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Abstracts

Age-related prevalence of open ductus arteriosus in full-term newborns

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Background: The ductus arteriosus (DA) is part of the fetal circulation. Normally the DA close shortly after birth, but for some neonates the closure is delayed. Little is known about the prevalence and timing of spontaneous DA closure in term born children.
Aim: The aim of this study was to evaluate the daily prevalence of open DA in term born neonates within the first 28 days after birth.
Method: Echocardiograms were collected in the Copenhagen Baby Heart Study with 25.000 examination in the database. The present study included term born neonates with an echocardiogram performed in the neonatal period, defined as day 0-28 after birth. Neonates with findings of other congenital heart defects than atrial septal defects were excluded. All echocardiograms were analyzed to diagnose an open DA.
Results: A total of 21,649 neonates were included in this study. The median age at examination was 11 days (IQR=4-18). In 485 neonates, an open DA (2.3%) were identified. In those examined at day zero (n=130), day two (n=1090), and seven (n=1080), an open DA were found in 36%, 8% and 0.6%, respectively. After day seven the prevalence of an open DA was stable around 0.6%.
Conclusion: This large-scale echocardiography study in healthy neonates showed a high prevalence of open DA on the first day of life, with a rapid decline to a prevalence of less than 1% at day seven remaining stable around 0.6% hereafter.

Novel candidate variant in the gene coding for receptor tyrosine-protein kinase erbB-2 is associated with left ventricular outflow tract obstruction defects in human

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Congenital heart defects (CHD) are the most common congenital malformations. Both genetic and environmental factors, such as blood flow during development, are known to contribute to disease development. The genetic predisposition is likely in most cases oligogenic, and currently, robust evidence for few predisposing genes for monogenic forms exist. Here we show evidence for a rare variant in the ERBB2 gene as potentially causal for CHD. ERBB2 is known to be essential for cardiac development in animal models, but so far human data are lacking. We studied a Finnish cohort of left ventricular outflow tract obstruction (LVOTO) patients and their families and identified a variant in ERBB2 (R569C) that segregated with disease in three unrelated families with multiple affected members. We performed functional studies, and show that the mutated receptor is functional, as NRG1 stimulation phosphorylates the receptor. However, a protein-protein interaction assay showed that the mutated receptor is mainly located in ER/mitochondria, whereas the wild type ERBB2 is located at the plasma membrane. This was confirmed by a flow cytometry analysis showing decreased receptor presence in the plasma membrane of patient derived cells. Zebrafish embryos expressing the R599C mutant allele demonstrated altered myocardium structure and reduced contractility compared to the wild-type allele or a mock control. Finally, we differentiated induced pluripotent stem cells (iPSCs) from a patient with the variant into cardiomyocytes. Single-cell RNA sequencing demonstrated reduced expression of genes related to heart development, muscle contraction and response to oxidative stress in patient cells compared to healthy controls. As endothelial cells (EC) are important during cardiac development, we also differentiated patient and healthy control iPSCs into ECs. Transcriptomic analysis showed significant differences in the expression of angiogenesis and vasculature development related genes in the patient cells. In summary, ERBB2 R599C variant segregates with CHD patients in three unrelated families with LVOTO defects. The variant influences location of the protein and causes compromised heart function in zebrafish embryos. We propose ERBB2 as a new candidate gene for CHD.

A web-based, innovative health promotion program for families with a history of pre-eclamptic pregnancy 8-12 years ago

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Pre-eclampsia is a pregnancy-related hypertensive disease affecting 2–3% of pregnancies in Finland. It increases the risk of premature hypertension and other cardiovascular diseases in children and mothers. Digital health approaches offer a cost-effective and easy-to-scale tool to support these families, but we still need more high-quality research to evaluate the effectiveness and feasibility of such interventions. We aim to promote child and maternal cardiovascular health with a web-based, long-term (12 months), family-centered lifestyle program/intervention by undertaking a randomized, controlled trial (FINNCARE). It is targeted at families where the mother had pre-eclampsia 8–12 years ago. We created an interactive web-based portal for the study in 2019 (HowSpace platform by Humap Software Ltd.). The intervention covers five target behaviors relevant to cardiovascular health: improving the quality of fat in the diet, increasing the consumption of foods rich in fiber, decreasing the use of salt, increasing physical activity, and reducing smoking. Every 1-2 weeks, families in the intervention group will have access to a new lifestyle-related theme and they will receive individual counseling and feedback from a nutritionist. During 2019-2023, 110 pre-eclamptic families participated in the lifestyle intervention, while 82 pre-eclamptic families belonged to the control group. We also included 92 families without pre-eclampsia. The process evaluation (reach, compliance, acceptability) will follow Medical Research Council guidance. The Howspace platform utilizes artificial intelligence and provides information on how the families use the web-based platform, e.g. the number of log-ins, time spent in the portal, the proportion of sessions completed, and the most interesting themes. The effectiveness assessment includes cardiovascular health, diet, physical activity, and smoking status. This trial provides, to our knowledge, the first evidence of whether a web-based, long-term, and family-centered lifestyle intervention could improve cardiovascular health in pre-eclamptic families. It offers a novel way to tackle the cardiovascular burden faced by these children and women. Possibilities to implement and test the web-based portal created in the current study, e.g in maternity and child health clinics, will be sought.

Offspring's Congenital Heart Defect As A Risk For Cardiovascular Morbidity In Women

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Background: Congenital heart defects (CHD) and adult cardiovascular disease (CVD) share common risk factors, such as obesity, diabetes mellitus, and pre-eclampsia. This raises the question: Could similar disease mechanisms underlie cardiac development and adulthood cardiovascular morbidity? We assessed the long-term risk of specific cardiovascular morbidity and mortality in women who had a child with CHD.
Methods: We used nationwide registers to form a cohort of all women who gave birth in Finland between 1986 and 2016 (N=702,439). Outcomes were CVD diagnoses or CVD related death. Exposure was the offspring's CHD. We followed health care records until death or end of 2016. Univariate and multivariate Cox regression models were used to analyze the CVD risk and the risk for CVD related death. Well-known CVD risk factors, such as diabetes mellitus, dyslipidemia, smoking, obesity, age, parity, pre-eclampsia, and preterm labor were used as covariates.
Results: A total of 27,299 (3.89%) women had at least one CVD diagnosis, with the first diagnosis at median age of 42 years (IQR 35-50). CVD diagnosis was present in 1002 (4,2%) women with a CHD child as compared to 26,297 (3,88%) women without a CHD child. Offspring's CHD was associated with increased risk for any CVD in the mother (adjusted HR (aHR) 1.19; 95% CI 1.12-1.27; $p<0.0001$). For specific CVD diagnoses, a CHD child increased the risk for hypertensive disorders (aHR 1.14; 95% CI 1.07-1.23) and atrial fibrillation (aHR 1.23; 95% CI 1.04-1.47). In addition, child's CHD was associated with maternal CHD (aHR 2.52; 95% CI 1.95-3.27). Offspring's CHD did not increase the risk for CVD related death.
Conclusion: In this nationwide cohort of Finnish women, having offspring with CHD was associated with an increased risk for CVD in general and specifically for hypertensive disorders and atrial fibrillation. These associations may indicate shared genetic risk, which may be relevant in further unraveling the pathophysiological events leading to CHD.

Outcome of transcatheter atrial septal defect closure in a nationwide cohort

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Background: Transcatheter (TC) atrial septal defect (ASD) closure has been the mainstay of therapy for secundum-type ASDs for over 20 years.

Aims: This nationwide cohort evaluated the long-term outcome of transcatheter closed ASDs.

Methods: The study enrolled every transcatheter ASD closure performed in Finland from 1999 to 2019. Five age, sex, and municipality-matched controls per ASD patient were gathered from the general population. The median follow-up period was 5.9 years (range 0-20.8). We used the hospital discharge register to gather all hospital visits and diagnoses. Closure complications and echocardiographic changes were collected from the electronic health records.

Results: Transcatheter ASD closure was performed in 1000 patients (68.5% females) during the study period. The median (range) age at the time of the procedure was 37.9 (1.8-87.5) years. ASD patients had an increased risk for new-onset atrial fibrillation (RR 2.45, 95% CI: 1.84-3.25), migraine (RR 3.61, 95% CI: 2.54-5.14), ischemic heart disease (RR 1.73, 95% CI: 1.23-2.45), ventricular fibrillation/tachycardia (RR 3.54 (95% CI: 1.48-8.43) and AV conduction disorder (RR 3.60, 95% CI: 1.94-6.70) compared to the control cohort. Stroke risk was not increased (RR 1.36, 95% CI: 0.91-2.03). Adverse events occurred in 6.3% (n = 63) of the patients, including four erosions and ten device embolizations.

Conclusion: After TC closure of ASD, patients had a higher risk of new-onset atrial fibrillation and migraine than controls without an ASD. As novel findings, we found an increased risk for ischemic heart disease, AV conduction disorders, and ventricular fibrillation/tachycardia.

The impact of basal region of interest on Global Longitudinal Strain

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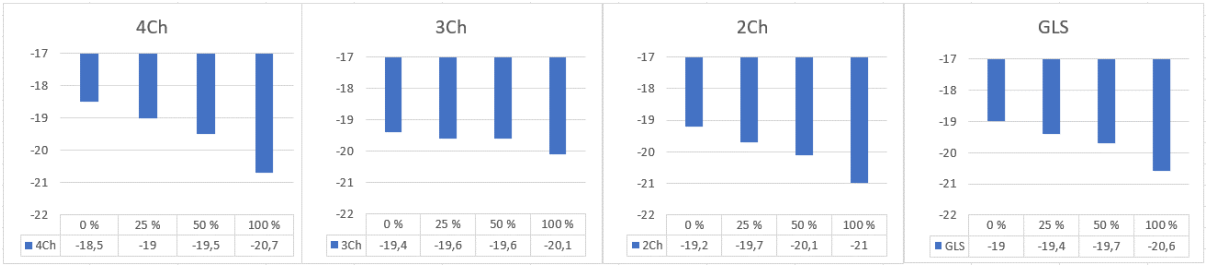
Aims: Studies on myocardial strain in neonates have shown the effect of acquisition parameters such as frame rate and frequency as well as image processing parameters such as smoothing, and drift compensation. How the placement of the basal levels of the region of interest affects strain measurements has not been presented. In this study we examine how global left ventricular strain is influenced by different definitions of the basal region of interest (ROI).

Methods and results: We examined 41 healthy neonates within the first days of life with transthoracic echocardiography. Strain was measured according to the recommendations for speckle-tracking echocardiography. Temporal and spatial smoothing as well as drift compensation were kept at default settings. ROI-width was set to cover the left ventricular myocardium. ROI was defined in two-, three-, and four-chamber views at four different distances from the mitral annulus, according to 0%, 25%, 50% and 100% of the length of the mitral leaflets. When defining the basal level of ROI more apical from the mitral valve annulus, global longitudinal strain increased from -19.0% to -20.6%. The increase in strain towards the apex was found in all three analysed planes, in segmental as well as global measurements.



Conclusion: In this study, we show that different offsets of basal ROI lead to significant differences in strain measurements. Therefore, consistent definition of the basal ROI across analyses is important to improve strain reproducibility.

Retrograde flow to the aortic root affects coronary perfusion and impedes cardiopulmonary performance in young Fontan patients.

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Background and Aim: Single ventricle function in Fontan circulation (FC) depends on systemic venous pressure, pulmonary vascular resistance and ventricular function. Since myocardial function is dependent on coronary perfusion we studied whether in FC retrograde flow from the Damus-Kaye-Stensel anastomosis to aortic root (AoR) affects cardiopulmonary performance (CPP).

Methods: 26 stable Fontan patients (14.4 ± 2.4 years) with right (RV, n=17) and left systemic ventricle morphology (LV, n=9) were studied. All RV patients had HLHS and were subdivided according to postnatal flow to the hypoplastic AoR being antegrade (RV-aAoR) or retrograde due to valve atresia (RV-rAoR). Anaerobic threshold (AT), maximal oxygen uptake maxVO2, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) were measured. These data were correlated with the postnatal size of aorta and current branch pulmonary artery size index (McGoon index). Mann-Whitney U-test and one-way ANOVA tested statistical difference

Results:

	LV-SVM (n9)	RV-aAoR (n8)	RV-rAoR (n9)	One-way ANOVA
SpO2%	94 ± 3	94 ± 4	93 ± 6	p=0.7412
AT (ml/kg/min)	21.5 ± 4.3	21.1 ± 4.3	18.6 ± 5.2	p=0.2795
VO2max (ml/kg/min)	32.5 ± 5.8	30.0 ± 4.2	25.4 ± 5.9	**p=0.0447**
McGoon	2.3 ± 0.4	2.0 ± 0.3	1.7 ± 0.4	**p=0.0110**
FVC (Z)	-1.20 ± 1.3	- 2.7 ± 1.9	-2.9 ± 0.9	p=0.0440
FEV1 (Z)	-1.0 ± 1.2	-3.2 ± 2.7	-3.3 ± 1.1	**p=0.0193**
FEV1/FVC, %	92	83	85	p=0.8432
Ao-asc (mm)	normal aorta & flow	5.9 ± 1.8	2.8 ± 1.1	**p=0.0221**
RPA (Z)	0.8 ± 1.0	0.6 ± 1.2	-0.09 ± 1.4	p=0.6769
LPA (Z)	2.0 ± 6.5	0.4 ± 0.7	-0.5 ± 1.7	p=0.4761

Patients with LV-morphology had superior VO2max compared to RV patients (p=0.044). In pulmonary function tests, FEV1 was significantly better in LV patients compared to both RV groups (p=0.0193). Forced vital capacity (FVC) was lowest in the HLHS-retro group (p=0.0228 against LV). The postnatal diameter of Ao-asc demonstrated a positive correlation with Vo2max (p=0.0362, $R^2$0.246).

Conclusions: Young Fontan patients with LV had better CPP over patients with HLHS. In the HLHS group, the patients with valvar atresia and retrograde aortic flow had the lowest maxVO2 and most restrictive lungs.

Pre-eclamptic children present with elevated blood pressure, arterial stiffness, and related peripheral artery media layer remodeling 8-12 years after birth (FINNCARE study)

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Background and aims: To study if pre-eclampsia (PE) children develop elevated blood pressure (BP) and arterial stiffness during preadolescent age, and if this is reflected in arterial wall, and influenced by body composition, anthropometrics, gestational and perinatal factors.
Methods: In 182 PE (46 early-onset) and 85 non-PE children office and 24-hour ambulatory BPs, anthropometrics and body composition, pulse wave velocity (PWV) were assessed, and arteries using ultra-high frequency ultrasound.
Results: PE children's office, central and 24-hour systolic BP (SBP) and pulse pressures (PP) were significantly elevated compared with non-PE, and this was pronounced in early-onset PE. Maternal gestational SBP and prematurity predicted PE's SBP, while PP remained elevated in PE after these adjustments. PP and local artery stiffness was related with adiposity. Central and peripheral PWVs were elevated in late-onset PE, and related with age, anthropometrics, and office SBP at follow-up, but not with maternal or perinatal factors. Peripheral artery media thickness (brachial, radial, and femoral) was independently predicted by 24-hour SBP and anthropometrics, particularly lean body mass. Carotid artery media thickness and lumen diameter were related with head circumference, but not with BP or adiposity. There were, however, no differences in anthropometrics, body composition, blood lipids and glucose, arterial morphology (layer thickness and lumen diameter) or local carotid artery stiffness between PE and non-PE groups. There were no independent associations between arterial wall layer thickness, stiffness and gestational or perinatal factors.
Conclusions: In-utero exposure to PE is related with elevated SBP/PP and arterial stiffness during preadolescent age. SBP is related with maternal gestational BP and prematurity and pronounced in early-onset PE. Arterial stiffness is related with adiposity and SBP at follow-up. Arterial wall layer thickness is not different in PE compared with non-PE, but SBP-related remodeling in peripheral media layer thickness suggests early progression of vascular disease. Strong relations between maternal and child BPs might be explained by shared genetic, in-utero, or postnatal lifestyle pathways.

Transcriptomic profiling of cardiac allografts reveals the key mechanisms of ischemia-reperfusion injury

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Background – Restoration of blood circulation into an ischemic cardiac allograft may paradoxically cause ischemia-reperfusion injury (IRI), which predisposes the transplant to various complications. While the pathogenesis of IRI is not well understood, new massive parallel sequencing methods enable investigation of the allograft transcriptome-associated signaling networks. Detailed knowledge on the underlying pathological mechanisms could yield novel treatment options.

Methods – We analyzed Next-Generation Sequencing data from myocardial transcriptome of 70 paired human heart transplant left ventricle biopsies, taken immediately before and one hour after reperfusion. The transcriptomic landscape of the cardiac allograft was composed based on the total gene expression at each time point. Gene set enrichment analysis (GSEA) was performed to investigate the pathway profile of reperfused cardiac allografts, and stringent statistical comparison of the time points was conducted to identify the key regulatory genes.

Results – The transcriptomic landscape indicated activation of a calcium signaling pathway before reperfusion, whereas signaling pathways related to inflammation and extracellular matrix (ECM) degradation were more dominant after reperfusion. GSEA confirmed that reperfusion induced activation of signaling pathways related to metabolic stress, structural integrity, and immune activation. A total of 13 genes (e.g. FOS, JUN, IL1B, and ICAM1) were identified as key regulators of pathophysiological processes associated with reperfusion. Validation with single-cell spatial analysis confirmed high expression of these genes in cardiac fibroblasts.

Conclusions – Our results demonstrate the transcriptomic changes associated with reperfusion of cardiac allografts including the related signaling pathways and key regulatory genes. These findings suggest that cardiac fibroblasts play a crucial role in transplantation associated IRI, and modulation of their cellular phenotype could be a therapeutic target for cardiac allograft patients.

Towards identifying risk for sudden death in hypertrophic cardiomyopathy associated with RASopathy

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Background: All risk assessment algorithms, and adult and Pediatric Cardiology Guidelines, specifically exclude patients with hypertrophic cardiomyopathy (HCM) associated with RASopathies such as Noonan syndrome from the application of risk assessment protocols for sudden cardiac death (SCD). As a result, a recent survey of European Pediatric Cardiologists found that there were hardly any such patients that received ICDs as a primary prophylaxis, and virtually all ICD-recipients had received their ICD after a resuscitated cardiac arrest. Yet in those patients with RAsopathy-HCM that survive infancy the risk of later sudden cardiac death is approximately the same as in non-syndrome HCM. This study aims to identify what clinical parameters might be most useful for risk assessment in pediatric RASopathy-HCM.

Methods: 51 patients with HCM associated with RASopathy, with at least 5 years of follow-up in survivors were studied with regard to clinical parameters associated with SCD.

Results: Overall median age at diagnosis was 0.3 [IQR 0,2-5.5], and duration of follow-up median 15y. SCD occurred predominantly in patients older at diagnosis, 6.5 [0.2-0.7]y, and those with no or mild outflow-obstruction. There were 9 patients with SCD, at a median age of 13.4 [10.2-22]y. Patients with subsequent SCD showed a severe phenotype already at diagnosis with maximal wall thickness Detroit Z-scores 6.5 [5.4-7.3] versus 4.1 [3.2-5.0], or Boston 2D-z-scores of 25.2 [19.2-34.0] versus 12.5 [6.7-21.7], and large ECG voltages and ECG Risk score 9 [5-1] versus 4 [3-7], and QTc 0.475 [0.416-0.522] versus 0.421-0.444; C-statistic for ROC-curve of QTc is 0.84 [0.66-1.00], p=0.007. Best discrimination was achieved around 7y of age with ECG Risk score 10 [7-11] versus 3 [3-8], C-statistic of the ROC-curve 0.86 [0.72-0.99]; p=0.006, and Boston 2D z-scores of 21.9 [18.4-23.6] versus 9.3 [6.3-14.1], C-statistic 0.81 [0.59-1.0]. HCM Risk-Kids gave less clear discrimination, 8.3 [5.4-10.1] versus 5.0 [3.1-7.7], with a C-statistic of 0.72 [0.49-0.95], p=0.12. Simple programmable ECG parameters such as limb-lead amplitude-duration product and 12-lead amplitude-duration product also shows promise with C-statistic of 0.95 [0.94-1.00], p=0.001 and 0.91 [0.79-1.0], p=0.001 respectively.

Conclusions: Patients with RASopathy-HCM that suffer a subsequent SCD have a notably abnormal phenotype already at diagnosis, and with a collection of a larger group of patients it should be possible to more clearly define optimal cut-offs for a high risk status to create a sound scientific basis for advising a primary prophylactic ICD-implantation, and for the optimal timing for this implantation. The AEPC working group on Basic Science, Genetics and Myocardial Disease hopes that Scandinavian Pediatric Cardiologists will join this effort.