AARHUS UNIVERSITY HEALTH

THE CARDIOVASCULAR NETWORK

Second annual meeting

September 9th 2021, from 14:00-17:15, followed by reception
Merete Barker auditorium, Lakeside Lecture Theatre, Aarhus University,
Bartholins Allé 3, 8000 Aarhus C

14:00 **Welcome** Jens Cosedis Nielsen, representing professor for the network

14:15 **Session 1: Electrophysiology - chair: Jens Cosedis Nielsen**

Ventricular tachycardia in repaired congenital heart disease Katja Zeppenfeld, Head of the clinical electrophysiology research and treatment centre in Leiden, The Netherlands, and Honorary Professor at Aarhus University and Department of Cardiology, Aarhus University Hospital

Experimental electrophysiology in pigs with myocardial infarction Claire A. Glashan, Department of Human Genetics, Leiden University Medical Centre (LUMC)

15:05 Coffee break and poster viewing

15:30 **Danish Cardiovascular Academy** Christian Aalkjær, Executive Managing Director

15:35 **Session 2: Epidemiology - chair: Christina Dahm**

High-density lipoprotein: Reconciling associations and functions Majken Jensen, Professor, Section of Epidemiology, University of Copenhagen

Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: Population based cohort study with 40 years of follow-up Jiong Li, Associate Professor, Department of Clinical Epidemiology, Aarhus University

16:20 **Session 3: Clones and companies - chair: Jacob Fog Bentzon**

Draupnir Bio – the development of an oral PCSK9 inhibitor for hypercholesterolemia Simon Glerup, CSO at Draupnir Bio and Associate Professor Department of Biomedicine, Aarhus University

Somatic mutations and clonal hematopoiesis in atherosclerotic cardiovascular disease José Javier Fuster, Biomedical Researcher, Assistant Professor, the Spanish Center for Cardiovascular Research (CNIC), Madrid, Spain

17:15 Reception and poster viewing

18:00 **Poster award**

Registration
At https://events.au.dk/cardiovascularnetworkannualmeeting2021. The deadline is August 29th.

OVERVIEW – POSTER PRESENTATIONS

Number	Group	Poster presenter	Time slot
1	I	Kristoffer Berg-Hansen	First break (@15:05)
2	I	Maria Hee Jung Park Frausing	First break (@15:05)
3	I	Daniel Fyenbo	First break (@15:05)
4	I	Laura Alonso Herranz	First break (@15:05)
5	I	Jakob Tarp	Second break (@17:15)
6	I	Jacob Valentin Hansen	Second break (@17:15)
7	I	Simon Gabriel Comerma Steffensen	Second break (@17:15)
8	I	Maja Fuhlendorff Jensen	Second break (@17:15)
9	I	Frederik Pagh Kristensen	Second break (@17:15)
10	II	Mathilde Emilie Kirk	First break (@15:05)
11	II	Thomas Weiss	First break (@15:05)
12	II	Lise Filt Jensen	First break (@15:05)
13	II	Rajkumar Rajanathan	First break (@15:05)
14	II	Niels Moeslund	Second break (@17:15)
15	II	Christian Staehr	Second break (@17:15)
16	II	Jie Zhang	Second break (@17:15)
17	II	Victor Tang Merit	Second break (@17:15)
18	II	Anders Meldgaard Kristensen	Second break (@17:15)

SESSION 1 - ELECTROPHYSIOLOGY

Ventricular tachycardia in repaired congenital heart disease

Katja Zeppenfeld
Department of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands
Honorary Professor at Aarhus University and Aarhus University Hospital

Advanced surgical techniques in various types of congenital heart disease (CHD) have improved survival into adulthood. Improved longevity of patients born with CHD has resulted in a high risk for late ventricular tachyarrhythmias leading to significant morbidity and mortality, despite excellent surgical results. These arrhythmias arise from complex arrhythmogenic substrates. Substrate formation depends on the coincidence of pathological myocardial remodelling and variable anatomical boundaries determined by the type of the defect and the surgical approach. Over the last decade(s) progress has been made to better understand the substrate for life-threatening arrhythmias, which has paved the way for better risk stratification, preventive interventions and curative treatment in subgroups of patients.

Experimental electrophysiology in pigs with myocardial infarction

Claire A. Glashan
Department of Human Genetics, Leiden University Medical Centre, Leiden, the Netherlands

Background: Ventricular tachycardia's (VT) after myocardial infarction (MI) are related to scars with complex geometry. Scar delineation and VT substrate identification relies on bipolar voltages (BV) and electrogram (EGM) characteristics. Early reperfusion therapy results in small, non-transmural scars which may not be identified using 3.5mm tip ablation catheters.
Purpose: To identify the value of combining EGM information provided by simultaneous mapping using micro- and conventional electrodes in the identification of post-MI (hidden) VT substrate.
Methods: Nine swine with early reperfusion MI were mapped using the QDot catheter which incorporates three micro-electrodes at the distal tip of the standard 3.5mm tip electrode. Systematic analysis of EGM recorded during sinus rhythm, RV pacing at 500ms, and during a short-coupled RV extra-stimulus (RVE) was performed and noted if one or two component signals were seen. The swine were sacrificed and mapping data was projected onto slices of the entire heart. Transmural biopsies corresponding to mapping points were assessed histologically.
Results: By combining the information from unipolar and bipolar voltage mapping (both conventional and micro) the sensitivity to delineate scar was increased to 93% (spec. 66%). If two component EGMs were present on the conventional EGM, they were always also visible on the micro EGM. On histology, an endocardial VM layer was typically separated by a layer of confluent fibrosis from epicardial viable myocardium. However, there were sites in which a second component was more clearly visible in the micro but was partially obscured within the decay artefact in the conventional EGM. These biopsies showed complex fibrotic changes on histology. Moreover, there were also sites in which a second component was only visible in the micro EGM. These sites typically showed thin layers of endocardial viable myocardium with large overlying epicardial viable myocardium.
Conclusion: The combined information provided by multi-size electrode voltage and EGM analysis increases the sensitivity with which areas of scar are identified and may allow, in conjunction with RVE, an estimate of non-transmural scar geometry and identification of ablation target sites using one catheter. The higher spatial resolution of the microelectrode allows for the identification of small near-field components which are either not picked up by the large-tipped electrodes or are obscured by the decay artefact produced in conventional EGM.

SESSION 2 - EPIDEMIOLOGY

High-density lipoprotein: Reconciling associations and functions

Majken Jensen
Section of Epidemiology, University of Copenhagen

Despite being a strong inverse risk factor for cardiovascular disease (CVD), recent drug trials did not find that raising high-density lipoprotein (HDL) levels was beneficial for CVD-risk reduction. This has spurred research of HDL functionality rather than absolute HDL cholesterol levels.
We have found that in contrast to the inverse association of the majority HDL with CVD, the presence of apolipoprotein CIII (apoC-III) on HDL renders HDL unprotective. Similarly, apoC-III also modifies the role of HDL in diabetes and insulin regulation.
In recent work we have continued to explore the complex constellation of lipid and proteins that makes up what we call "HDL". We have investigated HDL subtypes defined according to other proteins associated with HDL (the HDL proteome) in relation to CVD. Finally, we will discuss the current expansion of the concept of HDL speciation by addressing subspecies of HDL based on proteins that have been identified as key risk factors for Alzheimer's disease and stroke in genome-wide association studies (APOE and APOJ) and metabolomics studies.
The potential for a fuller understanding of the concept of HDL through both observational association studies and HDL function studies will be reviewed in this lecture.

Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: Population based cohort study with 40 years of follow-up

Jiong Li
Department of Clinical Epidemiology, Aarhus University

Objective: To evaluate the associations between maternal diabetes diagnosed before or during pregnancy and early onset cardiovascular disease (CVD) in offspring during their first four decades of life.
Design: Population based cohort study.
Setting: Danish national health registries.
Participants: All 2 432 000 liveborn children without congenital heart disease in Denmark during 1977-2016. Follow-up began at birth and continued until first time diagnosis of CVD, death, emigration, or 31 December 2016, whichever came first.
Exposures for observational studies: Pregestational diabetes, including type 1 diabetes (n=22 055) and type 2 diabetes (n=6537), and gestational diabetes (n=26 272).
Main outcome measures: The primary outcome was early onset CVD (excluding congenital heart diseases) defined by hospital diagnosis. Associations between maternal diabetes and risks of early onset CVD in offspring were studied. Cox regression was used to assess whether a maternal history of CVD or maternal diabetic complications affected these associations. Adjustments were made for calendar year, sex, singleton status, maternal factors (parity, age, smoking, education, cohabitation, residence at childbirth, history of CVD before childbirth), and paternal history of CVD before childbirth. The cumulative incidence was averaged across all individuals, and factors were adjusted while treating deaths from causes other than CVD as competing events.
Results: During up to 40 years of follow-up, 1153 offspring of mothers with diabetes and 91 311 offspring of mothers who did not have diabetes were diagnosed with CVD. Offspring of mothers with diabetes had a 29% increased overall rate of early onset CVD (hazard ratio 1.29 (95% confidence interval 1.21 to 1.37); cumulative incidence among offspring unexposed to maternal diabetes at 40 years of age 13.07% (12.92% to 13.21%),

difference in cumulative incidence between exposed and unexposed offspring 4.72% (2.37% to 7.06%)). The sibship design yielded results similar to those of the unpaired design based on the whole cohort. Both pregestational diabetes (1.34 (1.25 to 1.43)) and gestational diabetes (1.19 (1.07 to 1.32)) were associated with increased rates of CVD in offspring. We also observed varied increased rates of specific early onset CVDs, particularly heart failure (1.45 (0.89 to 2.35)), hypertensive disease (1.78 (1.50 to 2.11)), deep vein thrombosis (1.82 (1.38 to 2.41)), and pulmonary embolism (1.91 (1.31 to 2.80)). Increased rates of CVD were seen in different age groups from childhood to early adulthood until age 40 years. The increased rates were more pronounced among offspring of mothers with diabetic complications (1.60 (1.25 to 2.05)). A higher incidence of early onset CVD in offspring of mothers with diabetes and comorbid CVD (1.73 (1.36 to 2.20)) was associated with the added influence of comorbid CVD but not due to the interaction between diabetes and CVD on the multiplicative scale (P value for interaction 0.94).

Conclusions: Children of mothers with diabetes, especially those mothers with a history of CVD or diabetic complications, have increased rates of early onset CVD from childhood to early adulthood. If maternal diabetes does have a causal association with increased CVD rate in offspring, the prevention, screening, and treatment of diabetes in women of childbearing age could help to reduce the risk of CVD in the next generation.

SESSION 3 – CLONES AND COMPANIES

Somatic mutations and clonal hematopoiesis in atherosclerotic cardiovascular disease

José Javier Fuster
Spanish Center for Cardiovascular Research (CNIC), Madrid, Spain

Accumulating evidence suggest that conventional cardiovascular risk factors are incompletely predictive of cardiovascular disease, as a substantial risk remains even when these factors are apparently managed well, particularly in the elderly population. In this context, age-related clonal hematopoiesis has emerged as a new, potent and independent risk factor for atherosclerotic cardiovascular disease and other cardiovascular conditions. Clonal hematopoiesis typically arises from an acquired mutation that confers a competitive advantage to a mutant hematopoietic stem cell, leading to its clonal expansion in the stem cell pool and its progeny of blood leukocytes. Human sequencing studies and experiments in mice suggest that this phenomenon, at least when driven by certain mutations, contributes to accelerated development of atherosclerosis and other cardiovascular conditions, mainly related to exacerbated inflammatory responses driven by mutant immune cells. However, there is a great need for further investigation into the epidemiology, biology and clinical implications of this clonal hematopoiesis. Both experimental approaches and clinical research efforts will be required to develop strategies for the management of this newly recognized risk factor for cardiovascular disease.

Draupnir Bio – the development of an oral PCSK9 inhibitor for hypercholesterolemia

Simon Glerup
Draupnir Bio and Department of Biomedicine, Aarhus University

Ischemic heart disease is the main cause of death worldwide and is accelerated by hypercholesterolemia characterized by increased levels of low density lipoprotein cholesterol (LDL-C). Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a potent circulating regulator of LDL-C through its ability to induce degradation of the LDL receptor (LDLR) in the lysosomes of hepatocytes. Only in the last few years, a number of breakthroughs in the understanding of PCSK9 biology have been reported illustrating how PCSK9 activity is tightly regulated at several levels by factors influencing its transcription, secretion, or by extracellular inactivation and clearance. Two humanized antibodies directed against the LDLR binding site in PCSK9 received approval by the European and US authorities and additional PCSK9 directed biologics are currently in clinical trials. However, so far the development of a once-daily oral PCSK9 inhibitor has proven challenging. Draupnir Bio is a spin out from Aarhus University and the Max-Planck Institute and is combining deep structural insight and novel biological understanding into PCSK9 to advance the development of an oral available small molecule PCSK9 inhibitor with the aim to transform the treatment of hypercholesterolemia.

POSTER GROUP I

1 Myocardial external efficiency in left ventricular pressure overload versus systolic dysfunction

Kristoffer Berg-Hansen, MD,[a,b] Jens Sörensen, MD, DMSc, Prof,[b,c,d] Nils Henrik Hansson, MD, PhD,[a] Roni Nielsen, MD, PhD,[a] Anders Hostrup Larsen, MD, PhD,[a] Jørgen Frøkiær, MD, DMSc, Prof,[b] Lars Poulsen Tolbod, MSc, PhD,[c] Lars Christian Gormsen, MD, PhD, Prof,[b,c] Hendrik Johannes Harms, MSc, PhD,[c] Henrik Wiggers, MD, DMSc, Prof[a,b]

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Background: Myocardial external efficiency (MEE) is the ratio of cardiac work in relation with energy expenditure. We studied MEE in patients with different etiologies and stages of heart failure (HF) to discover the role and causes of deranged MEE. In addition, we explored the impact of patient characteristics such as sex, body mass index (BMI) and age on myocardial energetics.
Methods: Cardiac energetic profiles were assessed with 11C-acetate positron emission tomography (PET) and left ventricular ejection fraction (LVEF) was acquired with echocardiography. MEE was studied in 121 participants: healthy controls (n=20); HF patients with reduced (HFrEF; n=25) and mildly reduced (HFmrEF; n=23) LVEF; and patients with asymptomatic (AS-asymp; n=38) and symptomatic (AS-symp; n=15) aortic stenosis (AS).
Results: Reduced MEE coincided with symptoms of HF irrespective of etiology and declined in tandem with deteriorating LVEF. Patients with AS-symp and HFmrEF had reduced MEE as compared with controls (22.2±4.9%, p=0.041 and 20.0±4.2%, p<0.001 vs. 26.1±5.8% in controls) and a further decline was observed in patients with HFrEF (14.7±6.3%, p<0.001). Disproportionate left ventricular hypertrophy was as a major cause of reduced MEE. Female sex (p<0.001), a lower BMI (p<0.001), and advanced age (p=0.01) were associated with a lower MEE.
Conclusions: MEE was reduced in patients with HFrEF, HFmrEF, and HF due to pressure overload and MEE may therefore constitute a treatment target in HF. Patients with LVH, advanced age, female sex, and low BMI had more pronounced reduction in MEE and personalized treatment within these patient subgroups could be relevant.

2 Temporary pacing is not associated with an increased risk of cardiac implantable electronic device infections

Maria Hee Jung Park Frausing, Jens Cosedis Nielsen, Jens Brock Johansen, Ole Dan Jørgensen, Thomas Olsen, Christian Gerdes, Jens Kristensen, Mads Brix Kronborg

Background: Temporary transvenous pacing (TTP) has been associated with an increased risk of cardiac implantable electronic device (CIED) infections, but there is little data to document this in contemporary populations.
Objective: To investigate the impact of TTP on rate of CIED infections in a nationwide cohort of Danish patients.
Methods: We identified all patients who underwent a first-time CIED implantation between 2009 and 2017 using the Danish Pacemaker and ICD Register. Patients were categorized according to TTP status at implantation and followed for one year. The primary end point was local or systemic CIED infection with

requirement for device system removal. The secondary end points were systemic CIED infections and hospitalization for infective endocarditis (IE).

Results: We included a total of 40,601 CIED patients. 2,952 were treated with TTP. The primary end point was met in 246 patients. Risk of CIED infection at one year was 0.61% for patients without TTP and 0.65% for patients with TTP, HR of 1.28 (95% CI 0.80-2.05) and adjusted HR 0.84 (0.50-1.41). More systemic CIED infections and IE hospitalizations occurred in TTP patients, however, these differences did not persist after confounder adjustment. Cumulative mortality at 1-year in TTP patients was 16.8% versus 8.4% in patients without TTP.

Conclusion: TTP was not associated with a higher rate of CIED infections. Patients treated with TTP had higher mortality, more systemic CIED infections, and more IE hospitalizations within first year of implantation. Most was attributable to an accumulation of other risk factors for infection among TTP patients.

3 Right ventricular lead position is not associated with clinical outcome in cardiac resynchronization therapy

Daniel B. Fyenbo, MD, PhD student[1, 2]; Anders Sommer, MD, PhD[3]; Charlotte Stephansen, MD, PhD[1]; Bjarne L. Nørgaard, associate professor, PhD, DMSc[1, 2]; Mads B. Kronborg, associate professor, PhD[1, 2]; Jens Kristensen, MD, PhD[1]; Christian Gerdes, MD, PhD[1]; Henrik K. Jensen, professor, PhD, DMSc[1, 2]; Jesper M. Jensen, MD, PhD[1]; Jens C. Nielsen, chair professor, PhD, DMSc[1, 2].

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Background: Cardiac resynchronization therapy (CRT) is a guideline-directed therapy for selected heart failure (HF) patients. However, up to 40% of patients derive no measurable clinical benefit from CRT. While the impact of left ventricular (LV) lead positioning has extensively been studied, far less is known about the optimal position of the right ventricular (RV) lead. Available studies regarding importance of RV lead positioning demonstrate divergent results. These studies all applied two-dimensional fluroscopy and chest radiography to assess lead position, which is inaccurate and only modestly reproducible as compared with three-dimensional cardiac computed tomography (CT). The aim of this study is to evaluate the association between different RV lead positions as assessed by cardiac CT and clinical long-term outcomes in patients receiving CRT.

Methods: We reviewed patient records of 278 patients formerly included in two prospective, randomized controlled trials for the occurrence of the pre-defined primary composite endpoint of HF hospitalization or all-cause death during long-term follow-up after CRT implantation. Outcomes were compared between RV lead positions (non-apical vs. apical and free wall vs. septal RV) using adjusted Cox regression analysis.

Results: During a median (interquartile range) follow-up of 4.7 (2.9–7.1) years, 130 (47%) patients met the primary composite endpoint. The risk of meeting the primary composite endpoint was not significantly different between patients with non-apical vs. apical RV lead position (adjusted hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.54–1.12, p = 0.17) and free wall vs. septal RV lead position (adjusted HR 1.03, 95% CI 0.72–1.47, p = 0.86).

Conclusions: In patients receiving CRT, the risk of HF hospitalization or all-cause death during long-term follow-up is not significantly associated with certain anatomical RV lead position as assessed by cardiac CT.

4 VCAM1 contributes to plaque formation by providing SMCs with increased survival and migratory capacity

Laura Alonso-Herranz[1], Stine Gunnersen[1], Esmeralda Armando Lewis[2], Martin Mæng Bjørklund[1], Julián Albarrán-Juárez[1], Laura Carramolino[2], Ernst-Martin Füchtbauer[3], Per Fogelstrand[4], Charlotte Brandt Sørensen[1], Jacob Fog Bentzon[1,2,5].

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Background: VCAM1 is expressed in human and murine atherosclerotic plaques. This adhesion molecule is known for its role in recruiting monocytes to the activated endothelium, and blockade of VCAM1 reduces atherosclerosis at least partly by mitigating this process. However, VCAM1 is also expressed by modulated smooth muscle cells (SMCs). Using a genetic strategy that selectively inactivated the Vcam1 gene in SMCs (Myh11-CreERT2; VCAM1ko-fl mice) we showed that SMC-expressed VCAM1 contributes to plaque development in atherosclerotic mice. In this study, we aim to shed light in the underlying mechanisms and its role in SMC phenotypic switching.

Methods: In order to further characterize the phenotype of SMCs lacking VCAM1, siRNA-mediated silencing experiments were performed in rat aortic SMCs. VCAM1-KD cells were then subjected to in vitro functional assays for migration (scratch assay), proliferation (EdU assay), and apoptosis (TUNEL staining), as well as gene expression analysis by qPCR.

Results: We tested several inflammatory signals for the induction of Vcam1 expression and showed that TNFα was the most potent trigger. The combination of two siRNAs against VCAM1 with a protocol of double transfection in two consecutive days efficiently knocked down Vcam1 gene expression in SMCs. VCAM1-KD SMCs presented diminished migratory capacity and reduced expression of contractile markers (i.e. Acta2, Tagln, Smtn). Further characterization of VCAM1-KD SMCs showed an increase in apoptosis (% of TUNEL+ cells) and accelerated proliferation (% of EdU+ cells). This increase in proliferation may try to counterbalance the higher apoptotic rate.

Conclusion: In the context of arterial disease, VCAM1 expression is triggered by inflammatory signals and plays a role in SMC phenotypic modulation, endowing SMCs with a higher migratory capacity and acting as a survival signal. Collectively, these processes may contribute to the development of plaques that we previously reported in atherosclerotic mice.

5 Physical activity and cardiovascular mortality in type 2 diabetes: A cross-country comparison

Jakob Tarp, Aarhus University, Mengyun Luo, The University of Sydney, Adriano Sanchez-Lastra, University of Vigo, Knut Eirik Dalene, Norwegian School of Sports Sciences, Borja del Pozo Cruz, University of Southern Denmark, Mathias Ried-Larsen, University of Copenhagen, Reimar Wernich Thomsen, Aarhus University, Ding Ding, The University of Sydney, Ulf Ekelund, Norwegian School of Sports Sciences

Background

The main physical activity recommendation for individuals with type 2 diabetes (T2D), do 150-300 minutes of minimum moderate intensity aerobic physical activity per week, is identical to the recommendation given to the general population. The evidence-base behind this recommendation is weak.

Methods

We identified individuals with prevalent T2D in the UK Biobank (UKB) and China Kadoorie Biobank (CKB) prospective cohort studies. Cause of death was obtained from registries. Self-reported leisure-time physical

activity was categorized as zero activity (reference), and activity below, at, or above the recommended level of 150-300 minutes. Individuals with prevalent CVD or cancer were excluded. Associations with cardiovascular mortality (ICD-10 codes I00-I99) were determined using multivariable-adjusted subdistribution hazard ratios (sHR) from Fine-Gray competing risk regression models. The continuous dose-response pattern was modelled using restricted cubic splines.

Results

We included 14,876 (mean (SD) age: 59.5 (7.2) years) and 17,459 (57.7 (9.7) years) men and women with T2D from UKB and CKB, respectively. During a median of 11.3 and 9.7 years of follow-up, 321 and 800 deaths from CVD were recorded. In UKB, sHRs for cardiovascular mortality were 0.86 (95%CI 0.60, 1.24), 0.80 (0.53, 1.21) and 0.69 (0.46, 1.03) below, at, and above physical activity recommendations, respectively. The same contrasts yielded similar magnitude of associations in CKB; 1.01 (0.69, 1.49), 0.82 (0.61, 1.10) and 0.72 (0.61, 0.85). The continuous dose-response analysis did not support an optimal threshold or point of no added benefit (p-values for non-linearity were 0.86 and 0.35).

Conclusions

In this cross-country comparison, leisure-time physical activity showed an inverse, and similar, association with risk of cardiovascular mortality in individuals with T2D. Meeting current physical activity recommendations were associated with an approximately 20% lower risk of cardiovascular mortality in both cohorts. Stronger associations were observed at higher activity levels with no support of an upper limit of benefit.

6 Perfusion changes in chronic thromboembolic pulmonary hypertension patients after balloon pulmonary angioplasty

Jacob Valentin Hansen[1], Mads Dam Lyhne[1], Simone Juel Dragsbæk[1], Jens Erik Nielsen-Kudsk[1], Asger Andersen[1].

[1]*Department of Cardiology, Aarhus University Hospital.*

Background

Around 5% of pulmonary embolism survivors develop chronic thromboembolic pulmonary hypertension (CTEPH). It is an overlooked and serious disease with a 3-year survival rate of only 10% if left untreated. CTEPH patients can be treated with balloon pulmonary angioplasty (BPA). This increases pulmonary perfusion in previously occluded areas of the lung instantly, unloading the right ventricle, but further changes over time have never been investigated. We aim to evaluate early and late changes in pulmonary perfusion after the BPA procedure using Dual Energy CT (DECT).

Methods

This is a prospective clinical study with repeated measurements. Patients (n=17) will undergo 4 DECT scans. The 1st scan is done before the 1st BPA procedure. The 2nd DECT scan is done the day after, and the 3rd scan is performed 2 – 4 weeks later. The final scan is performed 3 months after the last BPA.

The primary endpoint is total, lung, and lobar blood volumes, automatically calculated from PBV maps using software.

Secondary endpoints are correlation between total, lung, and lobar blood volumes and invasive hemodynamics, biomarkers, and clinical parameters.

Perspectives

If we gain a greater understanding of lung perfusion changes over time after BPA, it may be possible to reduce the number of procedures needed, reducing both peri- and post-procedural risks and complications.

Further investigating the feasibility of dual-energy CT in pulmonary vascular diseases may lead to better and faster diagnostics, better monitoring of treatment response, greater understanding of the diseases, and may reduce the need for specialist assessment.

7 Erectile dysfunction and altered contribution of KCa1.1 and KCa2.3 channels in penile tissue of type-2 diabetic db/db mice

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Background: Activation of endothelial small conductance calcium-activated K+ channels (KCa2.3) and intermediate conductance calcium-activated K+ channels (KCa3.1) leads to vascular relaxation. Our previous studies have shown that endothelial KCa2.3 down-regulation in corpus cavernosum diminishes erectile function.
Aim: We hypothesized that in type-2 diabetic mice KCa2.3 channel function is impaired in erectile tissue.
Methods: Erectile function was measured, and corpus cavernosum strips were mounted for functional studies, and processed for qPCR and immunoblotting.
Results: In anesthetized diabetic db/db mice, erectile function was markedly decreased compared to non-diabetic heterozygous db/+ mice, and the impairment was even more pronounced compared to normal C57BL/6 mice. qPCR revealed KCa2.3 and KCa1.1 channel expressions were upregulated in corpus cavernosum from db/db mice. Immunoblotting showed down-regulation of KCa2.3 and KCa1.1β subunits in the corpus cavernosum from db/db mice. Acetylcholine relaxations were impaired while relaxations induced by the nitric oxide, donor SNP were unaltered in corpus cavernosum from db/db compared to C57BL/6 and db/+ mice. Apamin, a blocker of KCa2 channels, inhibited acetylcholine relaxation in corpus cavernosum from all experimental groups. In the presence of apamin, acetylcholine relaxation was markedly decreased in corpus cavernosum from db/db versus C57BL/6 and db/+ mice. Iberiotoxin, a blocker of KCa1.1 channels inhibited acetylcholine relaxation in corpus cavernosum from C57BL/6 and db/+ mice, while there was no effect in tissue from db/db mice.
Conclusions: Our results suggest that the contribution of iberitoxin-sensitive KCa1.1 channels to relaxation in corpus cavernosum is markedly reduced, while the larger contribution of apamin-sensitive KCa2 channels to endothelium-dependent relaxation in corpus cavernosum appears to be compensatory. The impaired KCa1.1 channel function may contribute to the impaired erectile function in diabetic db/db mice.

8 Molecular and physiological mechanisms behind anion-exchanger AE3-mediated regulation of the QT interval

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Short QT syndrome (SQTS) is a rare, genetically determined, severe cardiac disease with a high risk of syncope, ventricular fibrillation, and sudden cardiac death. In 2017, we discovered a variant in the SLC4A3 gene, which encodes the cardiac chloride-bicarbonate exchanger AE3, is associated with SQTS in patients. In zebrafish hearts, this variant leads to defected targeting of AE3 to the cell membrane, decreased chloride-bicarbonate exchange and increased intracellular pH, along with shortened QT interval. Previously, only six other genes, all encoding cation channels, have been known to be implicated in SQTS. Thus, the discovery of a SQTS-associated AE3 variant identifies a completely new disease mechanism for the development of SQTS.

In this study, we aim to create an optimized zebrafish model to facilitate in-depth functional characterizations of novel AE3 variants and investigate the molecular mechanism by which altered SLC4A3 function affects QT interval duration. Human AE3 exists as both full-length and truncated cardiac-specific variants. Through gene

structure analysis and PCR-analysis, we will investigate whether both variants exist in zebrafish. Using this knowledge, we will design and generate novel knockout zebrafish lines and knockin zebrafish carrying selected AE3 variants. These zebrafish models will be used to explore the molecular and physiological mechanisms involved in AE3-mediated regulation of the QT interval, which will involve extensive molecular and physiological measurements on zebrafish hearts both in vivo and ex vivo, and will include recordings of ECG as well as intracellular pH, action potential and calcium changes in cardiomyocytes.

If successful, this project will provide valuable insights into the mechanisms behind AE3 involvement in the development of inherited heart disease and bring knowledge on the molecular and physiological role of AE3 in the regulation of QT interval and thereby potentially facilitate the development of brand-new treatment options for a large group of heart patients suffering from SQTS.

9 Triglyceride levels in early type 2 diabetes and risk of cardiovascular disease: A Danish cohort study

Frederik Pagh Kristensen, MD[1], Diana Hedevang Christensen, MD, PhD[1], Kevin Kris Warnakula Olesen, MD, PhD[2], Michael Maeng, MD, PhD[2], Henrik Toft Sørensen, MD, PhD, DMSc[1], Reimar Wernich Thomsen, MD, PhD[1]

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Background: The REDUCE-IT trial showed that triglyceride (TG)-lowering treatment with icosapent ethyl reduces risk of cardiovascular disease (CVD). TG-rich lipoprotein levels are often increased (TG >1.7 mmol/L) in patients with prevalent type 2 diabetes (T2D). Data are scarce regarding TG levels in newly diagnosed T2D patients, their association with a subsequent CVD diagnosis, and the prevention potential of icosapent ethyl in real-world settings.

Methods: Using population-based register data, we studied 63,091 individuals residing in Northern and Central Denmark diagnosed with incident T2D during 2002–2016. Patients were classified according to their achieved TG level 6 months after their first diabetes record: normal (<1.7 mmol/L, reference), moderate (1.7-2.3 mmol/L), and high (>2.3 mmol/L). Patients were followed until a CVD event (myocardial infarction, ischemic stroke, coronary revascularization, or cardiac death), using Cox proportional hazards regression to compute adjusted hazard ratios (aHRs), while controlling for CVD risk factors.

Results: In our cohort, 24% of patients had moderate and 22% had high TG levels 6 months after T2D diagnosis. The incidence rates of CVD per 1000 person-years (median follow up time 5.7 years) were higher in the high TG group than in the normal TG group across all outcomes: 6.3 vs 5.0 for myocardial infarction, 7.0 vs 6.3 for ischemic stroke, 9.2 vs 6.7 for coronary revascularization, and 10.1 vs 9.3 for cardiac death. The aHRs in patients with high TG were 1.23 (95% CI 1.09-1.37) for myocardial infarction, 1.20 (1.08-1.33) for ischemic stroke, 1.24 (1.12-1.36) for coronary revascularization, and 1.23 (1.13-1.34) for cardiac death. The number needed to treat with icosapent ethyl to prevent one CVD event was 32.

Conclusion: Hypertriglyceridemia is common in newly diagnosed T2D patients. Increased TG is associated with increased CVD risk. Early TG reduction with icosapent ethyl may have routine clinical care CVD preventive effects.

POSTER GROUP II

10 Effects of Repetitive Pulmonary Emboli and Inhibition of Endogenous Fibrinolysis in a Porcine Model

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening complication of acute pulmonary embolism (PE). It is characterized by unresolved thrombi and persistent increased pulmonary arterial pressure. Treatment options are few and the exact underlying pathophysiological mechanisms remain unclear. However, it is theorized that recurrent emboli and impaired endogenous fibrinolysis play a role in the development of CTEPH after acute PE. We hypothesize that repetitive PE's and concomitant administration of tranexamic acid in a porcine model will induce chronic thrombi and pulmonary hypertension resembling CTEPH.
Methods: Six Danish slaughter pigs will be included. Baseline evaluation is performed before consecutive autologous PEs are injected until mean pulmonary arterial pressure is doubled. This is repeated after three, six and ten days. After one month a long-term evaluation is performed and tissue samples of heart and lungs are acquired for analysis. Tranexamic acid is administered throughout the experiment. Effects of the interventions will be evaluated by computed tomography pulmonary angiography, right heart catheterization, bi-ventricular pressure-volume loops, hemodynamic values, and blood samples.
Results: Preliminary data from pilot study will be presented if available.
Perspectives: This study will evaluate the effects of repetitive PE's combined with inhibition of endogenous fibrinolysis in a porcine model. Potentially, this can lead to an animal model of CTEPH, and hereby create opportunities of further investigation of the pathogenesis and possible treatment options.

11 Outcomes of isolated tricuspid valve surgery in contemporary practice

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Background
Isolated tricuspid valve surgery is rarely performed and has been associated with high mortality and morbidity. The aim of this study was to describe clinical outcome and functional capacity following isolated tricuspid valve surgery in contemporary practice.
Methods
We conducted a retrospective cohort study including all patients who underwent isolated tricuspid valve surgery at our institution from 2013 through 2019. Our cohort was identified using the Western Denmark Heart Registry. Postoperative outcomes were evaluated using patients' medical records. Clinical and echocardiographic status were reported for patients who survived beyond one year.
Results
We included 43 patients (mean age 65.2 ± 13.8, 39.5% female). Twelve (27.9%) had prior cardiac surgery. Up to 90-day follow-up, no patient died, and major morbidity was limited to four patients (9.3%) requiring pacemaker implantation and one patient requiring two reoperations. Within one year, four patients (9.3%)

died. Nine Patients (20.1%) required a single readmission for cardiac reasons during median follow-up of 38.4 months (IQR 30.9 months).
All patients that survived beyond one year (n=39) completed clinical follow-up. At follow-up, 38 of 39 (97.4%) patients were NYHA I or II compared to 12 of 39 (30,8%) preoperatively (p=0.001). Presence of edema and intensity of diuretic treatment were significantly reduced (p=0.005, and p=0.008 respectively). Echocardiographic follow-up showed significant improvement of tricuspid valve dysfunction in all patients.
Conclusion
Our results suggest that isolated tricuspid valve surgery can be performed safely and greatly improve patients' functional status. Our findings support the importance of optimal surgical timing and patient selection.

12 Cyclic Mechanical Stretch Regulates Vascular Smooth Muscle Cell Phenotype

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The phenotypic modulation of vascular smooth muscle cells (SMCs) plays a significant role in atherosclerosis and other cardiovascular diseases. Differentiated SMCs in the media wall of blood vessels shift from a contractile phenotype towards other phenotypes with reduced expression of contractility-associated genes. Other phenotypic changes include increased migration, proliferation, and the production of alternative extracellular matrix (ECM) proteins. A similar shift in the SMC phenotype is observed in classical culture systems, where physiological signals such as the mechanical stretching of the vessels elicited by the pulsating blood flow are absent. We have established an in vitro setup where SMCs can be cultured in conditions that more accurately simulate healthy or diseased arteries. First, human SMCs were cultured on flexible silicon-membranes coated with ECM substrates associated with a healthier (laminin and collagen-IV) or a more pathological (collagen-I and fibronectin) SMC phenotype. Then, we exposed the SMCs to different types of mechanical stretch. We compared the gene expression, proliferation, and migration of SMCs subjected to physiological stretch, supraphysiological stretch, and static conditions. Our results showed that cyclic stretch regulates the SMC phenotype through changes in their inflammatory signaling pathways. Static conditions or supraphysiological stretch induces an upregulation of several inflammatory molecules, including chemokines and adhesion molecules, compared to physiological stretch. These changes were accompanied by changes in proliferation and migration, but they seem to be independent of the ECM substrate. Therefore, this in vitro setup can be used as a platform to replace the extensive experiments in mice and will allow us to investigate and understand how mechanical cues control the phenotypic modulation of SMCs.

13 Short QTc in Mouse Model for Migraine: A Link between Migraine and Cardiovascular Morbidity

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Background:
Migraine with aura, is associated with cardiovascular morbidity. However, the molecular mechanism underlying this comorbidity remains to be studied to provide new improved preventive and therapeutic strategies for migraineurs. We have, therefore, acquired a mouse model for familial hemiplegic migraine type 2 (FHM2) to assess the cardiac function in hereditary migraine.
FHM2 mice are heterozygous for the FHM2-associated mutation (G301R) in the gene encoding the α2-isoform of Na+,K+-ATPase leading to decreased expression of α2-isoform, but upregulation of α1-isoform of Na+,K+-ATPase in hearts.

We hypothesized, that abnormal Na+/K+ transmembrane transport will affect excitability of cardiomyocytes and thus, electric properties of the heart.

Method:

Six-month-old FHM2 mice were compared to matched wildtype (WT) mice.

Telemetric electrocardiogram (ECG) from mice was acquired in active and resting period; 20:00-22:00 and 12:00-14:00, respectively.

Furthermore, ECG (10 minutes) was recorded from isoflurane-anesthetized mice at rest and during electric stimulation of the right atrium with a stepwise increment of stimulation frequency (10-12 Hz).

Subsequently, Mitchell' formula was applied to correct the QT interval.

Results:

Telemetric ECG data indicated significantly shorter QTc from FHM2 mice in both active- and resting periods when compared to WT mice. QTc was also significantly shorter in isoflurane anesthetized FHM2 mice. This suggests a shortened period for ventricular depolarization and repolarization of FHM2 hearts in comparison with the control.

Following electric cardiac pacing, the time from electric stimulation to QRS-complex was significantly shortened in FHM2 mice suggesting cardiac conduction abnormalities.

Conclusion:

In conclusion, FHM2 mice have shortened QTc, at least in part due to faster conduction of action potentials. Further investigation is required to elucidate the underlying molecular mechanism for this conduction abnormality.

14 High oxygen is beneficial on cardiac contractility after normothermic regional perfusion

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Background

Normothermic regional perfusion is a new method for in-situ reperfusion of potential donor organs after circulatory death with a heart-lunge machine. By reperfusion of the donor heart with oxygenated blood to restore it is possible to restore contractilty. We investigated the effects of high (HOX) versus low oxygenation (LOX) during NRP on donor heart function in a porcine model.

Methods

The Nineteen pigs (80 kgs) were anesthezied, connected to a heart-lung machine, and subjected to a 15-minute anoxic cardiac arrest followed by cardiac reanimation on NRP with subsequent assessment for 180 minutes post-NRP. The animals were randomized before NRP to a FiO2 of either 1.0 or 0.21 increasing to 0.40. Haemodynamic data was obtained by invasive blood pressure measurements and bi-ventricular pressure volume catheters. Biochemical analysis included blood gas, inflammation and oxidative stress analysis.

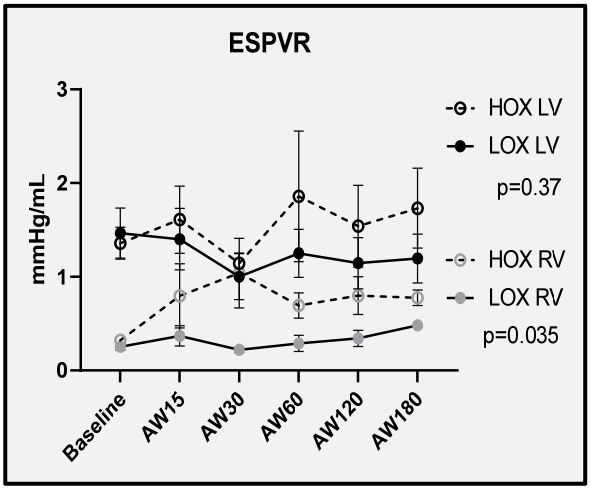
Results

Eight of nine animals in the HOX and seven of ten in the LOX group were successfully weaned from NRP ($p = 0.30$). Cardiac output, mean arterial pressure, central venous pressure, and pulmonary capillary wedge pressure were all comparable to baseline in the animals weaned from NRP. Right ventricular end-systole

elastance (Ees) was significantly improved in the HOX compared to the LOX group (p = 0.013) whereas left ventricular Ees was preserved to baseline and similar between the groups. CKMB as a marker of myocardial damage increased more in the LOX group than HOX group, while pro-inflammatory markers tended to have a greater increase in the HOX than the LOX group. No difference was found in oxidative stress between groups.

Conclusion

All hearts weaned from NRP showed acceptable haemodynamic function for transplantation. Hearts exposed to low oxygenation showed more myocardial damage and tended to have poorer contractile performance than hearts reperfused with high oxygen.



15 Mutations in the Na,K-ATPase link cardiovascular disease and familial migraine

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Background: Epidemiological studies have identified migraine with aura as a risk factor for developing cardiovascular disease. The underlying mechanism is unknown. The Na,K-ATPase α_2 isoform, encoded by the *Atp1a2* gene, is important for cardiac function. We hypothesized that mutation in the *Atp1a2* gene, which is associated with familial hemiplegic migraine type 2 (FHM2), may partially explain the association between migraine and cardiovascular disease, and we aimed to uncover the underlying mechanism.

Methods: Cardiac function in heterozygous mice carrying the FHM2-associated mutation ($\alpha_2^{+/G301R}$ mice) were compared with matched controls *in vivo* by cardiac MRI with hyperpolarization. Blood pressure was assessed telemetrically. Mitochondrial function was measured by respiometry and oxidative stress was assessed by malonedialdehyde measurements. The underlying mechanism was uncovered by analysis of proteomics data and Western blot analysis.

Results: Reduced expression of the Na,K-ATPase α_2 isoform and increased expression of the α_1 isoform was observed in hearts from $\alpha_2^{+/G301R}$ mice. Left ventricular dilation and reduced ejection fraction was shown in hearts from $\alpha_2^{+/G301R}$ mice (Fig. 1) and this was associated with reduced nocturnal blood pressure. Amplified signalling through the Na,K-ATPase-dependent Src/Ras/Erk1/2 pathway was observed in hearts from $\alpha_2^{+/G301R}$ mice and this was associated with mitochondrial uncoupling, increased oxidative stress, and increased level of lactate.

Conclusion: Our findings suggest that *Atp1a2* is a susceptibility gene for heart disease and thereby provide a link between migraine-associated mutation and cardiovascular disease. We suggest that FHM2-associated cardiac dysfunction is mediated via Na,K-ATPase-dependent ROS signalling through the Src/Ras/Erk1/2 pathway.

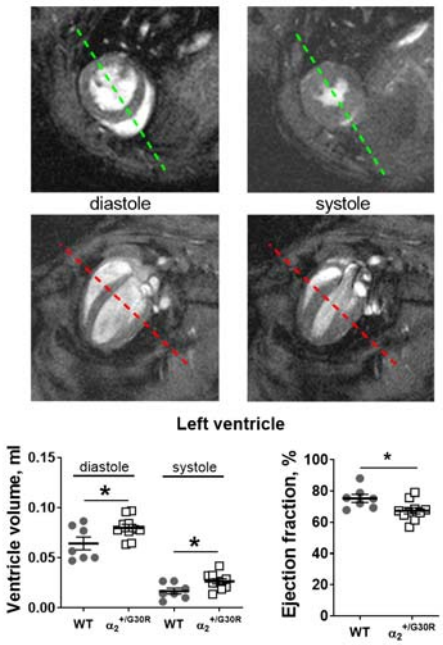

Figure 1. Ventricular dilation and decreased ejection fraction in hearts from $\alpha_2^{+/G301R}$ mice. Cardiac structure and function were assessed by cardiac resonance imaging.

16 Associations between self-reported or measured anthropometric variables and cardiometabolic biomarkers in a Danish cohort

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Background

It is easy and cost-effective to ask study participants to self-report height and weight and self-reported anthropometry is therefore widely used in epidemiological studies. However, it is questioned to what degree self-reported adiposity indices are a solid proxy of measured indices in terms of estimates of health outcomes. The current study aimed to quantify the agreement between self-reported and measured anthropometrics, including height, weight, body mass index (BMI), weight circumference (WC), and weight-to-height ratio (WHtR) in a contemporary cohort of adults, and to assess whether anthropometric indices misreporting yielded inaccurate estimates of associations with cardiometabolic biomarkers.

Methods

Self-reported and measured anthropometric variables were obtained from the Diet, Cancer, and Health-Next Generation Cohort (n=39,514). Pearson correlations and Lin's concordance correlations evaluated the correlation between self-report and measured anthropometrics. Misreporting in relation to age, sex and smoking status was investigated. Multivariable regression models and ROC analyses were used to assess the associations of cardiometabolic biomarkers with self-reported and measured general obesity and abdominal obesity.

Results
Self-reported height was overreported by 1.07 cm, weight was underreported by 0.32 kg on average, which led to self-reported BMI 0.42 kg/m2 lower than measured. Self-reported and measured height, weight, BMI, WC and WHtR were highly correlated (r=0.98, 0.99, 0.98, 0.88, 0.86, respectively). Associations between self-reported indices and cardiometabolic biomarkers were comparable to associations assessed with measured anthropometrics.
Conclusions
The self-reported anthropometric indices were reliable when estimating associations with metabolic biomarkers.
Key messages
This study found overall agreement between self-reported and measured anthropometric variables.

17 Pulmonary vasodilatation in the prolonged phase of acute pulmonary embolism in pigs

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Background: Acute pulmonary embolism (PE) causes increased pulmonary vascular resistance (PVR) that leads to an increased strain on the right ventricle. Experimental studies have shown PVR reduction within 12 hours of onset of PE, when administering pulmonary vasodilatory drugs. However, the effects beyond 12 hours remains unknown. This study aims to investigate if the effects of the pulmonary vasodilatory drugs, sildenafil and oxygen, are preserved in the days following experimental intermediate-high risk PE.
Methods: Six Danish slaughter pigs will be included. The study is designed as repeated measurements so each animal will serve as their own controls.
Day 1: Baseline computed tomography (CT) scans and hemodynamic evaluation will be recorded. Animals will then receive consecutive autologous PE until mean pulmonary artery pressure is doubled. At stable conditions, hemodynamics are recorded before sildenafil and oxygen are administered. Effects are measured 30 min later.
Day 2 and 3: Animals are evaluated before and after sildenafil and oxygen treatment. Euthanisation after day 3.
Results: The project will commence 1st of September 2021. Preliminary results will be presented if available.
Conclusion: This study will provide novel insight into the contribution of pulmonary vasoconstriction in the days following acute PE and the potential effects of the pulmonary vasodilators sildenafil and oxygen. This may provide knowledge and contribute to the designs of future clinical trials of acute PE.

18 Serial intravital imaging reveals supportive role of renal interstitial cells in recovery from acute kidney injury

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Increasing evidence suggests a link between acute kidney injury and progression to chronic kidney disease (AKI-CKD-transition). While wound healing from AKI leads to myofibroblast-activation from renal interstitial cells, myofibroblast-driven self-perpetuating tubulointerstitial fibrosis is a suggested key mechanisms for AKI-CKD-transition. To unravel the potentially deteriorating character of myofibroblasts, we tracked renal interstitial PDGFRβ-cell dynamics in ischemia-reperfusion injury (IRI)-induced AKI in the same kidney over time using serial intravital 2-photon microscopy.

We performed unilateral 21 minutes IRI followed by abdominal imaging window implantation for serial imaging of the same kidney regions for up to 3 weeks (N=8). To test for myofibroblast differentiation, we performed ex vivo staining for αSMA on the same tissue regions as previously imaged in vivo. PDGFRβ-CreERT2-Salsa6F reporter mice identified PDGFRβ- cells by tdTomato expression.

IRI-induced proximal tubule (PT) injury was associated with abundant necrotic tubular cell death, as detected by in vivo Propidium Iodide staining. From D1, PDGFRβ-cells accumulated around injured PTs peaking with an increase of 352% in PDGFRβ-cell number at D7. PDGFRβ-cell recruitment was most prominent in severely damaged PTs, which displayed epithelial vacuolization and nuclear karyolysis from D4. Among the karyolitic tubule population, 46% of the affected nephrons failed to recover, resulting in persistent, but locally restricted PDGFRβ-cell recruitment, which stained positive for αSMA. PDGFRβ-cell accumulation around recovering tubules drastically decreased to 223% by day 14 and remaining PDGFRβ-cells stained negative for α-SMA on D20.

This is the first study to track dynamic PDGFRβ-cell dynamics in IRI-induced injury and regeneration in the same renal tissue over time. Our data indicate locally restricted PDGFRβ-cell accumulation and differentiation to myofibroblasts in injured tissue regions. We did not observe myofibroblast-encroaching and deterioration of healthy nephrons. On the contrary, myofibroblast accumulation appeared reversible in successfully regenerating nephrons, suggesting a key role of these cells in renal wound healing.