ABSTRAKTER PRESENTERT PÅ HØSTMØTET

ORALE PRESENTASJONER

Unexpected identification of Fabry disease among patients with the clinical diagnosis of hypertrophic cardiomyopathy in Iceland

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Purpose: The aim of this study was to investigate the prevalence of Fabry disease (FD) among all hypertrophic cardiomyopathy (HCM) patients in Iceland.

Methods: 137 patients with clinically diagnosed HCM were studied; 76 carried the MYBPC3 c.927-2A>G founder mutation; the remaining 61 underwent targeted sequencing of 8 HCM genes and the α-galactosidase A gene (GLA). If a GLA sequence variant was found, then the enzyme activity of plasma and leukocyte alpha-galactosidase A (α-Gal A) and the urine concentration of globotriaosyleramide (Gb3) were measured. In vitro protein expression was performed in cases of new mutations. Patients were evaluated clinically and kidney function tests made. Brain and cardiac MRI was performed on patients with GLA sequence variants.

Results: Eight of the 137 patients (5.8%) had pathogenic GLA mutations, 5 males and 3 females, all without sarcomeric gene mutations. Age at LVH diagnosis was 46 ± 10 years (34-59), left ventricular wall thickness was 24 ± 5 mm (19-36). Two pathogenic mutations were identified. The I232T mutation was found in 3 patients from two families. In vitro protein expression showed 32% α-Gal A activity compared to wild type (WT). I232T was related to late onset disease with cardiac and cerebral manifestations. The D322E mutation was found in 5 patients from two families. In vitro protein expression showed 3% α-Gal A activity compared to wild

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type (WT). D322E seems to cause almost the classical form of FD. Familial studies allowed the diagnosis of FD in 12 additional patients: 2 males with classical FD, 3 males with cardiomyopathy as the only manifestation of FD, 7 young females without Fabry manifestations.

Conclusions: In Iceland, the prevalence of FD is high (about 6%) among patients with a clinical HCM diagnosis. Our results underscore the importance of considering FD in the differential diagnosis of unexplained LVH and presumed HCM.

Expression of selected genes in aspirated coronary thrombi in patients with acute myocardial infarction

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Background: Reports on the content of aspirated coronary thrombi have until now mainly focused on structural and cellular components.

Objectives: Investigate the genetic expression of selected mediators and proteases actively involved in plaque rupture, platelet and neutrophil cell activation, coagulation, fibrinolysis and inflammation in aspirated coronary thrombi from patients with acute myocardial infarction.

Patients/Methods: In this cross-sectional study, RNA from coronary thrombi in 67 subjects with acute myocardial infarction was isolated. Gene expression arrays of selected markers were performed by RT-PCR with relative quantification.

Results: Twenty of 22 markers were expressed in > 50% of the samples. The relative quantification of P-selectin correlated negatively to total ischemic time (p = 0.01), while genes related to fibrinolysis (t-PA, u-PA, PAI-1), inflammation (PTX3, CXCL9, MCP-1, IL18, TNF-alfa) and plaque instability (MMP-2 and TIMP-1) correlated positively to total ischemic time (all < 0.05). Long ischemic time (>4.0 hours) associated with a relative reduction in the expression of P-selectin and a relative increase in the expression of t-PA, u-PA, PAI-1, PTX3, CXCL9, MCP-1, IL18, TNF-alfa, MMP-9 and TIMP-1. The presence of type 2 diabetes increased PAI-1 expression 3.2-fold (adjusted p=0.033), while the presence of hypertension reduced IL-8 and TIMP-1 to about half-fold. Smoking and overweight did not affect any markers.

Conclusions: The coronary thrombi were highly genetic active. The expression profile changed along with ischemic time and with the presence of type 2 diabetes mellitus and hypertension. These observations contribute to increased insight into the genetic aspects of coronary atherothrombosis, which may have implications for future management of acute MI.

Modest effects of exercise training on HbA1c and VO2peak in patients with type 2 diabetes and coronary artery disease: a randomised clinical trial

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Background: Few studies have investigated the effects of exercise training in patients with both type 2 diabetes and coronary artery disease (CAD). We investigated the effects of 12 months combined aerobic and resistance training on glycemic control and exercise capacity in these patients, hypothesising that exercise would improve HbA1c and VO2peak.

Methods: Patients with type 2 diabetes and CAD (n=137) were randomised to exercise or normal follow-up. The training program consisted of 150 minutes weekly group-based and individual exercises. HbA1c was measured before and after the intervention. Changes in VO2peak, ventilatory threshold (VT) and time to exhaustion (TTE) were assessed by cardiopulmonary exercise testing (CPET). Between group differences in changes were calculated by one-way ANCOVA. "Intention to treat" (ITT) and «per protocol» (PP) analyses were performed.

Results: One hundred and twenty-three patients completed the study (ITT), and nine patients were excluded from the PP analyses due to low exercise adherence (<40%). No between group differences in changes were observed in HbA1c or VO2peak, whereas VT and TTE increased significantly (p=0.046 and p=0.034) (PP). The relative increase in VT and TTE was significantly larger than in VO2peak (12.8% and 13.7% vs. 4.5%). Presence of advanced vascular disease (previous AMI and/ or diabetes microvascular complications) interacted with the treatment principle with respect to changes in HbA1c and VO2peak (p=0.036 and p=0.063), and in the strata of patients without advanced

vascular disease (n=46) the exercise group did improve these parameters compared to controls (p=0.052 and p=0.035).

Conclusions: No significant effects of exercise training were observed on HbA1c or VO2peak levels, although VT and TTE increased significantly indicating improved exercise performance and capacity. Patients without advanced vascular disease did improve both HbA1c and VO2peak, implying that the degree of vascular disease influences exercise responses in patients with type 2 diabetes and CAD.

Clinical presentation predicts coronary atheroma necrotic core reduction in patients undergoing aerobic exercise intervention

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Background: Vulnerable coronary lesions are characterized by a large amount of necrotic core (NC). We have previously demonstrated a significant reduction in NC in patients on optimal medical treatment following moderate continuous exercise or aerobic interval training for 12 weeks (in press, clinicaltrials.gov, NCT01228201). In a post-hoc analysis we assessed clinical variables at baseline that could predict NC reduction.

Methods: NC was measured with radiofrequency intravascular ultrasound, and analyzed at an independent Core Laboratory. Baseline explanatory variables included age, sex, anthropometrics, medication, endothelial function, blood biomarkers and clinical presentation (stable angina pectoris or non-ST elevation acute coronary syndrome, NSTEACS). Variable screening was performed using random forest analysis (bootstrap, n=2000) following dichotomization of the outcome (NC change) into reduction or no change/increase. Significant variables were further analyzed using multivariate linear regression with NC change as a continuous variable (mm^3).

Results: In the random forest analysis, significant variables at baseline for NC reduction were use of angiotensin enzyme inhibitors/angiotensin II receptor antagonist, and clinical presentation. In linear regression, only clinical presentation remained significant (p=0.011, Rsquared 0.90). The median change in NC was -4.94 (-10.33;-1.33) mm^3 in patients with stable angina pectoris, and 1.03 (-4.29;3.71) mm^3 in patients with NSTE-ACS (between-group difference p=0.01). Mean NC volume at follow-up was 7.19 (1.87;12.50) mm^3 higher in patients with NSTE-ACS compared to stable angina pectoris. NC volume was reduced in 17 patients (94%) in the stable angina group compared to 8 patients (44%) in the NSTE-ACS group (between-group difference p=0.01).

Conclusions: Reduction of coronary atheroma NC in patients undergoing aerobic exercise may be strongly dependent on clinical presentation, and was much more frequent in patients with stable angina pectoris in our cohort. Based on our data, it could be hypothesized that an increased pro-inflammatory load renders patients with NSTE-ACS more resistant to exercise-induced plaque stabilization.

Heart rate during maximal exercise testing in patients with permanent atrial fibrillation

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Aims: To investigate the relation between heart rate (HR) response to exercise and exercise capacity (peak VO2) in patients with permanent atrial fibrillation (AF), with and without rate-reducing drug treatment.

Methods: Sixty patients (mean age 71±9 years, 18 women) with permanent AF and normal left ventricular function were included in the study. All received diltiazem 360 mg, verapamil 240 mg, metoprolol 100 mg and carvedilol 25 mg once daily for three weeks, in a randomized sequence. At baseline and on the last day of each treatment period, the patients underwent a maximal cardiopulmonary exercise test on a bicycle ergometer.

Results: Treatment with all four rate-reducing drugs lowered HR both at rest and during all stages of exercise and recovery, compared to baseline (p<0.001 for all) (Figure 1). In multivariate regression analysis, adjusting for age, gender, BMI, ejection fraction and FEV1, peak VO2 remained positively correlated to the heart rate reserve (difference between HR at peak exercise and resting HR, divided by the resting HR)(r=0.40, p<0.001) and inversely correlated to the relative increase in HR during the four minutes warm-up phase (r=-0.22, p<0.001).

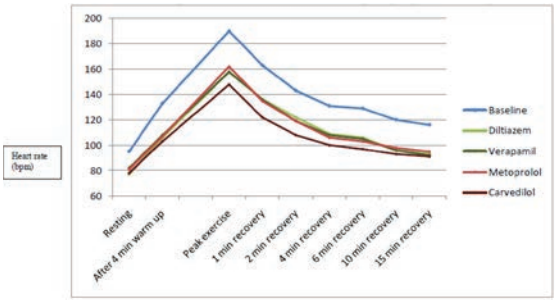

Figure 1. Heart rate during the exercise tests, at baseline and with the different drugs.

Conclusion: Preserved HRR was correlated to better exercise capacity while excessive HR response to minor exercise was predictive of reduced exercise capacity in patients with permanent AF.

POSTER-PRESENTASJONER

Non-Invasive Myocardial Work Index Identifies Acute Coronary Occlusion in Patients with Non-ST-Segment Elevation – Acute Coronary Syndrome

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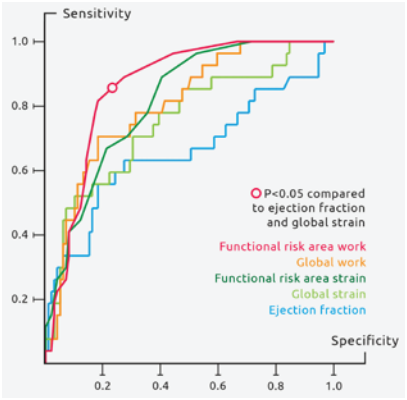
Introduction: Acute coronary artery occlusion (ACO) occurs in approximately 30% of patients with non-ST-segment elevation – acute coronary syndrome (NSTE-ACS). We investigated the ability of a regional non-invasive myocardial work index (MWI) to identify ACO.

Methods and Results: Segmental strain analysis was performed before coronary angiography in 126 patients with NSTE-ACS. Left ventricular (LV) pressure was estimated non-invasively using a standard waveform fitted to valvular events and scaled to systolic blood pressure. MWI was calculated as the area of the LV pressure-strain loop. Empirical cut-off values were set to identify segmental systolic dysfunction for MWI (<1700 mmHg %) and strain (>-14%). The number of dysfunctional segments was used in ROC analysis to identify ACO. 27 patients suffered ACO. The presence of ≥4 adjacent dysfunctional segments assessed by MWI was significantly better than both global strain and ejection fraction at detecting the occurrence of ACO (P<0.05). Regional MWI had a higher sensitivity (81% vs. 78%) and especially specificity (82% vs. 65%) compared to regional strain. Logistic regression demonstrated that elevated systolic blood pressure significantly decreased the probability of actual ACO in a patient with an area of impaired regional strain.



Conclusions: The presence of a region of reduced myocardial work in patients with NSTE-ACS identified patients with ACO, and was superior to all other parameters. The regional MWI was able to account for the influence of systolic blood pressure on regional contraction. We therefore propose that MWI may serve as an important clinical tool for selecting patients in need of prompt invasive treatment.

Cardiac resynchronization therapy in left bundle branch block improves right ventricular function

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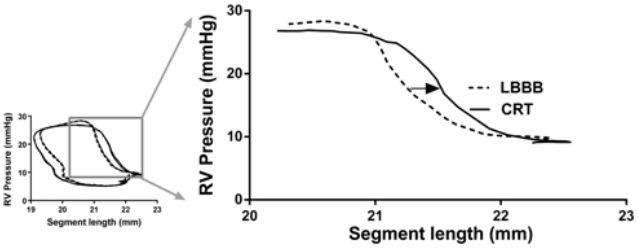
Purpose: Right ventricular (RV) function has been recognized as a predictor of clinical response to cardiac resynchronization therapy (CRT) during left bundle branch block (LBBB). In an experimental setting, we aimed to study the impact of CRT on RV function during LBBB.

Methods: In 6 anaesthetised dogs with LBBB induced by radio frequency ablation, we applied CRT with one electrode on the right side of the interventricular septum and one epicardially on the LV lateral wall. RV pressure was measured by a micromanometer in the RV cavity and segmental length (SL) by sonomicrometry in the RV free wall. The area of the RV pressure-SL loop was used as an index of regional work in the RV free wall. Pre-ejection RV shortening, measured at 50 % increase of RV pressure, was calculated in percentage of peak systolic shortening.

Results: Induction of LBBB was associated with a reduction in RV free wall work from 41±13 to

29±16 mmHg*mm (P<0.05). This was in part due to distortion of the pressure-SL loop with marked pre-ejection shortening (33±14 %) of total shortening. CRT increased segmental work to 41±15 mmHg*mm, P<0.05 and RV dP/dt max increased from 361±78 to 446±76mmHg/s (P<0.05). Neither maximum RV pressure (28±3 vs. 27±3mmHg, NS) nor total shortening (8±3 vs. 8±3 %, NS) was changed by CRT. However, the RV pre-ejection shortening decreased substantially to 13±12 % (P<0.05 vs. LBBB) of total shortening (figure).



Conclusions: During LBBB there is ineffective contraction in the RV free wall as approximately 1/3 of the contraction occurs during low pressure prior to ejection. The efficiency was improved by CRT, which markedly increased regional work in the RV free wall. The findings suggest that improvement in RV function may be important for success of CRT in LBBB.

Pro-arrhythmic consequences of hypokalemia in atrial cardiomyocytes

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Up to 20% of hospitalized patients exhibit hypokalemia, and mortality in these patients is 10 times higher than in those with normal potassium levels. Many studies have observed an association between hypokalemia and atrial fibrillation. We hypothesized that lowered extracellular K+ levels promote ectopic beats in atrial myocytes by triggering early and delayed afterdepolarizations. Our previous work has shown that when [K+] is reduced from 5.0 mM to 2.7 mM, rat ventricular cardiomyocytes briefly exhibit depressed Ca2+ transients followed by a recovery and overshoot of Ca2+ transient amplitude. In addition to larger Ca2+ transients at steady-state, we observed that ventricular cells exhibited spontaneous Ca2+ waves during hypokalemia, which generate delayed afterdepolarizations. In rat atrial cardiomyocytes exposed to the same protocol, the majority of cells exhibited early spontaneous release during the decline of the Ca2+ transient consistent with early afterdepolarizations. Approximately half of atrial cells exhibited a biphasic response of Ca2+ transient amplitude and spontaneous Ca2+ waves at steady state, which was reminiscent of observations made in ventricular cells. Remaining atrial cells exhibited a monophasic decrease in Ca2+ transient amplitude. Our work in ventricular cells has shown that the biphasic response is dependent on the presence of the alpha-2 isoform of the Na+-K+ ATPase in the t-tubules. Since we observed that t-tubules are present in about half of rat atrial myocytes, we believe that it is these tubulated cells which exhibit biphasic responses during hypokalemia. Importantly, increased occurrence of both Ca2+ waves and early spontaneous Ca2+ release events in atrial cells during hypokalemia was largely reversed upon return to normal extracellular K+ levels. These results support the notion that increasing blood K+ levels may have therapeutic value in patients with atrial fibrillation, and we are currently investigating this hypothesis in a parallel clinical study.

Rosuvastatin induced carotid plaque regression in patients with inflammatory joint diseases: The RORA-AS study

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Background: Patients with rheumatoid arthritis (RA) and carotid artery plaques (CP) have increased risk of acute coronary syndromes. Statin treatment with low density lipoprotein cholesterol (LDL-c) goal <1.8 mmol/L is recommended for patients with CP in the general population. In the ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory

joint diseases (RORA-AS) study, the aim was to evaluate the effect of 18 months intensive rosuvastatin treatment on change in CP height.

Methods: Eighty-six patients (60.5% female) with CP and IJD [RA (n=55), ankylosing spondylitis (n=21) and psoriatic arthritis (n=10)] were treated with rosuvastatin to obtain LDL-c goal. CP height was evaluated by B-mode ultrasound.

Results: Age was 60.8±8.5 years (mean±SD). At baseline, median number and height of CP was 1.0 (range 1-6) and 1.80 mm (IQR 1.60, 2.10). Change in CP height after 18 months rosuvastatin treatment was -0.19±0.35 mm (p<0.001). Baseline and change in LDL-c was 4.0±0.9 mmol/L and -2.3±0.8 mmol/L (p<0.001). Mean LDL-c level during 18 months rosuvastatin treatment was 1.7±0.4 mmol/L. The degree of CP height reduction was independent of the LDL-c level exposure during the study period (p=0.36). Attainment of LDL-c <1.8 mmol/L or the change in LDL-c did not influence the degree of CP height reduction (p=0.44 and p=0.46, respectively). The higher the CP was at baseline - the larger height reduction after 18 months with rosuvastatin treatment (p<0.001). Joint disease activity during the study period was inversely associated with change in CP height (p=0.02), so that patients with the highest disease activity had the smallest change in CP height and vice versa.

Conclusion: This is the first clinical study showing that intensive lipid lowering with statin induced regression of atherosclerosis in patients with IJD. Our results indicate that disease activity may influence the effect of anti-atherosclerotic treatment.

Hypertrophic cardiomyopathy in a large cohort of MYBPC3 c.927-2A>G founder mutation carriers

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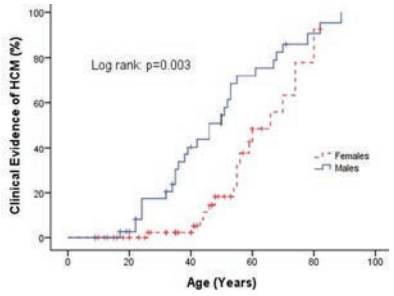
Purpose: Most hypertrophic cardiomyopathy (HCM) cohort studies are characterized by great heterogeneity of sarcomeric protein gene mutations. The aim of this study was to determine the penetrance and clinical disease expression in a large cohort of patients and relatives carrying the same MYBPC3 c.927-2A>G founder mutation, arising more than 500 years ago.

Methods:The initial study population comprised 88 probands carrying the MYBPC3 c.927-2A>G. Additionally, 223 first degree relatives accepted to undergo genetic testing and clinical evaluation, including echocardiography.

Results:Out of 223 family members, 95 c.927-2A>G mutation carriers were identified, of whom 47 (50%) were clinically affected with left ventricular hypertrophy (LVH) ≥13 mm. The penetrance was age related (34% <40 years versus 61% ≥ 40 years, p=0.009) and greater in males (67%) than females (35%, p=0.001). Gender specific, cumulative age related penetrance is shown in the figure below.

Neither males nor females were affected until age 17 and by age ≥80, more than 90% of individuals were affected. The degree of LVH among the relatives ranged from 13 mm to 28 mm, none had left ventricular outflow tract gradient ≥30 mmHg at rest. The pattern of septal hypertrophy was reverse curve in 67% of patients, neutral in 21%, apical in 5.8%, and 3.5% had sigmoid septum.



Conclusions: HCM related to the MYBPC3 c.927-2A>G founder mutation is mainly late onset and shows gender specific penetrance. Other genetic or environmental factors must play an important role in disease phenotype.

C-reactive protein is associated with peak oxygen uptake, but not with endothelial function: The HUNT 3 Fitness Study

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Background: Biomarkers of inflammation, particularly C-reactive protein (CRP), have received attention as predictors of cardiovascular disease (CVD). Some studies suggest that CRP participates actively in atherogenesis. The aim of the

present study was to investigate whether CRP (a marker of general inflammation), neopterin (a marker of activated macrophages), and lactoferrin (a marker of activated neutrophils) are associated with aerobic fitness, endothelial function, and the metabolic syndrome, in self-reported healthy respondents.

Methods: A cross-sectional association study included 1432 men and women from the HUNT 3 Fitness Study. 740 respondents identified as having the metabolic syndrome were age- and sex-matched with 692 controls from the same cohort. Associations between the biomarkers of inflammation and aerobic fitness (VO2peak = peak oxygen uptake during treadmill test), endothelial function (FMD = flow-mediated dilation), and the metabolic syndrome, were analyzed by linear and logistic regression.

Results: CRP was strongly associated with metabolic syndrome, male gender, and VO2peak (Figure 1, all $p<0.005$). In gender-stratified analyses, smoking was associated with CRP only in men ($p<0.005$). There was no association between FMD and CRP ($p=0.34$). Lactoferrin was associated with metabolic syndrome ($p<0.005$), but neither neopterin nor lactoferrin were associated with VO2peak or FMD. In logistic regression, the metabolic syndrome was strongly associated with male gender, lactoferrin and VO2peak ($p<0.005$). Each 1 ml*kg-1*min-1 increase in VO2peak corresponded to a ≈ 6 % risk reduction for the metabolic syndrome.

Conclusions: CRP was clearly associated with VO2peak and the metabolic syndrome, but not with FMD. Based on these findings, we hypothesize that aerobic fitness may have a significant effect on low-grade inflammation in a population without CVD. We hypothesize that a modest increase in aerobic fitness may protect against a detrimental clustering of CVD risk factors as in the metabolic syndrome.