PRESENTERTE ABSTRAKTER PÅ HØSTMØTET

Reason For Not Being Operated Affects Survival In Patients With Severe Aortic Valve Stenosis

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Introduction: Deciding whether to undergo aortic valve replacement(AVR) in patients with severe aortic valve stenosis(AS) can be challenging. Based on the reasons for not being operated on, we conducted a 3-year mortality-analysis in patients who were referred to medical treatment after evaluation of AVR.

Methods: Patients >18 years of age with severe AS (AVA < 1.0cm^2, aortic peak velocity > 4.0m/s and aortic mean pressure gradient > 40mmHg) referred for evaluation of AVR at our tertiary centre were included in a prospective cohort. Covariates investigated in uni- and multivariable analyses were: age, NYHA-class, diabetes mellitus, left ventricular ejection fraction(LVEF) and reason for not undergoing AVR(REASON-NOT).

Results: Of 480 included patients, 351 underwent surgical AVR, 38 transcatheter AVR, and 91 remained non-operated. We identified 3 main reasons for not undergoing AVR and established 3 groups accordingly: group (1) absence of symptoms, (2) high risk-benefit ratio, and (3) patient refusal despite recommended AVR. Three-year mortality was higher in unoperated than in operated patients [44 of 91(48.4%) vs. 44 of 389(11.3%), p<0.01]. Furthermore, 3-year mortality in the established groups were: (1) 10 of 34 (29.4%), (2) 25 of 37 (67.6%), and (3) 9 of 20 (45.0%), p=0.16. For unoperated patients, univariable analyses demonstrated that NYHA class III or IV (Hazard ratio, HR [95% CI] 2.09 [1.16-3.79], p=0.02), and below normal LVEF (HR 3.34 [1.78-6.29], p<0.01) and REASON-NOT (HR 1.79 [1.24-2.57], p<0.002) were associated with 3-year mortality. In multivarible analysis, below normal LVEF (HR 2.66 [1.23-5.57], p=0.01) and REASON-NOT (HR 1.67 [1.13-2.48], p=0.01) remained independent predictors.

Conclusions: This study demonstrates that AVR significantly reduces 3-year mortality in patients with severe AS. Furthermore, the poor prognosis reported among patients categorized as asymptomatic underlines the importance of a careful symptom-assessment. Awareness of the high mortality risk associated with refusing AVR should be conveyed to patients considering this option.

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Atrial Fibrillation prevalence and comorbidity in the Akershus Cardiac Examination (ACE) 1950 Study

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Background and rationale: The prevalence of atrial fibrillation (AF) is rising in many countries; however there is little data on the epidemiology of AF in Norway. In this work, we aimed to characterize prevalence of AF in relation to cardiovascular risk factors and concomitant cardiovascular disease (CVD) in middleaged Norwegians.

Methods: The ACE 1950 Study enrolled all men and women in Akershus County born in 1950, and the participants were subjected to an extensive baseline examination, including ECG, and detailed medical history of previous or concurrent AF or other CVD.

Results: We included 3706 of 5827 eligible subjects (64 %) and 203 subjects reported either previous or concurrent AF (5.5%). AF was more prevalent among men than women (7.3% vs. 3.6%; p<0.001), and AF subjects were taller and heavier than subjects without AF. Subjects with AF had higher prevalence of cardiovascular risk factors or established CVD (Table 1).

Conclusion: The prevalence of AF in a Norwegian 64-year-old population cohort was 5.5%. There were significant gender differences, and subjects with AF were taller, heavier and had higher prevalence of cardiovascular risk factors and established CVD.

Table 1 – Atrial Fibrillation characteristics and comorbidity, compared with non-AF population

AF population (n=203)	Non-AF population (n=3505)	p-value	
Height, cm, ±SD Men Women	180.5 ±7.0 167.8 ±6.7	178.7 ±6.4 165.3 ±5.9	<0.01 <0.01
Weight, kg, ±SD Men Women	92.9 ±15.6 76.9 ±15.8	88.3 ±13.6 72.8 ±13.4	<0.001 0.02
Body Mass Index (BMI), ±SD	28.1 ±4.9	27.1 ±4.4	<0.01
Obesity, BMI≥30, %	35.5	21.9	<0.001
Hypertension, %	66.0	58.2	0.03
Myocardial infarction, %	9.9	3.9	<0.001
Coronary heart disease, %	15.8	6.6	<0.001
Heart failure, %	9.4	1.2	<0.001
Diabetes mellitus, %	12.3	10.4	0.38
Stroke, %	6.4	3.6	0.04
COPD, %	7.9	7.0	0.63
Obstructive sleep apnoea, %	10.8	5.9	<0.01
eGFR, CKD-EPI, ±SD	80.0 ±13.9	83.1 ±11.8	<0.001

Pro-coagulant activity during exercise testing in patients with coronary artery disease

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Background: Strenuous exercise may trigger myocardial infarction through increased pro-coagulant activity. We intended to investigate whether patients referred for exercise testing, who were found to have angiographically verified coronary artery disease (CAD), have a more hypercoagulable profile during exercise testing compared to those without CAD.

Materials and Methods: Patients with symptoms suggestive of stable CAD were examined with exercise electrocardiography on bicycle ergometer. Venous blood samples were taken at rest and within 5 minutes after end of exercise. The following haemostatic variables were analysed: tissue factor pathway inhibitor (TFPI) activity and antigen, prothrombin fragment 1+2 (F1+2), D-dimer and endogenous thrombin potential (ETP). The latter was measured by the calibrated automated thrombogram (CAT) assay and the others with ELISAs. All participants underwent conventional coronary angiography. CAD was defined as having any degree of atherosclerosis.

Results: Out of 106 patients enrolled (62 males, mean age 62±10 years), 70 were found to have angiografically verified CAD. Mean exercise duration was 10:06 ± 4:11 min and mean metabolic equivalent (MET) 6.7 ± 1.8, with non-significant differences between the two groups. A significant increase from baseline to after exercise testing was observed in all measured markers in the total population ($p \leq 0.002$ for all). The increase remained significant in all markers except for D-dimer ($p = 0.071$) when adjusting for change in hematocrit. In patients with angiographically verified CAD, total TFPI was significantly lower at baseline compared to patients without CAD (median value 67.4 and 76.6 ng/ml respectively, $p = 0.027$). However, no significant differences in changes of the measured markers during exercise were observed between the two groups.

Conclusion: Pro-coagulant activity increased during strenuous exercise testing in patients with symptoms suggestive of CAD, however the hypercoagulable state observed, was not more pronounced in patients with angiographically verified CAD compared to patients without CAD.

Arrhythmias in catecholaminergic polymorphic ventricular tachycardia type 1 are associated with heart rate, but requires sympathetic stimulation

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Background

Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1) is caused by mutations in the gene encoding the cardiac ryanodine receptor (RyR2). RyR2 is the main Ca^{2+} release protein in the sarcoplasmic reticulum (SR) in cardiomyocytes. Patients with CPVT1 have

increased propensity for ventricular arrhythmias in situations associated with increased heart rate, such as physical or psychological stress. However, the role of heart rate and sympathetic stimulation for the development of arrhythmias in CPVT1 is not completely understood.

Methods and results

ECGs from 17 patients with CPVT1 were recorded during a bicycle stress-test. During the stress-test, the frequency and severity of ventricular arrhythmias increased with heart rate. In a subset of 4 patients treated with an ICD, atrial or ventricular electrode pacing did not induce premature ventricular beats (PVC), even at higher heart rates than the threshold for occurrence of PVCs during the bicycle stress-test.

Whole-cell Ca^{2+}imaging was performed in isolated ventricular cardiomyocytes from mice with the RyR2-R2474S missense mutation (RyR2-RS) and wild-type (WT) littermates. Increased frequency did not reveal differences between RyR2-RS and WT. However, during ISO-exposure, Ca^{2+} wave and Ca^{2+} spark frequency was higher in RyR2-RS compared to WT. Ca^{2+} waves developed at a lower SR Ca^{2+} content in RyR2-RS compared to WT ($p<0.05$).

In a computational model of mouse cardiomyocyte electrophysiology, RyR2 Ca^{2+} sensitivity was fit to recapitulate the experimental RyR2-RS-phenotype with regard to Ca^{2+} wave frequency and time to first Ca^{2+} wave. In this model, interplay between CaMKII-dependent RyR phosphorylation and SR Ca^{2+} reloading determine the propensity for Ca^{2+} wave development.

Conclusion

The propensity for ventricular arrhythmias in patients with CPVT1 is associated with heart rate. However, our results show that beta-adrenergic stimulation is the necessary factor for arrhythmia development in CPVT1. The results support beta-blocker treatment as first line therapy and could have implications for ICD programming.

Exercise training as anti-arrhythmic therapy in catecholaminergic polymorphic ventricular tachycardia type 1

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The results presented in this abstract have recently been published in two original articles:

1) Effects of Individualized Exercise Training in Patients with Catecholaminergic Polymorphic Ventricular Tachycardia Type 1, Manotheepan et al. Am J Cardiol 2014

2) Exercise training prevents ventricular tachycardia in CPVT1 due to reduced CaMKII-dependent arrhythmogenic Ca^{2+} release, Manotheepan et al. Cardiovasc Res 2016

Aims: Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1) is caused by mutations in the cardiac ryanodine receptor (RyR2) that lead to ventricular tachycardia triggered by acute physical or psychological stress. Combining clinical and experimental approaches, we have explored whether the chronic effects of exercise could stabilize RyR2 and prevent arrhythmias.

Method and results: Six patients with CPVT1 were included in a 12-week program of exercise training at an individualized and safe level, and were compared to seven other patients with CPVT1 for which lifestyle advice was unchanged. All patients performed repeated bicycle exercise testing throughout the study period. Aerobic capacity (VO_{2max}) in the exercise training patients increased by 13±3%, and no adverse events occurred. Interestingly, threshold heart rate for ventricular arrhythmias increased in the exercise training patients compared to the controls.

To investigate the mechanisms underlying the clinical observations, mice with the CPVT1-causative missense mutation *Ryr2*-R2474S (RyR-RS) underwent two weeks of treadmill interval training. Exercise training increased VO_{2max} in RyR-RS mice by 10±2%. Importantly, exercise training RyR-RS mice showed fewer episodes of ventricular tachycardia than sedentary animals. This coincided with lower propensity for RyR2-dependent arrhythmogenic Ca^{2+} release events in individual cardiomyocytes from these animals. Further results indicated stabilized RyR from reduced oxidation of the key RyR regulating kinase CaMKII.

Conclusion: Our pilot clinical data indicate a beneficial effect of individualized exercise training at a safe level for patients with CPVT1. This is supported by experimental data that suggests a mechanistic explanation for this effect. These results should motivate further research on the acute and chronic effects of exercise training on RyR-function in CPVT1 and other cardiac diseases.

CRT Survey II – Preliminary results

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Background

Cardiac Resynchronisation Therapy (CRT) reduces mortality and morbidity in patients with heart failure and electrical dyssynchrony and therefore receives strong recommendations in current guidelines. However, despite these recommendations, the increase in CRT implantation rate has been modest across Europe. Therefore, actions to increase awareness of the indications for CRT are needed.

Purpose

Two ESC associations, EHRA and HFA, have designed CRT Survey II to describe clinical practice regarding implantation of CRT devices in ESC member countries.

Methods

Patients enrolled are both those with new implantations of a CRT-P/CRT-D and those with upgrades. A patient related electronic case report form (eCRF) is completed at each enrolment. This eCRF includes patient demographics, aetiology of heart failure, ECG morphology and QRS duration, indication for CRT implantation, procedural details, complications, and discharge status.

Results

CRT Survey II began collecting data on 1st October 2015 and is currently operating in 42 countries with over 8100 patients included. The Survey will continue until 10 000 patients have been included. Preliminary demographic results of the first 7000 patients are shown in table one.

Table 1 – Preliminary Demographic results for CRT Survey II

Patient Demographics	**Europe** (n≅ 7100)	**Norway** (n≅ 290)
Age (yrs)	68.38 ± 10.70	68.88 ± 10.19
Intrinsic QRS duration (ms)	157.15 ± 26.60	153.77 ± 28.37
Gender, male (%)	75.9	80.2
Pre-implant rhythm, sinus (%)	68.8	59.4
QRS morphology, LBBB (%)	72.9	60.8
Primary HF aetiology, Ischaemic (%)	44.3	47.2
Type of device, CRT-P (%)	30.8	30.2
Upgrades, n (%)	23.0	23.1
Loop diuretic, n (%)	80.4	66.2
ACE inhibitor/ARB, n (%)	85.9	90.9
MRA (aldosterone antagonist), n (%)	62.0	42.0
Betablocker, n (%)	88.9	87.5

Conclusion

The data collected in CRT Survey II should help to identify the major obstacles to implementation of CRT therapy and thus create a basis for enhancement of therapy access. Ultimately, we hope that the results will serve to increase CRT implementation for appropriate heart failure patients in Europe.v

Patient and procedural characteristics in the newly established coronary invasive center at Akershus University Hospital

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Introduction. Akershus University Hospital (AHUS) serves a population of 500 000, as the largest provider of acute medical care in Norway. This and need for increased invasive capability in the South-East health region of Norway facilitated a new coronary invasive center at AHUS, opened in November 2015. Established in collaboration with the Department of Cardiology, Oslo University Hospital, it operates weekdays within regular working hours, without onsite backup of a cardiac thoracic surgeon and is for the time being not part of the regional emergency STEMI-call.

Objectives. Review the first one thousand invasive procedures of 2016 at AHUS.

Methods. Systematical review of patient and procedural data from the Norwegian registry for invasive cardiology (NORIC) from 04.01.16 to 02.08.16.

Results. A total of 898 patients underwent 1017 procedures in the period. Mean age was 65,4 years (28-96 years), with men dominating 66,7% vs. 33,3% (Table 1). There was a relative high number of diabetics (23,7%), patients treated for hypertension (50,0%), hypercholesterolemia (54,3 %), active or former smokers (66,4%). Almost 30% had prior myocardial infarction and respectively 8,7% and 35,7% had prior CABG- or PCI-treatment.

Acute coronary syndrome (ACS) was the most common indication for performing invasive procedure (53,2%) (Table2). Furthermore, 70,8% of all procedures were performed as subacute and 40,8 % resulted in interventional treatment. Single radial access was used in 94,8% of the procedures.

Total number of laboratory complications was 12 (1,2%), specific listing is presented in Table 3. There was one periprocedural death.

Conclusion. Invasive procedures at our center are performed dominantly in the subacute setting in patients with high pretest risk of ACS. In coherence with modern standards we rapport a high number of single radial access, a low number of laboratory complications and a high intervention rate.

Table 1 Baseline characteristics of the study population	
Characteristics	All (n=898)
Women, n (%)	299 (33,3%)
Men, n (%)	599 (66,7%)
Mean age all, years	65,4
Mean age women, years	67,9
Mean age men, years	64,2
Diabetes melitus, n (%)	213(23,7%)
Hypertension, n (%)	449 (50,0%)
Statin users, n (%)	488(54,3%)
Smokers, n (%)	167 (18,6%)
Previous smokers, n (%)	429 (47,8%)
Prior PCI treatment, n (%)	321 (35,78%)
Prior CABG treatment, n (%)	78 (8,7%)
Prior myocardial infarction, n (%)	266 (29,6%)
Ejection fraction < 40%, n (%)	86 (9,6%)
Peripheral arterial disease, n (%)	47 (5,2%)

Table 2 Procedure characteristics	
	All (n=1017)
Indication for invasive investigation	
NSTEMI, n (%)	346(34,0%)
UAP, n (%)	174(17,1%)
Stable coronary disease, n (%)	166(16,3%)
Unspesified chest pain, n (%)	117(11,5%)
STEMI, n (%)	21(2,1%)
Other, n (%)	193(19,0%)
Urgency	
Elective, n (%)	272(26,7%)
Subacute, n (%)	720(70,8%)
Acute, n (%)	25(2,5%)
Procedure	
Angiography, n (%)	602(59,2%)
Angiography + PCI, n (%)	351(34,5%)
PCI, n (%)	64(6,3%)
Access point	
Art.radialis dxt, n (%)	929(91,4%)
Art.radialis sin, n (%)	36(3,5%)
Other, n (%)	52(5,1%)

Table 3 Overview of all laboratory complications, n (% of all procedures)	
Iatrogenic aortic dissection, n (%)	2(0,2%)
Dissection of a coronary artery resulting in procedural myocardial infarction, n (%)	2(0,2%)
Unexpandable stent, n (%)	1(0,1%)
Lost stent, n (%)	2(0,2%)
Allergic incidences, n (%)	1(0,1%)
Occluded artery, n (%)	4(0,4%)

Is ECG useful in the clinical evaluation of patients with severe aortic stenosis?

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Aims

To explore the usefulness of the electrocardiogram (ECG) in the clinical evaluation of patients with severe aortic valve stenosis (AVS), and the association between left ventricular hypertrophy (LVH) in ECG, biomarkers (NT-pro-BNP, Troponin T) and outcome.

Methods

The Severe Aortic Stenosis Study is a cohort study of 480 patients with severe AVS referred for evaluation for aortic valve replacement (AVR) at Oslo University Hospital, Rikshospitalet. Clinical routine data from 367 patients recruited between May 2010 and March 2013 were analyzed; Resting 12-lead ECG, transthoracic echocardiography (TTE) and blood samples. LVH in ECG was assessed by Sokolow-Lyon criteria (SL), Cornell Voltage Product (CVP), Gubner-Ungeleider Index (GI) and Romhilt-Estes Point Score System (RE), and related to peak aortic flow velocity (Peak AV) and left ventricular mass index (LVMI) assessed by TTE, to biomarkers and to clinical outcome. Unoperated and AVR patients were analyzed separately.

Results

LVH was found by echo LVMI in 42% and by ECG in 49% of the patients (25% by CVP, 20% by SL, 19% by RE and 13% by GI). RE correlated statistically significant, but only fairly, with the three other ECG criteria for LVH (Pearson's coefficients r=0.29-0.37), CVP vs GI correlated moderately (r=0.49), while SL correlated neither with GI or CVP. LVH by echo LVMI and ECG correlated statistically significant, but only fair (r=0.16-0.32), ECG with NT-pro-BNP correlated poorly to fair (r=0.16-0.34). Peak AV velocity correlated statistically significantly, but poorly to SL, RE and GI (r=0.16-0.20). LVH in ECG and high NT-pro-BNP were associated with high odds ratios for adverse outcome in both patient groups (Table 1).

Conclusions

The various ECG algorithms for detecting LVH in patients with severe AVS perform differently. ECG gives additional information for the evaluation of patients with severe AVS.

Table 1. Odds Ratio on outcomes									
Op		Mace				Mortality			
		p	Non Op	p	Op	p	Non Op	p	
ECG (Y)	LVH in ECG	1,9	0,056	2,3	0,178	1,6	0,127	3,0	0,044
	Sokolow-Lyon Criteria	1,1	0,861	1,4	0,689	1,2	0,607	1,7	0,480
	Cornell Voltage Product	2,2	0,025	1,8	0,389	1,7	0,093	14,6	0,002
	Gubner-Ungeleder Index	1,6	0,331	0,9	0,858	2,1	0,047	2,6	0,255
	Romhilt-Estes Criteria	1,2	0,599	0,9	0,886	1,4	0,334	1,6	0,476
Echo	Peak AV Velocity*	0,8	0,466	1,1	0,918	0,8	0,568	0,8	0,593
	LVMI (Y)	0,9	0,698	1,6	0,471	1,6	0,112	1,1	0,821
Hormones	NT-pro-BNP*	1,5	0,246	4,6	0,048	3,1	0,000	6,0	0,002
	hs-TnT*	1,3	0,423	2,2	0,268	3,3	0,000	3,0	0,054

*Op: operated patients, Non Op: non operated patients, Mace=Major adverse cardiac events (all cause mortality, TIA/stroke, acute myocardial infarction), Y: positive for LVH criterion; LVMI: female >95 g/m², male >115 g/m², *: higher than median value; p: p-value; NT-proBNP: N-terminal pro brain natriuretic peptide; hs-TNT: high sensitive troponin T*