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ABSTRACTS

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Biatrial activation patterns and hemodynamics during Bachmann's bundle pacing: Learnings from a porcine model.

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Abstract

Background: Right atrial appendage (RAA) pacing impairs atrioventricular (AV) coupling and is associated with atrial fibrillation and adverse outcomes. Bachmann bundle (BB) pacing restores the interatrial conduction delay, but its acute hemodynamic impact remains unclear.

Objective: To characterize atrial activation and immediate hemodynamic effects of BB versus RAA pacing in a porcine model under AV-synchronized and non-synchronized conditions.

Methods: Six Landrace pigs underwent high-density biatrial electroanatomical mapping and invasive pressure monitoring of left atrium (LA), left ventricle (LV), right ventricle (RV), and femoral artery. A sequential activation- and pace-mapping workflow was used to identify the BB area. Total atrial activation times and P-wave characteristics were compared during BB and RAA pacing. Hemodynamic responses were assessed during non-AV-synchronized pacing in all pigs and during AV-sequential pacing with His bundle active-fixation lead capture in three pigs.

Results: BB pacing reproduced sinus P-wave duration and morphology (72.6±9.1 vs 73.0±8.6ms), whereas RAA pacing significantly prolonged P-wave duration (106.2±17.5ms; P=0.001). Total atrial activation time was shorter with BB versus RAA pacing (142.8±18.5ms vs 167.2±25.6ms; P=0.006), with disappearance of slow conduction zones seen during RAA pacing. Without AV-synchronization, BB pacing increased mean LV, RV, femoral pressures and LV dP/dT versus RAA pacing and baseline, without raising LA pressure. Under AV-sequential pacing, BB pacing modestly reduced intracardiac pressures relative to RAA pacing while preserving higher LV contractility versus baseline.

Conclusions: In this porcine model, BB pacing shortens atrial activation and confers immediate hemodynamic advantages over conventional RAA pacing, supporting BB as a physiological atrial pacing target.

Sex differences in surgical treatment of infective endocarditis: A NIDUS registry study

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Background

Lower surgical rate of female patients with infective endocarditis (IE) has been consistently reported, yet the reasons remain poorly understood. We aimed to characterize sex differences use, timing and indications of surgical treatment in patients with left-sided IE.

Methods

We identified all patients with left-sided IE from the NatIonal Danish endocarditis stUdieS (NIDUS) registry with left-sided IE. Baseline clinical, echocardiographic and microbiological characteristics were compared between male and female patients undergoing surgery. We assessed the prevalence of surgical indication and time from diagnosis to surgery according to sex. A class 1 indication for surgery was defined as uncontrolled infection, heart failure or embolization. Indication for surgery included patients with a vegetation >10 mm. Further, analysis of in-hospital and 6-month mortality rate was performed with logistic regression and cox-regression (male as reference)

Results

We included 3,017 patients, of whom 996 (33%) were female and 2,021 (66%) were male. Valve surgery was performed in 148 (14.9%) females compared with 514 (25.4%) males. The groups had comparable time from diagnosis to surgery and similar rates of prosthetic valve IE (25.7% vs 27.0%). Surgically treated females were older (70.1 years (57.5-75.1) vs. 66.3 years (55.1,72.7), less often self-reliant in activities of daily living (87% versus 93.9%) than males and more frequently had *S. aureus* IE (29.1% vs 22.8%). Despite this risk profile, female patients less often met a Class I indication for surgery (42.6% vs 48.6%). When analyzing patients with either a Class I indication or a vegetation >10 mm, 34% of female patients and 51% of male patients were surgically treated. The most common reasons to refrain from surgery despite indication was *estimated poor prognosis* (26% vs 30%), *hemodynamic instability* (5.9% vs. 3.5%) or *death before surgery* (3.8% vs 3.3%). Female patients had significant higher in-hospital mortality rate (21% vs 17.0%, p<0.01) but not in unadjusted analysis (OR: 1.15 (95% CI 0.94-1.42). Female patients had higher unadjusted 6-month mortality rate than males (31.9% vs 25.9%) but not in unadjusted analysis (HR: 1.08 (95% CI 0.94-1.25).

Conclusion

Surgery for IE is less common in female patients than male patients even when a surgical indication is present. Male patients had higher rates of class 1 indication for surgery and female patients were generally older and less self-reliant. When accounting for sex-specific differences, outcomes were similar.

The SGLT2 inhibitor, Dapagliflozin, Decreases Mitochondrial Oxygen Consumption in a Murine Model of Heart Failure with Preserved Ejection Fraction

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Background: Globally, the prevalence of hypertension and metabolic disease, including diabetes mellitus, is rapidly rising. These factors are important contributors to the development of heart failure with preserved ejection fraction (HFpEF). It is well-known that sodium-glucose cotransporter-2 inhibitors (SGLT2i) possess cardioprotective properties in heart failure. SGLT2i have previously been proposed to mediate cardiac protection by shifting substrate utilization towards fatty acid oxidation with subsequent generation of ketone bodies. Nevertheless, SGLT2i-related changes in glucose metabolism within HFpEF remain to be further elucidated.

Hypothesis: SGLT2 inhibition alters cardiac mitochondrial respiration during glucose utilization, thereby attenuating the progression of HFpEF.

Methods: Male C57Bl/6j mice were assigned to; I) vehicle-treatment receiving a normal diet, II) vehicle-treatment receiving a western diet (WD) combined with N-nitro-1-arginine methyl ester (L-NAME, 600 mg/kg/day) in the drinking water; and III) treatment with a SGLT2i (dapagliflozin; 10 mg/kg diet (DAPA)) in chow combined with WD and L-NAME for 6 weeks.

Echocardiography was conducted prior to the initiation of the intervention period and repeated at the end of the study. At sacrifice, mitochondrial respiration in cardiac tissue was assessed using the OROBOROS O2k-FluoRespirometer. $P<0.05$ is considered statistically significant.

Results: The E/e' ratio, a parameter for diastolic function, was increased in the HFpEF-group compared to controls and this was improved with DAPA towards control values ($P=0.042$ and $P=0.51$, respectively, n=7-9). Furthermore, mitochondrial oxygen consumption in cardiac tissue from the HFpEF-group was significantly increased compared with controls, though this was normalized with DAPA treatment ($P=0.008$ and $P=0.003$, respectively, n=6-9).

Conclusion: Decreased mitochondrial oxygen consumption may contribute to the cardioprotective effects of SGLT2i in HFpEF.

Rationale and design of a Danish Pragmatic Randomized Trial of Nutritional Supplements in Heart Failure: DANUTRIO-HF

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Background: Despite advances in heart failure (HF) treatment, patients continue to face substantial residual risk. Prior small-scale trials of patients with HF with reduced ejection fraction (HFrEF) have suggested that daily intake of the nutritional supplement coenzyme Q10 (CoQ10) may reduce the incidence of HF-related adverse events. Observational studies indicate associations between low serum concentrations of the mineral selenium and poor prognosis in HF. Additionally, a mechanistic trial has linked the nutritional supplement selenium to improvement in ejection fraction and quality of life score in HFrEF. DANUTRIO-HF will evaluate the effectiveness of CoQ10 vs. placebo and, separately, selenium vs. placebo in reducing the composite of HF hospitalizations and cardiovascular death in HF patients.

Methods: DANUTRIO-HF is an investigator-initiated, nationwide, registry-based, event-driven, 2x2 factorial randomized, double-blinded trial in patients with HF. Patients are randomized 1:1 to CoQ10 (100 mg twice daily) vs. placebo, and 1:1 to selenium (100 µg twice daily) vs. placebo. Potential participants are identified through the Danish Administrative Health Registries using a validated algorithm for identifying HFrEF, though inclusion is independent of ejection fraction. The trial employs a decentralized design with digital recruitment, asynchronous consent, communications through the governmental electronic letter system, and registry-based data collection with no physical visits. Trial interventions are mailed directly to patients biannually, and self-administered questionnaires are sent digitally to assess quality of life, disease burden, and study compliance. The primary endpoint is time-to-first HF hospitalization or cardiovascular death. The study is event-driven and will target 708 primary events by initially randomizing 4,044 participants. A sub-study involving 600 participants will explore the potential underlying effects of CoQ10 and selenium over two visits (baseline and after one year) with echocardiography, blood samples, and a 6-minute walking test.

Discussion: The pragmatic study design of DANUTRIO-HF substantially reduces trial costs, pioneering novel methods to evaluate interventions that might otherwise remain untested due to limited economic incentives. By lowering financial barriers, this approach enhances opportunities for independent research and promotes broader access to evidence-based therapies.

Conclusions: This trial will answer whether the nutritional supplements CoQ10 and/or selenium can improve the quality of life and longevity of patients with HF, potentially leading to affordable new treatment options. Conversely, negative findings may prevent patients from spending money on supplements marketed as cardioprotective with limited efficacy.

Investigating the effect of somatic mutations on smooth muscle cell clonal expansion

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Our lab recently found that somatic mutations and expanded mutated clones are a frequent feature of human Atherosclerosis, suggesting that mutation-driven clonal expansion may play an important role in plaque development. Our data point to vascular smooth muscle cells (SMCs) as a key contributing cell type.

My project focuses on understanding how somatic mutations affect SMC behavior during atherosclerosis progression. We hypothesize that SMCs acquire mutations that provide a selective advantage, promoting clonal expansion and influencing plaque growth and stability.

To study this, we combine mutational profiling of human plaque tissue with experimental studies in both plaque-derived cells and commercially available human SMCs. Using targeted sequencing approaches, we identify and spatially map mutations detected by whole-exome sequencing (WES) within human plaques, allowing us to investigate how mutated clones are distributed throughout the tissue and relate to plaque composition.

We also culture cells directly from freshly isolated human plaques and follow their development over multiple passages under different growth conditions. By tracking changes in the mutational landscape over time, we investigate how environmental cues may affect clonal dynamics and mutation-driven expansion in plaque-derived cells.

In addition, we perform siRNA-mediated knockdown experiments in commercially available human SMCs targeting genes affected by mutations identified in human plaques. Together, these approaches aim to move beyond mutation discovery and towards understanding how plaque-associated mutations may contribute to disease biology.

By integrating sequencing data from human plaques with experimental studies in cultured SMCs, this project aims to provide new insight into the mutational landscape of atherosclerosis and the mechanisms driving clonal expansion in vascular disease.

Understanding the cardiovascular consequence of type 2 diabetes mellitus: an exercise cardiac magnetic resonance imaging study

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Background: Type 2 diabetes mellitus (T2DM) is a major metabolic disease with profound cardiovascular consequences. Patients with T2DM have an increased risk of heart failure and are particularly prone to developing heart failure with preserved ejection fraction (HFpEF). In T2DM, HFpEF-related myocardial abnormalities, including impaired myocardial blood flow, diffuse myocardial fibrosis and altered cardiac function, are thought to develop years before clinical heart failure becomes apparent. Current cardiac assessments may miss early, functionally relevant diabetic cardiac disease in this high-risk population, as conventional cardiac imaging is primarily performed at rest despite symptoms typically occurring during physical activity. Assessing cardiac function under increased circulatory demand may therefore be essential to understand early disease mechanisms in T2DM and the pathways that may ultimately lead to HFpEF. Exercise cardiac magnetic resonance imaging (MRI) offers a unique opportunity to address this gap by integrating assessment of myocardial fibrosis, myocardial blood flow and cardiac function during a physiological challenge that reflects activities of daily living.

Methods: Patients with T2DM and age- and sex-matched healthy control subjects will be recruited. Cardiac structure and function, myocardial perfusion and diffuse myocardial fibrosis will be assessed using cardiac MRI, including extracellular volume mapping as a surrogate marker of diffuse fibrosis. Participants will subsequently perform in-scanner supine cycling using an MRI-compatible ergometer, aiming to achieve 60% of heart rate reserve.

Perspective: By integrating measures of myocardial perfusion, diffuse fibrosis and cardiac function during physiological stress, the study may help clarify whether microvascular dysfunction or myocardial fibrosis is more closely associated with impaired cardiac reserve in T2DM. Furthermore, sex-specific analyses may improve understanding of whether men and women with T2DM differ in the mechanisms linking diabetic myocardial disease to reduced exercise cardiac performance.

S100A8/A9 signaling molecules from epicardial adipose tissue as a driver of cardiac fibrotic remodeling

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Aim:

To investigate how S100A8/A9 proteins secreted from epicardial adipose (EAT) influence fibrotic remodeling in cardiac tissue.

Background:

EAT is visceral fat linked to increased bodymass index (BMI), atrial fibrillation (AF), and inflammation. During obesity, EAT releases inflammatory molecules that affect cardiomyocytes and fibroblasts leading to fibrosis in the atria, disrupting electrical conduction, promoting AF, and creating arrhythmogenic substrates. S100A8/A9 proteins, elevated in obesity and AF, are involved in inflammation and are Ca^{2+}-binding molecules that activate Toll-like receptor 4, upstream of the NLRP3 inflammasome, which is linked to cardiac fibrosis. Preliminary data suggest that S100A8/A9 proteins are elevated in EAT from the left atrial appendage (LAA) of obese patients, but the role of EAT-derived S100A8/A9 in cardiac fibrosis remains unclear.

Methods:

Left atrial biopsies with EAT will be collected from patients with normal (BMI) < 25 and from patients with obesity (BMI >30) at Rigshopitalet. A part of the tissue will be incubated to obtain the secretome, and S100A8/A9 protein levels in both EAT and the secretome will be analyzed by proteomic analysis.

Atrial fibroblasts will be incubated with or without recombinant S100A8/A9 protein for 24 hours. Fibroblasts will then be harvested and analyzed via mass spectrometry to examine NLRP3 inflammasome signaling pathways using bioinformatic analysis.

healthy myocardial tissue from donor hearts, acquired from patients with normal weight in London, will be sliced and mounted as "living myocardial tissue", and incubated with S100A8/A9 proteins for 48 hours. Slices from the same tissue will be used for baseline measurements and time matched controls. Conduction velocity and electrical heterogeneity will be assessed in the living myocardial tissue by utilizing a multi-electrode array system. Following electrophysiological measurements, tissue will be stained to assess collagen, fibroblast proliferation and differentiation, as well as cardiomyocyte morphology.

The E-wave Propagation Index as a Marker of Apical Blood Flow in Patients with Cryptogenic Stroke

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Background

In approximately 25% of ischemic stroke events, an underlying cause remains undetected. A potential underdiagnosed cause of cryptogenic stroke (CS) could be either left ventricular (LV) microthrombi or spontaneously resolved LV thrombi, which increases the risk of systemic thromboembolism five-fold. The E-wave propagation index (EPI) is a novel echocardiographic risk marker for LV thrombus formation

Purpose

To investigate whether patients with cryptogenic stroke exhibit lower EPI, as an indicator of either transient LV thrombi or LV microthrombi, as compared to a control group.

Methods

This was a case-control study comparing patients with CS with age- and sex-matched controls in a 1:3 ratio. Patients with CS were sampled from a prospective cohort study (n: 54), in which they underwent implantation of an implantable loop recorder for atrial fibrillation screening. Controls were recruited from a general population study, and excluded participants with a history of heart failure, atrial fibrillation, valve disease, pacemaker, and cerebrovascular disease. The EPI was measured as the ratio of the velocity time integral of early transmitral inflow to LV diastolic length. Linear regression was applied to calculate the adjusted mean differences after adjusting for potential clinical and echocardiographic confounders.

Results

This study included 54 patients with CS and 162 controls. The groups were well-matched in terms of age (mean age 54 years) and sex (57% men), and no clinical differences were noted between the groups. Of note, atrial fibrillation was detected with prolonged rhythm monitoring in 13 (24%) of the patients with CS. Patients with CS had significantly worse systolic (LVEF 52.1% vs 56.1%, $p<0.001$) and diastolic function (E/e' 7.6 vs. 5.7, $p<0.001$). Additionally, patients with cryptogenic stroke exhibited significantly higher EPI (1.7 vs. 1.4, $p<0.001$). The unadjusted mean difference was 0.32 (95% CI: 0.23-0.43). This difference persisted in multivariable adjustments. Similar findings were noted in the subgroup of patients who remained free of atrial fibrillation (adjusted mean difference of 0.41 (95% CI: 0.28-0.53).

Conclusion

Compared to an age- and sex-matched control group, patients with CS did not exhibit lower EPI, indicating that this measurement may not be useful in resolving the underlying cause of CS. The findings could reflect a greater degree of diastolic dysfunction in patients with CS.

Post-resuscitation cerebral ischemia is associated with vasospasm and capillary failure after experimental asphyxial cardiac arrest

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Aims: Neurological injury is the primary cause of disability and death after cardiac arrest (CA). This study aimed to investigate cerebral microcirculation after return of spontaneous circulation (ROSC) following asphyxial CA. We hypothesized that contraction of pericytes post-ROSC compromises cerebral capillary blood flow**.**

Methods: Transgenic C57BL/6 mice (*n*=19) were studied, in which pericytes were fluorescently labeled via PDGFRβ promoter-driven expression. Chronic cranial windows over the sensory cortex were implanted 3-weeks prior to the experiment. Four minutes of asphyxial CA was followed by cardiopulmonary resuscitation. Two-photon microscopy assessed cerebral capillary velocity, vessel diameter, capillary flow stalling, and mean transit-time (MTT) in the same cohort of mice at both 3 and 24 hours post-ROSC.

Results: Of 13 mice in the CA group, 9 achieved ROSC; 6 and 5 mice survived to 3 and 24 hours post-ROSC, respectively. Arterial blood pressure was similar between groups 3 and 24 hours post-ROSC. At 3 hours post-ROSC, pial arteries and penetrating arterioles were constricted compared with sham (arteriole diameter: 12.18 µm [95% CI: 10.99–13.37] vs. 15.64 µm [13.76–17.53] in CA and sham, P<0.003). Similarly, 1st and 2nd-3rd order capillaries showed reduced diameters 3 hours post-ROSC (1st order diameter: 3.87 µm [3.52–4.24] vs. 5.33 µm [4.79–5.87] in CA and sham, P<0.002). The post-ROSC vasoconstriction was associated with slower red blood cell velocities throughout the capillary network (for 6th-10th order capillaries; 0.72 mm/sec [0.37-1.06] vs. 1.38 mm/sec [1.09-1.68], P<0.05) and increased capillary flow stalling (incidence: 30.01% [20.46-39.56] vs. 16.23% [10.91-21.56] in CA and sham, P<0.01). Artery-to-vein MTT and capillary transit-time heterogeneity were increased 3 hours post-ROSC. By 24 hours post-ROSC, vessel diameters, blood flow velocity, MTT, and capillary stalling were not different compared with sham.

Conclusion: Cerebrovascular vasospasm 3 hours post-ROSC was associated with impaired cerebral microcirculation and increased capillary flow stalling.

Electrical, structural, and inflammatory features of atrial fibrillation in a *dsc2l* heterozygous zebrafish model.

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Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with electrical, structural and inflammatory remodeling of the atria. Emerging evidence suggests that alterations in desmosomal proteins contribute to cardiac dysfunction and arrhythmogenesis. Desmocollin-2 (DSC2), encoded by the human DSC2 gene, is a key component of the cardiac desmosome, playing a critical role in cell-cell adhesion and myocardial integrity.

Hypothesis: Mutations in desmosomal proteins impair cell adhesion, promote inflammation and alter cellular metabolism, ultimately leading to electrical disturbances in the heart.

Methods: To investigate the role of desmosomal dysfunction in AF, a CRISPR-Cas9 *dsc2l* heterozygous zebrafish model carrying premature stop-codon mutation was generated and validated by sequencing.

Results: To investigate the functional consequences of heterozygous loss of *dsc2l*, electrocardiographic recordings were performed at 4, 6, 8, and 12 months post-fertilization (mpf). These revealed an electrophysiological phenotype detectable as early as 4 mpf in *dsc2l* heterozygous fish. Loss of desmosome integrity can lead to defects in electrical coupling, and to investigate this, we performed in vivo calcium imaging using 5 days post-fertilization (dpf) wild-type and heterozygous larvae. The calcium imaging results at 5 dpf did not show any significant defect in the heterozygous *dsc2l* larvae, suggesting the need for further analysis in later stages. Future studies will investigate the localization of various desmosomal components in *dsc2l* mutant fish and ultrastructural alterations at later stages, however, preliminary data using transmission electron microscopy (TEM) analysis at 2 mpf identified possible glycogen accumulation within atrial muscle fibers, suggesting an early metabolic switch associated with disease onset. In parallel, transgenic reporter lines were used to investigate macrophage distribution in and around the cardiac tissue in wild-type and heterozygous fish at 5, 14 and 40 dpf. These results were in-conclusive and will need further investigations.

Endothelial STING-IFN-I Signaling Drives Atherogenic Inflammation and Disrupts Cholesterol Homeostasis

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Background and Aims: Despite major advances in lipid-lowering therapies, residual inflammatory risk continues to drive progression of atherosclerotic cardiovascular disease (ASCVD). As key orchestrators of vascular inflammation and barrier function, endothelial cells represent an important yet insufficiently explored therapeutic target. STING (Stimulator of Interferon Genes), a cytosolic adaptor involved in innate immune and type I interferon signalling, is well recognized in immune cells, but its endothelial-specific contribution to vascular inflammation and atherogenesis remains unclear. Here, we aimed to define the role of endothelial STING signalling in endothelial inflammatory remodelling and vascular dysfunction in ASCVD.

Methods and Results: Single-cell transcriptomic profiling identified expression of key components of the STING-type I interferon (IFN-I) signalling axis within endothelial cells (ECs), suggesting their capacity to mount STING-dependent inflammatory responses. This response was confirmed in vitro, where stimulation of human endothelial cells (HECs) with the STING agonist cGAMP activated IFN-I signalling, as demonstrated by increased expression of interferon-stimulated genes, including ISG15. Bulk RNA sequencing further revealed that endothelial STING activation was associated with dysregulated cholesterol homeostasis and enrichment of inflammatory pathways. Consistent with these transcriptomic findings, STING activation tended to increase lipid accumulation in vitro and promoted a pro-inflammatory endothelial phenotype, characterized by upregulation of VCAM-1 and ICAM-1, together with increased secretion of CXCL10. These effects were abolished by genetic deletion of key STING signalling mediators, including STING and IRF3, confirming pathway specificity. Notably, in addition to cGAMP, native LDL also appeared to activate STING-IFN-I signalling in HECs, as reflected by increased expression of IFN-I-related genes, including ISG15 and CXCL10, and induction of adhesion molecule protein expression. These findings suggest that, beyond cytosolic DNA sensing, lipid-related stimuli may also contribute to endothelial STING-IFN-I activation.

Conclusions: Together, these findings implicate endothelial STING-IFN-I signalling as a lipid-responsive inflammatory pathway that may contribute to vascular dysfunction in cardiometabolic disease.

Comparison of findings from pre-angiographic cardiovascular magnetic resonance in patients with suspected NSTEMI with and without previous MI

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Background - Previous studies have investigated the use of cardiovascular magnetic resonance (CMR) for diagnosis of acute MI in patients with suspected NSTEMI. However, there is limited evidence regarding the utility of CMR in patients with prior myocardial infarction (MI), in whom old MI scars may complicate the identification of an acute MI. Native T1/T2 mapping can detect myocardial oedema and differentiate between old and acute MI as well as non-ischaemic myocardial injury.

Purpose - To characterize CMR findings in a prospective cohort of patients with suspected NSTEMI, comparing the distribution of findings between patients with and without previously documented MI.

Methods - Consecutive patients with suspected NSTEMI referred for ICA were prospectively enrolled for comprehensive CMR including cine, native T1/T2 mapping, and late gadolinium enhancement (LGE) prior to ICA. CMR diagnoses were categorized as: normal, chronic scars only (ischaemic or non-ischaemic), acute non-ischaemic, acute MI. Acute MI was defined as elevated T1 (>1100 ms) and T2 (>55 ms) with corresponding ischaemic-pattern LGE. Wall motion abnormalities in the absence of edema or LGE were classified as chronic coronary syndrome (CCS). All readers were blinded to clinical and angiographic data. Differences were assessed using the Kruskal-Wallis test and pairwise Mann-Whitney U tests.

Results - A total of 107 patients (age 67.7 ± 11.4 years, 65% male) were included, of which 25 (23%) had a history of previous MI. In patients without previous MI (n=82), CMR identified acute MI in 29%, whereas 23% had normal findings and 17% had acute nonischaemic findings (Figure 1). In patients with previous MI (n=25), the rate of acute MI findings was 32%, and chronic findings (ischaemic or non-ischaemic scars) were numerically more prevalent compared to those without prior MI (44% vs. 26%). Five patients (4.7%) were classified as CCS. Peak troponin T levels (ng/L) differed significantly by CMR category ($p < 0.001$) (Figure 2): Patients with acute MI findings had the highest levels (376, 152–1040), which were significantly higher than those with chronic ischaemic (127, 67–233; p=0.002), chronic non-ischaemic (104, 67–157; p=0.001), and acute non-ischaemic findings (171, 87–307;p=0.02). Patients with normal CMR findings had the lowest troponin levels (68, 34–121), which was also significantly lower than those with acute non-ischaemic findings (p=0.007).

Conclusions - In patients with suspected NSTEMI and previous MI, nearly half had chronic scars with no signs of oedema, and the rate of acute MI was similar (32 vs 29%) to patients without prior MI. Troponin T levels were higher in patients with CMR signs of acute MI and acute non-ischaemic injury. CMR frequently identified non-acute or non-ischaemic pathology in patients managed as acute NSTEMI and may be used to differentiate acute MI from chronic scars, regardless of previous MI history.

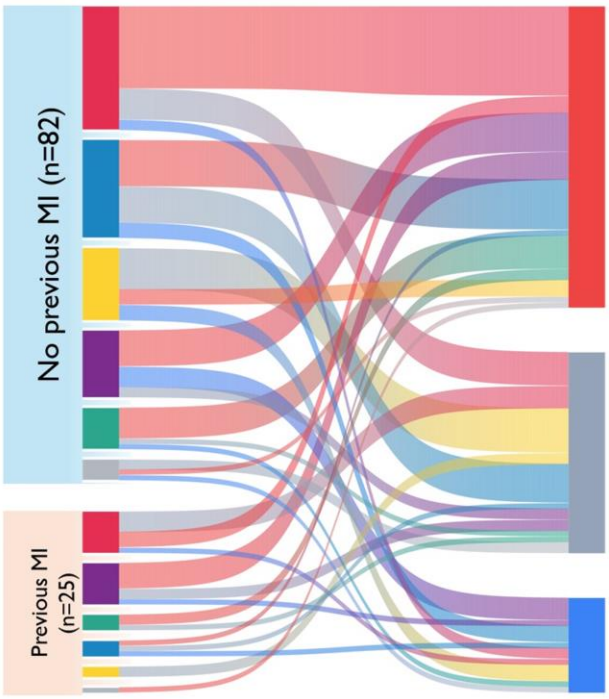

Figure 1. CMR Findings and ICA-guided Management by Previous Myocardial Infarction History This figure presents the final Cardiac Magnetic Resonance (CMR) findings stratified by the presence (n=25) or absence (n=82) of a documented previous myocardial infarction (MI). Diagnoses are listed in descending order of total frequency. Tabular data are presented as n (relative subgroup percentage) followed by the distribution of clinical interventions (PCI / No intervention / CABG). Acute MI findings were the most common diagnosis overall, showing similiar prevalence (29 vs 32%) across both groups. Chronic findings were sub-classified based on tissue characterization; Chronic ischaemic scar was more prevalent in patients with a known history of MI (32% vs 16%), whereas Normal CMR findings were more frequent in those with no prior history (23% vs 12%). Despite these numerical variations, global distribution differences were not statistically significant ($p > 0.05$). Total cohort intervention rates were 50% for PCI, 34% for medical management/no intervention, and 16% for CABG.

ICA- guided management	No Prev MI (n=82) *n (%) PCI/None/CABG*	Prev MI (n=25) *n (%) PCI/None/CABG*	Total (n=107) *n (PCI/None/CABG)*
Acute MI	24 (29%) 16/6/2	8 (32%) 3/4/1	32 (19/10/3)
Normal	19 (23%) 9/7/3	3 (12%) 1/1/1	22 (10/8/4)
Chronic ischaemic scar	13 (16%) 7/2/4	8 (32%) 5/2/1	21 (12/4/5)
Acute non-ischaemic	14 (17%) 3/8/3	2 (8%) 0/2/0	16 (3/10/3)
Chronic non-ischaemic scar	8 (10%) 6/1/1	3 (12%) 2/1/0	11 (8/2/1)
Non-acute CCS	4 (5%) 1/2/1	1 (4%) 1/0/0	5 (2/2/1)
Total	**42/26/14**	**12/10/3**	**54/36/17**

Characterization of a fibrotic HFpEF-like mouse model and response to finerenone treatment

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Background: Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome. Despite its rising prevalence, effective treatment options remain limited. Myocardial fibrosis is presumably a hallmark of HFpEF, contributing to increased ventricular stiffness and impaired diastolic function. Finerenone, a selective non-steroidal mineralocorticoid receptor antagonist, has demonstrated cardioprotective and antifibrotic effects in cardiovascular and renal diseases; however, its efficacy in HFpEF remains incompletely understood.

Aim: This study aimed to develop a multi-hit mouse model exhibiting HFpEF-like features including marked myocardial fibrosis, and to investigate the effects of chronic finerenone treatment**.**

Methods: Eight-week-old male C57BL/6N mice underwent a 16-week HFpEF-inducing protocol (HFpEF group). To induce obesity and hypertension, mice were fed a high-fat diet (60% fat) and administered L-NAME (1 g/L) via drinking water. Four weeks into the protocol, a subcutaneous minipump was implanted to deliver phenylephrine (10 µg/kg/day) for four consecutive weeks. After 13 weeks, a subgroup of HFpEF animals received finerenone (10 mg/kg/day) P.O. for three weeks (FIN group). The HFpEF (n=15) and FIN (n=7) groups were compared to an untreated, age-matched control group (n=14). Following the 16-week period, cardiac function was assessed in vivo using echocardiography and exercise capacity testing. Myocardial fibrosis was quantified through histopathological assessment**.**

Results: After 16 weeks, both the HFpEF ($p<0.0001$) and FIN ($p=0.0135$) groups showed significantly higher body mass than controls. The HFpEF group exhibited preserved ejection fraction (EF) and a trend toward increased left ventricular wall thickness ($p=0.0569$). In contrast, FIN-treated animals showed a significant reduction in EF ($p=0.0018$) and no increase in wall thickness compared to controls. Elevated filling pressures were trending toward an increased E/e' ratio in the HFpEF group ($p=0.0746$), which was not observed in the FIN group. Finally, both HFpEF and FIN groups demonstrated reduced exercise capacity and significantly increased myocardial fibrosis compared to control animals.

Conclusion: We developed a novel multi-hit mouse model displaying key HFpEF-like features, including preserved EF, exercise intolerance, and marked myocardial fibrosis. While finerenone improved indices of ventricular remodelling and diastolic filling pressures, the concomitant reduction in EF suggests that structural modulation does not necessarily translate into improved global cardiac performance in this specific model. These findings highlight the need for further mechanistic investigation.

Symptoms of anxiety and depression after out-of-hospital cardiac arrest: an exploratory dyadic analysis of survivors and their cohabiting spouses or partners from the BOX trial

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Abstract

Aim: The objectives were to: i) compare symptoms of anxiety and depression between survivors and cohabiting spouses/partners, and ii) investigate characteristics associated with higher scores of anxiety and depression in both parts, respectively.

Methods: This observational exploratory substudy used three-month follow-up data from the *Blood Pressure and Oxygenation Targets after Cardiac Arrest* (BOX)-trial, restricted to cohabiting survivor-partner dyads. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS-A anxiety, HADS-D depression). Paired comparisons were used to examine differences within the dyad, and multivariable linear regression models applied separately for survivors and spouses/partners to investigate associations between characteristics and symptom burden, reported as β with 95% confidence intervals (CI).

Results: Among 321 eligible OHCA survivors, 200 survivor-partner dyads were included. Median HADS-A scores were 4 (IQR 1-7) in survivors and 5 (IQR 1-8) in spouses/partners (p=0.107). Median HADS-D scores were 1 (IQR 0-4) and 1 (IQR 0-3), respectively (p=0.290). In adjusted regression analyses among survivors, higher age was associated with lower scores of HADS-A (β -0.065, 95% CI -0.125;-0.025; p=0.012) and HADS-D (β -0.040, 95% CI -0.090;-0.00; p=0.037). In sensitivity analyses, poorer self-rated health was associated with higher scores of HADS-A and HADS-D in both parts, and poorer *survivor* self-rated health was associated with higher scores of HADS-D among spouses/partners.

Conclusion: Symptoms of anxiety and depression did not differ in survivors and their spouse/partners. Higher age was associated with lower scores of anxiety and depression among survivors, and poorer self-rated health with higher symptom-scores in both.

Women with pregestational adiposity - a high-risk population - The PRE-STORK baseline data

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Background and aims

Pregestational overweight and obesity affect more than 40% of all women and associates with adverse pregnancy, neonatal outcomes, long-term maternal and offspring health risk. Pregnancy induces insulin resistance, increased blood pressure and hyperlipidemia, and additional metabolic dysfunction-associated steatotic liver disease (MASLD) may worsen these conditions. Although women with pregestational adiposity may exhibit cardiometabolic parameters within the normal range, subclinical abnormalities may become unmasked or exacerbated during pregnancy, potentially increasing health risks for both mother and offspring. We therefore aimed to estimate the prevalence of subclinical and clinical cardiometabolic abnormalities in women with pregestational adiposity and investigate if these abnormalities are BMI dependent.

Material and methods

This study presents baseline data from the PRE-STORK trial, including women with BMI 25-44 kg/m^2 seeking pregnancy. Pregestational cardiometabolic health, was assessed by BMI, insulin resistance (HOMA-IR), hepatic steatosis measured by Fibroscan® controlled attenuation parameter (CAP), blood pressure, lipids and low-grade inflammation assessed by high-sensitive CRP (hsCRP). The prevalence of women exceeding subclinical and clinical cut-off values was estimated according to international guidelines from, The European Association for the Study of the Liver and The European Society of Cardiology respectively. Simple linear regression models examined associations between anthropometric measures and metabolic parameters.

Results

The included women (n=259) had a mean age of 30.6 years and BMI of 32.6 kg/m². The prevalence of subclinical, clinical insulin resistance and prediabetes was 27.7% (95% CI 22.3–33.7), 33.6 % (95% CI 27.9–39.8) and 1.9% (95% CI 0.7–4.7) respectively. Steatosis/MASLD was present in 38.9% (95% CI 32.8–45.3) and the majority of these were categorized as S3-steatosis (CAP>280 dB/m). Subclinical hypertension and hypertension were present in 19.0% (95% CI 14.5–24.4) and 5.4% (95% CI 3.1-9.1), respectively. Furthermore, 23.7% (95% CI 18.8–29.5) and 29.6% (95% CI 24.1–35.6) presented with subclinical and clinical LDL-hypercholesterolemia and 40.4% (95% CI 30.6–51.1) had low-grade inflammation. All metabolic parameters, except LDL-cholesterol, increased with BMI, with similar associations across anthropometric measures (figure).

Conclusion

A great proportion of women with pregestational adiposity have cardiometabolic abnormalities, which may increase the risk of unmasking cardiometabolic disease during pregnancy - highlighting the need for targeted preconception preventive strategies.

Chamber specific calcium abnormalities in a desmin arrhythmia model.

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Mutations in *DES*, which encodes the intermediate filament protein desmin, are a recognized cause of atrial and ventricular cardiomyopathies, yet the chamber-specific origins of these pathologies remain poorly understood. Here, using a zebrafish model, we define the primary and secondary drivers of cardiac dysfunction arising from partial desmin loss by integrating high-resolution imaging, developmental phenotyping, functional electrophysiology, and molecular profiling across multiple life stages. We find that the atrium is uniquely vulnerable with early calcium handling defects, which persist into adulthood. These defects are accompanied by a prolonged P-wave duration and higher frequency of arrhythmic events. These abnormalities coincide with the expansion of an ectopic conduction network, increased collagen deposition, and slowed electrical activation. In contrast, ventricular tissue primarily exhibits structural hallmarks of Z-disk disruption and a reduction in average conduction velocity, without the early functional instability observed in the atrium. Together, these findings demonstrate that partial desmin deficiency elicits distinct pathogenic trajectories in the two cardiac chambers, with the atrium showing the earliest and most pronounced defects. This chamber-specific sensitivity underscores the need for early and continuous monitoring of atrial function in individuals carrying *DES* variants.

Low-dose GLP1-RA as a metabolic intervention in obesity-induced atrial fibrillation

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Aim and Hypothesis: Obesity is a major risk factor for atrial fibrillation (AF), yet effective strategies to prevent or treat obesity-induced AF remain limited. Glucagon-Like Peptide-1 Receptor Agonists (GLP1-RA) have demonstrated cardiometabolic benefits but their direct effects on atrial structure and AF susceptibility are unclear. We hypothesize that low-dose GLP1-RA reduces AF susceptibility and atrial remodeling independently of weight loss through anti-inflammatory and metabolic pathways. **Methods:** Göttingen minipigs (n=16) will undergo 3 months of western-style diet to induce a 50 % weight gain followed by a 3-month weight-stabilization period with adjusted calorie intake. Subsequently, pigs will be randomized to receive low dose GLP1-RA (n=8) or placebo (n=8) for 3 months while body weight is kept stable. Assessments will be performed at baseline, post-weight gain, post-weight stabilization and post-treatment. The primary endpoint is 72 hours AF burden measured using Ellipse implantable cardioverter-defibrillators. Secondary endpoints include epicardial adipose tissue volume by cardiac magnetic resonance imaging (MRI) and atrial tissue composition from biopsies. At the study's conclusion, electroanatomical mapping will be used to characterize atrial electrophysiological remodeling. Ex vivo MRI of explanted hearts and postmortem histology will quantify atrial fat infiltration and myocyte-adipose-fibrosis composition. **Perspectives:** This study will provide novel insights into obesity-induced atrial remodeling and assess GLP1-RA's potential as a therapeutic intervention against AF. If successful, the findings would support the evidence that metabolic pathways drive atrial disease progression and help clarify whether metabolic modulation represents a potential treatment approach in obesity-associated AF.

Prehospital Prediction of Myocardial Infarction Within Seven Days of an Emergency Call for a Medical Complaint: Development and Temporal Evaluation of Machine Learning Models

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Objective: To develop and temporally evaluate prehospital models for predicting 7-day myocardial infarction (MI) and to assess the added value of vital signs and 12-lead ECG beyond dispatch data.

Methods: Nationwide retrospective cohort study using the Danish Prehospital Medical Record System of all emergency ambulance dispatches, linked to the Danish Nationwide ECG Cohort and national hospital and mortality registries. We included 522,241 adults aged 18–100 years assessed by an ambulance for a medical complaint (development 2017–2022, evaluation 2023–March 2024). The outcome was MI within 7 days of index assessment. Predictor sets were "Benchmark" (demographics, symptoms, ambulance response), "+Vitals" (Benchmark + vital signs) and "+ECG" (Benchmark + vital signs + ECG features). The isotonic-calibrated random forest performed best in cross-validation and was evaluated.

Results: In the main evaluation cohort (N = 79,411, MI ≤7 days 3.0%), adding vital signs to benchmark provided marginal improvement in performance (area under the receiver operator characteristic curve (AUC) 89.9 (95% confidence interval, 89.3–90.4) vs 88.8 (88.2–89.4), Brier 2.50 (2.41–2.59) vs 2.56 (2.47–2.65)) with small decision impact at 1–5% thresholds (Δnet benefit (NB) ×100 ≤0.2). In the ECG evaluation subcohort (N = 19,343, MI 8.1%), +ECG outperformed +Vitals (AUC 88.5 (87.7–89.4) vs 81.5 (80.5–82.5), Brier 4.82 (4.58–5.06) vs 6.56 (6.30–6.82)). At 5% risk threshold, the +ECG model achieved the highest net benefit (NB×100 5.5), with higher sensitivity (90.3%), positive predictive value (PPV) (17.6%), a lower test-positive rate (41.6%), and fewer missed events (7.91/1,000) than +Vitals (NB×100 5.0, sensitivity 85.5%, PPV 16.2%, 12.10 misses/1000) and Benchmark (NB×100 4.9, sensitivity 87.7%, PPV 14.5%, 10.08 misses/1,000). Largest clinical gains were seen in dyspnoea (AUC 82.3 +ECG vs 63.5 +Vitals), where at 5%, +ECG yielded the best net benefit (NB×100 2.5), high sensitivity (89.0%), and fewest misses (5.89/1,000). In chest pain, +ECG improved efficiency at 5% (PPV 24.3%, test-positive 48.1% vs 16.2% and 77.0% with Benchmark) with modest sensitivity reduction (90.9% vs 97.2%) and higher NB (NB×100 9.8 vs 9.1). Overall, 16% of MI patients (N = 1,449) had no prehospital ECG, including 11.2% (N = 775) of chest pain and 34.4% (N = 201) of dyspnoea MIs.

Conclusion: ECG findings substantially improved prehospital prediction of MI and were particularly valuable in patients with dyspnoea, among whom ECGs are not routinely obtained. Vital signs added only limited incremental information beyond dispatch data.

Project on genetics of cardiovascular disease in Greenland

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Similar abstract was also presented in Danish at the Greenlandic health conference, Nunamed 2025

Background: Genetics substantially influences cardiovascular disease (CVD) risk, and genetic research has strong potential to improve the understanding, prevention, and treatment of CVD. However, most genetic studies of CVD have been conducted in populations of European or East Asian genetic ancestry, leaving the genetic architecture of CVD in other populations, including the Greenlandic population, unexplored[1]. Genetic contributions to disease vary across populations. For example, type 2 diabetes risk in European populations is influenced by hundreds of variants with small individual effects, whereas fewer variants with larger effects have been identified in the Greenlandic population, increasing their potential utility for precision medicine[2,3]. This project aims to investigate the genetic determinants of CVD in the Greenlandic population.

Methods: We will conduct the first genome-wide association studies (GWAS) of CVD using genetic and nationwide health registry data from approximately 6,000 participants from the Greenlandic Public Health Surveys. Complementary analyses will use two European cohorts, the UK Biobank and the Copenhagen Hospital Biobank, to perform gene-based replication of candidate loci and evaluate causal relationships between relevant endophenotypes and CVD outcomes.

Expected Results: We hypothesize that the genetic architecture of CVD differs in the Greenlandic population compared with European and Asian populations. We expect to identify one or more population-specific genetic variants with relatively large effects on CVD risk. Such variants may provide novel insights into disease mechanisms and reveal potential therapeutic targets. In addition, known CVD-associated variants may differ substantially in allele frequency and population impact, while some variants may show similar frequencies and effects across populations.

Conclusions: A comprehensive characterization of the genetic contribution to CVD in the Greenlandic population, and comparison with other populations, may improve understanding and prevention of CVD in Greenland. As the first study of genetic determinants of CVD risk in Greenland, this project will also contribute to reducing disparities in genetically informed healthcare and precision medicine.

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Coronary High-Intensity Plaque Signal-Intensity Ratio (CHIPS) for detection of flow-limiting coronary stenoses in comparison to Fractional Flow Reserve (FFR)

Authors:

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Introduction: Magnetic Resonance imaging using iT2-prep BOOST (1) is a newly developed technique for identification of unstable coronary artery disease (CAD). Hyperintense regions identified on T1-weighted plaque imaging that correspond to coronary atherosclerotic lesions can be quantified relative to the signal intensity of the vessel wall, yielding a normalised metric referred to as the coronary hyperintense plaque signal (CHIPS) ratio. A greater quantity of methaemoglobin, which arises from intraplaque hemorrhage or plaque rupture, creates a greater ratio and thus more advanced disease. This could be used to characterise intra-plaque characteristics non-invasively and without use of radiation and contrast agents. However, validation is required in order to verify efficacy.

Methods: FFR measured using coronary computed tomography angiography or invasive coronary angiography were obtained from 26 coronary vessels with suspected CAD. CHIPS was acquired from lesions with ≥ 50 % luminal stenosis via use of iT2-prep BOOST. The diagnostic performance of CHIPS was compared to FFR. A significance threshold of <0.80 was used for FFR and ≥1.33 for CHIPS.

Results: There were 12 FFR positive and 18 CHIPS positive coronary lesions. Sensitivity and NPV of CHIPS as compared to FFR was 1. Specificity of CHIPS as compared to FFR was 0.57 (95% CI: 0.29 - 0.823) whilst PPV was 0.67 (95% CI: 0.41 - 0.87). The diagnostic accuracy was 0.77 (95% CI: 0.56 - 0.91) and AUC was 0.79 (95% CI: 0.65-0.92).

Discussion: CHIPS identified all flow-limiting coronary lesions. There was however a tendency to overestimate disease prevalence as compared to FFR. Further investigation in a larger cohort will be required to determine the precise diagnostic precision and optimal threshold of significant disease before iT2-BOOST and CHIPS can be used in a clinical context.

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Sustained use of oral versus transdermal postmenopausal hormone therapy and cardiovascular events in women with diabetes - an observational target trial emulation

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Background and aims

In postmenopausal women with diabetes, the effect of hormone therapy (HT) remains unclear. We emulated a target trial using observational data to compare oral and transdermal HT, investigating the risk of cardiovascular events in women with diabetes.

Materials and Methods

Using the Danish nationwide registries, we emulated a target trial from 1998-2024, investigating combined oestrogen-progestogen HT use in women aged 45-60 years. HT exposure was based on redeemed prescriptions and time zero was defined as the date of prescription redemption corresponding to either oral or transdermal combined HT. Women were followed from time zero until the first diagnosis of the composite outcome (arterial or venous thrombosis or cardiovascular death), emigration, death from other causes, or 31 January 2024. The five year risk and risk difference of the primary outcome following two, three, four and five years of sustained HT treatment, respectively, was calculated using longitudinal minimum loss-based estimation (LTMLE), accounting for baseline and time varying confounders.

Results

We included 668 women with diabetes, 362 initiating oral therapy and 306 initiating transdermal therapy. The mean age at time zero was comparable between the two arms at 51.1 (SD 3.3) and 51.2 (SD 3.1) years in the oral and transdermal arm, respectively. Oral initiators had a lower income compared to transdermal initiators, while educational status and comorbidities were similar. At five years, 13 women in the oral arm had experienced the composite outcome, whereas the number was 5 in the transdermal arm. Following five years of sustained oestrogen-progestogen treatment, the five year risk of the composite outcome was 6.1% (95% CI: 3.2% to 8.9%) in the oral arm and 0.3 (95% CI: 0.0 to 0.6) in the transdermal arm, corresponding to a statistically significant five year risk difference of -5.8% (95% CI: -8.6% to -2.9%), in favor of sustained transdermal HT treatment. The corresponding risk differences at five years were -4.5% (95% CI: -7.2% to -1.9%) following four years of sustained HT treatment, -3.4% (95% CI: -5.5% to -1.3%) following three years of sustained HT treatment, and -1.4% (95% CI: -2.5% to -0.2%) following two years of sustained HT treatment.

Conclusion

In women with diabetes initiating combined oestrogen-progestogen HT, sustained treatment with transdermal administration was associated with a decreased risk of cardiovascular events at five years compared to oral administration. This risk difference increased with increasing length of sustained HT treatment.

Characterisation of the protein composition and histone modification in neutrophil and eosinophil extracellular traps.

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Extracellular traps (ETs) are released by neutrophils (NETs) and eosinophils (EETs) during inflammation and play a role in the pathology of inflammatory diseases. NETs are composed of chromatin decorated with histones and anti-microbial proteins, such as myeloperoxidase (MPO) and elastase, while the protein composition of EETs has not been well studied. Various studies highlight a role for extracellular histones in promoting tissue damage and disease, e.g. in atherosclerosis. In this study, we used a proteomic approach to compare the protein composition of NETs and EETs, and examined whether the histones contain post-translational modifications (PTMs), which could influence their reactivity. The NETs were isolated from purified neutrophils stimulated with calcium ionophore (A23187) using different DNA digestion times (15 or 5 min) to create different NET sizes. The abundance of histones and MPO was significantly higher in small sized NETs compared to large sized NETs. Interestingly, NET size was not associated with the presence of other NET associated proteins, like neutrophil elastase, α-enolase and transketolase. In contrast, the protein composition of EETs released by purified eosinophils stimulated with A23187 was significantly different from the proteins detected in NETs. Eosinophil cationic protein, eosinophil peroxidase (EPO) and different types of proteoglycans were the most abundant proteins in EETs and not identified in NETs, while MPO and Histone H4 were significantly elevated in NETs. PTMs of histones were determined, particularly on Tyr88 in histone H4, which was brominated in EETs and chlorinated in NETs, consistent with the formation of hypobromous acid by EPO and hypochlorous acid by MPO. These results show for the first time that ETs from eosinophils contain different proteins and histone modifications than NETs, which could be important in determining the cellular nature of ETs in vivo and assessing their wider role in disease.

Cardiac remodelling and functional status after cardiac resynchronization therapy: upgrade from right ventricular pacing and de novo

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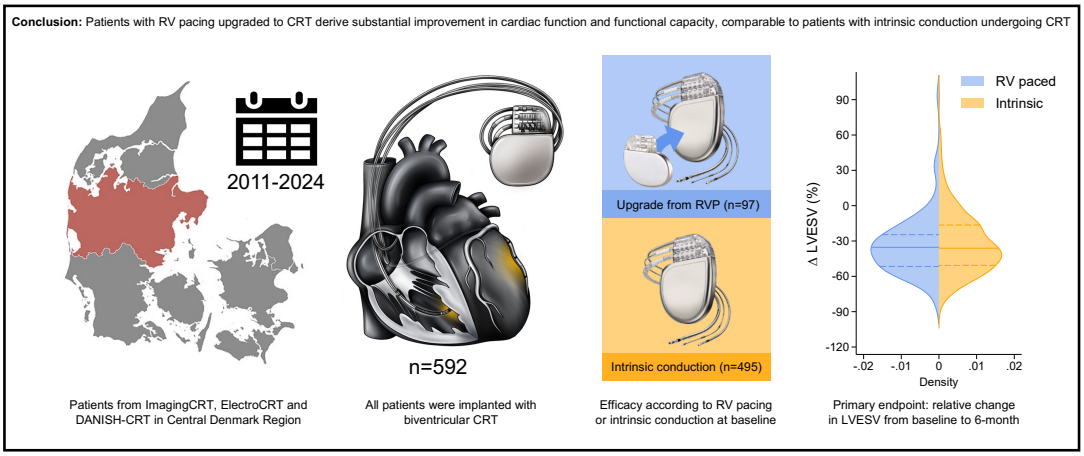
Background: Patients with heart failure considered to be induced or worsened by chronic right ventricular (RV) pacing commonly undergo upgrade to a cardiac resynchronization therapy device (CRT). Upgrades comprise 25-30% of CRT procedures, even though most evidence rest on de novo

Purpose: The purpose of this study was to compare the effect size of improvement in cardiac function and functional capacity from CRT implantation to 6-month follow-up between patients with RV pacing and intrinsic conduction at baseline.

Methods: We included patients from three randomized controlled trials; the ImagingCRT, ElectroCRT and DANISH-CRT trials (age ≥40 years, left ventricular [LV] ejection fraction [LVEF] ≤35% and prolonged QRS). All patients received biventricular CRT. The primary endpoint was change in LV end-systolic volume (LVESV) from baseline to 6-month follow-up. Secondary endpoints included change in QRS duration, LVEF, LV end-diastolic volume, LV mass index, left atrial volume index, N-terminal prohormone of brain natriuretic peptide, six-minute walk test, quality of life questionnaires, New York Heart Association functional class and use of loop diuretics.

Results: We included 592 patients; 97 (16.4%) with RV pacing and 495 (83.6%) with intrinsic conduction at baseline. We found significant relative reduction in LVESV from baseline to 6-month follow-up for patients with RV pacing (-34±25%) and intrinsic conduction (-32±26%) with no between-group difference (mean difference -2%, 95% CI [-8;4], p=0.469). There was significant absolute improvement in LVEF in patients with RV pacing (14±9) and intrinsic conduction at baseline (13±9) with no difference between them (mean difference 1, 95% CI [-1;3], p=0.356). Reduction in QRS duration was larger with RV pacing compared with intrinsic conduction (-38±26 versus -26±24 ms). We found significant improvements in the remaining secondary endpoints, with no difference between the groups.

Conclusion: Patients with RV paced QRS morphology who are upgraded to a CRT device derive substantial improvement in cardiac function and functional capacity, comparable to patients with intrinsic conduction undergoing CRT.



High-intensity interval training improves endothelial function in patients with Ischemia with no Obstructive Coronary Arteries (INOCA)

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BACKGROUND INOCA is characterized by coronary microvascular dysfunction and endothelial impairment, yet no evidence-based treatment protocol currently exists. HIIT has been shown to improve vascular function through increased shear stress and enhanced nitric oxide bioavailability, making it a mechanistically plausible therapeutic candidate for this patient group. **OBJECTIVES** The purpose of this study was to investigate the effects of 12 weeks (60-minute, 3x weekly) high-intensity interval training (HIIT) on endothelium-dependent and endothelium-independent vascular conductance and oxidative stress in patients with Ischemia with no Obstructive Coronary Arteries (INOCA). **METHODS** Twenty INOCA patients (11 females, 9 males) were randomized to the 12-week supervised exercise treatment (ExT) or maintenance of current lifestyle (MnT). Nineteen individuals without INOCA (CON) were included for baseline comparison. Endothelium-independent and endothelium-dependent vascular conductance were assessed by intraarterial infusion of adenosine (ADO) and acetylcholine (ACH) respectively, via brachial artery catheterization. Handgrip exercise with vitamin C infusion was used to assess the contribution of oxidative stress to vascular function. Data were analyzed using linear mixed models. **RESULTS** Following the 12-week intervention, maximal oxygen uptake (VO_2max) increased significantly in ExT (Δ2.3 mL/kg/min, p=0.009), but not in MnT (p=0.348). The ADO response was unchanged following the intervention in either group (all p>0.05). A significant dose × group interaction was observed at the highest ACH dose following the intervention (p=0.042), with ExT showing an increase in vascular conductance of Δ3.03 mL/min/mmHg, while MnT showed no change. No significant group difference was observed in the vitamin C protocol (p=0.672). **CONCLUSIONS** 12 weeks of HIIT significantly improved endothelium-dependent vascular conductance in patients with INOCA, while endothelium-independent vasodilation and oxidative stress-related vascular function showed no improvement with exercise training. These findings suggest that exercise training may represent a promising non-pharmacological intervention for improving vascular endothelial function in INOCA.

Developing a Model System to Investigate Tissue Specific Extracellular Vesicles *in Vivo*

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Extracellular vesicles (EVs) are small lipid bilayer-enclosed particles released by cells into body fluids. EVs carry both nucleic acids and proteins that can be used for crosstalk between organs such as the heart and kidneys in health and disease. Yet all cells release EVs, and kidney- and heart-derived EVs account for only a small fraction of the total EV pool. Thus, although cell-type-specific EVs represent a promising avenue for studying organ crosstalk, identifying cell-type-specific plasma EV markers remains a major challenge.

To address this issue, we developed a novel approach to isolate cell type–specific EV markers both *in vitro and in vivo* through chemically labeling cell-type-specific EV surface proteins. This was done by creating a fusion protein containing the EV marker CD9, the peroxidase APEX2, and a peptide epitope (ALFA)-tag. To test the system *in vitro,* HeLa cells were transfected to produce a stable expression of the fusion protein. Cells were incubated with biotin and H_2O_2 for 10 min, fixed and stained with Streptavidin, Alexa Fluor™ 568 conjugate and FluoTag-X2 anti-ALFA-Atto-643. Importantly, only cells transfected with the construct had positive staining for the ALFA-tag and cells were only streptavidin positive upon biotin addition. Successful isolation of EVs from biotinylated cells by PEG precipitation and size exclusion chromatography (SEC) isolation was demonstrated by Western blotting for CD63, another EV marker. Streptadivin-HRP was used to investigate biotinylation and showed some positive staining in all groups, though cells with the construct showed positive biotinylation in other fractions. To allow isolation of tissue-specific EVs in vivo, we generated a strategy for Cre-dependent expression of the CD9-APEX2 fusion protein. First, recombinant adeno-associated virus (rAAV) 8 was used to deliver a liver-specific Cre recombinase (rAAV8-Tbg-Cre, $1{\cdot}10^{12}$ viral genomes). One month later rAAV9 ($1{\cdot}10^{12}$ viral genomes) encoding the fusion protein was introduced using an IV injection. A Cre-dependent GFP virus was used as a recombination control. 14 days post AAV9 injection spot plasma samples were collected and EVs were isolated by an AcouTrap microfluidics device. After isolation EVs were biotinylated with biotin-tyramide and H_2O_2 for 1 min and analyzed by western blotting. The presence of EVs was investigated by flotillin-1 (EV-specific marker) and was confirmed in all groups. Importantly, biotinylation assessed with streptavidin-HRP, was only detected in groups carrying the fusion protein.

This work demonstrates the validity of the approach and the initial *in vivo* studies suggest that targeting the liver specific EVs is feasible. Further developments and validation are ongoing before detailed comparisons of tissue specific EV surface markers and cargo can be compared in health and disease.

Haemodynamic Effects of Nitroglycerin-induced Vasodilation in Acute Heart Failure: A Clinical Study

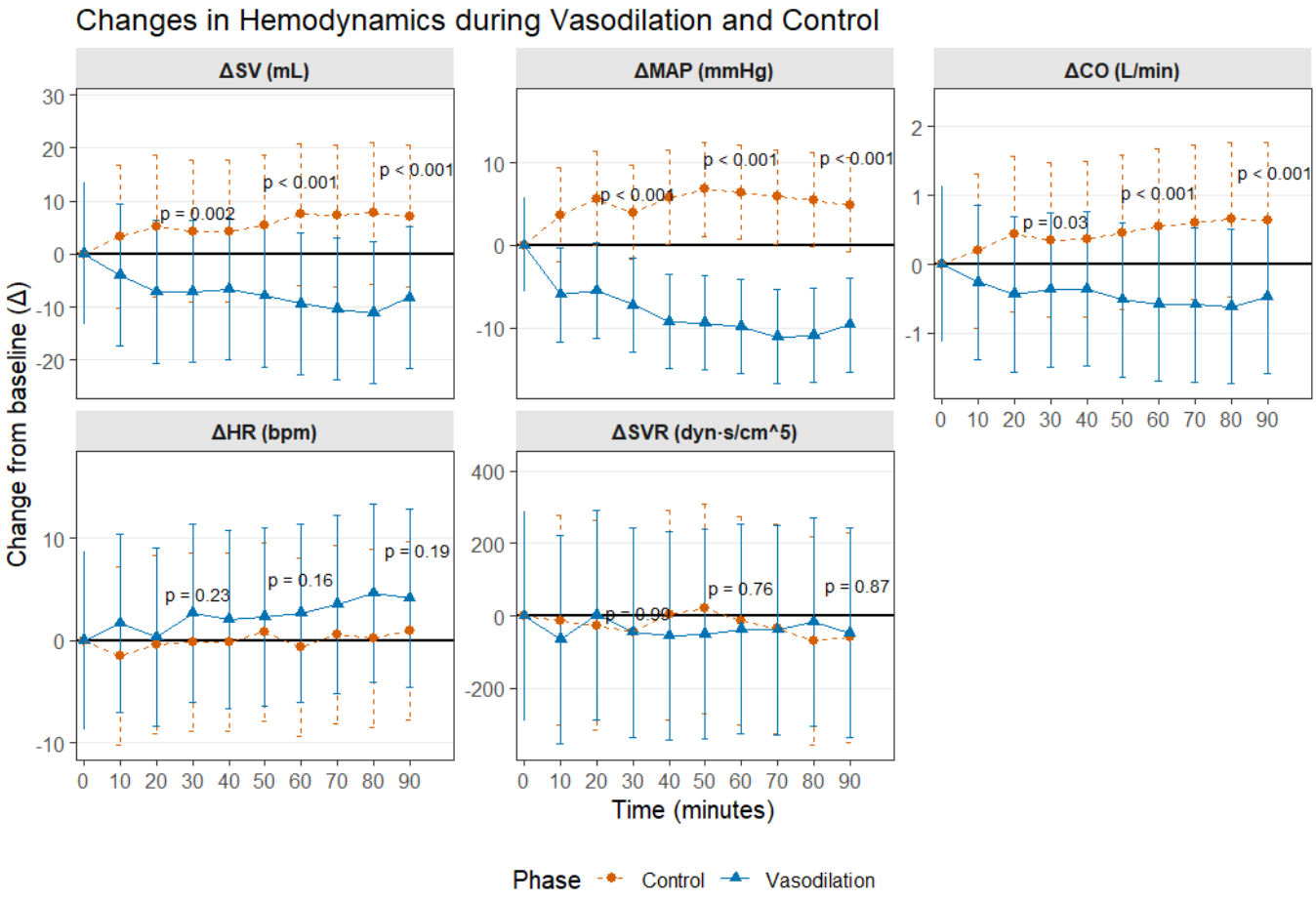
Authors: *Jasmin Dam Lukoschewitz, Frederik F. Lau, Ekim Seven, Jesper Kjærgaard, Jens Hove, Nicolai Bang Foss, Johannes Grand*

Background: Acute heart failure is a life-threatening clinical syndrome associated with high one-year mortality. Selected patients may benefit from intravenous nitroglycerin therapy; however, the haemodynamic response to nitroglycerin-induced vasodilation remains poorly characterised.

Methods: In this interventional study, patients hospitalised with acute heart failure and a systolic blood pressure >85 mmHg were enrolled. Nitroglycerin was per protocol titrated to achieve a 20–30% reduction in mean arterial pressure (MAP) for 90 minutes, followed by a 90-minute control phase. Haemodynamic parameters were continuously monitored using an arterial waveform analysis (PulseCO™). The primary outcome was change in stroke volume from baseline. Secondary outcomes included changes in MAP and urine output.

Results: Twenty-one patients were included (mean age 78 ± 11 years; 52% male). Pulmonary oedema was the cause of admission in 24%, while 76% presented with acute decompensated heart failure. The median time from hospital admission to initiation of the intervention was 24 hours (20–27 hours). Following achievement of vasodilatory steady state, the median nitroglycerin dose was 5 µg/kg/min. Stroke volume decreased during nitroglycerin infusion from 79 mL (95% CI: 66-92) at baseline to 71 mL (95% CI: 57-84) at 90 minutes (−8 mL, −11%) and increased to 79 mL (95% CI: 66–93) during the control period ($p < 0.001$). MAP decreased from 79 mmHg (95% CI: 73–85) to 69.5 mmHg (95% CI: 64–75) during vasodilation (−9.5 mmHg; −12%) and increased to 74.5 mmHg (95% CI: 69–80) during the control phase ($p < 0.001$). Urine output increased more rapidly during vasodilation than during the control phase (136 mL (95% CI: 105.6-166.3) vs. 67.4 mL (95% CI: 36.1-98.6); $p < 0.001$). The overall cohort and baseline haemodynamic were heterogeneous, but the directional response to vasodilation was broadly consistent.

Conclusion: Vasodilation with intravenous nitroglycerin reduced stroke volume and mean arterial pressure and were associated with increased urine output during vasodilation in patients with acute heart failure.



Mechanistic insights into microvascular dysfunction in INOCA using human resistance arteries

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Ischaemia with no obstructive coronary arteries (INOCA) is characterised by symptoms of myocardial ischaemia in the absence of significant coronary artery disease on angiography and predominantly affects women. INOCA encompasses two endotypes, microvascular dysfunction and vasospasm, but the underlying mechanisms remain poorly understood. In an ongoing clinical study, paired gluteal biopsies from patients with INOCA and age-matched controls are used to isolate small resistance arteries for ex vivo myography and proteomic analyses. Vascular segments are assessed for endothelial-dependent relaxation, smooth muscle responsiveness, and pharmacological vasoactivity to evaluate peripheral microvascular function and identify disease-related differences. Preliminary analyses reveal sex-dependent differences in noradrenaline-induced vasoconstriction in patients, suggesting altered adrenergic responsiveness as a contributor to INOCA heterogeneity.

The broader project will examine vascular adaptations in patients with INOCA in response to exercise training and/or colchicine treatment, an established anti-inflammatory drug. Complementary preclinical studies in rats are being conducted to further investigate the vascular effects of colchicine and its potential role in modulating cardiovascular physiology. Together, these studies aim to provide mechanistic insights into INOCA pathophysiology and pave the way for more effective treatments and improved patient outcomes.

Sex Differences in Microvascular Function in Subjects with INOCA and Controls

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BACKGROUND: Postmenopausal women exhibit an increased susceptibility to ischemia with no obstructive coronary arteries (INOCA) and endothelial dysfunction compared with men. The decline in estrogen levels following menopause is thought to reduce vasoprotective effects, thereby contributing to microvascular dysfunction. However, sex-specific differences in isolated human resistance arteries remain insufficiently explored.

OBJECTIVE: This study aimed to investigate sex differences in vascular responses to vasoconstrictive and vasodilatory agents in isolated small resistance arteries.

METHODS: A total of 25 participants, 15 women and 10 men aged 67±10 and 68±8 respectively, were included. Five of the women and four of the men were diagnosed with INOCA. Resistance arteries (100–500 µm in diameter) were isolated from gluteal adipose tissue biopsies and mounted in a wire myograph. Vessels were exposed to increasing concentrations of noradrenaline (NE), endothelin-1 (ET-1), isoprenaline, adenosine, and acetylcholine (ACh). To assess mechanisms of ACh-mediated vasodilation, vessels were treated with L-NG-nitro-arginine-methyl-ester (L-NAME), polyethylene glycol-catalase (PEG-catalase), and a cocktail of TRAM-34, apamin, and indomethacin, followed by repeated ACh dose–response assessment.

RESULTS: Women exhibited significantly greater sensitivity to ET-1 compared with men, as indicated by a higher pEC50 (P = 0.034), while maximal responses did not differ between sexes. No sex differences were observed in responses to NE, isoprenaline, adenosine, or ACh. ACh-mediated vasodilation was significantly reduced following combined inhibition (cocktail + L-NAME) in both men (~30%) and women (~20%), whereas inhibition with L-NAME alone, cocktail alone, or PEG-catalase had no effect.

CONCLUSION: These findings demonstrate sex-specific differences in sensitivity to ET-1, but not to other vasoactive agents. Despite inhibition of nitric oxide, prostacyclin, and EDHF pathways, residual ACh-mediated vasodilation persisted in both sexes, suggesting the involvement of alternative vasodilatory mechanisms.

Risk factors, survival and discharge after cardiac surgery across age groups: a multicenter retrospective study

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ABSTRACT

Objectives
Elderly cardiac surgery patients typically present with more comorbidities and reduced physiological reserves. In high-income countries, the proportion of individuals aged 80 years and older is projected to double between 2021 and 2050. This study aimed to compare survival outcomes across age groups undergoing cardiac surgery. Specifically, we sought to evaluate index hospitalization and 1-year survival across age groups, characterize discharge patterns and their association with long-term outcomes, and assess whether established risk factors for mortality demonstrate age-specific effects.

Methods
This retrospective study analyzed prospectively collected data from cardiac surgery patients at the Department of Cardiothoracic and Vascular Surgery, Odense University Hospital and the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital. Perioperative clinical variables were retrieved from Western Denmark Heart Registry (WDHR). Survival was evaluated using the Kaplan-Meier estimator, with log-rank tests for group comparisons, applying Bonferroni-Holm correction for multiple comparisons. Multivariate survival analysis was performed using Cox proportional hazard regression.

Results
The analysis included 27,311 cardiac surgery patients. Multivariate Cox regression analysis identified age ≥60 years, preoperative kidney dysfunction, COPD, extracardiac arteriopathy, intraoperative RBC transfusion and urgent/emergency surgery as significant predictors of increased 1-year mortality.

Conclusions
Octogenarians achieved 95% index hospitalization survival and 90% 1-year survival, with similar outcomes for home discharge and transfer to another hospital. Emergency surgery (HR 3.83, P <0.001), advanced age (HR 3.43 P <0.001), and preoperative kidney dysfunction (HR 2.29 P <0.001) were the strongest mortality predictors. These findings support that cardiac surgery can be performed safely in carefully selected octogenarians.

Where does intramyocardial adipose tissue come from?

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Background: The myocardium is a complex architectural composite of cardiomyocytes, connective tissue, and adipose deposits. While epicardial adipose tissue (EAT) is known to surround the heart, intramyocardial adipocytes - small fat cells embedded directly within the muscle - represent a critical area of study. These cellular "islands" are hypothesized to physically reorganize 3D muscle fiber orientation, potentially creating anatomical substrates for conduction disturbances and arrhythmias.

Methods: This project utilizes both pig atrial tissue and human atrial biopsies harvested during open-chest surgery. This study utilizes histology, proteomics and high-resolution structural data acquired via Phase-Contrast Tomography at the MAX IV Laboratory.

Results: Using Phase-Contrast Tomography at an unprecedented resolution for the human heart, we demonstrate for the first time that intramyocardial adipose tissue is entirely embedded in 3D within the myocardium. Our findings indicate that obesity is a primary driver in the development and expansion of intramyocardial adipose tissue within the atria. The observed lack of physical contact between intramyocardial adipose tissue and EAT suggests a distinct developmental origin, prompting further investigation. Our analysis reveals a significant association (80%) between intramyocardial adipose tissue and myocardial vessels. This leads us to propose that these adipocytes are perivascular in nature, potentially originating from a small stem cell niche within the vessel wall that has been pushed toward an adipogenic fate.

Future perspectives: We are moving closer to a comprehensive understanding of intramyocardial adipocytes and their developmental origins. While their specific role in pathology remains less explored, this study establishes the fundamental knowledge necessary to bridge that gap. Future research will focus on elucidating how these adipocytes contribute to the development and progression of cardiac disease.

Remote Detection of Paroxysmal Atrial Fibrillation in Racehorses Using Smartphone-Enabled Implantable Loop Recorders

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Paroxysmal atrial fibrillation (pAF) affects both humans and horses and is an important cause of poor performance in Standardbred racehorses. While persistent atrial fibrillation is easily diagnosed by standard electrocardiography (ECG), pAF remains diagnostically challenging due to its intermittent nature. Implantable loop recorders (ILR) monitor heart-rhythm continuously and store episodes of arrhythmia. Until now, ILR data collection in horses has relied on manual device interrogation, but the LINQ II system (Medtronic) allows owners to connect to the ILR via a smartphone app and remotely transmit rhythm reports to the veterinarian.

In this study, 26 standardbred racehorses were recruited: two research horses with tachypacing-induced AF, two client-owned horses with naturally occurring persistent AF and 22 client-owned racehorses without known arrythmias. Each horse was equipped with a Medtronic LINQ II ILR. Rhythm reports were transmitted through the CareLink™ Network and downloaded for analysis.

ILR implantation was safe and without complications. The device detected pAF in one of the 22 horses without already diagnosed arrythmias, and 23 of the ILRs successfully connected to CareLink™ Network. The remaining three devices required manual data transmission. The ILR detected AF in all horses with persistent and induced AF, although AF burden was underestimated in persistent AF (mean burden 42.6%). In induced AF, minute-by-minute sensitivity was 68.2% and specificity 100%, suggesting incomplete episode capture rather than failure to detect AF.

Smartphone-enabled ILRs provide a safe and promising approach for remote detection of pAF in racehorses. Clinically, this may improve diagnosis of intermittent arrhythmias in horses with unexplained poor performance. It also enables future studies on AF burden, triggers and progression in a unique large animal model with naturally occurring disease.

Dietary Medium-Chain Triacylglycerol Induces Erythropoietin and initiation af erythropoeisis even in the absence of hepatic ketogenesis

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Background and aim: Erythropoietin (EPO) stimulates erythropoiesis. Beyond hypoxia, exogenous administration of the ketone body, beta-hydroxybutyrate (BHB), was recently shown to increase circulating EPO levels. We recently demonstrated that a modest, nutritionally induced endogenous rise in BHB via medium-chain triacylglycerol (MCT) intake elevated circulating EPO by 38% within 8 days in humans. Here, we investigated tissue-specific EPO regulation following acute MCT ingestion and whether chronic MCT intake initiates erythropoiesis and hematological adaptations in mice. We further assessed if MCT mediates these effects using liver-specific 3-hydroxy-3-methylglutaryl-CoA synthase 2 knockout (LiKO) mice, incapable of producing BHB.

Material and methods: C57Bl/6JRj wild-type (WT) or LiKO mice were subjected to either an acute oral gavage with MCT oil, long-chain triacylglycerol (LCT) oil, or water as control, or 6 weeks intake of MCT- or LCT-enriched high-fat diets. Blood and tissues were collected to assess hematological effects, circulating BHB and EPO levels, and tissue signaling.

Results: Acute MCT administration increased circulating BHB levels by 706% (MCT: 2.5±0.2mmol/l vs. LCT: 0.3±0.0, $p<0.001$) compared with acute LCT administration, and a 113% higher renal *Epo* mRNA after 2 hours ($p=0.045$), compared with placebo.
Chronic MCT intake increased basal circulating BHB by 62% ($p<0.001$) and EPO by 37% ($p=0.008$) compared with LCT-fed mice, with a positive correlation between BHB and EPO levels ($r=0.66$, $p=0.001$). This was accompanied by 31% higher phospho-STAT5 in bone marrow ($p=0.015$), while renal protein content of HIF-1α/2α, remained unchanged ($p>0.05$). MCT fed mice showed higher reticulocyte count (13%, $p=0.0216$), immature reticulocyte fraction (26%, $p=0.060$), and mean corpuscular volume (3%, $p<0.001$), with lower red cell distribution width (-9%, $p<0.001$). LiKO mice did not increase BHB with MCT, however, despite hereof LiKO MCT-fed mice had higher reticulocyte count (18%, $p=0.021$), immature reticulocytes (30%, $p<0.001$), mean corpuscular volume (2%, $p=0.026$), but also red cell distribution width (3%, $p=0.044$) than WT mice.

Conclusion: MCT intake increases circulating EPO and initiates erythropoiesis, with the kidney as a key site of transcriptional induction. This is accompanied by enhanced bone marrow signaling and production of younger and more uniform erythrocytes. Notably, mice incapable of hepatic ketogenesis show an even greater erythropoietic response, indicating that the effect of MCT is at least partly independent of ketone bodies. This suggests that medium-chain fatty acids, rather than ketones alone, may drive this regulatory axis of erythropoiesis, highlighting a potential nutritional approach to modulate erythropoiesis.

Low-grade Inflammation, Left atrial strain and Risk of Atrial Fibrillation in the General Population.

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Background: Echocardiographic measures of impaired left atrial (LA) structure and function are associated with atrial fibrillation and flutter (AF). Low-grade inflammation determined by high-sensitivity c-reactive protein (hsCRP) is increasingly recognized as a marker of cardiovascular risk. The prognostic value of hsCRP for determining subclinical LA dysfunction and subsequent risk of AF needs further examination.

Purpose: The aim of this study was to determine whether plasma levels of hsCRP were associated with LA structure and function and subsequent incident AF.

Methods: A prospective community-based cohort had blood samples analyzed and underwent echocardiographic examination from 2011-2015. Persons with a diagnosis of AF at baseline were excluded (n=138), as were those without an available measured hsCRP (n=723) and a CRP-level >10 mg/l (n=114). HsCRP was stratified into groups with “low”, “average” and “high” hsCRP (respectively <1, 1-3 and >3 mg/l). HsCRP was logarithmically transformed for the linear regression analyses.

We used uni- and multivariable linear regressions to analyze the association between log(hsCRP) and echocardiographic measures of LA structure and function including peak atrial longitudinal strain (PALS), left atrial conduction strain (LACS), peak atrial contraction strain (PACS) and left atrial volume index (LAVi). Outcome was incident AF, and follow-up was completed in 2018. Multivariable Cox regression was used for the outcome analyses and the models were adjusted for clinical and echocardiographic characteristics.

Results: We included 3,613 participants (mean age 57.9 years, 56.6 % women). Median hsCRP in the entire cohort was 1.12 mg/l (IQR 0.65-2.03). When stratified according to increasing level of hsCRP, the median age and prevalence of comorbidities increased across the groups. The “high” hsCRP group, had more women, larger BMI’s and higher prevalence of smoking and comorbidities.

In univariable analyses, increasing levels of log(hsCRP) was associated with a decline in PALS and LACS and increase in PACS and LAVi. (Figure) PALS, LACS and PACS remained significantly associated with hsCRP in multivariable analyses.

During a median follow-up of 4.96 years, 126 (3.6 %) of the participants were diagnosed with AF. In the multivariable Cox model, the “high” hsCRP-group was associated with a significantly higher risk of developing AF (Hazard Ratio 2.42 (1.05-5.59)) compared to the “low” hsCRP-group independent of echocardiographic measures of LA structure and function (Table). No effect modification was found between hsCRP and any of the measures of LA strain or LAVi.

Conclusion: In a sample from the general population with no previous history of AF, increasing levels of hsCRP were significantly associated with impaired LA function determined by echocardiographic measurement of LA strain. A hsCRP >3 mg/l was significantly associated with a higher risk of AF independent of echocardiographic measures of LA structure and function.

Olink Proteomics: What are we measuring?
The unexplainable plasma protein measurements from Proximity Extension Assays

Authors
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Abstract
Proximity extension assays are now extensively used to measure plasma proteomes on population scale, yet thorough technical validation is not uniformly available for all platforms and measured targets. Here we systematically assess Olink Explore protein targets (n=2,922) with exceptionally low variance explainability (n=411) by integrating genetic associations, cross-platform concordance and tissue and peptide atlases. We identify a subset of targets (n=96) that likely lack robust or quantitative plasma signals, revealing assay- and tissue-specific limitations with implications for panel composition, statistical power and interpretation of large-scale population proteomics studies.

The acute impact of an increased left ventricular afterload on left and right atrial electrophysiology to understand atrial fibrillation in patients with aortic stenosis

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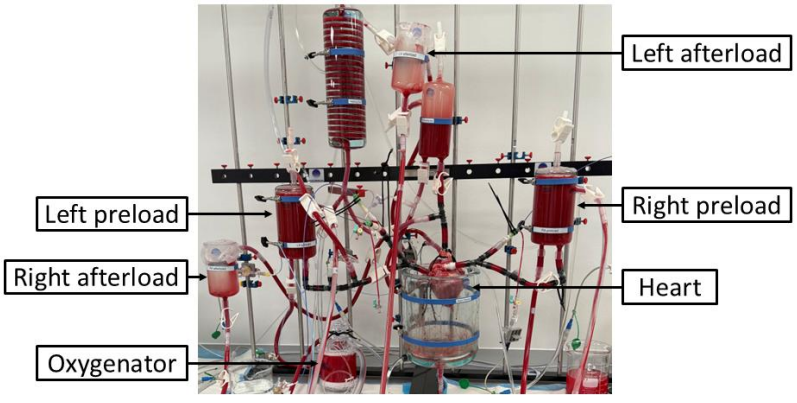
Atrial fibrillation (AF) occurs a in third of patients with severe aortic stenosis (AS), and the underlying AF mechanisms are often ascribed to increased left atrial pressure due to increased left ventricular afterload. Moreover, close to half of patients suffering from severe aortic stenosis present with right ventricular dysfunction suggesting a mechanical crosstalk between ventricles. However, the effect of increased left atrial pressure on the right atrium is still unknown.

It is known that a coupling between the heart's electrophysiology and mechanical function exists, in which a mechanical stimulus directly alters the electrophysiology through stretch-activated ion channels. We therefore hypothesize, that an increased left atrial pressure caused by aortic stenosis, will mechanically impact the right atrium, through the atrial septum. This will act as a mechanical stimulus, disturbing right atrial electrophysiology through changes in refractoriness and conduction, ultimately creating a proarrhythmic substrate.

We test this in a whole-organ setting using an ex-vivo porcine working-heart setup (Figure 1). Each pig is placed under general anaesthesia with propofol and fentanyl (15mg/kg/h and 5µg/kg/h) and whole blood (2L) is collected. Following antegrade infusion of cardioplegia the heart is explanted and installed in a perfusion system with a 1:3 perfusate of whole blood:Tyrode´s solution, mimicking the physiological circulation and allowing physiological loading of all four heart chambers. A 249-electrode grid, allows for high-resolution electrophysiology measurements of the myocardium, providing detailed depolarization maps of both atria. Additionally, an endocardial grid electrode catheter, inserted into the right atrium through the superior vena cava, is used to measure the effective refractory period. Electrophysiology recordings are performed during left afterload pressure modulation, right preload pressure modulation, as well as with and without induction of acute aortic stenosis. To induce aortic stenosis, a ligature is placed around the aorta, just distal to the aortic valve. The ligature is tightened until the left ventricular outflow is reduced and the left afterload is increased.

With this we intend to gain new insights into the underlying mechanism of arrhythmic complications in AS, potentially aiding the design of better treatment options for patients with concomitant AS and AF.

Figure 1



Coronary function and capillary density do not change in mice with HFpEF

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Introduction: Coronary microvascular dysfunction (CMD) is associated with developing cardiomyopathies, especially heart failure with preserved ejection fraction (HFpEF). Although the pathogenesis of HFpEF is poorly understood, patients with diastolic dysfunction together with a coronary flow reserve (CFR) <2 have a 5-fold increase of HFpEF hospitalizations later in life. It highlights the need of developing translational animal models with a focus on CFR to understand the connection between CMD and HFpEF progression.

Aim: This study investigates coronary function by quantifying CFR together with capillary density in a HFpEF mouse model.

Methods: C57BL6/NRj male mice were randomized to 16 weeks of diet. One group (n=24) received high fat diet (HFD) and water with 1g/L of L-NAME, a nonselective inhibitor of nitric oxide synthase. A control group (n=23) received normal chow and water. Exercise test was quantified by running distance on a treadmill, CFR was assessed in vivo by pulse wave velocity and ex vivo in isolated hearts. Capillary density was assessed by CD31 lectin histology.

Results: Ejection fraction was similar in HFpEF mice and controls (60±9 versus 57±12%; P>0.05). HFpEF mice ran a shorter distance than control mice in the exercise intolerance test (201±89 versus 290±90 m; P=0.001). CFR in vivo (HFpEF: 2.8±0.4 and controls: 2.6±0.6; P=0.2) and ex vivo (HFpEF: 4.7±2.1 and controls: 4.4±1.5; P=0.64) were similar in the two groups. Capillary density staining shows no difference between the groups (HFpEF: 2974±150 versus controls: 2990±263 capillaries/mm^2; P=0.9).

Conclusion: In the present study we do not observe changes in coronary flow nor in capillary density in mice with HFpEF as compared to controls.

Multimodal CMR evaluation of pulsed field versus radiofrequency atrial ablation: Acute and chronic lesion characteristics with histological validation

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Background: In contrast to thermal radiofrequency ablation (RFA), pulsed field ablation (PFA) preferentially ablate cardiomyocytes while sparing non-myocardial structures.
Aim: This study aimed to compare characteristics of acute and chronic ablation lesions in the right atria induced by RFA and PFA using cardiac magnetic resonance imaging (CMR).
Methods: A right atrial intercaval line was ablated in 28 female Danish Landrace pigs, using the same catheter, administering either focal RFA (F-RFA, Group 1, n=14) or focal PFA (F-PFA, Group 2, n=14). Ablation lesions were assessed using 3D CMR scans, specifically non-contrast enhanced T1-weighted long inversion time (TWILITE), T2-weighted (T2w) imaging, and late gadolinium enhancement (LGE). Baseline imaging was performed immediately after ablation, with follow-up imaging conducted 6 weeks post-procedure. All lesions underwent histological analysis, and MRI-derived lesion widths were compared with histological measurements obtained at the 6-week time point to determine the level of agreement between imaging and histology.
Results: Acute F-RFA lesions showed well-demarcated coagulative necrosis with hemorrhage, whereas acute F-PFA lesions exhibited subtler lesions with contraction-band necrosis. At 6 weeks, both modalities formed transmural fibrous scars, with F-PFA lesions remaining nearly twice as wide as F-RFA lesions (mean difference 11.1 mm, 95% CI: 5.3 to 16.9 mm,p = 0.0016). T2w and LGE visualized acute lesions in both groups, while TWILITE identified the necrotic core only in acute F-RFA lesions. At 6 weeks, lesions were detectable by LGE but not by T2w or TWILITE scans. LGE demonstrated lesion shrinkage in both groups, yet F-PFA lesions remained wider regardless of SIR thresholding.
Blant-Altman analysis determined that the best agreement with 6-week histology was achieved using LGE scan (SIR>1.1) for F-PFA (mean bias of 0 mm with LoA: -19 to 19 mm) and 6-week LGE (SIR>1.0) for F-RFA (mean bias of 2 mm and LoA: -13 to 18 mm).
Conclusion: F-RFA and F-PFA lesions show distinct characteristics in histology and CMR. To estimate true mature ablation lesion width with CMR, different scan timing (earlier for F-PFA and later for F-RFA), rather than signal thresholding, results in accurate lesion visualization.

Proteogenomics as a tool to identify plasma proteins and genes causing and predicting coronary atherosclerosis and abdominal aortic aneurysms. A substudy under the Danish Cardiovascular Screening Study – DANCAVAS

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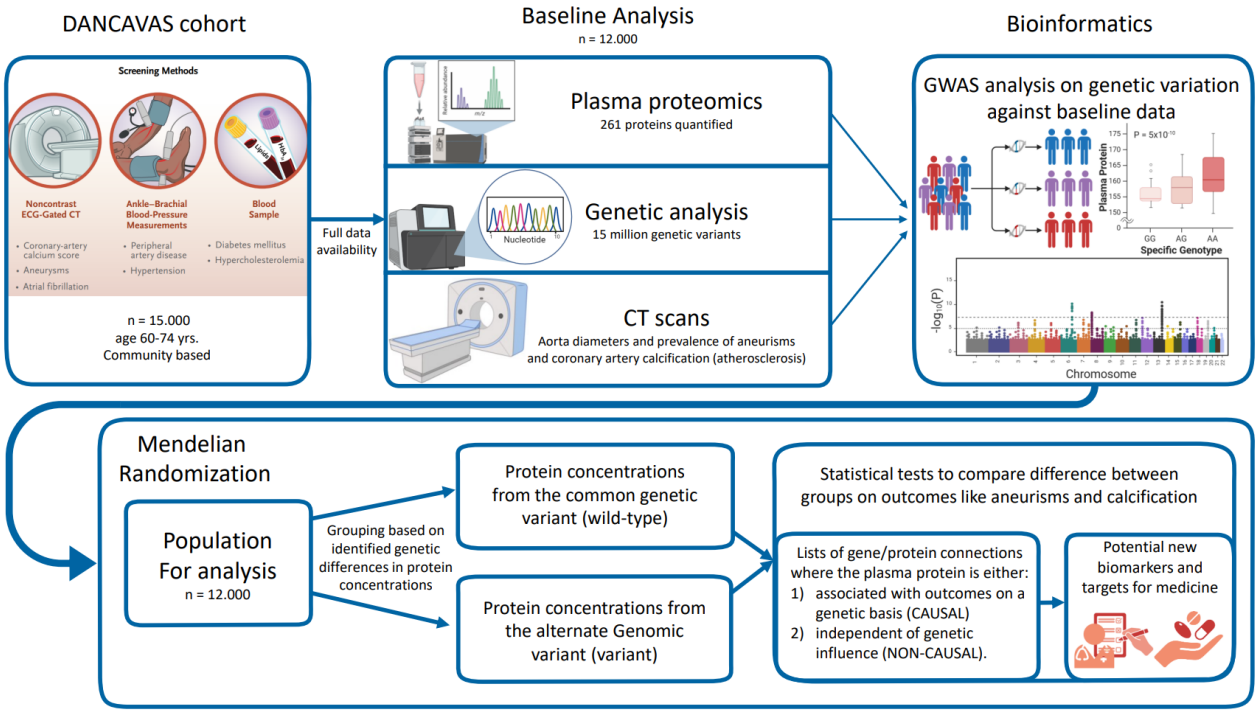
Cardiovascular diseases such as coronary atherosclerosis and abdominal aortic aneurysm are major causes of illness and death in Denmark, particularly among older adults. Although some biological mechanisms are known, many genetic and molecular links remain unclear. This project aims to uncover how genetic variants and blood protein levels are associated with cardiovascular disease, to improve diagnostics and identify potential treatment targets.

We use existing data from 12.000 participants in the Danish cardiovascular screening study DANCAVAS, which includes CT scans, health and medication records, and long-term follow-up data on disease and mortality. Participants underwent comprehensive cardiovascular screening approximately a decade ago, with data on risk factors and quality of life collected at baseline. National registry data provides follow-up over 7–9 years.

Our specific aims are:

- To identify genetic variants associated with plasma levels of hundreds of proteins.
- To examine how these proteins relate to one another, to disease status, and to clinical risk factors.
- To find new protein and genetic markers that help explain disease mechanisms and predict cardiovascular risk.

We analyze 15 million DNA variants per individual and apply modern proteomic techniques to measure plasma proteins. Bioinformatics methods such as genome-wide association studies and Mendelian Randomization are used to assess causal relationships between genetic variation, protein expression, and disease.



Characterization of 3D Smooth Muscle Cell Spheroids: A Human Relevant Model for Smooth Muscle Cell Phenotypic Modulation in Atherosclerosis.

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Background: Atherosclerotic cardiovascular disease remains the leading cause of mortality worldwide. Plaque progression is largely driven by expansion and phenotypic modulation of vascular smooth muscle cells (SMCs) from a quiescent contractile state toward a range of mesenchymal phenotypes. However, conventional 2D culture systems fail to capture the complexity of SMC plasticity in disease , limiting their translational relevance.

Objective: To develop and characterize a 3D human smooth muscle cell spheroid system to model disease-relevant phenotypes.

Methodology: Human coronary artery SMCs (HCASMCs) and rat aortic SMCs were cultured in ultra-low attachment plates to generate 3D spheroids. Human spheroids were stimulated with vehicle, PDGF-BB, or TGF-β1 for four days, and spheroid formation and kinetics were assessed by bright-field imaging over time. At the endpoint, spheroids were sectioned and analysed by immunofluorescence for the contractile marker SM22, the synthetic marker lumican (LUM), and the proliferation marker Ki67. Human and rat spheroids were comparatively analyzed to evaluate inter-species differences.

Results: HCASMC spheroids formed within 24 hours, and spheroid size decreased over time across all experimental groups. TGF-β1 increased spheroid size and enhanced $SM22^{+}$ cell abundance, consistent with a contractile phenotype. In contrast, PDGF-BB induced larger,less compact spheroids compared with controls, suggesting a migratory phenotype. Cells expressing the contractile marker SM22 localized preferentially to the spheroid periphery, while the fibroblast-like marker LUM was expressed throughout the spheroid across all treatments. Comparative analysis demonstrated marked interspecies differences, with rat SMC spheroids exhibiting approximately 4-fold greater surface area and increased $Ki67^{+}$ cells relative to human spheroids, indicating enhanced proliferative activity.

Conclusion: This 3D HCASMC spheroid model recapitulates stimulus-dependent phenotypic switching and highlights functional differences between human and rat spheroids, underscoring the limitations of rodent systems in translational vascular research. Overall, the model provides a physiologically relevant, human-based platform for studying SMC plasticity and contributions to atherosclerosis. Future studies will investigate spheroid functional properties and SMC transcriptional regulators to further strengthen its mechanistic and therapeutic screening potential.

TARGETING SMAD7 REPROGRAMS SMOOTH MUSCLE CELLS TOWARD A CONTRACTILE PHENOTYPE AND PROMOTES PLAQUE STABILITY IN ATHEROSCLEROSIS

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Background and aim: Smooth muscle cell (SMC) phenotypic plasticity critically shapes atherosclerotic plaque remodeling and stability[1–3], yet its transcriptional control remains incompletely understood. Genetic studies implicate *SMAD7* in coronary artery disease risk[4–6], but its function in vascular SMCs is unknown. Here, we investigated how SMAD7 regulates SMC phenotypic state and atherosclerotic lesion progression.

Results: siRNA-mediated *Smad7* knockdown in cultured vascular SMCs promoted a contractile, quiescent phenotype, characterized by increased contractile marker expression, enhanced cytoskeletal organization and collagen gel contraction, and reduced proliferation and migration. To define its role in vivo, we generated SMC-specific *Smad7* knockout mice and induced atherosclerosis using PCSK9-mediated hypercholesterolemia. Despite elevated plasma cholesterol, *Smad7*-deficient mice developed smaller plaques relative to cholesterol burden, with reduced macrophage accumulation and increased collagen deposition—hallmarks of enhanced plaque stability. Single-cell RNA sequencing of atherosclerotic lesions revealed that *Smad7* loss altered SMC state transitions, retaining cells in contractile-like states while reshaping stress-responsive and osteochondrogenic transcriptional programs. Mechanistically, SMAD7 functions as a molecular brake on SMC phenotypic reprogramming by restraining TGFb-SMAD2/3 signaling involved in contractility and matrix remodeling.

Conclusion: Together, these data identify SMAD7, a coronary artery disease GWAS gene, as a key regulator of SMC plasticity and plaque stability, highlighting opportunities for disease-modifying therapy beyond cholesterol lowering.

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Long-term Angina-Related Healthcare Utilization in Women with ANOCA and Impaired Coronary Flow Velocity Reserve

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Background
Most women evaluated for angina have no obstructive coronary artery disease (ANOCA), yet many have persistent symptoms, and the long-term burden of angina-related healthcare utilization remains poorly defined. Coronary microvascular dysfunction (CMD), reflected by impaired coronary flow velocity reserve (CFVR), is common in ANOCA and may contribute to ongoing angina.
We aimed to quantify recurrent angina-related hospital contacts and diagnostic testing in women with ANOCA and to examine whether impaired CFVR is associated with increased long-term healthcare utilization.

Methods
We conducted a registry-based follow-up study of women with ANOCA from the iPower cohort (2012-2018), a prospective study of women with angina, left ventricular ejection fraction >45%, and no obstructive coronary artery disease on invasive coronary angiography. CFVR was assessed at baseline using transthoracic Doppler echocardiography.
Women were stratified according to baseline CFVR (<2.25 vs. ≥2.25). Using Danish National registries, we identified angina-related hospitalizations (>1 day), outpatient contacts and ischemia-related procedures (coronary angiography, coronary CT angiography, stress echocardiography, positron emission tomography and myocardial perfusion scintigraphy).
The primary endpoint was a composite of recurrent angina-related hospitalizations, outpatient contacts, and ischemia-related procedures. Recurrent events were analyzed using the Andersen-Gill extension of the Cox proportional hazards model: Hazard ratios (HRs) therefore reflect the total burden of events, rather than time to first event.
Analyses were performed unadjusted and with multivariable adjustment for cardiovascular risk factors (age, BMI, hypertension, diabetes, smoking, dyslipidemia, atherosclerosis and baseline angina severity using the Seattle Angina Questionnaire).

Results
Among 1,681 women (CFVR ≥2.25: n=958; CFVR <2.25: n=723), impaired CFVR was associated with higher angina-related event rates. The composite event rate was 11.48 vs. 7.31 per 100 person-years in women with impaired and preserved CFVR, respectively (p<0.001). In unadjusted analyses, impaired CFVR was associated with increased recurrent events (HR 1.46, 95% CI 1.14-1.86), remaining significant after multivariable adjustment (HR 1.47, 95% CI 1.10-1.97).
Hospitalizations were nearly doubled in women with impaired CFVR (adjusted HR 1.80, 95% CI 1.00-3.24). Ischemia-related procedures were also significantly increased (HR 1.28, 95% CI 1.02-1.60).

Conclusion
Among women with ANOCA, impaired CFVR is associated with increased recurrent angina-related healthcare utilization, independent of cardiovascular risk factors and baseline symptom severity. This suggest that CMD identifies a phenotype characterized by a higher burden of hospital contact and diagnostic testing. Recognition of CMD may therefore improve risk stratification and inform more targeted management strategies in this population.

Development of a Controlled *In Vitro* Oxidative Stress Model in 2D hiPSC-Derived Cardiomyocytes for Target and Therapeutic Validation

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Oxidative stress is a phenomenon caused by elevated intracellular levels of reactive oxygen species (ROS) that disrupt redox homeostasis and cause damage to lipids, proteins, and DNA. While transient ROS increases can act as signalling molecules, sustained or excessive ROS elevation impairs cellular function and promotes mitochondrial dysfunction, senescence, and cell death.

The aim of this project was to develop a controlled *in vitro* oxidative stress model using human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes to mimic disease-associated redox dysregulation, quantify transient ROS accumulation overtime, and support downstream human-relevant target and drug validation.

To induce ROS production, two different approaches were evaluated: i) treatment with three different perturbagens (doxorubicin, dimethyl succinate, and menadione), or ii) small interfering RNA (siRNA)-mediated knockdown of a mitochondrial health-related gene (*TAZ*) encoding for the TAFAZZIN protein. TAFAZZIN was selected as the target for the siRNA experiment, as reduced TAFAZZIN activity has been described to result in mitochondrial dysfunction and heightened vulnerability to oxidative stress. For both approaches, titration experiments were performed to identify optimal concentrations and stimulation conditions. Transient ROS generation was quantified through live-cell imaging using the CellROX Deep Red dye, enabling sensitive and time-resolved readouts of transient oxidative stress generation. To assess therapeutic relevance and assay responsiveness, the ROS-scavenging/counteracting agents N-acetylcysteine (NAC) and elamipretide (a cardiolipin-stabilizing peptide that targets mitochondria) were tested within the model for their ability to attenuate ROS levels.

Results showed that oxidative stress was elevated under both perturbagen-driven and *TAZ* knockdown conditions. Co-treatment with NAC or elamipretide reduced the ROS signal, demonstrating that the developed assay reliably reproduces and enables efficient evaluation of oxidative-stress modulation in human cardiomyocytes.

Overall, an *in vitro* oxidative stress assay was successfully established and validated in hiPSC-derived cardiomyocytes, providing a sensitive human-relevant platform for testing oxidative-stress modulators and for mechanistic understanding of novel drug targets.

Cardiac Biomarkers for Detecting Cardiac Impairment in Patients with COPD

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Objective: Chronic obstructive pulmonary disease (COPD) and cardiac dysfunction frequently coexist and present with overlapping symptoms. We investigated whether N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hs-TnI) levels could identify echocardiographic abnormalities in patients with COPD.

Methods: We studied 787 participants from a large prospective cohort study of cardiovascular disease in COPD patients. Bloodwork and echocardiography were performed at the visit. Logistic regression analyses were utilized to evaluate associations between biomarker levels and abnormal echocardiograms (defined as LVEF <50% or presence of diastolic dysfunction according to the 2016 ASE guidelines).

Results: Among 787 participants, the mean forced expiratory volume in first one second was 49% of predicted. The mean age was 70 years, 52% were female, and 37% had abnormal echocardiograms. Patients with abnormal echocardiograms were older, had significantly more comorbidity, and elevated NT-proBNP and hs-TnI compared to patients with normal echocardiograms. Patients with abnormal echocardiograms did not have more dyspnea than participants with normal echocardiograms. Logistic regression revealed significant associations between NT-proBNP, hs-TnI, and echocardiographic abnormalities, even after adjusting for potential confounders (OR: 2.00 (1.47-2.72), p<0.001 for NT-proBNP cutoff, 82.2 ng/L). Subgroup analysis confirmed these associations in patients with moderate to severe dyspnea.

Conclusion: In patients with stable COPD, cardiac biomarkers such as NT-proBNP and hs-TnI may help identify individuals with a higher likelihood of cardiac abnormalities on echocardiography, supporting their potential use in earlier detection of cardiac impairment in this population.

Perfusable Artery-On-Chip model: combined environmental stimuli drive arterial cells towards atherosclerosis.

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Introduction

Atherosclerosis is defined as a dysregulation of arterial cells' behaviour. Through phenotypic switches, endothelial cells (ECs), vascular smooth muscle cells (vSMCs) and monocytes jointly participate in plaque formation within the sub-endothelial space.[1] Disease onset and progression have been described to involve numerous biochemical and mechanical stimuli but also inter-cellular signalling.[2] In vivo, arterial cells must react simultaneously to all pathophysiological parameters, a condition which is complex to replicate in vitro, constituting a setback for fundamental biology research but also for drug testing devices. Here, we propose a new 3D perfusable artery-on-chip model. Its multilayered tubular architecture with co-culture of vSMC and ECs better replicates the in vivo arterial organisation while its modular matrix and perfusable design enables the replication of biochemical and mechanical disruptions found in atherosclerosis.

Methods

Using a two-needle templating method, we cast a vSMC-laden matrix made of fibrin, bovine aorta dECM or bovine dECM methacrylate. The resulting hollow tubular network can subsequently be perfused and its lumen wall seeded with a monolayer of endothelial cells. The multilayered co-culture is subjected to atherotypical reductions in wall shear stress (10 to 1 dyn/cm^2) but also matrix stiffening (UV stiffening of the methacrylated dECM network) or biochemical cues (disrupting iron level increase). The artery constructs may be stained and analysed in situ; however, cells may also be extracted from the hydrogel for flow cytometry or downstream RNA expression analysis.

Results

Following mechanical stimulation, Endothelial cells and vascular smooth muscle cells respectively adopted mesenchymal-like and foam cell-like phenotypes, both hallmarks of plaque formation in vivo. In situ we observed localised disruption of the endothelial layer dependant on the underlying vSMC network with the accumulation of low-density lipoproteins within vSMCs and their loss in expression of the contractile marker alpha-smooth muscle actin. Moreover, decrease in shear stress conjugated with iron loading triggered ferroptotic cell death, a phenomenon suspected to enable necrotic core formation in vivo. Ex situ, the intracellular accumulation of reactive oxygen species showed significant variations depending on matrix stiffening, shear stress and endothelial cell interactions.

Conclusion

Our new complex artery-on-chip model enabled the stimulation of arterial cells by complex pathophysiological stimuli and successfully replicated in vivo findings, thus proving its relevance as a drug testing device for atherosclerosis. Furthermore, these results highlight the importance of stimulus coalescence when probing disease-relevant mechanotransduction pathways. We believe that this in vitro model is uniquely positioned to better understand the complex environmental cues found in vivo.

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Reversing Severe Persistent Childhood-onset Obesity with Semaglutide: The RESETTLE Randomized Controlled Trial

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Introduction: Young adults with persistent childhood-onset obesity represent a high-risk population. Hospital-based pediatric obesity care can improve adiposity, but responses are heterogeneous, and sustained remission is challenging. We investigated the effects of adding semaglutide to hospital-based obesity care in young adults who still have obesity following pediatric obesity care. **Methods**: We conducted a randomized controlled trial with young adults aged 18-28 years from The HOLBAEK Study cohort. Participants were recruited into four participant groups based on childhood weight development (Fig. 1A): *low response* to non-pharmacological pediatric obesity care (BMI SDS reduction < 0.1) and adult obesity (current BMI ≥ 30 kg/m^2); *medium response* (BMI SDS reduction > 0.25 and current BMI ≥ 30); *high response* (BMI SDS reduction > 0.5 and current BMI < 30); and a *normal BMI development* group. Average pediatric obesity care duration was 3.7 years (SD 2.5). Participants in the low and medium response groups were randomly assigned 2:1 to receive semaglutide 2.4 mg s.c. once weekly or placebo adjunct to non-pharmacological obesity care for 68 weeks. Primary endpoint was change in BMI. Key secondary endpoints included cardiometabolic biomarkers, body composition, and MRI-quantified visceral and liver fat, tested hierarchically. **Results**: A total of 246 participants were included (23±3 years, 41% male). Of these, 162 participants were randomized 2:1 to semaglutide or placebo, with 152 (94%) attending final visit. At inclusion, participants in the low and medium response groups had impaired cardiometabolic health compared with the high response and normal BMI development groups. Mean change in BMI from baseline to week 68 in the low response group was -19.0% [95% CI: -23.4, -14.5], p<0.0001, for semaglutide compared with placebo and -19.0% [-23.7, -14.3], p<0.0001, in the medium response group (Fig. 1B). Semaglutide improved health outcomes compared with placebo in the low and medium response groups: total fat mass; -17.4 kg [-21.5; -13.3] and -15.1 kg [-19.9; -10.2]; metabolic syndrome z-score; -0.80 [-1.03; -0.57] and -0.58 [-0.81; -0.35]; visceral fat; -47.7% [-55.2; -39.0] and -40.5% [-54.2; -22.8]; and liver fat; -39.4% [-54.1; -20.0] and -33.7% [-49.9; -12.4], respectively, p≤0.0058 for all outcomes. **Conclusion**: Young adults with severe persistent childhood-onset obesity and a high cardiometabolic risk profile had substantial health improvements after treatment with semaglutide 2.4 mg vs. placebo as an add-on to hospital-based obesity care. Treatment effects were irrespective of prior response to non-pharmacological pediatric obesity care.

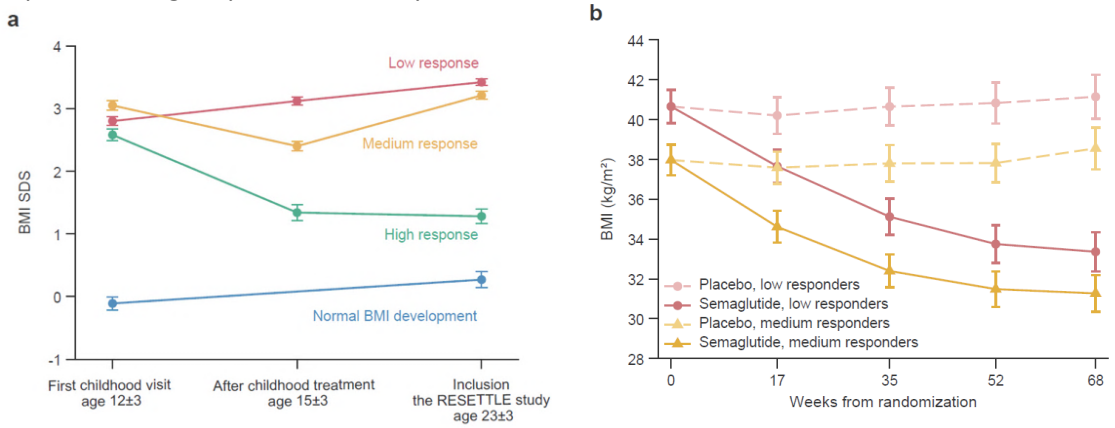

Figure 1. Panel **a)** BMI (SDS) ± SEM and mean age (years) ± SD at first and last visit at The Children's Obesity Clinic and inclusion in the RESETTLE trial: low response (n = 82), medium response (n = 80), high response (n = 34), and normal BMI development (n = 50). Panel **b)** the intention-to-treat estimated BMI ± SEM of participants in the low and medium response groups randomized to semaglutide or placebo treatment from week 0 (at inclusion) to week 68 (end of trial).

Investigating the role of titin-truncating variants in cardiac fibrosis development using heterozygous zebrafish mutants

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Titin is the largest sarcomeric protein and is expressed in all striated muscle. Truncating variants of this protein (TTNtvs) are strongly associated with dilated cardiomyopathy, and more recently with atrial fibrillation. The clinical impact of these variants depends on the location within the protein. Variants in the A-band are consistently more deleterious, while I-band variants are thought to be associated with a milder phenotype. Using a zebrafish model of an I-band truncating mutation in *ttn.2,* our group has previously shown an increase in interstitial cardiac fibrosis, which can significantly impair heart function, and has directly been linked with atrial fibrillation. Despite these insights, the relationship between the TTNtv locations and disease progression remains poorly defined. A systematic mapping of disease progression associated with I- band versus A-band truncations is still lacking.

In our study, we will use existing heterozygous zebrafish mutants of TTNtvs to investigate how mutations in the I- and A-band drive phenotype development, with a specific focus on fibrosis development. We will determine whether the distinct phenotypic difference between the two variants leads to a conserved or divergent fibrotic response over time.

To answer this question, we will perform histological analysis of cardiac tissue at defined timepoints corresponding to the onset of electrophysiological and structural abnormalities, enabling a direct correlation between functional decline and fibrotic remodelling. To identify the molecular mechanisms underlying fibrosis, we will apply integrated proteomics and RNA-sequencing approaches, to both mutant lines. This strategy will resolve the signalling pathways that drive fibrotic remodelling and establish whether these pathways are shared or distinct between I-band and A-band truncating variants.

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Reducing cardiometabolic burden in persistent childhood-onset obesity with semaglutide: the RESETTLE randomised trial

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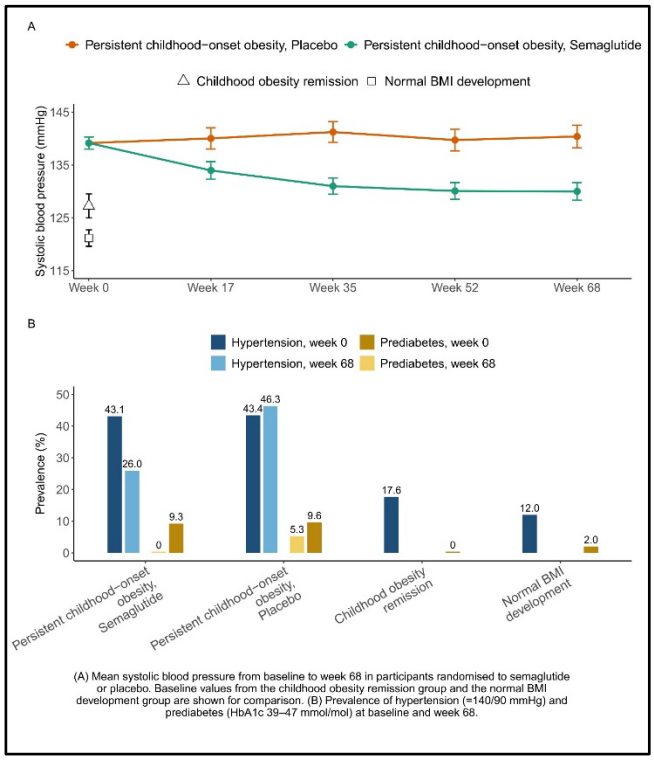
Background and aims: Young adults with persistent childhood-onset obesity represent a high-risk population for early onset cardiometabolic disease. Hospital-based paediatric obesity care can improve adiposity, but sustained remission may be difficult to achieve. We investigated the effects on cardiometabolic health of adding semaglutide to hospital-based obesity care in young people who still have obesity following paediatric obesity care and compared this to peers without obesity.

Materials and methods: This investigator-initiated, double-blinded, randomised, placebo-controlled trial included young adults aged 18-28 years from The HOLBAEK Study cohort with persistent childhood-onset obesity. Participants were randomised in a 2:1 ratio to semaglutide 2.4 mg once weekly or placebo for 68 weeks. Repeated measurements included anthropometry, office blood pressure, HbA1c and high-sensitive C-reaction protein (hsCRP). For baseline comparisons two sex- and age matched reference groups were included: young people with childhood obesity remission (n = 34) and young people with normal BMI development (n=50). Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg and prediabetes as HbA1c 39 - 47 mmol/mol.

Results: We included 162 participants with persistent childhood-onset obesity (59% females, age: 22.5±3.0 years, BMI: 39.3±6.0kg/m2). Semaglutide led to relevant reductions in SBP by -10.4 mmHg [-14.5;-6.3] p<0.001, DBP by -5.9 [-8.3; -3.4], p<0.001, HbA1c by -3.0 mmol/mol [-4.6; -1.5], p<0.001 and hsCRP by -51.3 % [-64.7; -32.7], p<0.001, compared with placebo (Fig 1A). Semaglutide treatment reduced the prevalence of hypertension from 43% to 26%, while it increased slightly in the placebo group. Prevalence of hypertension was 18% in the childhood obesity remission group and 12% in the normal BMI development group. The prevalence of prediabetes in persistent childhood-onset obesity decreased from 9% to 0% with semaglutide treatment and from 10% to 5% with placebo (Fig 1B). Prediabetes was not observed in young adults with childhood obesity remission.



(A) Mean systolic blood pressure from baseline to week 68 in participants randomised to semaglutide or placebo. Baseline values from the childhood obesity remission group and the normal BMI development group are shown for comparison. (B) Prevalence of hypertension (=140/90 mmHg) and prediabetes (HbA1c 39–47 mmol/mol) at baseline and week 68.

Conclusion: Young adults with persistent childhood-onset obesity carry a substantial cardiometabolic risk burden despite their young age. In persistent childhood-onset obesity semaglutide markedly improved glycaemia, blood pressure and systemic inflammation and reduced prevalence of hypertension and prediabetes moving towards
levels observed in peers without obesity.

Structural and functional studies of TRPV2 with the inhibitor valdecoxib

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The large transient receptor potential vanilloid (TRPV) sub-family of ion channels is known for their cation selectivity. TRPV2 responds to noxious heat, mechanic stretch, cannabinoids and inflammation [1,2] and 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. Thus, there is significant interest in advancing the understanding of TRPV2.

In this study, two different techniques of membrane protein solubilization are explored for rTRPV2 purified from *P. Pastoris*; detergent solubilization and reconstitution into Nanodiscs. Incorporation into Nanodiscs provide a high protein stability. Brief incubation with the selective antagonist, valdecoxib, yielded the cryo-EM structure of 3.6 Å resolution in detergent. The structure reveals classic TRPV features, including the vanilloid pocket.

Whole-cell patch clamp electrophysiology shows effects of probenecid and 2-APB with 100 µM valdecoxib. The experiments confirm the selective antagonistic effect of valdecoxib efficiently 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 different cardiovascular pathologies.

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Title: Left Ventricular Mass in Children with Obesity Following Obesity Treatment

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Background: Increased left ventricular mass (LVM) is a complication of obesity that has also been observed in children. However, data on how LVM relates to growth, development, and changes in degree of obesity during childhood remain sparse.

Purpose: We aim to assess LVM in children with obesity at baseline and after 18 months of obesity treatment compared to population-based controls.

Methods: In this longitudinal study, we included 141 children aged 10-14 years: an obesity group (n=92) from the HOLBAEK Study entering obesity treatment, and a population-based controls (n=49) recruited from local schools. We obtained anthropometrics, cardiac MRI, and dual-energy x-ray absorptiometry (DXA) data at baseline and at 18 months follow-up. LVM and LV volumes were derived from short-axis stack of cine SSFP cardiac MRI and indexed to height$^{2.7}$ (LVMi)

Results: The obesity group and population-based controls were similar in age (12.3 years vs. 12.5 years, p=0.8) and differed significantly in measures of obesity including body mass index standard deviation score (3.10 vs. 0.1, p<0.001) and DXA-derived fat percentage (46.6% vs. 26.0%, p<0.001). At baseline, the obesity group had 23% higher LVMi (24.8 vs. 20.1 g/m$^{2.7}$, p<0.001) but similar ejection fraction (66.9% vs 67.1%, p=0.6). A total of 92 children (obesity group n= 50; population-based controls n= 42) participated in the follow-up. The full longitudinal analyses of change in LV mass and diastolic function are ongoing and will be presented.

Conclusion: Children with obesity have significantly elevated LVM compared to population-based controls. The ongoing longitudinal analysis will examine whether reduction in degree of obesity following treatment initiation is associated with LVM normalization, which may provide insights for early cardiovascular prevention strategies.

Cost reductions with oral step-down antibiotic treatment in patients with endocarditis (POET)

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BACKGROUND: Infective endocarditis (IE) has traditionally required up to six weeks of in-hospital antibiotic treatment. In the Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis (POET) trial, oral step-down antibiotic treatment in clinically stable patients with left-sided IE reduced hospital length of stay by 16 days. The POET trial informed the 2023 ESC guidelines with implementation of oral step-down treatment.

AIM: To conduct a cost analysis using the POET cohort to estimate differences in hospitalization-related costs, bed days, and outpatient visits between conventional in-hospital IV antibiotic treatment and oral step-down antibiotic treatment.

METHODS: The POET trial was a Danish multicenter study including 400 patients with left-sided IE. Patients were randomized after prespecified stabilization criteria were reached. In-hospital treatment costs used the average bed-day cost at the Department of Cardiology, Rigshospitalet (€879 per day). Outpatient visit costs were estimated at €159 per visit based on Danish national data. Costs related to medication, microbiology, imaging and broader societal factors were not included.

RESULTS: Median time from the diagnosis of IE to randomization was 17 days [IQR 12–24]. After randomization, the median hospital length of stay was 19 days [IQR 14–25] for the conventional IV group and 3 days [IQR 1–10] for the oral step-down group, a difference of 16 days. The 199 patients assigned to conventional IV treatment used 3,781 in-hospital bed days, whereas the 201 patients assigned to oral step-down treatment used 603 in-hospital bed days, a difference of 3,178 bed days. In the oral step-down group, the reduced in-hospital stay (16 days) resulted in mean savings of €14,064 per patient. Patients receiving oral step-down treatment had a mean of 4.8 additional outpatient visits until completion of antibiotic therapy, equivalent to a total of 965 visits and total costs of €153,403. The estimated net saving associated with oral step-down treatment was €13,301 per patient or €2,673,460.8 in total.

CONCLUSIONS: Oral step-down treatment may reduce hospital bed use and healthcare costs in appropriately selected patients with IE while maintaining the clinical benefits shown in the POET trial.

Prognostic Performance of the National Early Warning Score and the Contribution of Systolic Blood Pressure in Patients with Acute Heart Failure

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Background: Patients with acute heart failure (AHF) are a heterogeneous group, highlighting the need for a reliable tool to identify patients at high risk of all-cause mortality. However, the prognostic utility of the National Early Warning Score (NEWS) in AHF remains limited, and the prognostic contribution of systolic blood pressure (sBP) within NEWS in AHF remains unclear.

Purpose: This study aimed to evaluate the prognostic value of NEWS, for predicting 1-year all-cause mortality in patients admitted with AHF, including analyses with and without sBP at admission, and to explore whether individual components of these scores independently predict long-term outcomes.

Methods: In this retrospective cohort study, consecutive patients admitted with AHF to the Emergency Department between March 10, 2020 and March 31, 2022 were included. Patients were stratified according to admission NEWS using a predefined cut-off (≥7 vs <7).

Results: Among 408 patients (mean age 75±12 years), one-year all-cause mortality was significantly higher in patients with NEWS ≥7 (log-rank p <0.001). In multivariable analysis, NEWS ≥7 was independently associated with increased mortality (HR 2.05, 95% CI 1.39 - 3.02). The overall discriminatory performance of NEWS was poor (AUC 0.59).

Conclusion: In patients admitted with AHF, a NEWS ≥7 at ED presentation was independently associated with increased one-year all-cause mortality. The overall discriminatory performance of NEWS was modest and largely driven by respiratory parameters, supporting its role as a pragmatic screening tool rather than a standalone instrument for individualized long-term risk prediction

A little pump goes a long way: Establishing cardiac fibrosis in mice for antifibrotic drug screening

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Introduction: Cardiac fibrosis is a key contributor to heart failure progression and arrhythmogenesis, yet there are no approved therapies that directly target fibrotic structural remodeling of the myocardium. Preclinical evaluation of antifibrotic strategies requires experimental models that recapitulate the gradual and diffuse fibrosis observed in clinical diseases. Angiotensin II (AngII) infusion is commonly used to induce cardiac fibrosis in rodents. This study aimed to establish an AngII-induced cardiac fibrosis model and investigate the potential antifibrotic properties of ABR-238901 (ABR), a selective S100A8/A9 blocker, and pirfenidone (PFD), a broad-spectrum antifibrotic agent used in lung diseases.

Method: Thirty-six 11-week-old male C57BL/6NCrl mice were included in an 8-week study comprising a 4-week induction period using AngII osmotic minipump implantation (Alzet 2004, 1.5 mg/kg/day) and a 4-week treatment period. At weeks 3 and 7, transthoracic echocardiography was performed under isoflurane anesthesia (2%). At week 4, pumps were explanted and animals were randomized into three treatment groups (n=11/group): vehicle, ABR (6 mg/kg/day) or PFD (86 mg/kg/day). Treatment was administered twice daily via i.p. injections. At week 8, atrial fibrillation (AF) inducibility was assessed using a burst pacing protocol via the jugular vein (20 rounds of 2 s at 50 Hz, with carbachol (0.5 mg/kg i.p.) administered prior to the final 10 rounds). Hearts were collected for histological and proteomic analyses, with cardiac interstitial fibrosis quantified using picrosirius red staining.

Results: Data are currently being analyzed and include echocardiographic assessment, evaluation of AF inducibility, histological assessment of myocardial fibrosis, and proteomic evaluation of ventricular tissue.

Discussion: AngII infusion is anticipated to induce a mild to moderate degree of cardiac fibrosis over 4 weeks, mimicking the progressive fibrotic remodeling observed in clinical disease rather than acute injury. Importantly, antifibrotic treatment was initiated following pump explantation and cardiac fibrosis establishment, thereby modeling a clinically relevant therapeutic scenario in which patients receive treatment after an established fibrotic diagnosis. This supports the translational relevance of the model for antifibrotic drug testing, addressing a critical unmet therapeutic need.

Conclusion: We anticipate that ABR and PFD will attenuate fibrotic remodeling and reduce AF susceptibility in this translationally relevant model of cardiac fibrosis.

Ketamine as neuroprotective agent after out-of-hospital cardiac arrest: rationale and design of the KETOHCA trial

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Background:

Comatose patients resuscitated from out-of-hospital cardiac arrest (OHCA) have a poor prognosis, with fewer than 50% surviving beyond 30 days, largely driven by hypoxic-ischemic brain injury. Current strategies to limit brain injury are initiated after hospital arrival, despite injury evolving from the early post-resuscitation phase. During this period, comatose patients often require prehospital intubation and sedation. There are no guidelines supporting the choice of sedative post-OHCA. A preliminary review of prehospital medical records showed that propofol was the most frequently used sedative, ketamine was rarely used, vasopressor use was higher among sedated patients, and non-sedated patients had poorer prognostic markers. The sedatives differ in their hemodynamic and neurophysiological profiles: propofol may aggravate post-resuscitation hypotension, whereas ketamine has shown preclinical neuroprotective signals and may support hemodynamic stability through its sympathomimetic effects. The comparative effects of ketamine and propofol on early cerebral injury and hemodynamic stability after OHCA remain unknown.

Purpose:

To describe the rationale and design of KETOHCA, an ongoing randomized controlled trial comparing prehospital sedation with ketamine versus propofol in patients resuscitated from OHCA.

Methods:

KETOHCA is an ongoing investigator-initiated, multicenter, randomized controlled trial conducted in three Danish regions. The trial will enroll 282 adult comatose patients resuscitated from OHCA of presumed cardiac origin with a primary shockable rhythm, sustained return of spontaneous circulation, mean arterial pressure ≥40 mmHg, and need for prehospital intubation and sedation. Patients are randomized 1:1 in the prehospital setting to intravenous or intraosseous esketamine ≥0.5 mg/kg or propofol ≥0.25 mg/kg. The primary endpoint is neuron-specific enolase 48 h after cardiac arrest. Secondary endpoints include all-cause mortality, Cerebral Performance Category, and modified Rankin Scale at discharge and 180 days. Exploratory endpoints assess hemodynamic instability, including vasopressor use, hypotension, and arrhythmias during prehospital and in-hospital care. As of 15 May 2026, 165 primary endpoint samples had been collected.

Conclusion:

KETOHCA is designed to determine whether prehospital sedation with ketamine, compared with propofol, reduces early post-resuscitation cerebral injury without compromising hemodynamic stability after OHCA. To our knowledge, the trial will provide the first randomized evidence to guide sedative choice in early post-resuscitation care. If positive, the trial could identify an immediately implementable neuroprotective strategy for patients who currently face high mortality and limited effective treatments.

Cardiomyocyte polyploidy and postnatal cell-cycle exit limit regeneration after ischemic injury

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Background
The specialized cells of the adult human heart are traditionally considered terminally differentiated and incapable of regenerating after injury. Polyploidy has long been viewed as the primary barrier to cardiomyocyte (CM) proliferation. In mice, CMs undergo their final round of true cell division within the first 1–2 days after birth, yet DNA synthesis continues for approximately two weeks, leading to binucleation through failed cytokinesis and subsequent polyploidization. Emerging evidence, however, suggests that CMs first enter a non-dividing, dormant state during development *before* polyploidization occurs. This early developmental dormancy may represent the true bottleneck limiting postnatal CM renewal. Despite its potential importance, the molecular mechanisms that govern the transition from proliferation to dormancy and ultimately to polyploidy remain poorly understood.
Aim
We aim to identify the molecular mechanisms that drive the transition of CMs from a proliferative state into dormancy and subsequent polyploidy, and to determine whether dormancy can be reversed or modulated to restore CM proliferative capacity and support regeneration after cardiac ischemic injury.
Methods
To distinguish dividing, dormant, and polyploid CMs, we use a cardiomyocyte-specific Cre/lox lineage-tracing system combined with a multicolor fluorescent reporter. Each CM permanently activates a single fluorescent label during development, allowing true cell division to be identified through clonal expansion, while polyploidization without division retains the label within a single enlarged cell. This system, together with cell-cycle markers, nucleation analysis, and single-cell transcriptomics, enables precise mapping of CM fate transitions and identification of pathways regulating proliferation, dormancy, and polyploidization.
Expected Results
We expect to define distinct transcriptional and cell-cycle states marking transitions between proliferative, dormant, and polyploid CMs, and to identify regulators that may be targeted to influence these states. Manipulating these pathways may reveal whether CM dormancy is reversible and whether proliferation can be restored safely to support regeneration after injury.
Perspective
By uncovering the mechanisms underlying CM dormancy and polyploidization, we may identify new therapeutic targets for stimulating endogenous heart regeneration and support future regenerative strategies for patients with myocardial injury.

Pudafensine, a monoamine reuptake inhibitor, promotes paracopulatory behaviors and increases genital flow in female rats

Simon Comerma-Steffensen, Elif Alan Albayarak, Geomar Sijas, Gregers Wegener, Ulf Simonsen

Female sexual dysfunction (FSD) has limited treatment options. Pudafensine, a monoamine-reuptake inhibitor, has shown pro-erectile effects in male rats and patients. We hypothesized that pudafensine promotes sexual behavior and increases rat female genitalia blood flow.

Female adult rats were estrous-synchronized and sexual behavior was evaluated, estrogen (E_2) and Follicle Stimulating Hormone (FSH) were measured. Other rats were anesthetized with pentobarbital, Laser Doppler measured blood flow in the clitoris and vagina, and pudendal arteries were isolated for myography.

Pudafensine (10 mg/Kg) increased paracopulatory behaviors (darts/hops). E_2 and FSH levels were in physiological ranges. In contrast to the vehicle, administration of increasing doses of pudafensine in the jugular vein dose-dependently increased clitoral blood flow, while vaginal flow was unaltered. Pudafensine concentration-dependently relaxed pudendal arteries.

We conclude that pudafensine increased paracopulatory sexual behaviors, and specifically increased blood flow in the clitoris and arteries. Pudafensine has a potential for treatment of women with FSD.

Beyond valve repair: the hidden psychological burden after mitral valve repair

Background: While mitral valve repair (MVr) for degenerative mitral regurgitation improves survival and functional outcomes, long-term postoperative psychological morbidity remains poorly characterized in large, contemporary population-based studies.
Purpose: To assess the incidence of new-onset psychopharmacological therapy following first-time MVr compared with a matched background population, and to examine whether associations persist beyond the immediate postoperative period.
Methods: Using Danish nationwide registries, we included all patients (≥18 years) undergoing first-time isolated MVr between 2000 and 2023. Patients were matched 1:4 to controls from the background population on age, sex, calendar year, and educational level. A new-user design was applied, excluding individuals with psychiatric diagnoses before index or psychopharmacological therapy 5 years before index. Outcomes were first-time prescription redemption of antidepressants, anxiolytics, hypnotics, or a composite thereof within 5 years following discharge. Cumulative incidence functions and multivariable Cox regression models were used to estimate associations, including in landmark analysis at 1 year.
Results: We identified 2,603 patients (median age 62.1 years, 73.9% male) and matched them to 10,404 controls. Patients had a higher prevalence of ischemic heart disease (15.8% vs 8.9%), congestive heart failure (18.1% vs 2.3%), and atrial fibrillation (37.7% vs 4.5%), but a lower prevalence of diabetes (3.7% vs 8.1%) compared with controls. Patients had a significantly higher 5-year cumulative incidence of first-time psychopharmacological therapy across all individual medication categories compared with controls, including antidepressants (9.1% vs 6.5%; adjusted HR (aHR) 1.39, 95% CI 1.15–1.69), anxiolytics (7.8% vs 4.8%; aHR 1.54, 95% CI 1.23–1.92), hypnotics (19.9% vs 7.73%; aHR 2.64, 95% CI 2.28–3.07), and the composite outcome (28.3% vs 15.5%, aHR 2.05; 95% CI 1.78–2.36). In the 1-year landmark analysis, the 5-year cumulative incidence remained significantly higher across medication categories, with attenuated hazard ratios (antidepressants: aHR 1.31, 95% CI 1.06–1.62; anxiolytics: aHR 1.20, 95% CI 0.92–1.56; hypnotics: aHR 1.20, 95% CI 0.99–1.47; composite outcome: aHR 1.25, 95% CI 1.08–1.44). For the composite outcome, similar associations were observed in both analyses: male sex and more recent calendar periods were associated with lower risk, whereas increasing age and most preoperative comorbidities were associated with higher risk.
Conclusion: Mitral valve repair is associated with an increased risk of new-onset psychopharmacological therapy compared with the background population. This excess risk persists beyond 1 year postoperatively, albeit attenuated, suggesting sustained psychological vulnerability. These findings highlight the need for mental health screening and support as part of long-term follow-up.

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Chronic Kidney Disease Progression After Cardiac Surgery: A Retrospective Multicenter Study

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Background
Chronic kidney disease (CKD) is a known risk factor for adverse outcomes following cardiac surgery and is linked to higher mortality and postoperative complications[1]. While detrimental effects of preexisting CKD on cardiac surgery outcomes are well-described, long-term kidney function trajectories remain poorly understood. This study aimed to describe CKD progression and kidney failure in cardiac surgery patients with preexisting CKD.

Methods
This retrospective observational multicenter study analyzed 27,485 adult cardiac surgery patients at Odense University Hospital (2000–2022) and Aarhus University Hospital (2008–2024), including 3,144 patients with preoperative CKD (stages G3a–G5). Clinical, biochemical and mortality data were obtained from national registries and laboratory systems. The study was approved by Regional and Directorate authorities in Region of Southern Denmark. Three KDIGO-defined outcomes were assessed: rapid progression (confirmed eGFR decline ≥5 mL/min/1.73m²/year), CKD stage progression (confirmed ≥25% eGFR drop with stage advancement), and kidney failure (confirmed eGFR less than 15 mL/min/1.73m²). Competing risk analysis accounted for mortality during median 7-year follow-up.

Results
CKD patients were older, more often female, had higher comorbidity burden and more frequent postoperative acute kidney injury (AKI). Five-year survival decreased with worsening baseline kidney function: 86.1% (stages G1–2), 70.6% (G3a), 61.3% (stage G3b), 45.4% (stage G4), and 51.9% (stage G5). Five-year cumulative incidence among CKD patients was 38.7% for rapid progression, 23.8% for CKD stage progression, and 5.5% for kidney failure. Notably, 43% of rapid progression, 39% of CKD progression, and 27% of kidney failure events occurred within the first year post-discharge. Males ≤70 years with stage G4 CKD experiencing postoperative AKI had highest risks across all outcomes (Fig. 1).

Conclusion
Cardiac surgery patients with preexisting CKD face substantial kidney disease progression risks, with postoperative AKI as the strongest accelerating factor. These findings highlight the need for structured follow-up and the need for investigation of early preventive treatments to improve long-term kidney outcomes in this vulnerable population.

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

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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-four diabetic patients with an increased risk of having microvascular disease will be included outside of the hospital sector. Twenty-two 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 four months of supervised HIIT-training or four months without any additional training. Baseline measurements (ex. MRI & LVEF) will be repeated after the intervention.

Risk of Out-of-Hospital Cardiac Arrest in incident diabetes mellitus

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Background: Individuals with diabetes mellitus have an elevated risk of cardiovascular disease. However, the long-term risk of out-of-hospital cardiac arrest (OHCA) remains insufficiently characterized, particularly across diabetes subtypes and levels of glycemic control. We aimed to investigate the long-term absolute risk of OHCA among individuals with incident type 1 diabetes (T1D) and type 2 diabetes (T2D).

Methods: In this nationwide register-based cohort study, we included all Danish residents aged <80 years between January 1, 2016, and December 31, 2023. Incident cases of diabetes were identified using validated algorithms and matched on date of diagnosis to individuals without diabetes. Participants were followed from the index date (diagnosis or matching) until OHCA, death, emigration, age 80 years, or end of follow-up. Absolute risk was estimated using cumulative incidence functions accounting for the competing risk of death, and cause-specific Cox regression models were used to estimate hazard ratios. Baseline hemoglobin A1c (HbA1c) was evaluated as a predictor of OHCA and mortality.

Results: Among approximately 6.7 million individuals in the source population, 166,871 incident diabetes cases and 665,645 matched controls were included. During follow-up, individuals with diabetes had a higher cumulative incidence of OHCA compared with matched controls. At 5 years, the absolute risk of OHCA was 1.0% (95% CI: 0.9–1.0) in individuals with diabetes, compared with 0.7% (95% CI: 0.7–0.8) in matched controls. Among individuals with prevalent cardiovascular disease at the time of diabetes diagnosis, the 5-year absolute risk of OHCA was 2.0% (95% CI: 1.8–2.2), compared with 1.4% (95% CI: 1.4–1.5) in matched controls. The increased absolute risk was primarily driven by T2D, as the 5-year risk of OHCA in individuals with incident T1D was comparable to that of matched controls. Restricted cubic spline analysis demonstrated a non-linear association between HbA1c and OHCA risk, with progressively increasing risk at higher baseline HbA1c levels.

Conclusions: In this nationwide study, incident diabetes was associated with an increased long-term risk of OHCA, particularly among individuals with T2D and those with pre-existing cardiovascular disease. Poor glycemic control at baseline was associated with a further increase in risk. These findings underscore the need for improved risk stratification and targeted preventive strategies addressing arrhythmic outcomes in individuals with diabetes.

Genetic subtypes of body composition have distinct biological and clinical features throughout life course

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INTRODUCTION: Body mass index (BMI) does not fully capture heterogeneity in body composition. Genetic analyses of body composition traits may reveal underlying biological mechanisms critical for cardiometabolic health.

OBJECTIVE: To characterize the genetic architecture of body composition traits.

METHODS: We conducted genome-wide (Nmax=560,000) and exome-wide association meta-analyses (Nmax=450,000) for body fat percentage (BFP) and fat-free mass index (FFMI). Genetic subtypes were defined using k-means clustering based on associations with BFP, FFMI, BMI, WHRadjBMI, and height. Genetic risk scores (GRSs) were constructed for each subtype and tested for associations with cardiometabolic traits and diseases in Fenland, EPIC-Norfolk, UK Biobank, and BioMe. Early-life effects were assessed in the ALSPAC study. Tissue and cell-type enrichment and effector gene prediction were conducted using five in silico approaches.

RESULTS: We identified 1,183 loci associated with BFP (443), FFMI (535), or both (205), clustering into six genetic subtypes: [C1] high BFP, low FFMI and BMI; [C2] high BFP, low FFMI and BMI with greater height; [C3] high BFP, FFMI, and BMI with low WHRadjBMI; [C4] very high BFP, FFMI, and BMI; [C5] high BFP and FFMI with shorter height; and [C6] high BFP, FFMI, and BMI. Larger body size subtypes (C4–C6) conferred greater cardiometabolic risk than higher relative adiposity subtypes (C1–C2), which were largely neutral, while the lower-body adiposity subtype (C3) was protective. Subtype features emerged by ~5 years of age. The genetic subtypes with higher overall body size [C4, C6] enrich for the brain and effector gene prediction points towards neuronal pathways and appetite regulation similarly to body mass index. The genetic subtypes with higher relative adiposity [C1, C2, C3] enrich for peripheral tissues spanning adipose, musculoskeletal and digestive tissues, and effector gene prediction pinpoint genes involved in extracellular matrix remodeling and muscle differentiation including the myostatin-ACVR2B pathway [C1], bone and cartilage biology [C2], and adipose expansion [C3]. We identified 22 rare coding variants (MAF<1%) with opposing effects on BFP and FFMI, including MSTN.

CONCLUSION: Genetic studies of body composition reveal subtypes with distinct cardiometabolic risk profiles that are not fully captured by BMI. Our findings suggest that that absolute adiposity confer greater cardiometabolic risk than relative adiposity. Furthermore, we identify genomic mechanisms regulating body composition that may offer therapeutically actionable targets.

Adiponectin Mimetic Peptide for Vascular Protection: Focus on Calcium Signaling in Endothelium and Vascular Smooth Muscle Cells

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Adiponectin possesses prominent therapeutic potential for cardiovascular disorders. The newly synthesized adiponectin mimetic peptide, namely the glycosylated adiponectin collagenous domain peptide (GlyACD), has emerged as a novel pharmacological tool to activate adiponectin signaling in the vasculature. Using pressure myography, we found that acute exposure to GlyACD induces anti-contractile effects in mouse mesenteric arteries and enhances endothelium-dependent relaxation via activation of the endothelial-derived hyperpolarizing factor (EDHF) pathway.

To elucidate the cellular mechanisms underlying the vascular protective effects of acute GlyACD exposure in vascular smooth muscle cells, simultaneous wire myography and ratiometric calcium imaging with Fura-2 LR/AM will be employed to comprehensively assess intracellular Ca^{2+} handling and Ca^{2+} sensitivity in arteries under both endothelium-intact and endothelium-denuded conditions. Additionally, this study aims to establish an optimized experimental protocol for characterizing endothelial calcium signaling in Fura-2 LR/AM-loaded *en face* arterial preparations. We also intend to explore the effects of metabolic stress and sex differences by applying the GlyACD to small arteries from male and female mice on either a normal diet or a high-fat/high-fructose diet for 10 weeks.

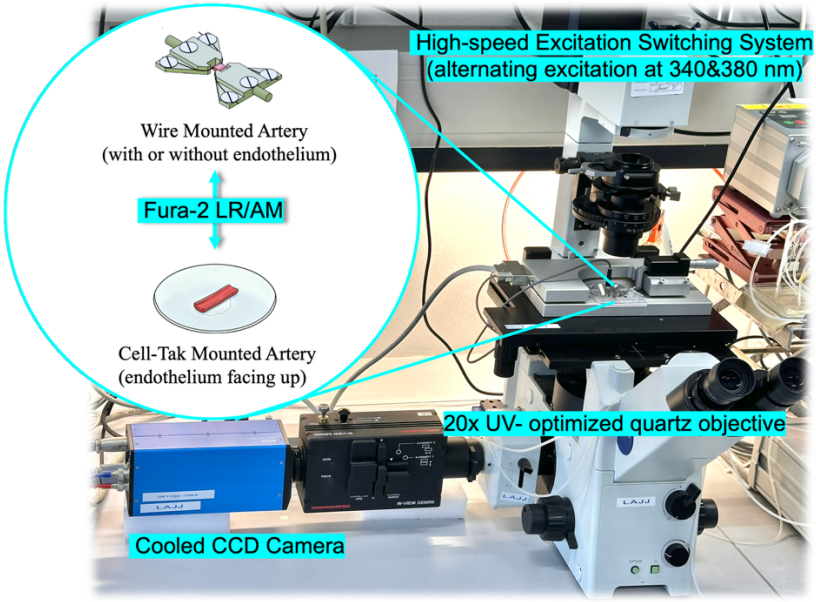

Figure: Schematic diagram of simultaneous wire myography and Fura-2 based ratiometric calcium imaging in small arteries

Plasma proteomic and lipidomic signatures of metabolic subtypes of obesity in children and adolescents

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Children and adolescents with obesity show substantial heterogeneity in cardiometabolic dysfunction. We investigated metabolic subgroups in 3,645 children and adolescents aged 4-20 years from the HOLBAEK Study and analyzed 1,216 plasma proteins quantified by mass-spectrometry, 164 by olink, and 227 lipid species to characterize subgroup differences and responses to lifestyle intervention.

Individuals with normal weight (n=1,581) or obesity (n=2,064) were stratified based on the presence of 0, 1, or ≥2 cardiometabolic risk (CMR) features (dyslipidemia, hypertension, insulin resistance, hyperglycemia, or hepatic steatosis). Among children with obesity, 32% had 0, 30% had 1, and 38% had ≥2 CMRs, compared with 70%, 25%, and 4.3% in normal weight. The obesity ≥2CMRs group had higher adiposity and more adverse cardiometabolic profiles. Complementary unsupervised clustering using continuous clinical variables identified clusters potentially driven by high levels of cholesterol or insulin resistance. Overall, 611 proteins and 113 lipid species differed across obesity metabolic subgroups, including several disease markers such as ALDOB, HAOX1, and ceramides. After one-year lifestyle intervention, children in the obesity 0CMR group showed the largest adiposity reduction, whereas 1CMR and ≥2CMR groups achieved cardiometabolic improvements. Multiple baseline proteins and lipids were associated with changes in cardiometabolic traits, with potential predictive value for changes in metabolic status.

Together, this study provides insights into metabolic heterogeneity in pediatric obesity, underscoring the importance of risk stratification for the management of cardiometabolic health.

Oestrus cycle dependent changes in vascular function underpin a novel mechanism in menstrual migraine

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Abstract

Classic migraine presents as a throbbing headache with cerebral artery vasodilation. Menstrual migraine (MM) is a subclassification of migraine. Since the 1970's, MM has been attributed to the withdrawal of estradiol (E2) at the onset of menses. We have recently demonstrated that a reduction in serum E2 in rodents enhanced arterial sensitivity to vasodilators.

Therefore, we proposed that an estrus cycle driven change in cerebrovascular reactivity enhances sensitivity to migraine induction via nitro triglyceride (NTG) in 9-week-old female C57BL/6J mice.

Via laser speckle contrast imaging, we observed an increase in cerebral blood flow at rest, and post migraine, a decrease in CGRP puncta, and a significant regulation of proteins associated with vesicular handling within the cerebral cortex in mice in a low serum E2 stage of the cycle.

Our findings reinforce the current model for MM, and provide novel insights into the protein changes associated with enhanced sensitivity to MM.

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