BF% cluster was linked to increased FM but decreased FFM, lower bone mineral density, and handgrip strength, favoring subcutaneous fat and showing a protective effect against type 2 diabetes and cardiovascular disease.

Our study highlights the distinct genetic architectures of BMI and BF%, providing new insights into obesity research.

Title: Epigenetic Insights into Drug-Induced QT Prolongation: A Multi-Omics Approach

Authors: Marlene Schouby Bentestuen*[1,2], Anna Szoszkiewicz* [3, 4], Juan Cordero-Solorzano [5,6,7], Christiane Gasse [1,2,8], Anna Starnawska [5,6,7]

** shared first*

Affiliations:

1. Psychosis Research Unit, Aarhus University Hospital Psychiatry, Aarhus, Denmark
2. Department of Clinical Medicine, Health, Aarhus University, Aarhus, Denmark
3. Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland
4. Doctoral School, Poznan University of Medical Sciences, Poznan, Poland
5. Department of Biomedicine, Health, Aarhus University, Aarhus, Denmark
6. The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark
7. Center for Genomics and Personalized Medicine, CGPM, and Center for Integrative Sequencing, iSEQ, Aarhus, Denmark
8. Department of Affective Disorders, Aarhus University Hospital Psychiatry, Aarhus, Denmark

Abstract

Objectives: Drug-induced QT prolongation (diQTP) is a significant clinical concern due to its potential to cause life-threatening arrhythmias. Common medications, such as antiarrhythmics, antidepressants, and antipsychotics, can lead to this condition. Although genetic variants are linked to diQTP, the mechanisms underlying susceptibility to diQTP remain poorly understood. Epigenetic factors may contribute to this susceptibility. However, few studies have investigated the role of epigenetic regulation in diQTP. We aimed to explore the interplay between genetic and epigenetic factors and their contribution to individual susceptibility to diQTP.

Methods: We analyzed diQTP-associated genes and single nucleotide polymorphisms (SNPs) identified in a recent systematic review. To investigate gene-specific epigenetic mechanisms, we queried two epigenome-wide association study (EWAS) databases for associations between DNA methylation at diQTP-associated genes and various traits or exposures. Genomic imprinting was assessed by examining the overlap between diQTP-associated genes and imprinted genes using two established databases. Additionally, we evaluated whether genetic variation in diQTP-associated genes influences gene expression or DNA methylation by determining if the identified SNPs function as methylation quantitative trait loci (mQTLs) and/or expression quantitative trait loci (eQTLs) in whole blood and cardiac tissue.

Results: The gene *KCNQ1* showed recurrent overlaps across the EWAS and imprinting databases, indicating its potential role in the epigenetic regulation of susceptibility to diQTP. Additionally, epigenetic variation in several other genes, including *CACNB2*, *CACNA1C*, *ZFHX3*, and *JPH3*, was significantly associated with multiple complex traits and exposures in the two EWAS databases. The traits most frequently associated with DNA methylation at these loci included aging, a known factor in QTc prolongation, as well as smoking, obesity, and type 2 diabetes, all of which are established risk factors for cardiovascular disease. Furthermore, we identified the diQTP-associated genetic variants in the gene *SCN5A* to act as an mQTL within cardiac tissue, supporting the potential role of epigenetics in mediating diQTP risk.

Conclusion: This study provides initial insights into the potential role of epigenetic mechanisms in diQTP, identifying key genes such as KCNQ1 that may influence susceptibility through altered DNA methylation and gene expression. Although no single dataset provided definitive conclusions, the consistency of findings across multiple sources suggests that epigenetic modifications could contribute to diQTP susceptibility. These findings highlight the importance of further research into the epigenetic landscape of diQTP to elucidate its complex genetic and environmental dynamics.

Longitudinal Assessment of Cardiac Function and Structure in a Chronic Equine Atrial Fibrillation Model

Mélodie Schneider[1], Charlotte Hopster-Iversen[1], Sofie Amalie Troest Kjeldsen[1], Simon Libak Haugaard[1], Sarah Dalgas Nissen[1], Rikke Buhl[1], Colin Schwarzwald[2]

[1]Department of Veterinary Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Taastrup, Denmark

[2]Clinic for Equine Internal Medicine, Vetsuisse Faculty, University of Zurich, Switzerland

Background
Horses serve as a unique translational model for atrial fibrillation (AF), sharing key features with the human condition, including common triggers and progressive remodeling. While AF-related contractile dysfunction is well described in humans, its temporal progression in this model remains unclear.

Aim
To track changes in cardiac function and size over time in a chronic equine AF model using advanced echocardiographic techniques.

Methods
In this longitudinal study, disease progression was followed in 10 horses with atrial high rate pacing induced AF and four sham-operated controls. Echocardiographic assessment was performed at baseline, 1 month, and 4 months using right parasternal long- and short-axis views. Measurements included two-dimensional echocardiography (2DE), motion mode (M-mode), and speckle tracking strain (2DST) to evaluate structural and functional cardiac changes.

Results
Contractile remodeling occurred early in AF horses, with a significant increase in left atrial area (from 89.7 ± 6.9 to 92.8 ± 6.8 cm² at 1 month, $p = 0.003$), a decrease in left atrial reservoir strain (from 17.8 ± 4.2% to 12.9 ± 3.1% at 1 month, $p = 0.0005$), and reduced left ventricular ejection fraction (from 67.5 ± 3.9% to 58.0 ± 5.7% at 1 month, $p = 0.0003$). No significant changes were observed in controls.

Conclusion
Atrial fibrillation induces significant changes in atrial size and function, and ventricular function within one month in this chronic equine model. These findings support early functional deterioration in AF and highlight the value of this model for studying disease progression and therapeutic interventions. Ongoing analysis will correlate echocardiographic strain with histological fibrosis at 4 months to further explore the relationship between structural and functional remodeling.

Nanoformulated eicosapentaenoic acid is a potent suppressor of macrophage pro-inflammatory responses *in vitro*

Nilsson MD[1], Hansen J[1], Hansen A[1], Tripodi GL[1], Muzammel H[2], Türeli E[3], Kerth P[4], Steffensen LB[1], Ejsing CS[5], Svenningsen P[1], Schini-Kerth V[2], Ketelhuth DFJ[1]

1 Cardiovascular and Renal Research Unit, Department of Molecular Medicine, University of Southern Denmark (SDU), Odense, Denmark
2 University of Strasbourg, Translational Cardiovascular Medicine UR 3074, 67000 Strasbourg, France.
3 MyBiotech, Ueberherrn, Germany
4 Preventor TBC GmbH, Pfungstadt, Germany
5 VILLUM Center for Bioanalytical Sciences, Department of Biochemistry and Molecular Biology, SDU, Odense, Denmark

Background and Aims: Atherosclerosis is characterized by chronic inflammation, largely driven by activated macrophages. Omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to influence macrophage activation and support inflammation resolution. However, the effects of different n-3 PUFA formulations, including varying EPA:DHA ratios, on macrophage-mediated inflammatory responses remain unclear. This study examined the impact of nanoformulated EPA and DHA, individually and combined, on pro-inflammatory cytokine production and cytotoxicity in THP-1–derived M1-like macrophages and primary human peripheral blood mononuclear cells (PBMCs) from healthy donors.

Methods and Results: Macrophages were generated from THP-1 monocytes by differentiation with PMA (100 ng/mL) for 24 hours, followed by a 24-hour resting period. Cells were then simultaneously treated with LPS (10 ng/mL) and stabilized nanoformulated EPA, DHA, or EPA:DHA mixtures (1.25:1 and 6:1) at concentrations ranging from 0.003% to 0.1%. Cytokine secretion was quantified by ELISA, and cytotoxicity was evaluated via LDH release. Initial screening showed that at 0.01%, all treatments reduced TNF and IL-1β levels, with EPA having the strongest effect. Individually, EPA and DHA were more effective than their combination, which along with DHA alone exhibited slightly higher cytotoxicity at this dose compared to EPA. A subsequent experiment using 0.01% EPA, DHA, and 6EPA:1DHA confirmed greater suppression of TNF and IL-1β by EPA and DHA alone, with low toxicity observed for all. Native (non-nanoformulated) EPA, DHA, and 6EPA:1DHA at 0.01% also lowered TNF, though less effectively than the nanoformulated oils, with no notable cytotoxicity. In PBMCs, dose titration identified 0.01% nanoformulated omega-3 as effective in reducing IFNγ, TNF and IL-1β, with minimal to no toxicity, under T-cell (PHA) and monocyte (LPS) stimulation, respectively.

Conclusion: This study demonstrates that nanoformulated EPA is a potent modulator of macrophage-driven inflammation, effectively suppressing the secretion of pro-inflammatory cytokines at non-cytotoxic concentrations. Combination formulations with DHA offered no added benefit and showed increased cytotoxicity at higher doses. These findings support EPA as the most bioactive n-3 PUFA tested and provide a strong rationale for extended kinetic profiling, mechanistic multi-omics studies, and forthcoming *in vivo* investigations to map the blueprint of EPA-driven inflammation resolution in atherosclerosis.

Human heart modeling for designing a self-powered leadless pacemaker

[1]Hasani, Milad*, [1]Rezaniakolaei, Alireza & [2]Riahi, Sam
*Lead presenter, e-mail: miha@energy.aau.dk
[1] Department of AAU Energy - Aalborg University, Aalborg, Denmark
[2] Department of Cardiology - Aalborg University Hospital and Department of Clinical Medicine - Aalborg University, Aalborg, Denmark

Background

Intracardiac leadless pacemakers should be replaced after a few years due to limited battery life. The energy harvesting methods can tackle this limitation by providing a sustainable energy source.

Aim

This project aims to design an endocardial energy harvester (EEH) to convert the kinetic energy of the human heart motion into electrical power for pacemaker devices. The efficiency and optimal design of the EEH depend on the motion at the endocardial implant site. This research develops cardiac digital twins based on a biventricular model using the finite element method, facilitating deriving 3D instantaneous translational and rotational motions at different endocardial sites.

Methods and results

A 3D biventricular solid geometry is constructed through an available point cloud[1] dataset of an actual human heart measured by MRI scanning (Fig. 1). The myocardial muscle fibers are implemented (in Fig. 2) with spatial helical arrangement derived from histological data and diffusion tensor imaging method. Electrophysiology propagation from the AV node throughout both ventricles is modeled to mimic natural cardiac contraction. The pericardial–epicardial boundary condition involves the effects of surrounding tissues' viscosity and elasticity. In addition to heart tissue, the hemodynamic is integrated into the model to simulate the fluid-structure interaction between blood flow and heart tissue. Although this model primarily focuses on the 3D simulation of ventricles, it also computes the blood circulatory network through a 0D formulation, including systemic and pulmonary pathways and both atria, to provide accurate blood flow at four heart valves. The heart contraction and relaxation, including the blood flow and electrophysiology propagation, are shown in Fig. 3.

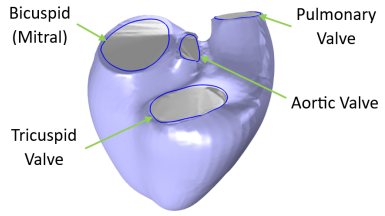


Fig. 1- The 3D solid geometry of a human heart derived from MRI scanning.

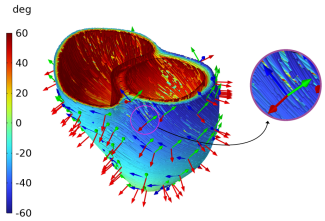


Fig. 2- The helical arrangement of myofibers with variable angle from epicardium to endocardium and from apex to basal.

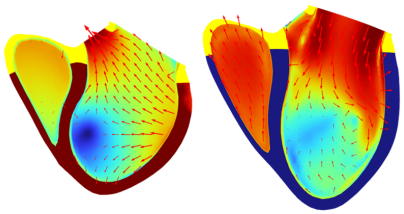


Fig. 3- The 2D cross-section of heart contraction (left) and relaxation (right), showing blood flow in two chambers and electrophysiology propagation in the myocardium.

Conclusions

The results indicate that the model effectively replicates actual heart motion in comparison to cine MRI data. The derived motion at different sites can be used to determine the optimal implant site for endocardial energy harvesting to supply sufficient power for intracardiac leadless pacemakers.

[1] A discrete set of data points in 3D space

Correlation between echocardiography and cardiac MRI for evaluation of cardiac function in a rat model of myocardial ischemia/reperfusion

Natalia Łopuszyńska[1], Ingrid Hunter[1], Sisse Andersen Nørgaard[1]
[1] Minerva Imaging, Oelstykke, Denmark.

Introduction: Accurate evaluation of cardiac function is essential in preclinical models of myocardial infarction. Echocardiography (ECHO) is widely used due to its accessibility, while cardiac MRI (cMRI) provides more precise measurements but is less available in most setups. This study aims to assess the correlation between echocardiography and cMRI in evaluating cardiac function in a rat model of myocardial ischemia/reperfusion (I/R) injury.

Methods: Nineteen male Lewis rats underwent the I/R surgery. A left thoracotomy was performed to expose the heart, and the left anterior descending (LAD) coronary artery was ligated for 30 minutes to induce ischemia, followed by reperfusion. ECHO was performed at baseline, day 2, and day 29 using the Vevo 3100 platform (Fujifilm VisualSonics). Images from PSLAX projections were acquired and analyzed using Vevo Lab. CMRI (Bruker, PharmaScan 70/16 US) was performed at baseline, 3 and 28 days after I/R surgery. Anatomical and functional parameters including ejection fraction (EF) were measured from the stack of six short-axis, retrospectively gated FLASH images evenly distributed along the long-axis of the left ventricle. On day 3 and 28 Late Gadolinium Enhancement (LGE) cMRI was applied to detect and measure infarct size (Figure 1C).

Results: Of the 19 animals, two (10.5%) were lost during anesthesia recovery, six (31.5%) were excluded due to absence of infarct on day 3 cMRI, and eleven (58%) were included in the full study based on confirmed infarct presence. On the day 28/29, EF decreased from 69.5 ± 1.9% to 56.4 ± 5.9 % (cMRI), and from 76.7 ± 4.7% to 49.5 ± 9.2% (ECHO PSLAX), depending on the measurement method (Figure 1A). A very strong correlation (r = 0.80) between cMRI and ECHO (PSLAX) results was observed. Mean infarct size, cMRI, at the acute phase (day 3) was 25.5 ± 7.4% of the LV myocardial volume and decreased to 21.0 ± 4.9 % on day 28 (Figure 1B).

Conclusions: A myocardial ischemia/reperfusion rat model was successfully implemented, and anatomical and functional parameters, including ejection fraction (EF), were measured using both cMRI and ECHO. A very strong correlation between EF measured by cMRI and by ECHO (PSLAX) was confirmed.

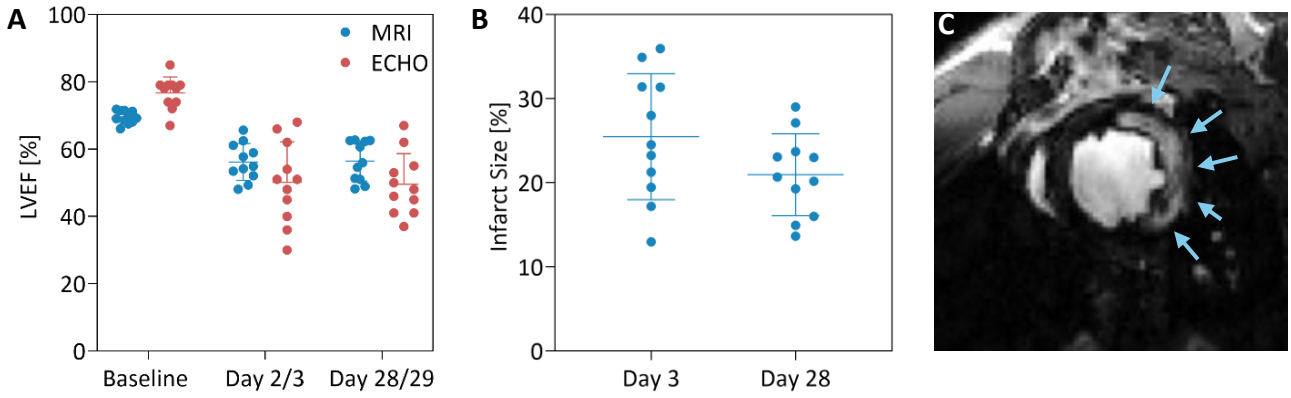


Figure 1. (A) LV ejection fraction (LVEF) measured with MRI (blue) and ECHO PSLAX (red), and (B) infarct size measured in myocardial I/R rat model (cMRI) at baseline, day 2/3 and 28/29 after surgery; (C) Representative late gadolinium enhancement (LGE) cMR image. Infarct is visible as hyperintense area marked with arrows.

Spatial mapping of protein degradation patterns in a mouse stroke model using N-terminal proteomics

Nicoline W. Thorsen[1], Lejla Becirovic[2], Kate L. Lambertsen[2], Michael J. Davies[1] & Luke F. Gamon[1,3].

1. Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark
2. Department of Neurobiology Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark
3. Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

Stroke is an acute vascular event where blood flow to the brain is compromised either due to blockage of- or injury to - the vessels that supply the brain. Age as well as a wide range of lifestyle factors such as smoking, diabetes, physical exercise etc. are important determinators for an individual's risk of stroke, similarly to atherosclerosis, which is considered the main cause of ischemic strokes. At the onset of stroke, quick action and treatment is crucial for assuring the best possible outcome as stroke can result in severe disabilities and in the worst case, death. Although stroke care is improving, a study from the Swedish population from 2019 showed that 2/3 of ischemic stroke patients would either be severely dependent or dead within 5 years of their acute episode.

The last couple of years, regulation of inflammation has been highlighted as a possible key player in the patients' outcome after stroke, with immune cell derived proteases seen to be significantly upregulated in and around the infarct area. However, as the mechanisms involved after onset of stroke, and the importance of these in prognosis and recovery, are not well understood, we hypothesized that using a N-terminal proteomics approach would provide new valuable insight into the proteolytic degradation patterns seen in stroke. In a pilot study, six fixed brain sections (fore- to mid-brain) from each of eight mice, which had undergone artery occlusion seven days prior to sacrifice, were prepared using a N-terminal proteomics workflow to allow for a spatial proteome and degradome map of the stroke area.

A similar N-terminal proteomics approach on lysed plaque tissue from humans has shown remarkable differences in proteolytic activity between patient groups determined by fragmentation. However, by utilizing fixed sections we hope to prove that; proteolytic fragments can be enriched from fixed sections from less starting material, protein degradation is variable between different regions within the stroke area as well as providing new insight into the tissue remodeling, inflammation and degradation pathways important in the resolution of stroke.

Lipoprotein(a) and risk of dementia: three cohort studies including 575,630 individuals

Peter E. Thomas[a,b,c], Signe Vedel-Krogh[a,b,c], Sune F. Nielsen[a,b], , Børge G. Nordestgaard[a,b,c], Ruth Frikke-Schmidt[a,b,c], Pia R. Kamstrup[a,b,c]

[a]Department of Clinical Biochemistry, Copenhagen University Hospital - Herlev and Gentofte, Denmark.
[b]The Copenhagen General Population Study, Copenhagen University Hospital - Herlev and Gentofte, Denmark.
[c]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
[d]Department of Clinical Biochemistry, Copenhagen University Hospital – Rigshospitalet, Denmark
[e]The Copenhagen City Heart Study, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Denmark.

Background and Aims: Dementia is a leading cause of death and disability, shares risk factors with atherosclerotic cardiovascular disease (ASCVD), and 45% of dementia cases may be preventable. High lipoprotein(a) is a risk factor for ASCVD and all-cause mortality while results for dementia are conflicting. With lipoprotein(a) lowering drugs in clinical trial, we tested whether lipoprotein(a) associates with risk of Alzheimer's disease (AD) and/or vascular-related dementia (VRD).

Methods: We included 539,478 individuals with plasma lipoprotein(a) measurements from the Copenhagen General Population Study, the Copenhagen City Heart Study, and the UK Biobank. *LPA* KIV-2 genotypes were available in 117,029 participants in the Copenhagen studies. During a maximum follow-up of 30.2 years, 6,404 developed AD, and 7,866 VRD.

Results: On continuous scales, lipoprotein(a) levels did not associate with risk of AD or VRD when not accounting for competing risks. When accounting for such, absolute risks of VRD increased with higher lipoprotein(a) levels in the UK Biobank (N=458,601; events=5,132; p=0.01), but not in the Copenhagen studies (N=80,877; events=2,734; p=0.4). Absolute risks at age 80 in UK Biobank individuals with lipoprotein(a) >95th vs. ≤50thpercentiles were 3.6% vs. 3.3% for VRD. In the Copenhagen studies, *LPA* KIV-2 number of repeats ≤5th vs. >50th percentile, determining lifelong high lipoprotein(a), associated with a hazard ratio for AD of 1.27(1.08-1.48).

Conclusions: Low lipoprotein(a) levels are not associated with risk of AD or VRD, indicating that pharmacological lowering of lipoprotein(a) is likely safe for risk of dementia. We cannot exclude that very high lipoprotein(a) increases risk of dementia.

Colchicine Assessment of Low-grade Inflammation and Biomarker Response in Atherosclerosis with Targeted Evaluation – The CALIBRATE trial (Protocol)

Rasmus Haahr[1], MD; Peter Dall Mark[2], MD, Ph.D.; Rasmus Ripa[2], MD, DMSc.;Eva I. B. Prescott[1], MD, DMSc.
[1]Dept. of Cardiology, Bispebjerg and Frederiksberg University Hospital. [2]Dept. of Clinical Physiology and Nuclear Medicine, Bispebjerg and Frederiksberg University Hospital.

Background

Colchicine has shown promise in large clinical trials as a potential treatment to mitigate residual inflammatory risk in patients with chronic coronary syndrome (CCS), and in 2024, colchicine was included in the ESC guidelines for the treatment of CCS. However, around the same time, three studies were published that cast doubt on colchicine's effectiveness in this patient population. These studies had various limitations, but nevertheless, they have left the role of colchicine in the treatment of cardiovascular disease uncertain.

Hypothesis

- Colchicine reduces vascular inflammation, as measured by [^{18}F]-FDG PET/CT (FDG-PET), in patients with CCS and low-grade inflammation.
- The effect of colchicine on vascular inflammation is dose dependent.
- Reductions in inflammatory biomarkers correlate with reductions in vascular inflammation.
- Decreases in perivascular inflammation, as assessed by the Fat Attenuation Index(FAI) on coronary computed tomography angiography (CCTA), correlate with decreases in vascular inflammation.

Design

86 patients are included in a prospective, randomized, placebo-controlled clinical study with a stepwise fixed dose-response design. Inclusions criteria are stable CCS patients (with myocardial infarction within 1–12 months), with low grade inflammation (hs-CRP ≥2 mg/L), Left Ventricular Ejection Fraction >45% and age >50 years.

Stepwise fixed doses will consist of two sequential 3-month phases. First phase: 0.5 mg colchicine or placebo once a day for 3 months; succeeded with a second phase: 0.5 mg colchicine or placebo twice a day for additional 3 months.

The intervention is evaluated at baseline, after the first phase, and after the second phase using a test panel consisting of FDG-PET, FAI assessed by CCTA, and inflammatory biomarkers.

The primary endpoint is change in arterial [^{18}F]FDG-uptake after 6 months of colchicine-treatment compared to placebo-treatment.

The Role of Diabetes and Hemoglobin A1c in Cardiac Surgery: Mortality and Kidney Function

Rasmus Bo Lindhardt[1,2], Sebastian Buhl Rasmussen[1,2], Peter Juhl-Olsen[3,4], Lars Peter Riber[2,5], Hanne Berg Ravn[1,2]

[1]Department of Anesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark
[2]Department of Clinical Research, Health Faculty, University of Southern Denmark, Odense, Denmark
[3]Department of Cardiothoracic- and Vascular Surgery, Anesthesia Section, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[5]Department of Cardiac, Thoracic and Vascular Surgery, Odense University Hospital, Odense, Denmark

Introduction
Diabetes Mellitus (DM) is a common comorbidity in cardiac surgery, affecting up to 40% of patients worldwide[1]. However, the prognostic value of the DM biomarker hemoglobin A_{1c} (HbA1c) remains unclear[2]. We aimed to evaluate the impact of preoperative HbA1c on postoperative mortality, acute kidney injury (AKI) and long-term chronic kidney disease (CKD) following cardiac surgery.

Methods
We included patients undergoing cardiac surgery at Odense University Hospital (2010–2022) and Aarhus University Hospital (2010–2024), identified through the Western Denmark Heart Registry. Clinical data were merged with biochemical records from regional laboratory databases. Only the patients' most recent surgery was included. Patients with missing preoperative HbA1c or kidney function data were excluded. Patients were categorized into four groups: HbA1c <48 mmol/mol without diabetes, HbA1c <48 mmol/mol with diabetes, HbA1c 48–52 mmol/mol, and HbA1c ≥53 mmol/mol. We used Cox regression, multinomial regression, and Fine-Gray regression models to analyze mortality, AKI, and CKD, respectively, adjusting for prespecified demographic and procedural variables.

Results
A total of 11,264 patients were included. Univariate survival analysis revealed a 5-year survival of 85% (95% CI: 84–86%), with significant variation across HbA1c groups. In multivariate analysis, patients in the highest HbA1c group had a more than 50% increased hazard of 5-year mortality compared to those in the lowest group (HR 1.52, 95% CI 1.28–1.81, p<0.001). Higher HbA1c levels were also associated with increased risk of AKI (all stages) in both univariate and multivariate analyses, with the highest HbA1c group showing relative risk ratios of 2.13–2.44 across AKI stages, compared to the lowest group. However, no significant association was observed between HbA1c and the development of CKD after adjusting for covariates including AKI.

Conclusion
Elevated preoperative HbA1c was independently associated with increased risks of postoperative mortality and AKI, but not with long-term CKD. These findings suggest that optimizing glycemic control prior to cardiac surgery may improve postoperative outcomes.

References
1. Navaratnarajah M et al. Effect of glycaemic control on complications following cardiac surgery: literature review. *J Cardiothorac Surg*. Jan 17 2018;13(1):10. doi:10.1186/s13019-018-0700-2
2. Jeppsson A et al. 2024 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg*. Dec 26 2024;67(1) doi:10.1093/ejcts/ezae355

Vesicle-mediated transport is a novel disease mechanism in congenital heart disease

Shermaine Tay[1], Karthik Aripaka[1], Oskar Kaaber Thomsen[2], Anne Kathrine Møller Nielsen[3], Osama Jamal Bin Amir Hussain[2], Enrique Audain[4], Marc-Phillip Hitz[4], Vibeke Hjortdal[3], Søren Tvorup Christensen[2], Lars Allan Larsen[1]

[1] Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark. [2] Department of Biology, University of Copenhagen, Copenhagen, Denmark. [3]Department of Cardiothoracic Surgery, Rigshospitalet, Denmark. [4] Department of Medical Genetics, Carl von Ossietzky University, Oldenburg Germany.

Congenital heart disease (CHD) affects approximately 1% of live births and includes a wide spectrum of structural abnormalities. While genetic studies have implicated various pathways in CHD, the precise molecular mechanisms remain poorly defined. By leveraging unpublished CHD genetic data and a systems-genetics framework developed in our lab, we identified vesicle-mediated transport (VMT) genes—*COPZ1, DCTN1, ANK3, SPTBN1, GOSR2* and *KIF11*—as novel CHD candidate disease genes. To explore their potential roles in cardiac development, we employed a combination of in vivo and in vitro approaches. RNA-seq analyses of developing zebrafish hearts revealed robust expression of all six genes. Notably, in situ hybridization further demonstrated enriched expression of *ank3b*, *sptbn1* and *kif11* within heart and brain regions. Subcellular localization studies in RPE-1 cells and P19CL6-derived cardiomyocytes further demonstrated that COPZ1 and ANK3 localize to the Golgi apparatus and ciliary base, indicating a possible role in Golgi-ciliary transport. Importantly, CRISPR-Cas9-generated zebrafish F0 mutants targeting *copz1, dctn1a* and *ank3b* exhibited a higher incidence of cardiac defects. Our ongoing work focuses on generating stable CRISPR-Cas9 zebrafish mutants to further investigate developmental mechanisms. Collectively, our findings support the emerging hypothesis that vesicle transport represents a previously unrecognized pathophysiological mechanism in CHD.

Phenotyping and characterization of a Danish Wild-type Transthyretin Amyloidosis Cardiomyopathy cohort: A cross-sectional study

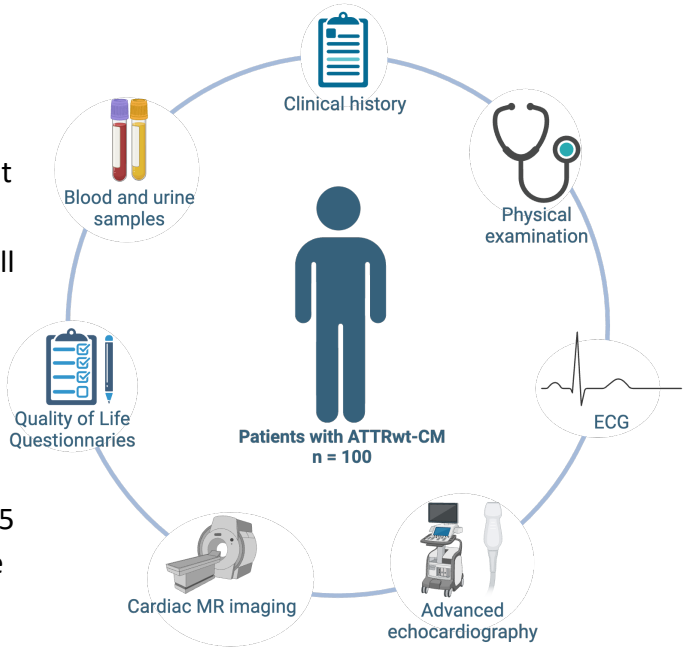
Sie Kronborg Fensman, MD, Aarhus University hospital (SKF) – presenting author
Principal supervisor Steen Hvitfeldt Poulsen, Professor, DMSci, PhD, MD, Aarhus University hospital (SHP)
Tor Skibsted Clemmensen, DMSci, PhD, MD, Aarhus University hospital (TSC)
Bjarke Follin, MSc, PhD, Specialist, Novo Nordisk, Denmark (BF)

Background: Wild-type transthyretin cardiac amyloidosis (ATTRwt-CM) is a progressive cardiomyopathy leading to heart failure, reduced quality of life (QoL) and increased mortality in elderly patients. ATTRwt-CM is caused by amyloid fibril deposition in the myocardium; amyloid fibrils form due to misfolding and aggregation of transthyretin (TTR).

Hypothesis: We hypothesize (1) that increased disease severity in patients with ATTRwt-CM is associated with reduced quality of life (QoL), and (2) that misfolded (misTTR) and fragmented (fragTTR) transthyretin are detectable in blood and/or urine samples from these patients, with levels correlating to disease severity. Disease severity will be evaluated based on clinical characteristics, biochemical markers, and diagnostic imaging findings within a contemporary ATTRwt-CM cohort.

Design: Prospective cross-sectional study

Setting: From the outpatient amyloidosis clinic at Aarhus University Hospital we will include 100 consecutive ATTRwt-CM patients representing all disease stages according to the National Amyloid Center system. A control cohort of 25 heart-healthy patients will also be included for comparison of mis-/fragTTR values.



Results: A total of 81 ATTRwt-CM patients and 25 healthy controls have been included. Results are pending.

Perspectives: This study will provide comprehensive insights into ATTRwt-CM characteristics and its impact on QoL. MisTTR and/or fragTTR show promise as a simple and harmless method for evaluating the clinical disease progression of ATTRwt-CM. Overall, the study may provide novel insights to guide future personalized treatment strategies and contribute to improving the prognosis of patients with ATTRwt-CM.

Multiparametric cardiac magnetic resonance imaging of myocardial infarction progression in Göttingen minipigs over 6 months

Signe Winther Hasler[1] and Natalia Łopuszyńska[1,*], Elin Sergi-Lindell[1], Micki Panda Bjørn Pengcheng Ji[1], Frederikke Tofteng[2], Michala Nordfalk[2], Sofie Troest Poulsen[2], Mette Flethøj Madsen[2]
[1] Imaging Department, Minerva Imaging, Ølstykke, Denmark. [*]Equal contribution.
[2]Large Animal Pharmacology Department, Minerva Imaging, Ølstykke, Denmark

Introduction: Preclinical large animal models are critical for translating scientific discovery to therapeutic applications. Knowledge of myocardial remodeling after myocardial infarction (MI) in Göttingen minipigs is sparse. The aim of the study is to investigate the progression of cardiac function and motion, tissue characteristics, and infarct size using cardiac magnetic resonance imaging (CMRI) from baseline (pre-MI induction) to 6 months post-MI induction.
Method: Eight female Göttingen minipigs underwent MI induction via 120-minute ballon occlusion in the LAD coronary artery. CMRI was conducted at baseline, 7, 28, 56, 84 and 180 days after MI using a 1.5T MRI scanner (GE Signa Artist). CMRI protocol included 2D bSSFP cinematic images for functional and strain analysis, T1 and extracellular volume (ECV) mapping for tissue characterization and early- and late-gadolinium enhancement (EGE, LGE) imaging for microvascular obstruction (MVO) and infarct size measurements. LVEF was also measured using echocardiography (echo) at all timepoints.
Results: At baseline, LVEF was 66±2% (mean±SD, estimated with MRI) and decreased to 45±7% 6 months after MI indicating heart failure with reduced ejection fraction (HFrEF) (Figure 1a), and a strong correlation was seen between MRI and echo (r = 0.85). All mean strain parameters showed reduced contractility, as mean radial strain decreased from 38±5% (baseline) to 25±5%, and circumferential and longitudinal strain increased from -21±2% and -20±1%, to -15±2% and -14±3%, respectively. Mean infarct size at day 7 was 26±6% of the LV myocardial mass and decreased to 16±6% at chronic stages (Figure 1b). EGE MRI showed MVO in all pigs on day 7 (Figure 1d), indicating adverse LV remodeling. Mean ECV increased from 21±3% in healthy myocardium to 76±14% in infarcted regions post-MI and remained elevated, indicating increased extracellular volumes and decreased cellularity (Figure 1c).
Conclusion: A HFrEF model was established and reference values for functional parameters and tissue characteristics values were successfully obtained in healthy and acute, sub-acute and chronic stages of the MI model.

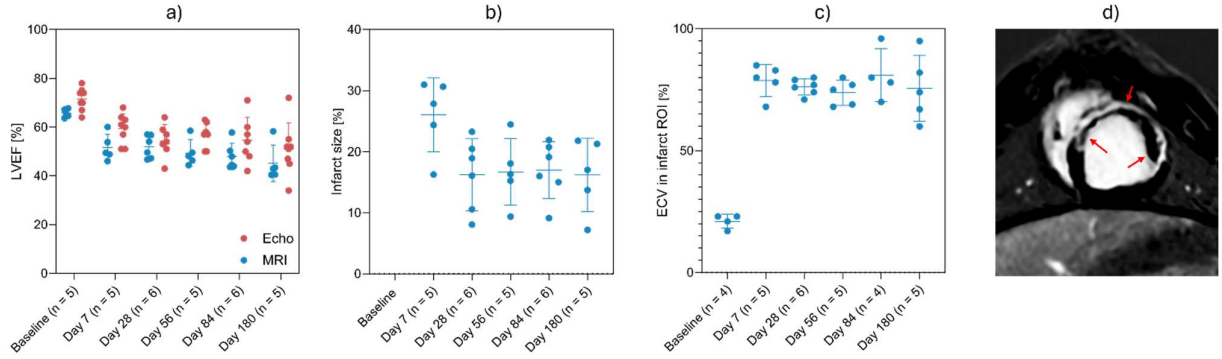


Figure 1 a) LV ejection fraction (LVEF, in %) measured with MRI (blue) and echocardiography (red), b) infarct size (in %), and extracellular volume fraction (ECV, in %) from pre-MI (baseline) to 6 months post-MI induction. d) Prescence of microvascular obstruction (MVO) in early-gadolinium enhancement (EGE) MRI on day 7 post-MI induction.

The impact of toxic sphingolipid ceramides accumulating in cerebrovascular endothelial cells on acute ischemic stroke outcomes in mice

Sohom Mookherjee[1], Jack Wilson[1], Michael Judge[1], Frederik Denorme[2], J. Alan Maschek[1], Liping Wang[1], Ying Li[1], Richard L. Proia[3], Paulo W. Pires[4], Robert A. Campbell[2], William L. Holland[1], Scott A. Summers[1], John David Symons[1]

1 Nutrition and Integrative Physiology, University of Utah, 2 Department of Emergency Medicine, Washington University in St. Louis, 3 NIDDK, 4 Department of Physiology, University of Arizona

Ceramides are toxic sphingolipids that accumulate during aging and obesity. Acute ischemic stroke (AIS) patients have reported high plasma ceramides levels, which correlate with higher prevalence of neurobehavioral and motor complications. Here, we hypothesize that accumulation of ceramides in cerebral endothelial cells (ECs), which constitute ~35% of brain cell subtypes, impact AIS complications. AIS in mice, evoked by 60-min transient middle cerebral artery (MCA) occlusion followed by 23-hr reperfusion, elevated ceramides in plasma and brain compared to sham-operated controls. Moreover, AIS-induced ceramides were elevated in cerebral EC-enriched but not non-EC (NEC)-enriched fraction of mice brain. MCAs with exogenous treatment of C2-ceramide had dampened acetylcholine-evoked vasodilation vs. vehicle treated arteries, implicating ceramide accrual could affect cerebrovascular endothelial dysfunction and impaired blood flow during AIS. Additionally, we observed that both exogenous and endogenous ceramide biosynthesis induced reduced basal and maximal mitochondrial oxygen consumption (OCR) of immortalized human brain microvascular ECs (hBMVECs), in Seahorse assay, implicating the role of these sphingolipids in disrupted mitochondrial function. *Degs1* is the gene encoding Dihydroceramide desaturase-1 (DES1), which catalyzes the crucial double bond addition in the EC-ceramide biosynthesis pathway. We deployed a cerebral EC-specific adeno-associated virus BR1 serotype (AAV-BR1) to deliver the Cre-recombinase (AAV-BR1-*Cre*) to *Degs1*$^{fl/fl}$ mice, enabling selective depletion of *Degs1* in cerebral ECs. Fourteen days after delivering AAV-BR1-*Cre* (Cre-Degs1) or AAV-BR1-Null vectors (Null-Degs1) to *Degs1*$^{fl/fl}$ mice, the EC-enriched and NEC-enriched fractions were isolated from cerebral homogenates. AIS-induced tissue injury, as well as motor and neurological deficits, were less severe in Cre-Degs1 vs. Null-Degs1 male mice, indicating that loss of cerebral EC-specific ceramide generation improves AIS outcomes. We also deployed AAV-BR1-*Cre* or Null vectors to mice that allow for overexpression of a fusion construct comprising the 3 serine palmitoyltransferase (SPT) subunits preceded by a fl-STOP-fl cassette enabling rapid induction of ceramides (fSPT mice). AIS-induced tissue injury, as well as neurological and motor deficits, were worse in male Cre-fSPT vs. Null-fSPT mice 14 days after receiving the respective vectors, implicating that cerebral EC-ceramide overproduction worsens AIS outcomes. Small molecule inhibitors of DES1 (CNT2130) developed by Centaurus Therapeutics, nearing phase I trials, have potential for AIS-treatment. *In vitro,* CNT2130 not only repressed the ceramide accrual during oxygen glucose deprivation and reoxygenation but also mitochondrial OCR during palmitate-induced ceramide lipotoxicity in hBMVECs. In conclusion, our findings suggest that AIS-induced cerebrovascular EC ceramide synthesis worsens infarct volume and neurobehavioral and motor complications by impairing arteriolar and mitochondrial efficiency, and that ceramide-lowering interventions could mitigate these outcomes.

Cardiac Troponin T elevations are frequent in five non-cardiac diseases

Sophie Sander Knudsen[1,2], R.B. Hasselbalch[1,2], N. Strandkjær[1,2], T. Krag[6], J. Vissing[6,7], H.P. Hansen[8], A. Hougaard[7,9], H. Bundgaard[3,4], K. K. Iversen[1,2,4,5]

Affiliations

1) Department of Cardiology, Copenhagen University Hospital - Herlev-Gentofte Hospital, Copenhagen, Denmark. 2) Department of Emergency Medicine, Copenhagen University Hospital - Herlev-Gentofte Hospital, Copenhagen, Denmark. 3) Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark. 4) Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. 5) Department of Internal Medicine, Copenhagen University Hospital - Herlev-Gentofte Hospital, Copenhagen, Denmark. 6) Copenhagen Neuromuscular Center, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. 7) Department of Clinical Medicine, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark. 8) Department of Nephrology, Copenhagen University Hospital-Herlev and Gentofte, Herlev, Denmark. 9) Department of Neurology, Copenhagen University Hospital-Herlev, Herlev, Denmark.

Introduction: Cardiac troponins (cTns) are the biochemical gold standard for detecting myocardial infarction. However, elevated levels—particularly of cardiac troponin T (cTnT)—are frequently observed in patients with non-cardiac conditions and no evident cardiac dysfunction. Emerging evidence suggests that cTnT may be released from skeletal muscle in patients with muscle pathology. This study aimed to investigate the prevalence and potential non-cardiac sources of cTnT elevation in five disease groups with previously described frequent elevations: sepsis, rhabdomyolysis, end-stage renal disease (ESRD), stroke, and major non-cardiac surgery (MNCS).

Methods: This single-center prospective cross-sectional study included patients from the five above mentioned disease groups over a 12-month inclusion period. Patients with any signs of cardiac disease were excluded. Patients were included within 48 hours of hospital admission. All patients underwent vital signs assessment, 12-lead electrocardiogram (ECG), echocardiography (Echo), and blood sample collection. Cardiac troponin T was measured at the patient's bedside with a point-of-care test. Patients with cTnT levels above 42 ng/L (99th percentile) were considered eligible for skeletal muscle biopsy.

Results: Of 194 patients eligible for inclusion, 31 (16%) showed signs of cardiac disease on either ECG or Echo. Among the 165 patients without signs of cardiac disease, elevated cTnT above the 99th percentile was found in 50 (30,3%) of patients; 69% (20/29) with ESRD, 54% (7/13) with rhabdomyolysis, 34 % (14/41) with sepsis, 16% (6/38) with MNCS and 7% (3/42) with stroke. The median cTnT was 81 ng/L (IQR: 53 – 152 ng/L). Muscle biopsies were obtained from 15 patients with elevated cTnT and analysis is currently ongoing.

Conclusions: Elevated cTnT is common across all five non-cardiac disease groups studied, most notably in ESRD and rhabdomyolysis. These findings highlight the need to further explore the mechanisms behind non-cardiac cTnT release. Skeletal muscle biopsy may help clarify whether potential skeletal muscle release of cTnT contributes to circulating cTnT in these patients.

Contact System Proteins as Biomarkers in Abdominal Aortic Aneurysm: Associations with Disease Status and Aortic Diameter

Stephanie T. D. Pham[1*], Jes S. Lindholt[2,3,4], Lasse M. Obel[2,3,4], Lars M. Rasmussen[2,4,5], José L. Martin-Ventura[6], Katrine Pilely[1], Yaseelan Palarasah[1].

[1]Department of Cancer and Inflammation Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark. [2]Elite Centre for Individualized Medicine in Arterial Diseases (CIMA), Odense University Hospital, Odense, Denmark. [3]Department of Cardiac, Thoracic, and Vascular Surgery, Odense University Hospital, Odense, Denmark. [4]Department of Clinical Research, University of Southern Denmark, Odense, Denmark. [5]Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark. [6]IIS-Fundación Jiménez-Díaz, Universidad Autonoma de Madrid; CIBER de Enfermedades Cardiovasculares, Madrid, Spain.

Background: The contact system is a tightly regulated cascade involving the plasma proteins FXII, prekallikrein (PK), High-molecular-weight kininogen (HK), and its primary inhibitor C1 inhibitor (C1-inh). Upon activation, the system initiates the intrinsic pathway of coagulation and promotes inflammation through the generation of cleaved HK (cHK) and the proinflammatory peptide bradykinin. A previous study found a positive correlation between thrombus size in abdominal aortic aneurysm (AAA) and PK-levels indicating involvement of the contact system in the disease AAA. Given that AAA is often asymptomatic, challenged by early diagnosis, and limited by treatment options, further understanding of the contact system in AAA could lead to improved therapeutic strategies for patients suffering from this critical condition.

Aim: This study aimed to assess systemic and local levels of contact system proteins in AAA and to assess their association with disease status and aortic diameter.

Methods: We conducted a case-control study including plasma samples from 52 cases with AAA and 60 controls without AAA. We have developed unique in-house assays capable of assessing activity status and inhibition within the contact system. Using these assays, plasma levels of FXII, PK, HK, cHK, and C1-inh were measured. The protein levels were compared between groups, and associations with AAA status and aortic diameter were analyzed using nonparametric tests, correlation analysis, and logistic regression adjusted for cardiovascular risk factors. The contact system proteins were additionally measured in 62 tissue samples from individuals with AAA and 40 tissue samples from individuals without AAA.

Results: In plasma samples, levels of PK, HK, and C1-inh were increased in individuals with AAA compared to controls. These proteins also showed significant correlations with abdominal aortic diameter and were independently associated with AAA. Levels of FXII and cHK showed no difference between AAA patients and individuals without AAA. In tissue samples, levels of all the contact system proteins were increased in AAA cases compared to controls, apart from C1-inh showing no difference between the AAA samples and the control samples.

Conclusions: Patients with AAA have elevated levels of PK, HK, and C1-inh in plasma and are independently associated with both the presence of AAA and aortic diameter. In tissue, patients with AAA have elevated levels of all contact system proteins besides C1-inh. These results indicate a difference of the contact system in AAA systemically versus locally. Our results suggest a potential role for the contact system proteins in AAA pathophysiology and risk stratification.

Patient Engagement in Pulmonary Embolism Research: Insights from a Post-PE Study

S.F. Lindegaard[1], N. Rolving[2], A.A. Højen[1]

[1]Danish Center for Health Services Research, Aalborg University Hospital, Aalborg Denmark

[2]Department of Physiotherapy and Occupational Therapy, Aarhus University Hospital, Aarhus, Denmark

Background: There is growing recognition of the significance of a close collaboration between patients, clinicians, and researchers to ensure that research and health service delivery effectively meets the needs of patients. However, there is limited understanding of best practices for patient engagement in research among patients with venous thromboembolism, and there is sparse knowledge about challenges to and facilitators of this process.

Purpose: To describe and explore the process and evaluate the impact of patient engagement in the development of a structured post pulmonary embolism care model (the Attend-PE model).

Method: This prospective embedded case study of patient engagement was conducted within a Danish post-PE research project. The study was based on observations, semi-structured interviews with patient representatives, clinician representatives and researchers, as well as written and visual materials from co-production processes. Data were analyzed using research questions guided by United Kingdom six Standards for Public Involvement; Inclusive opportunities, Working together, Support & learning, Governance, Communications and Impact.

Result: Involvement of patient representatives played a crucial role throughout the research project. They contributed to defining research questions, designing the project, co-producing of the Attend-PE model and disseminating result. A patient research partner was actively involved in the steering committee, ensuring patient perspectives were included in high-level decision-making. While patient engagement was high during the co-production of the Attend-PE model, the involvement was lower in the selection of outcomes, feasibility testing, and implementation. Nevertheless, ongoing participation provided patients with valuable insight into the research process, even when their involvement varied across different research stages, enhancing them to engage effectively when needed.

Important facilitators of patient engagement were related to “Inclusive opportunities” and “Support and learning”. Patients highlighted the importance of being a part of the process, working together as a team, and being prepared for the work. Important challenges to patient involvement related to “Communication” and “Governance”, including poor expectation alignment and the use of medical language in communication about clinical elements in the care, where clinician often dominated the discussions.

Conclusion: Patient engagement has been invaluable in the development of the Attend-PE model that reflects patient needs and experiences. While challenges exist, the benefits from patient engagement outweigh initial barriers. Researchers should actively integrate patient engagement in their projects, even with limited prior experience. Addressing barriers, such as expectation alignment and communication can further optimize patient engagement in future research.

Glycerol-3-Phosphate Phosphatase as a Potential Therapeutic Target for Cardiovascular Disease

Stine Tillebæk Søndergaard[2,4], Signe Dissing Hansen[1], Frederik Teilfeldt Hansen[2], Clarisse Chiche-Lapierre[2], Emilie Grupe[4] Aske Bredow Bojesen[2], Ping Song[3], Jørgen Kjems[3] & Jane Stubbe[4]
[1]Aalborg University, Department of Chemistry & Bioscience & Department of Health, Denmark, [2]Idun Biologics ApS, Denmark, [3]Aarhus University, iNANO, Denmark, [4]Southern Denmark University, Institute of Molecular Medicine

Obesity, which affects over a billion people globally, contributes significantly to diabetes and cardiovascular disease (CVD). Glycerol-3-phosphate phosphatase (G3PP) dephosphorylates glycerol-3 phosphate into glycerol, preventing triglyceride build-up and mitochondrial oxidative stress. Cellular metabolism, which is influenced by epigenetic reprogramming and environmental fac tors, critically affects CVD progression. This project explores the therapeutic potential of G3PP in CVDs, such as atherosclerosis and abdominal aortic aneurysm (AAA). Published data indicate that G3PP expression levels in human white adipocytes correlate with obesity (e.g. BMI, waist circumference and circulating triglycerides) and inflammatory markers (Circulating C-reactive protein, CRP), suggesting that G3PP could play a detoxifying role in obesity. A high-fat diet modulates G3PP and hepatic G3PP loss in rodents, leading to TG accumulation, elevated proinflammatory cytokine production, and elevated circulating TG levels. G3PP is broadly expressed in humans, but its role in arterial walls and macrophages during CVD remains unstudied.

Our aim is to investigate the endogenous regulatory mechanism of G3PP and its potential as a therapeutic target for detoxifying cells from nutrient-induced stress, using targeted delivery of encapsulated G3PP mRNA in lipid nanoparticles (LNPs) to the artery wall and activated macrophages.

Our preliminary results, confirms that G3PP is expressed in vascular smooth muscle cells (VSMCs) and macrophages. The endogenous expression of G3PP did not change when grown in high glucose for 8 h (25 mM and 50 mM) compared with 5.5 mM or osmotic controls using mannose (25 mM and 50 mM). Based on patient data set (GSE57691), we found increased expression of G3PP in large AAAs compared to aortic controls. A similar trend was observed in our murine AAA model, suggesting a therapeutic potential. We plan to use lipid nanoparticles to selectively deliver G3PP mRNA to endothelial cells and activated macrophages in the diseased aorta of our angiotensin II-induced AAA model, enabling precise gene modulation in otherwise undruggable targets.

In conclusion, our preliminary data suggest that Glycerol-3-Phosphate Phosphatase (G3PP) may play a role in metabolic health and the modulation of cardiovascular disease processes. While still early, these findings point to G3PP as a potentially important factor in regulating obesity-related inflammation and triglyceride accumulation. Ongoing and future studies will aim to further characterize the underlying mechanisms and assess the feasibility of tissue-specific targeting strategies.

Albumin is an important contributor to indoxyl sulfate-mediated endothelial dysfunction

Authors: Søren H. Elsborg[1], Anna Vingborg[2], Vladimir Matchkov[2], Lene N. Nejsum[1], Henricus A.M. Mutsaers[1] and Rikke Nørregaard[1,3]

[1]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.
[2]Department of Biomedicine, Aarhus University, Aarhus, Denmark.
[3]Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark.

Background: Chronic kidney disease (CKD) is characterized by the accumulation of metabolic end-products in the blood, including Indoxyl sulfate (IxS). In CKD patients, elevated plasma levels of IxS are associated with an increased risk of cardiovascular disease (CVD) due to its harmful effects on endothelial cells. In plasma, albumin acts as a carrier for IxS that hinders its clearance via dialysis. However, whether albumin contributes IxS toxicity is currently unknown.

Objective: This study investigates how albumin influences the pathophysiological effects of IxS on the vasculature.

Hypothesis: Albumin facilitates IxS transport in endothelial cells and modulate its cellular toxicity.

Methods: Endothelial cells (EA.hy926) were exposed to either IxS, 4% human serum albumin (HSA), or in combination for different time intervals. Fluorescence microscopy was used to visualize IxS and HSA localization, as well as the intracellular trafficking of endocytosed IxS in cells transfected with GFP-tagged markers for early (Rab5) and recycling endosomes (Rab11). Western blot analysis was performed to assess the induction of phosphorylation events by IxS and HSA. For the ex vivo studies, 11-13-week-old male C57BL/6J mice were fed a western diet (WD, n=6) or a control diet (n=9) for 6 weeks. The proximal abdominal aorta was dissected from these mice, and ~2 mm segments were mounted on a wire myograph. The aorta segments were treated with IxS and HSA or HSA alone for 40 min.

Results: Microscopy revealed colocalization of IxS and HSA in vesicle-like structures. IxS was detected in Rab5-positive early- and Rab11-positive recycling endosomes, but only in the presence of HSA. Furthermore, IxS+HSA treatment increased C-Jun phosphorylation in endothelial cells after 40 compared to HSA alone, but not after 10 min. IxS treatment increased the vascular tonus of aorta segments in the control mice only.

Summary of results and conclusion: Our findings suggest that albumin facilitates IxS endocytosis into endothelial cells. In the presence of HSA, IxS was transported into early and recycling endosomes, potentially triggering C-Jun activation. Moreover, IxS induced a contractile phenotype in aortic segments. In summary, these results suggest that albumin may directly contribute to IxS-induced vascular dysfunction in CKD patients, exacerbating CVD risk.

Advancing Aortic Valve Repair: Surgical and Biomaterial Innovations in a Translational Porcine Model

Tanita Drejer Jeppesen[1,2], Johannes Høgfeldt Jedrzejczyk[1,2], Søren Nielsen Skov[1,2], J. Michael Hasenkam[1,2], Leila Louise Benhassen[1,2], Peter Johansen[1,2,3].

[1]Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark.
[2]Department of Clinical Medicine, Aarhus University, Denmark.
[3]Department of Electrical and Computer Engineering, Faculty of Technical Sciences, Aarhus University, Denmark.

Background:
Aortic valve insufficiency remains a common and serious cardiac condition. While valve replacement is the standard treatment, it is associated with a 50% complication rate within ten years, compared with just 12% following aortic valve repair. Our research aims to improve feasibility and outcomes of aortic valve repair.

Methods and Results:
During the PhD project, we developed and tested the Aortic Phlex-ring — an open annuloplasty ring — in an 80 kg porcine model. The ring preserved physiological aortic root dynamics and demonstrated promising hemodynamic performance. These findings were presented at last year's DCA Summer Meeting. A three-month survival study is currently approaching completion, including histological and immunological evaluation of host response and tissue remodeling.

Annuloplasty is essential for durable valve repair, yet it is frequently insufficient when used alone. In many cases, additional reconstruction of the valve leaflets is necessary to restore full valve competence. Building on the model established through the Aortic Phlex-ring project, our research now expands toward the development and evaluation of novel materials for aortic leaflet reconstruction — a critical next step in advancing comprehensive valve repair techniques.

To support this, we are developing a novel semi-synthetic bioscaffold composed of gelatin, polycaprolactone (PCL), and polyethylene terephthalate (PET), designed to combine early resorption with long-term structural support. To evaluate this material, we will use our already established pulsatile left heart chamber model simulating physiological conditions to evaluate different leaflet repair techniques. Surgical approaches such as the Ozaki, Berra, and Tambrallimatch techniques will be tested and compared with native porcine aortic roots. The setup allows real-time assessment of valve function using echocardiography, endoscopy, pressure catheters, and flow measurements. Once the scaffold is finalized, it will be tested within the same platform.

Conclusion:
This project provides a robust translational platform for advancing aortic valve repair from preclinical evaluation. By combining surgical technique refinement with biomaterial development, we aim to improve the durability and clinical applicability of aortic valve repair procedures — especially benefiting younger patients through less invasive and longer-lasting treatment options.

Targeting the novel HCO_3^- sensor RPTPγ for neuroprotection in ischemic stroke

Tarannum Ara, Department of Biomedicine, Aarhus University

Vladimir Matchkov, Department of Biomedicine, Ebbe Boedtkjer, Department of Biomedicine, Aarhus University

Abstract

This study investigates the role of receptor protein tyrosine phosphatase gamma (RPTPγ), a bicarbonate (HCO_3^-) sensor, in neuroprotection during ischemic stroke. RPTPγ mediates intracellular signalling in response to extracellular acid-base disturbances, a critical aspect of ischemic pathology. Given that ischemic stroke is characterised by local hypoxia and ischemia, acid-base imbalance plays a critical role in determining the fate of salvageable brain tissue, particularly the penumbra. The disruption of pH homeostasis during ischemia contributes to neuronal damage, making acid-base regulation a key therapeutic target. Previous findings from our laboratory indicate that individuals carrying loss-of-function variants in RPTPγ exhibit a significantly increased risk of stroke, suggesting its protective role.

To explore this further, we assessed stroke susceptibility in RPTPγ knockout (KO) mice compared to wild-type (WT) controls. Our results demonstrate an increased vulnerability to ischemic injury in KO mice. Analysis revealed a higher stroke frequency in male KO mice, while the effect in females, though present, was not statistically significant, pointing toward potential sex-specific factors such as hormonal and physiological differences. Additionally, KO mice exhibited significantly higher neurological scores, often necessitating earlier humane endpoints compared to WT controls. These findings highlight the significance of RPTPγ in influencing stroke severity and support continued investigation into its underlying mechanisms and potential as a therapeutic target.

Naturally occurring COL1 fragments induce COL3 formation at physiological concentrations in 3D PEG hydrogel model with human ventricular cardiac fibroblasts

T. Chrysoulidou[1,2], H. Devos[2,3,4], H. Mischak[5], A. Latosinska[5], F. Genovese[2]

[1]Institute of Biomedical Sciences, University of Copenhagen - Copenhagen (Denmark), [2]Nordic Bioscience - Herlev (Denmark), [3]Centre of Systems Biology, Biomedical Research Foundation of the Academy of Athens - Athens (Greece), [4]Laboratory of Biology, University of Athens School of Medicine - Athens (Greece), [5]Mosaiques Diagnostics GmbH - Hannover (Germany)

Background: Cardiovascular diseases are the leading cause of death worldwide, accounting for approximately 17.9 million fatalities every year. A common feature across many cardiac pathologies is fibrosis, which involves changes in ECM turnover. This process can generate collagen fragments, either from the pro-peptides (signifying collagen synthesis) or from the main collagen chain (signifying collagen degradation). One of the collagens that increases significantly in early-stage heart fibrosis following myocardial infarction (MI) is collagen type III (COL(III)) [1]. Previous work by Magalhães et al. demonstrated that not only was there unexpectedly little overlap between naturally occurring peptides in blood and urine of the same individuals, identified using mass spectrometry, but also that the respective abundances of overlapping peptides did not correlate. One exception that stood out was COL(I)-derived peptides[2], leading to the conclusion that blood-derived peptides pass the glomerular filter but are reabsorbed in the tubules. This shows that COL(I)-derived peptides are potentially bypassing typical absorption within the renal tubules, further suggesting that they may possess signalling activity. Finally, Wu et al. and Feng et al. investigated peptide sequences that target specific receptors and discovered that, among other functions, they regulate ECM remodelling [3,4].

Aim: Based on the collection of the aforementioned findings, nine of the most abundant naturally occurring urinary COL(I)-derived peptides were synthesised and tested for their biological effects on COL(III) turnover, in a 3D *in-vitro* cardiac fibroblast model.

Methods: Human ventricular cardiac fibroblasts (HCF-v) were cultured in pre-cast PEG hydrogels over a 10-day period in fibroblast basal medium, under stimulated conditions with nine COL(I) peptides in physiological human circulating concentrations. The assessment of COL(III) formation was conducted in the cell supernatant at day 0, day 3, day 6, and day 10 by using competitive enzyme-linked immunosorbent assay (ELISA).

Results: Stimulation with seven of the nine peptides enhanced matrix assembly and remodelling, as assessed by the elevated levels of the fragments of COL(III) formation when compared to vehicle.

Conclusion: COL(III) plays a significant role in cardiac fibrosis, and it is involved in the early stages of cardiac remodelling following a MI. We tested the effect of nine COL(I) peptides on COL(III) levels in an *in-vitro* 3D human ventricular fibroblast model. Our experiment found that naturally occurring COL(I) fragments demonstrated similar pro-fibrotic response of rapid COL(III) production when used as stimulants on cardiac fibroblasts, suggesting that these peptides are relevant in cardiomyopathies and merit further investigation.

Small vessel disease of the brain and heart. A perfusion PET study of training effects

Primary Investigator & Presenting Author: Thomas Ehlig Hjermind Justesen
Main Supervisor: Lisbeth Marner
Secondary Supervisors: Eva Prescott & Carl-Johan Boraxbekk
Affiliation: Department of Clinical Physiology and Nuclear Medicine, Bispebjerg Hospital

Introduction: Over the last decades the diagnostics and treatment of cardiovascular large vessel disease has improved significantly. Yet, the majority of elderly patients with ischemic heart disease do not have large-vessel heart disease and it seems that small vessel disease may explain a large fraction of these cases as well as the cardiovascular morbidity in the elderly, especially in females. Hence, the current development in diagnostics and treatments of ischemic heart disease does not address the most common subtype of ischemic disease seen in elderly patients.

Objective: The main objectives are: 1) Evaluate if small vessel disease is a systemic disease with affection of heart and brain in the same individuals 2) improve our understanding of how small vessel disease of not only the brain but also the heart may lead to cognitive dysfunction, and 3) to examine whether improvements in cardiorespiratory fitness (VO2-max) through supervised training can reverse or limit cognitive dysfunction.

Methods: Forty-eight diabetic patients with signs of beginning microvascular disease will be included from the Steno Center at Herlev Hospital. Twenty-four healthy controls will be included from internet advertisements. Perfusion of the hearts and brain ($[^{15}O]H_2O$ PET), brain MRI, cognitive capacity, LVEF and VO2-max will be assessed at baseline. After baseline testing, we will compare the results from the diabetic patients with the healthy controls. The diabetic patients will then be randomized to either five months of supervised HIIT-training or five months of supervised passive stretching. Baseline measurements (ex. MRI & LVEF) will be repeated after the intervention.

Increased health care utilization prior to sudden cardiac death in the general population

Authors: T. Skjelbred[a], B.G. Winkel[a], G. Gislason[b,c], T.H. Lynge[a], J. Tfelt-Hansen[a,d]

Affiliations: [a]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [b]Department of Cardiology, Herlev and Gentofte Hospital, Hellerup, Denmark; [c] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [d]Section of Forensic Genetics, University of Copenhagen, Copenhagen, Denmark

Background: Despite advancements in cardiovascular care, predicting and preventing sudden cardiac death (SCD) in the general population remains a major challenge. Near-term prevention of SCD relies on identifying persons in immediate risk of a lethal arrhythmia before cardiac arrest. This study aimed to evaluate health care contact patterns before SCD and death from other causes, compared to a matched background population.

Methods: We analyzed the entire Danish population in 2010, identifying SCD cases using Danish death certificates and discharge summaries, yielding 6,767 SCD cases. All deaths in 2010 (n=53,120) were matched with four controls (n=212,480) from the background population based on age, sex, and comorbidities (atrial fibrillation, heart failure, ischemic heart disease, chronic kidney disease, chronic obstructive pulmonary disease, and cancer). We assessed health care contacts both to general practitioners (GP) and hospitals in the year preceding the index date. Logistic regression was used to estimate odds ratios (OR) for health care contact in the 14 days prior to SCD.

Results: In the year before SCD, weekly health care contact rates increased among cases but remained stable in controls. GP contact rates in controls remained at ~21% per week, whereas among SCD cases, they rose from 24% per week (one year prior) to 39% in the final week before death. Similarly, hospital visit rates increased from 4% to 9% in SCD cases, while remaining stable in controls. There were higher rates of health care utilization, both at hospitals and general practice, in deaths that were non-sudden. In the two weeks preceding death, SCD cases had significantly higher odds of GP contact (OR: 4.3, 95% CI: 4.1–4.6) and hospital contact (OR: 3.2, 95% CI: 3.0–3.5) compared to controls.

Conclusion: Health care contact rates doubled in the year leading up to SCD, with a marked increase in the final weeks. SCD cases were 4.3 times more likely to contact a GP and 3.2 times more likely to visit a hospital in the two weeks before death. These findings highlight the need for improved near-term SCD risk stratification, potentially integrating health care utilization patterns in primary and secondary care in novel SCD prevention strategies.

Titel: Deep Cardiometabolic Pheno-Genotyping of CAD risk in Children with Normal Weight and Obesity.

Authors: Trine Obel[1,2,3], Morten AV Lund[1,2,3], Niels Vejlstrup[2], Michael Christiansen[4], Jens-Christian Holm[3] Torben Hansen[5], Thomas Jespersen[1].

Affiliations: [1]Department of Biomedical Sciences, University of Copenhagen, Denmark; [2]Department of Cardiology, Rigshospitalet, Denmark; [3]Department of Pediatrics, The Children's Obesity Clinic, Holbæk Hospital, Denmark; [4]Statens Serum Institut, Copenhagen, Denmark; [5]Novo Nordisk Foundation Centre for Basic Metabolic Research, University of Copenhagen, Denmark.

Background

Early genetic risk stratification using polygenic risk scores (PRS) can identify individuals at high lifetime risk for coronary artery disease (CAD) from early life. Childhood is crucial for establishing cardiovascular (CV) health, offering significant preventive potential. However, understanding how genetic predisposition to CAD is associated with adverse phenotypes in children, especially with obesity, remains unclear. Current CAD prognostic tools focus on adults and conventional CV risk factors. Our recent study of 4,000 Danish children found that high PRS for CAD did not increase conventional CV risk factors in children with normal weight but did in those with obesity, suggesting childhood obesity amplifies genetic risk.

Hypothesis

Genetic predisposition to CAD is linked to adverse CV phenotypes in children with normal weight, and childhood obesity amplifies this association.

Methods

This cross-sectional study will recruit 400 children with normal weight aged 8-18 years. Participants will undergo advanced cardiometabolic profiling, including carotid ultrasound and MRI. Genetic profiling and PRS calculation will be performed in this cohort and in an existing cohort of 400 children with obesity who have undergone identical phenotyping.

Results

Inclusion is ongoing, with 30/400 participants included. Results are expected by early 2027.

Perspectives

Identifying an overlooked subgroup at high risk for CAD could improve and personalize cardiovascular prevention and treatment guidelines starting from childhood.

Combined use of cardioprotective glucose-lowering drugs and statins for primary prevention of atherosclerotic cardiovascular disease in individuals with type 2 diabetes: A nationwide cohort study

Tummas Ternhamar[1,2,3], Mia Ø. Johansen[2,3,4], Børge G. Nordestgaard[1,2,3], Shoaib Afzal[1,2,3]

[1]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Borgmester Ib Juuls Vej 73, Elevator 7, 4th Floor, N5, Herlev DK-2730, Denmark. [2]The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Denmark, [3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark, [4]Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

Aim:

Clinical guidelines recommend statins for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in type 2 diabetes, but the role of cardioprotective glucose-lowering drugs, including sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, remains unclear. Furthermore, the importance of combining cardioprotective glucose-lowering drugs and statins was not tested in a trial. We hypothesized that combining cardioprotective glucose-lowering drugs and statins in a primary prevention setting is associated with lower risk of ASCVD than using either drug alone.

Methods:

Using Danish nationwide registers, we identified individuals in Denmark with type 2 diabetes and no preexisting ASCVD treated with only metformin between December 2012 through 2021. With an active comparator design, we followed 59,795 individuals initiating a cardioprotective glucose-lowering drug or a cardioneutral dipeptidyl peptidase-4 inhibitor and compared: i) dipeptidyl peptidase-4 inhibitor, ii) cardioprotective glucose-lowering drug, iii) dipeptidyl peptidase-4 inhibitor and statin, and iv) cardioprotective glucose-lowering drug and statin. The primary outcome was time to first ASCVD including myocardial infarction, coronary revascularization, ischemic stroke, peripheral arterial disease, or coronary death.

Results:

During mean follow-up of 3.2 years, 2,546 individuals experienced first time ASCVD. Compared with dipeptidyl peptidase-4 inhibitor (no use of statin or cardioprotective glucose-lowering drug) the multivariable adjusted hazard ratios for ASCVD were 0,87(95% confidence interval:0.76–0.98) for cardioprotective glucose-lowering drug alone, 0.69(0.63–0.77) for statin alone, and 0.64(0.56–0.73) for cardioprotective glucose-lowering drug and statin combined.

Conclusions:

In individuals with type 2 diabetes without preexisting ASCVD, statin alone was associated with substantially lower risk of ASCVD than cardioprotective glucose-lowering drug alone, while combination of the two drug classes was associated with similar ASCVD risk as statin alone.

A novel cardiac-specific lncRNA lnc900 modulates hypertrophic responses in cardiomyocytes

Vignesh Gnanaskandan[1], Dennis M Krüger[1], Susanne Burkhardt[1], Izzatullo Sobitov[4,5], Niels Voigt[4,5], Antje Ebert[5], Andre Fischer[1,2,3]

[1]Department for Systems Medicine and Epigenetics, German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany

[2]Cluster of Excellence "Multiscale Bioimaging: from Molecular Machines to Networks of Excitable Cells" (MBExC), University of Göttingen, Germany

[3]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany

[4]Institute of Pharmacology and Toxicology, University Medical Center Göttingen, Göttingen, Germany

[5]German Center for Cardiovascular Research (DZHK) partner site Göttingen, Germany

Cardiomyocytes, the primary cellular component of the myocardium, are responsible for the contractile function of the heart. Under pathological conditions, they undergo cardiac remodelling which is an adaptive turned maladaptive mechanism leading to hypertrophy and deregulation of several important pathways. Long non-coding RNAs (LncRNAs) have emerged as regulatory molecules and have been studied exclusively in the physiological and pathological processes of cardiac hypertrophy. In this study, we describe and characterize an human cardiomyocyte specific lncRNA *lnc900*. We found that *lnc900* is upregulated in cardiomyocytes treated with Endothelin-I (ET-1) and also found to be dysregulated in *in vitro* models of Dilated (DCM) and Hypertrophic Cardiomyopathy (HCM). Silencing *lnc900 in vitro* attenuates ET-1 induced hypertrophy where reduced expression of hypertrophic markers were observed. RNA-Seq analysis after *lnc900* knockdown, revealed downregulation of important pathways contributing to calcium signalling and cell survival. Electrophysiological recordings show reduced sodium and calcium peak currents after *lnc900* knockdown. These findings suggest that *lnc900* plays a critical role in regulating hypertrophic responses and calcium signalling in cardiomyocytes, providing a mechanistic link between the lncRNA and cardiac remodelling under pathological conditions. Its dysregulation in the DCM and HCM model, further implicates it in the molecular pathways contributing to disease progression, offering new insights into the role of lncRNA in cardiomyocyte dysfunction. These findings not only enhance our understanding of this lncRNA but also provide potential therapeutic targets for heart diseases.

Keywords : LncRNAs; cardiomyocytes; hypertrophy

Qiangxinyin formula protects against isoproterenol-induced cardiac hypertrophy

Zhong-Yan Zhou, Yu Wang

Department of Pharmacology and Pharmacy & State Key Laboratory of Pharmaceutical Biotechnology, LKS faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Regions of China

Abstract

Heart failure is a life-threatening cardiovascular disease and characterized by cardiac hypertrophy, inflammation and fibrosis. The traditional Chinese medicine formula Qiangxinyin (QXY) is effective for the treatment of heart failure while the underlying mechanism is not clear. This study aims to identify the active ingredients of QXY and explore its mechanisms protecting against cardiac hypertrophy. We found that QXY significantly protected against isoproterenol (ISO)-induced cardiac hypertrophy and dysfunction in zebrafish. Eight compounds, including benzoylmesaconine (BMA), atractylenolide I (ATL I), icariin (ICA), quercitrin (QUE), psoralen (PRN), kaempferol (KMP), ferulic acid (FA) and protocatechuic acid (PCA) were identified from QXY. PRN, KMP and icaritin (ICT), an active pharmaceutical ingredient of ICA, prevented ISO-induced cardiac hypertrophy and dysfunction in zebrafish. In H9c2 cardiomyocyte treated with ISO, QXY significantly blocked the calcium influx, reduced intracellular lipid peroxidative product MDA, stimulated ATP production and increased mitochondrial membrane potential. QXY also inhibited ISO-induced cardiomyocyte hypertrophy and cytoskeleton reorganization. Mechanistically, QXY enhanced the phosphorylation of Smad family member 2 (SMAD2) and myosin phosphatase target subunit-1 (MYPT1), and suppressed the phosphorylation of myosin light chain (MLC). In conclusion, PRN, KMP and ICA are the main active ingredients of QXY that protect against ISO-induced cardiac hypertrophy and dysfunction largely via the blockage of calcium influx and inhibition of mitochondrial dysfunction as well as cytoskeleton reorganization.

Keywords

Heart failure, Cardiac fibrosis, Cardiac hypertrophy, Calcium overload, Traditional Chinese medicine, Zebrafish

Corresponding to Prof. Yu Wang (yuwanghk@hku.hk)

Notes

Notes

Get in touch with the DCAcademy team during the meeting:

Thomas Jespersen	Executive Managing Director	thojes@sund.ku.dk / +45 24 80 51 90
Christian Aalkjær	Scientific Senior Advisor	ca@biomed.au.dk / + 45 30 45 43 06
Emil Toft Brøndum	Chief of Operations	etb@biomed.au.dk / + 45 22 56 90 52
Nanna Cathrine Brinch	Communications Manager	ncb@biomed.au.dk / + 45 93 52 18 01
Pernille Højvang Nielsen	Course Manager	pehn@biomed.au.dk / + 45 20 78 22
Lise Klarholt	Course and Event Manager	lk@biomed.au.dk / + 45 20 37 42 14
Arnela Saljic	Course Coordinator	arnela@sund.ku.dk / + 45 42 36 04 11
Elena Bouzinova	Course Coordinator	elbo@biomed.au.dk / + 45 28 26 77 87
Andrea Carla Forsyth	Student Assistant	acf@cc.au.dk

Danish Cardiovascular Academy