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CASD 001

Drugs with effects in reduction of oxidative stress, platelets hyperactivity, hypercoagulability status and incidence of sudden death in ACS

Elena Bobescu[a], Mariana Radoi, Dan Dobreanu, Liliana Rogozea, Bianca Doka, Geanina Catanescu
[a]*Brasov,Romania. E-mail: elena_bobescu@yahoo.com*

Purpose In patients with non ST elevation acute coronary syndrome (ACS), sudden cardiac death and other major acute cardiovascular events (MACE) were evaluated in relation with administration of drugs with complementary mechanisms in reduction of oxidative stress, platelets hyperactivity and hypercoagulability status.

Methods Two hundred and forty patients (pts) with ACS were divided in two groups: Group A treated with drugs with complementary mechanisms mentioned above: nebivololum, zofenoprilum, rosuvastatinum, trimetazidine and omega-3 polyunsaturated fatty acids; Group non A treated with drugs without mentioned proprieties: metoprololum, enalaprilum, simvastatinum. All other drugs for ACS treatment were simillar on both groups. Biomarkers for platelets hyperactivity (ASPItest, ADPtest by MULTIPLATE), hypercoagulability status (von Willebrand factor activity), oxidative stress (Total antioxidant status) and MACE were evaluated at 1 year of follow up. Statistic analysis: multiple regression, chi square test.

Results

	Group A	Group non A	*p*
Total ACS patients -240	115 (47.9%)	125 (52.1%)	ns
Cardiovascular death	3 (2.6%)	10 (8.0%)	ns
Sudden cardiac death	1 (0.9%)	9 (7.2%)	0.025
Nonfatal AMI	5 (4.3%)	18 (14.4%)	0.025
Stroke	2 (1.7%)	3 (2.4%)	ns
Recurrent angina with readmission	10 (8.7%)	36 (28.8%)	0.005
ASPItest >30 U	26 (24.3%)	48 (38.4%)	0.05
ADPtest >50 U	10 (8.7%)	16 (12.8%)	ns
Von Willebrand factor activity >169.7%	11 (9.6%)	32 (25.6%)	0.01
Total antioxidant status <1.3 mM	12 (10.4%)	35 (28.0%)	0.01

AMI, acute myocardial infarction; ADPtest, adenosine diphosphate test; ASPItest, aspirin test.

Conclusions In patients with ACS a significantly reduced incidence of sudden cardiac death, acute myocardial infarction, recurrent angina with readmission, inadequate response to aspirin, high von Willebrand factor plasma value and low total antioxidant status serum values was observed in group treated with drugs with complementary mechanisms in comparison with control group.

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Keywords Sudden death incidence, drugs mechanisms in ACS.

CASD 002

Cardiac muscarinic receptor overexpression in Sudden Infant Death Syndrome

Pascal Bousquet[a], Angelo Livolsi, Nathalie Niederhoffer, Catherine Olexa-Zorn, Walid Mokni
[a]*Strasbourg, France. E-mail: pascal.bousquet@unistra.fr*

Purpose Sudden Infant Death Syndrome (SIDS) refers to the death of an infant <1 year of age that remains unexplained after rigorous case investigation and represents the leading cause of infant death. No biological abnormalities of the peripheral vago-cardiac system have been demonstrated to date. The present study aimed to seek such abnormalities in SIDS victims. To this end, the cardiac expression of muscarinic receptors and acetylcholinesterase (AchE) enzyme activity were investigated.

Methods Left ventricular samples and blood samples were obtained from autopsies of SIDS victims ($n = 9$) and children deceased from non cardiac causes (control group, $n = 11$). Total muscarinic receptor density was assessed in cardiac tissues using radioligand binding experiments with [3H]NMS, a selective muscarinic receptor ligand. AchE enzyme activity in erythrocytes was assayed colorimetrically.

Results The total cardiac muscarinic receptor density was more than double that found in controls (171.0 ± 95.3 vs. 74.5 ± 21.5 fmol/mg protein). Of note, muscarinic receptor densities were above control in eight out of nine SIDS samples. Average erythrocyte AchE activity was also significantly increased in SIDS victims (5.8 ± 1 vs. 4.6 ± 1 units/ml erythrocytes). Looking at the evolution of cardiac muscarinic density and AchE activity with age in SIDS compared to controls, it appeared that (i) most differences between the two groups occurred before the age of 5–7 months and (ii) the larger the alterations in vagal regulation, the earlier the age of death.

Conclusion An overexpression of muscarinic receptors has been observed in SIDS hearts. AchE was upregulated in SIDS, which may appear as an attempt to oppose the increased muscarinic receptor density to maintain the sympatho-vagal balance. This is the first demonstration of a peripheral vago-cardiac disorder in SIDS. It suggests that cardiac muscarinic receptor overexpression may represent a biological vulnerability to SIDS.

Keywords infant sudden death, cardiac muscarinic receptors.

CASD 003

Sudden cardiac death: Molecular autopsy and clinical management of relatives

Laura Ferrero-Miliani[a], Niels Morling, Henning Bundgaard, Gyda Lolk Ottesen, Rune Frank-Hansen [a]*Copenhagen, Denmark.*
E-mail: laura.ferrero@forensic.ku.dk

Sudden Cardiac Death (SCD) may be caused by several dominantly inherited heart diseases. The relatives to a SCD victim have a 50% chance of carrying the same genetic variation responsible for the disease and may also suffer a SCD if left undiagnosed and untreated. As many of the diseases related to SCD present neither signs nor symptoms it is important to follow a systematic approach in order to identify affected relatives. This includes a systematically performed autopsy, toxicology testing and the collection and storage of tissue from the deceased in order to perform a molecular autopsy. Between August 2009 and July 2010, 300 autopsies in people under 50 years of age were performed at the Department of Forensic Medicine at the University of Copenhagen. According to the data collected on the autopsy report, a substantial proportion of these deaths were likely to have been caused by an inherited heart disease. In these cases, it is important to follow a diagnostic algorithm for clinical management of the SCD victim's relatives. Here we illustrate the advantages and pitfalls of this approach.

Keywords SCD, molecular autopsy, genetic heart disease.

CASD 004

Screening for familial hypertrophic cardiomyopathy: a cost-effectiveness analysis

Anneke Hendrix[a], Arend Mosterd, Pieter Doevendans, Jan Post, Michiel Bots, Jacoba Greving
[a]*Utrecht, The Netherlands. E-mail: a.hendrix@umcutrecht.nl*

Background Information on the balance between the beneficial and harmful effects of genetic cascade screening for hypertrophic cardiomyopathy (HCM) is scarce. We aimed to evaluate the potential benefits, harms and cost-effectiveness of genetic cascade screening in relatives of HCM mutation carriers.

Methods and Results A decision analytical model was developed to compare genetic cascade screening to no screening in relatives of HCM mutation carriers and in relatives of victims of sudden cardiac death (SCD) in whom HCM was diagnosed with post-mortem investigation. Cohort age of the relatives was taken as 20 years and 45 years. Univariable and probabilistic sensitivity analyses addressed uncertainty in all model parameters. In 20-year-old relatives, screening prevented almost half of the SCD events (6% vs. 12%), increased life expectancy (44.0 vs. 42.7 years), increased quality-adjusted life-years (QALY) (30.2 vs. 29.9 QALYs) but also increased costs (€13 218 vs. €580 per patient). The costs of screening were €44 657 per QALY gained. Cost of screening were >€150 000 per QALY gained if age at screening was 45 years. The cost-effectiveness strongly improved when screening was performed in relatives of SCD victims diagnosed with HCM (€17 901 per QALY in 20-year-old relatives and €30 178 per QALY in 45-year-old relatives).

Conclusion Genetic cascade screening in relatives of HCM mutation carriers appears to be more cost-effective in 20-year-old relatives than in 45-year-old relatives. Screening of relatives of SCD victims in whom HCM was diagnosed strongly improved cost-effectiveness. These findings are relevant for the development of guidelines on screening for HCM.

Keywords hypertrophic cardiomyopathy, cost-effectiveness, genetic cascade screening.

CASD 005

Comparison of indicators metabolic syndrome among male smokers, Iran

Leila Jamshidi[a], Seif Asghar
[a]*Hamedan, Iran. E-mail: jamshidi.leila@gmail.com*

Introduction Worldwide non communicable diseases are increasingly recognized as a major cause of morbidity and mortality. They are accounted for 35 million of 58 million global deaths from all causes in 2005. Tobacco use, an unhealthy diet, physical inactivity increases the risk of heart attacks and strokes. People with the metabolic syndrome are at increased risk of coronary heart disease

Purpose The aim of this study was to determine the clustering pattern of metabolic variables among smoker and non smoker individuals and the inter relatinship between these risk factors.

Material and Method One hundred and twenty-eight smokers and 255 non smoker healthy males aged 30–78 years participated in this study. Standard questionnair was completing regarding smoking habits, medications, past medical history, physical activity, blood pressure, fasting blood suger, total cholestrol HDL, triglycerides .

Results We have found significant differences between M.S and C.H.D. The prevalence of M.S was 31%. The bivariable correlation between metabolic syndrome. Variables in both smoker and non smoker. Among the studied variables WHR showed a significant positive association ($P < 0.05$) with FBS, SBP, DBP, TG among smoker and non smoker.

Conclusion Although many cardiovascular disease can be treated or prevented many people die from CVDs. Reducing cigarette smoking, body weight, blood pressure, blood cholesterol, and blood glucose all have a beneficial impact on major biological cardiovascular risk factors. Behaviours such as stopping smoking, taking regular physical activity and eating a healthy diet promote health and have no known harmful effects.
Keywords metabolic syndrome, smokers.

CASD 006

Implantable cardioverter defibrillator (ICD) treatment and cardiac death after percutaneous transluminal septal myocardial ablation (PTSMA) in hypertrophy

Morten Jensen[a], Morten K. Jensen, Ole Havndrup, Steffen Helqvist, Henning Kelbæk, Erik Jørgensen, Christian Hassager, Lars Køber, Henning Bundgaard
[a]*Copenhagen, Denmark. E-mail: mortenjensen@dadlnet.dk*

Reports on long term risk of cardiac death after PTSMA are sparse. We assessed the long term prevalence of ICD indication and cardiac death in HOCM patients treated with PTSMA.
Methods Survival data and ICD recordings from a consecutive cohort of HOCM patients treated with PTSMA was obtained from in-hospital and national registries. All available patients were risk stratified according to current guidelines by Holter-monitoring, exercise test, clinical- and echocardiographic examination. Left ventricular wall thickness ≥30 mm (WT), unexplained syncope (US), non-sustained ventricular tachycardia (NSVT), family history of sudden death (<40 years of age) (FH) and abnormal blood pressure response (ABPR) (patients <50 years) were considered risk factors for sudden cardiac death (SCD). Presence of two risk factors or VT was considered indication for ICD treatment.
Results Seventy-two patients were treated with 2.6 ± 0.9 (mean ± SD) ml alcohol per PTSMA procedure. Four patients had ICD indication before the procedure. In the follow up period of 4.0 ± 2.6 years three patients had an ICD implanted. Twelve patients died before follow up (seven cardiac deaths) and eight refused participation in the risk stratification program. In 52 patients entering the program the distribution of risk factors were: FH – 0%, WT – 2%, ABPR – 43%, NSVT – 19%, US – 6% and VT – 2%. ICD indication was found in four patients (8%), and only one out of five examined ICD patients had two risk factors at follow up. The 5 year cardiac mortality was 11%, while the 5 year survival free of ICD indication and cardiac death was 79% (*Figure 1*).
Conclusion Severely affected HOCM patients treated with PTSMA remain at increased cardiac risk at long term. However, this risk is comparable to the risk of similar HOCM populations.
Keywords PTSMA, ICD, cardiac death, risk factors.

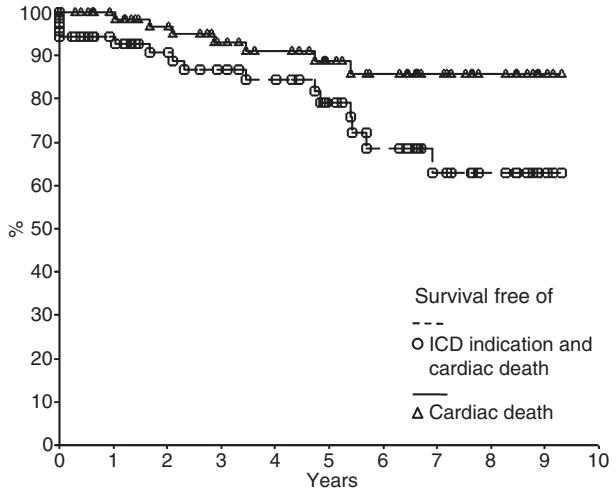

Figure 1 Survival free of cardiac death and implantable cardioverter defibrillator (ICD) indication.

CASD 007

Reduced risk of sudden cardiac death after alcohol septal ablation (ASA) in patients with hypertrophic obstructive cardiomyopathy

Morten Jensen[a], Christian Prinz, Dieter Horstskotte, Frank van Buuren, Thomas Bitter, Lothar Faber, Henning Bundgaard
[a]*Copenhagen, Denmark. E-mail: mortenjensen@dadlnet.dk*

Background The myocardial infarction induced by alcohol septal ablation (ASA) in patients with hypertrophic obstructive cardiomyopathy (HOCM) has been considered a potential arrhythmogenic substrate that may affect the risk of sudden cardiac death (SCD).
Methods The five risk factors (RF) for SCD in HCM were evaluated at baseline and 1.0 ± 1.8 years after ASA in a dual-center cohort of 465 HOCM patients (age 56 ± 14 years) with a post-ASA follow-up of 8.4 ± 3.9 years. Patients with ≥2 RFs are considered at high-risk (SCD-rate ~4% per year).
Results The 1, 5 and 10 years survivals free of SCD were 99.5% (CI 99–100%), 97% (CI 95–98%) and 96% (CI 94–98%), i.e. the annual SCD rate was 0.4%. ASA reduced the prevalences of abnormal blood pressure response (BPR) (23–9%, $P < 0.001$), syncope (26–2%, $P < 0.001$), non-sustained ventricular tachycardia (NSVT) (23–17%, $P = 0.047$) and maximal wall thickness (MWT) ≥30 mm (7–2%, $P < 0.001$). A family history of SCD in 19% was unchanged. Presence of ≥2 RFs was reduced from 25 to 8%. Patients with ≥2 pre-ASA RFs had an annual SCD-rate of 0.6%. We identified a modified RF-score; (i) family history of SCD, (ii) pre-ASA MWT ≥30 mm, (iii) post-ASA NSVT and (iv) post-ASA syncope. Patients with ≥2 of these RFs ($n = 22$; 7%) had reduced 10 years survival free of SCD (89%) compared to patients with <2 RFs ($n = 299$; 99%; Log Rank $P = 0.007$).
Conclusions ASA reduced the incidence of SCD and prevalences of the RFs for SCD as compared to the pre-ASA risk stratification. A modified RF-score for patients treated with ASA is proposed.
Keywords alcohol septal ablation, sudden cardiac death, RIsk stratification.

CASD 008

Cystic tumor of the atrioventricular node: syncope followed by death in a 9 year-old girl

Frederikke Kasper[a], Seija Ylijoki-Sørensen, Jytte B. Lundmose, Lia M. Pedersen
[a]*Aalborg, Denmark. E-mail: fredestrikke@hotmail.com*

Cystic tumor of the atrioventricular node (CTAVN) is a rare cardiac tumor. We report a case of a previously healthy 9 year-old girl, presenting with syncope caused by complete atrioventricular (AV) block. She was treated with isoprenalin, temporary pacemaker, hypothermia and antibiotics. Despite intensive treatment, she died of multiple organ failure after 2 days. All the microbiological and toxicological tests were negative. CT scans of the brain and thorax were inconclusive in terms of etiological diagnosis. At the autopsy, macroscopic examination of the heart and other organs was also inconclusive. Histology of the conduction system showed a microscopic CTAVN as the cause of death. CTAVN is a rare cause of AV block and cardiac arrest, but should be considered in cases of unexplained death.
Keywords cystic tumor of the AV-node.

CASD 009

G-Protein coupled inwardly rectifying potassium current contributes to ventricular repolarization

Bo Liang[a], Jakob D. Nissen, Morten Laursen, Hanne B. Rasmussen, Morten Grunnet, Søren-Peter Olesen, Thomas Jespersen
[a]*Copenhagen, Denmark. E-mail: boliang@sund.ku.dk*

Background The G protein-coupled inwardly rectifying potassium (GIRK) channel has a prominent role in modulation of heart electrical excitability, stabilizing resting membrane potential (RMP), and atrial action potential repolarization. However, the functional role of GIRK channels in ventricles is unclear. Recent evidence shows that GIRK current is underestimated in ventricles. Thus, GIRK current might be of greater physiological and pathophysiological relevance than previously thought in ventricles.
Objective The purpose of this study was to investigate the expression of GIRK channels in ventricles, as well as the functional role of GIRK current in ventricular repolarization.
Methods and Results Immunofluorescence experiments demonstrated that GIRK4 was localized in t-tubules, outer cell membrane, and intercalated disks in both atria and ventricles in mice. GIRK4 was localized only in intercalated disks in rat ventricle, whereas it was localized in intercalated disks and outer cell membrane in rat atria. In contrast, GIRK4 was localized in t-tubules and intercalated disks in human endocardium and epicardium, but absent in midcardium. Ex vivo experiments on rat ventricular tissue showed that N6-Cyclopentyladenosine (CPA) and acetylcholine (ACh) shortened the action potential duration (APD) and that APD shortening was recovered by either the highly selective GIRK channel blocker rTertiapin Q (TTQ), or the selective adenosine A1 receptor antagonist DPCPX, or the selective muscarinic M2 receptor antagonist AF-DX 116. TTQ prolonged APD in the absence of G-protein coupled receptor (GPCR) activation. CPA also hyperpolarized the RMP, an effect which could be recovered by TTQ. In contrast, TTQ depolarized RMP in the absence of GPCR activation.
Conclusion GIRK4 are differentially expressed in mice, rat, and human ventricle, and GIRK4 was found heterogeneously expressed across the human ventricular wall. Ex vivo studies shown GIRK current contributed to ventricular repolarization, suggesting GIRK channels to have a functional role in ventricular electrical activity.
Keywords ion channel, repolarization, GIRK.

CASD 010

Is asystole during tilt testing association with significant arrhythmia?

Jesper Mehlsen[a], Louise Brinth, Anne-Birgitte Mehlsen
[a]*Frederiksberg, Denmark. E-mail: jesper.mehlsen@frh.regionh.dk*

The study investigated the outcome of Holter-monitoring in a large group with recurrent syncope presenting with asystole during a head-up tilt test.
One hundred and fourteen consecutive patients (73 women, mean age: 32.6 year (±14.4)) were included and submitted to 20 min of head-up tilt to 60 °C followed by sublingual nitroglycerin with continued tilting for 15 min or till the occurrence of syncope. RR-intervals and blood pressure were measured continuously. All patients had a normal 12-lead ECG and the initial hemodynamic response to head up tilt was normal. Forty-eight hour Holter monitoring was offered if it had not been done previously. Twenty-four hour heart rate variability was quantified by standard deviations (SDNN) of normal RR-intervals and by the difference between successive normal beats (RMSSD).

Syncope occurred after a tilt period of 16 min (range: 0.4–30) and asystole lasted for 21 s (range: 3.4–82.2 s). Asystole was preceded and followed by arrhythmia in 47 and 93 subjects, respectively. The arrhythmias consisted of junctional rhythm in 70%, second, or third degree atrioventricular block in 10, and 16%, respectively and atrial fibrillation in 3%. The arrhythmias following asystole lasted for up till 10 min. Holter-monitoring showed relative pauses in 16, absolute pauses in 3, short episodes of supraventricular tachycardia in 30 and ventricular tachycardia lasting 13 beats in one patient. Stratifying heart rate variability as

being above or below the upper confidence limits for SDNN and RMSSD did not result in any significant differences between groups with respect to duration of asystole or type and duration of the associated arrhythmia.

Holter monitoring in patients with cardioinhibitory syncope revealed a number of primarily benign arrhythmias such as relative pauses and self terminating supraventricular tachycardia. Only in one subject with non-sustained ventricular tachycardia of short duration did the observations lead to further investigations.

Keywords syncope, arrhytmia, cardioinhibition.

CASD 011

Tpeak-Tend interval and Tpeak-Tend/QT ratio as markers of lone atrial fibrillation

Jonas B. Nielsen[a], Morten S. Olesen, Stig Haunsø, Jesper H. Svendsen, Anders G. Holst
[a]*Copenhagen, Denmark. E-mail:jonas.bille.nielsen@gmail.com*

Aims We have recently shown that incomplete right bundle branch block is associated with lone atrial fibrillation (AF), indicating that disturbances in cardiac electrophysiology in lone AF patients may be present not only in the atria, but also in the ventricles. In this study we hypothesized that early-onset lone AF would be associated with changes in elements of the QT-interval.

Methods and Results This case-control study was conducted to compare electrocardiogram (ECG) markers of ventricular repolarization from patients with early-onset lone AF to a healthy control population. One hundred and twenty five paroxysmal or persistent lone AF patients (84% males, median age 37) and 250 gender matched healthy controls (84% males, median age 39) with a sinus rhythm ECG were included. Lone AF patients had both a significantly shorter Tpeak-Tend interval (lead V2: 79.7 vs. 94.0 ms; $P < 0.001$) and a decreased Tpeak-Tend/QT ratio (lead V2: 0.211 vs. 0.243; $P < 0.001$) compared to controls. In multivariable analysis adjusted for conventional risk factors, Tpeak-Tend/QT ratio was strongly and independently associated with early-onset lone AF (odds ratio for below vs. above median 0.31; 95% confidence interval 0.17–0.56; $P < 0.001$).

Conclusions We are the first to report that a shortened Tpeak-Tend interval and a decreased Tpeak-Tend/QT ratio during sinus rhythm is strongly and independently associated with early onset lone AF.

Keywords Tpeak-Tend interval, atrial fibrillation, arrhythmia.

CASD 012

Building a platform for diagnosing long QT syndrome in the horse

Philip J. Pedersen[a], Jørgen K. Kanters, Dan A. Klærke, Rikke Buhl
[a]*Frederiksberg, Denmark. E-mail: philip@life.ku.dk*

Background Long QT syndrome (LQTS) is an genetic disorder characterized by prolonged QT interval in the ECG. Patients are predisposed to syncopal episodes and sudden cardiac death. Mutations in KCNQ1 and KCNH2 genes coding the Iks and Ikr repolarizing K+ currents in the heart are responsible for more than 90% of cases. Up to 68% of sudden death events in racehorses do not have lesions sufficient to account for the death on necropsy and are suspected of exercise-induced acute cardiovascular failure. The objective of our work is to build a genetic background for diagnosing LQTS in the equine population aiming to use QT interval as a clinical biomarker for the disease.

Methods MRNA was extracted from equine ventricular myocytes. From cDNA full length KCNH2 DNA products could be amplified using RACE PCR. The DNA was sequenced (GenBank: HM641824.1) and cloned for expression in Xenopus oocytes where two-electrode voltage clamp (TEVC) was performed.

Reference values for the equine QT interval were determined by analyzing ECGs from 30 Swedish trotters. Stable heart rate (HR) areas were localized and QT intervals were measured manually. A piecewise regression model gave the best description of the QT interval in the horse as a function of the HR (RR interval).

Results The equine KCNH2 sequence is 99% homologous with the human. TEVC confirmed that the equine KCNH2 channel is functional and have electrophysiological properties resembling the human channel.

With our QT interval model we found that for a trotter QTc adjusted for an RR interval of one second is approximately 475 ms for a stallion, 452 ms for a mare and 443 ms for a gelding.

Conclusion Using the obtained reference QTc value it is now possible to assign suspected equine LQTS patients to genetic testing before an event of syncope or sudden cardiac death occur.

Keywords horse, heart, QT interval, long QT syndrome.

CASD 013

Effect of clopidogrel in STEMI

Marek Prech[a], Ewa Bartela, Aleksander Araszkiewicz, Igor Jeremicz, Magdalena Janus, Malgorzata Pyda, Aleksandra Kutrowska, Marcin Jezierski, Witold Laskowski [a]*Leszno, Poland. E-mail: mmprech@wp.pl*

Pharmacologic treatment that facilitates primary coronary angioplasty in STEMI patients is still being investigated.

Aim To assess rate of aborted myocardial infarction (MI) in STEMI patients pretreated with 600 mg of clopidogrel.

Material and Methods We studied 305 consecutive STEMI patients referred to our department for primary coronary angioplasty. Inclusion criteria were: (i) chest pain persisting for >30 min, (ii) ST-segment elevation >1 mm in ≥2 contiguous leads, (iii) admission within 12 h of symptoms onset, (iv) pre-treatment with triple regimens: 600 mg of clopidogrel, aspirin and heparin (bolus of 5000 IU iv). Aborted MI was defined as maximal CK-MB ≤2× upper limit of normal level. Relationships between rate of aborted MI and initial TIMI flow in infarct-related artery, total ischemic time, clopidogrel to balloon time and ST-segment total resolution were analyzed.

Results Thirty-one patients (10.1% of the whole group) met criteria of aborted MI. Patients with aborted MI did not differ with respect to total ischemic time (231.2 ± 129.3 vs. 240.4 ± 132.3 min; NS) or clopidogrel to balloon time (93.4 ± 32.6 vs. 100.5 ± 36.9 min; NS) when compared to rest of group. Initial TIMI flow ≥2 (87.0 vs. 28.1%; $P < 0.001$) and early ST-segment resolution (74.2 vs. 24.1%; $P < 0.001$) were significantly more often observed in them. Logistic regression model showed initial TIMI flow ≥ 2 (OR 10.65; $P < 0.0001$) and early ST-segment resolution (OR 2.78; $P < 0.05$) but not short ≤ 2 h) total ischemic time (OR 1.24; NS) as independent predictors of limitation of myocardial necrosis.

Conclusions Initial TIMI flow ≥2 and early ST-segment resolution are the predictors of limitation of myocardial necrosis.

Keywords aborted myocardial infarction, clopidogrel, TIMI.

CASD 014

Prevalence of early repolarization in population. The Czech post-MONICA study

Jiri Prochazka[a], Peter Wohlfahrt, Vera Adámková
[a]*Prague, Czech Republic. E-mail: prochazka.jiri.dr@volny.cz*

For many years early repolarization (ER) was considered to be an innocent ECG finding with benign prognosis. Recently ER in inferior leads was found to be associated with increased risk of idiopathic ventricular fibrillation and cardiovascular death.

Aim The aim of our study was to find out the prevalence of ER in inferior leads in a representative sample of the Czech population.

Methods On 12-lead electrocardiogram from 603 individuals from the Czech post-MONICA study (1% random population sample of the Czech population) we assessed the J-point elevation over 1 mm in II, III, aVF leads.

Results In a random population sample of the Czech population 10 subjects out of 603 had ECG signs of early repolarization in inferior leads, what represents 1.7% prevalence. Compared with individuals without ER signs, those with ER were more often males (70% vs. 40%, $P < 0.05$), were taller (180.5 ± 3.6 vs. 170.7 ± 9.3, $P < 0.01$), had lower resting heart rate (58.2 ± 10.1 vs. 67.0 ± 10.5, $P = 0.01$) and shorter QTc interval (400.9 ± 21.8 vs. 423.7 ± 22.6, $P < 0.01$). There was no age difference between groups.

Conclusion We have described for the first time the prevalence of early repolarization in the Czech population. We have confirmed the association of ER with male gender and slower heart rate. The QTc shortening in individuals with ER supports the common origin of syndromes with local or global repolarization abnormalities – J wave syndromes (ER, Brugada syndrome, and short QT syndrome).

Keywords early repolarization, prevalence, J wave syndromes.

CASD 015

Familial co-aggregation of premature death and early-onset cardiovascular disease

Mattis Flyvholm Ranthe[a], Lisbeth Carstensen, Nina Øyen, Jacob Tfelt-Hansen, Michael Christiansen, William McKenna, Jan Wohlfahrt, Mads Melbye, Heather Boyd
[a]*Copenhagen, Denmark. E-mail: FLY@ssi.dk*

Background Arrhythmias are important causes of morbidity and death. Since arrhythmias in the young are often associated with inherited cardiac disease, premature cardiac deaths in the family might signal an increased risk of cardiovascular disease. We examined the effect of a family history of premature death on the risk of early-onset cardiovascular disease (CVD).

Methods Using Danish national registers, we established a cohort of persons born in 1950–2008 and identified those with a family history of premature death (<60 years). Individuals were followed for development of early-onset CVD (<50 years). Poisson regression estimated incidence rate ratios (IRRs) and 95% confidence intervals (CIs).

Results Thirty nine lacks eighty-five thousand three hundred and one persons were followed for 89 294 258 person-years; 129 825 and 5214 persons were diagnosed with any CVD and ventricular arrhythmia (VA), respectively. IRRs (CI) for any CVD and VA given premature cardiac deaths in first-degree relatives were 1.72 (1.68–1.77) and 1.94 (1.70–2.20), respectively. In contrast, the corresponding IRRs given non-cardiac deaths were only 1.12 (1.10–1.14) and 1.21 (1.11–1.31). With ≥2 cardiac deaths, the IRRs for CVD and VA were 3.30 (2.77–3.94) and 6.18 (3.32–11.50), respectively, and the relative risks of these conditions before age 35 years given cardiac deaths in relatives aged <35 years were 3.62 (2.93–4.47) and 11.1 (6.29–19.6), respectively. Deaths in grandparents conferred lower risks as compared to parents.

Conclusion Family history of premature death was consistently and significantly associated with risk of early-onset CVD, suggesting a genetic contribution to early-onset CVD and an inherited cardiac vulnerability. These results should inform clinical and genetic evaluations and treatment in families with a history of premature death.

Keywords arrhythmia, premature death, familial aggregation, epidemiology.

CASD 016

Anti-aldosterone therapy also to mild heart failure and servere hypertension

Luis Ruilope[a]
[a]*Madrid, Spain. E-mail: ruilope@ad-hocbox.com*

In recent times the capacity of aldosterone blockers to improve the outcome of patients with HF and a diminished left ventricular function was shown in RALES and EPHESUS studies. This year the capacity of eplerenone to improve the outcome of patients with mild hypertension has also been shown. The expansion of the need of the use of aldo blockers has also come with the demonstration of these drugs to facilitate BP control in resistant hypertension and also in the capacity to decrease proteinuria and improve renal outcome in patients with CKD.

Keywords heart failure, hypertension, anti-aldosterone drugs, resistant hypertension.

CASD 017

CAV3 variants detected in an unselected nationwide cohort of Sudden Infant Death Syndrome (SIDS) cases

Golnaz Sadjadieh[a], Bo G. Winkel, Anders G. Holst, Stig Haunsø, Morten S. Olesen, Jacob Tfelt-Hansen
[a]*Copenhagen, Denmark. E-mail: golle_s@yahoo.dk*

Purpose Mutations in the CAV3 gene have previously been associated with LQTS and SIDS. The purpose of this study was to determine the incidence of CAV3 variants in a nationwide unselected cohort of SIDS cases.

Methods Death certificates of all infant deaths, and autopsy reports in all sudden unexpected infant deaths (<1 year) in a 7-year period (2000–2006), were collected and read. Deaths fulfilling the SIDS criteria, in which DNA were available for genetic testing, were included in the study ($n = 66$). The coding sequence of CAV3 was investigated using intronic primers, high resolution melting curve analysis, and direct sequencing.

Results One non-synonymous mutation, T78M, was found in a single case (1.5%) of SIDS. This mutation was in a highly conserved residue, was not found in control subjects ($n = 210$) and have previously been described in LQTS and SIDS cohorts. Three common polymorphisms, L9L (24%), N33N (45.6%), and F41F (46.5%) were likewise found in the cohort.

Interestingly, the prevalence of possible disease causing CAV3 mutations in this unselected nationwide SIDS cohort does not differ significantly from those found in previous highly selected SIDS cohorts.

Conclusion In a nationwide unselected cohort of SIDS cases, 1.5% had a non-synonymous possible disease causing CAV3 mutation not found in control subjects. This study suggests that genetic screening of CAV3 is important in SIDS cases and should be included in a molecular autopsy.

Keywords CAV3, LQT syndrome, SIDS, nationwide.

CASD 018

Efficacy of caevedilol in patients with congestive heart failure associated with various heart diseases

Masahito Sakai[a]
[a]*Takeo, Japan. E-mail: caj33660@pop17.odn.ne.jp*

Introduction Among medical therapies for heart failure beta-blockers were associated with a relatively higher mortality reduction than other drugs. However, the treatment dose of carvedilol may vary among different ethnic groups. We have beta-blockers aggressively for various congestive heart failure (hypertensive heart disease). In the present study, we investigated a low dose of carvedirol was effective in the various forms of CHF.

Methods This study included congestive heart failure patients (HHD 28, IHD 20, VHD 9, DCM 3, HOCM 1, unknown 20) in whom carvedilol was initiated between December 2007 and December 2010. They composed 36 men and 44 women, aged 35–85 years (median age, 70 years). Carvedilol was initiated at a dose of 2.5 mmg/day and every week there after with a target dose of 10 mg/day.

The study prospectively assessed the efficacy and adverse reactions based on the changes in symptoms, cardiothoracic ratio (CTR), left ventricular ejection fraction (LVEF), and human brain natriutetic peptide (BNP). The mean follow up period was 10 months.

Results The mean CTR decreased from 65.5 ± SD3.2% to 60.2 ± SD2.5% and the mean LVEF improved from 40.5 ± SD2.5% to 65.2 ± SD4.2%.

In the cases of poor LV function, LVEF improved 30.5 ± SD5.2% to 60.5 ± SD3.5%. Mean BNP levels showed a decrease from 305.5 ± SD5.2 pg/ml to 150.3 ± SD6.3 pg/ml.

Conclusions Carvedilol has been effective in various forms heart failure. In particular, cavedilol therapy improved heart failure with preserved systolic function and clinical performance and reduced BNP levels.

Keywords β-blocker.

CASD 019

ECG based blood potassium estimates

Stefano Severi[a], Cristiana Corsi, Sanjay Kharche, Johan DeBie, Raffaella Bloise, Carlo Napolitano, Silvia G. Priori, Antonio Santoro, David Mortara
[a]*Bologna, Italy. E-mail: stefano.severi@unibo.it*

The aims of the study were to develop a method quantifying serum potassium concentration ([K+]) from T-wave analysis, validate it on dialysis patients undergoing rapid [K+] variations and test the estimator on LQT2 patients, where the link between [K+] and ECG is disrupted.

We analyzed Holter ECG acquired from 13 hemodialysis (39 sessions) and 7 LQT2 patients. The two most significant eigenleads were used to calculate the T-wave downslope and amplitude during each beat. A 2-min window median value of the ratio of the T-wave slope to amplitude (TS/A) was used to estimate [K+]. Reference values were obtained from blood samples. An ECG-based potassium estimator (KECG) was defined as a quadratic function of TS/A and compared to the reference. Data from 33/39 sessions gave consistent results. In six sessions the presence of a systematic error inhibited reliable estimates. Patient specific calibration allowed good agreement in all patients (error: −0.04 ± 0.61 mM). In contrast, [K+] was significantly underestimated in LQT2 patients (error: 1.24 ± 0.75 mM, $P < 0.01$).

Preliminary results show the KECG estimates can be an effective tool for hyper/hypokalemic risk patient monitoring. Data from LQT2 patients suggest that IKr dependence on extracellular potassium is crucial in determining the link between [K+] and T wave morphology.

Keywords potassium, ECG.

CASD 020

Inhibition of SK channels in human atria tissue

Lasse Skibsbye[a], Erik Wettwer, Torsten Christ, Ursula Ravens, Morten Grunnet, Thomas Jespersen
[a]*Copenhagen, Denmark. E-mail: lassesk@sund.ku.dk*

Background Atrial fibrillation (AF) is associated with increased morbidity and mortality and is in addition the most prevalent cardiac arrhythmia. Our group has previously shown that pharmacological inhibition of Small Conductance Ca^{2+}-activated K+ (SK) Channels exhibit anti-arrhythmic effects in different species including rat, guinea pigs and rabbit ex vivo as well as in vivo.

Methods The present study was devoted to evaluate, whether pharmacological inhibition of SK channels would have any effect on the human atrial action potential morphology. These studies were done on intact human cardiac muscle strips obtained from patients undergoing valve displacement or by-pass surgery.

Results In this study we show that inhibition of SK channels exhibit pharmacological effects on human atrial tissue, acutely isolated from right atrial appendages. Two chemically and mechanistically different SK channel inhibitors significantly increased the atrial action potential duration and the atrial effective refractory period in tissue from both patients in sinus rhythm and atrial fibrillation.

Conclusion The functional role of SK channels in human atrial tissue was demonstrated by two different SK channel inhibitors NS8593 and UCL1684, thereby indicating that these channels might constitute a new target for anti-arrhythmic treatment.

Keywords Ca^{2+}-activated K+ Channels, SK channels, atrial fibrillation, human atrial tissue.

CASD 021

A mouse model of hypertrophic cardiomyopathy with a high frequency of sudden cardiac death

Weihua Song[a], Emma Dyer, Lorenzo Monserrat, Dominic Wells, Steven B. Marston
[a]*London, UK. E-mail: whsong@imperial.ac.uk*

We have created a transgenic mouse that expresses the ACTC E99K mutation in cardiac actin at 50% of total actin. Patients with this mutation have apical hypertrophy. Sudden cardiac death was reported in 8/61 carriers with five deaths in a single family. The transgenic mice showed high mortality; 42% of females and 22% of males died within a short period (28–45 days old). Survivors had almost normal mortality. A 40 days old female mouse was seen having sudden death. The mouse behaved as normal before it was gently held. Within around 20 s, the mouse suddenly went through sustained and violent limb clonic jerking and head bobbing to fetal posture and stretching for a couple of time before freezing. The heart and lung were immediately collected and fixed. The lung was not fully expanded but there were no fluid accumulation in the thorax cavity. The molecular phenotype of the ACTC E99K mutation is an increase in myofibrillar Ca^{2+}-sensitivity, similar to most HCM-causing mutations. It has been proposed that this is sufficient to alter Ca^{2+}-homeostasis and thereby to increase the probability of potentially fatal arrhythmias. ECG recordings of anaesthetised survivor mice showed significant higher frequency of atrial ectopic beats, atrial flutter, flattened or negative T wave, and abnormal intraventricular conduction blockage (double or deep S waves). This mouse model is potentially very useful in the study of the origin of SCD in HCM. The high proportion of SCD at a consistent age indicates a link with growth and maturation. The higher probabilities of SCD in females may be related to the different action potential duration in males and females and the presence of a significant proportion of survivors for the mutation on a hybrid C57BL\6 × CBA\Ca background indicates an important role of genetic background in determining the SCD phenotype.

Keywords sudden cardiac death, hypertrophic cardiomyopathy, cardiac actin, Ca2 + -sensitivity.

CASD 022

Mitochondrial function in survivours of cardiac arrest treated by therapeutic hypothermia

Nis Stride[a], John Bro-Jeppesen, Steen Larsen, Jesper Kjærgaard, Flemming Dela, Christian Hassager
[a]*Copenhagen, Denmark. E-mail: nis.stride@gmail.com*

Background The Post-cardiac arrest syndrome comprises brain injury, myocardial dysfunction, systemic ischemia/reperfusion response and persistent precipitating pathology. These entities are managed in the ICU according to empirically based treatment algorithms but their molecular background is still largely unknown. Ischemia/reperfusion has been shown to cause excessive production of free oxygen radicals (ROS) (O_2-, H_2O_2, OH−) which can lead to mitochondrial dysfunction.

Animal models have shown that therapeutic hypothermia ameliorates the mitochondrial dysfunction observed in cerebral and myocardial ischemic events and mild therapeutic hypothermia is recognized as part of a treatment strategy for comatose survivors of cardiac arrest, possibly reducing the generation of ROS within the mitochondria of target tissues.

Hypothesis We speculated that therapeutic hypothermia would generally protect the mitochondria of all cells against oxidative stress and that a body core temperature of 33 °C would preserve mitochondrial function better than therapeutic hypothermia at 36 °C.

Method A subset of 20 patients from the TTM-study are currently having biopsies performed (m. quadriceps femoris) 24 h after initiation of hypothermia. High resolution respirometry allows for assessment of the individual complexes of the electron transport chain (ETC). The intactness of the outer mitochondrial membrane and the degree of coupling between ETC and oxidative phosphorylation

(in which ATP is produced) is evaluated. The capacity of the mitochondrial creatine kinase enzyme system is assessed from ADP titration protocols in the presence and absence of creatine after application of Michaelis-Menten enzyme kinetics to the resulting dose-response curves. The expression of enzymes involved in the defense against ROS (superoxide-dismutase, glutathione-peroxidase, manganese-dismutase) are measured via RT-PCR and Western Blotting and will be performed when patient inclusion has been finalized.
Status Forteen patients have been included, but the results have not yet been evaluated due to investigator blinding.
Keywords therapeutic-hypothermia, mitochondria.

CASD 023

A review of consecutive cardiac arrests in 2002 and 2007 at a regional hospital in Denmark: a retrospective cohort study

Henriette Ullerup-Aagaard[a], Søren Nielsen, Mikkel Brabrand
[a]*Odense C, Denmark. E-mail: h_ullerup@hotmail.com*

Background Most of the available literature on cardiac arrests is dealing with treatment. In this cohort study, we have sought to describe the events surrounding cardiac arrests such as time, cause, initial rhythm, and the final outcome.
Methods Retrospective analysis of all consecutive cardiac arrests at Sydvestjysk Sygehus Esbjerg in the years 2002 and 2007. The events were initially identified using a registry in the Department of Anesthesia on all patient contacts. Using a unique personal identification number on all patients, we retrieved the charts and nurses notes and extracted the relevant data.
Results We included 267 cardiac arrests, 175 out-of-hospital and 91 in-hospital arrests. The cardiac arrests were distributed with 24% in daytime (08–16), 20% in the evening (16–00) and 26% at night (00—08). The causes of cardiac arrests were acute coronary syndrome in 24%, respiratory insufficiency in 13%, hypotension in 5%, arrhythmias in 3%, other causes in 15% and unknown in 40%. The initial rhythm was asystole in 58%, pulseless electrical activity in 18%, pulseless ventricular tachycardia/ventricular fibrillation in 15%, rhythm with perfusion in 2% and unknown in 7%. In three patients, the treatment was stopped because of a Do Not Attempt Resuscitation order in the chart. In 64 patients (20%) the treatment was stopped due to return of spontaneous circulation and 30 (47%) patients survived to discharge.
Conclusion Cardiac arrests at Sydvestjysk Sygehus Esbjerg occur around the clock with an even distribution during the day, evening and night. Most cardiac arrests are caused by acute coronary syndrome and respiratory failure. We most often witnessed asystole as the presenting rhythm.
Keywords cardiac arrest.

CASD 024

A novel SCN5A mutation found in a young sudden unexplained death patient

Yinman Wang[a], Bo Gregers Winkel, Mads Hollegaard, David Hougaard, Stig Haunsø, Morten S. Olesen, Jacob Tfelt-Hansen
[a]*Copenhagen, Denmark. E-mail: wswangyinman@yahoo.com.cn*

Background Sudden unexplained death (SUD) is characterized by sudden death with negative autopsy. Studies have shown that gain or loss of functions of LQT genes have association with this disease.
Aim To investigate the roles of three major LQT genes (KCNQ1, KCNH2, and SCN5A) in 27 young SUD cases, and find potential molecular genetic predisposition to SUD.
Method and Results A population based study enrolled 27 patients from 1 to 35 years died suddenly with negative autopsy. Healthy people without cardiac disease were used as controls. The whole-genome DNA was amplified in triplicates using genomic DNA extracted from the dried blood spot at birth. Genetic analysis of KCNQ1, KCNH2, and SCN5A were performed using light scanner and Big Dye chemistry on a DNA analyzer 3730. The coding regions and splice junctions were sequenced bidirectional. One missense mutation P1177L in SCN5A was identified in one male patient aged 20 years. The mutation was not found in 1100 controls or in public available databases. P1177L mutation located in highly conserved residue (*Figure 1*) and was predicted to be possibly damaging using Polyphen prediction software.
Conclusions A novel SCN5A gene mutation (P1177L) seems to predispose to death in a case of SUD in young male
Keywords sudden unexplained death, SCN5A, sudden cardiac death.

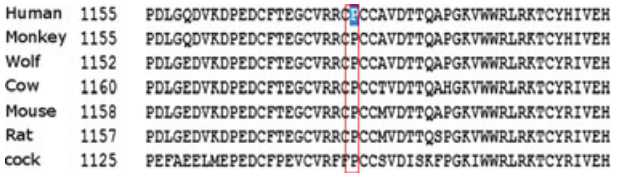

Figure 1 P1177L mutation located in highly conserved residue.

CASD 025

Cardiac ion channel mutations in the sudden infant death syndrome

Ronald Wilders[a], Eva C. Klaver, G. Marja Versluijs
[a]*Amsterdam, The Netherlands. E-mail: r.wilders@amc.uva.nl*

Sudden infant death syndrome (SIDS) is characterized by the sudden death of an infant that occurs during sleep and remains unexplained despite thorough examination. Postmortem genetic analysis ('molecular autopsy') of SIDS cases has revealed a number of cardiac ion channel mutations that are associated with arrhythmia syndromes, including the long QT syndrome, Brugada syndrome and short QT syndrome. Mutations have been found in genes directly encoding (subunits of) cardiac ion channels as well as in related genes, including KCNQ1, KCNE1, KCNH2, KCNE2, KCNJ8, SCN5A, SCN3B, SCN4B, CAV3, GPD1-L and SNTA1. More than half of the reported mutations are related to the cardiac sodium channel. In addition to mutations in the alpha-subunit encoding gene, SCN5A, there are mutations in the beta-subunit encoding genes SCN3B and SCN4B and in the 'regulatory genes' CAV3, GPD1-L and SNTA1. Approximately 30% of the reported mutations occur in the potassium channel genes KCNQ1, KCNE1, KCNH2, KCNE2, KCNJ2 and KCNJ8. Combining data from population-based cohort studies, we conclude that at least one out of five SIDS victims carries a mutation in a cardiac ion channel-related gene and that the majority of these mutations are of a known malignant phenotype.
Keywords sudden infant death, ion channelopathies, long QT syndrome, Brugada syndrome.

CASD 026

Evaluation of sudden death and non-haemorrhagic stroke and their association with HIV protease inhibitor (PI) usage

Signe W. Worm[a], David Kamara, Peter Reiss, Matthew Law, Antonella d'Arminio Monforte, Andrew Phillips, Lene Ryom, Francois Dabis, Rainer Weber
[a]*Copenhagen, Denmark. E-mail: sww@cphiv.dk*

Objective The FDA has issued warnings that several PIs, used for the treatment of HIV, may have an effect on the electric conductivity of the heart (ECG abnormalities: prolongation of PR- and QT-interval). In the general population, such abnormalities may lead to an excess risk of sudden death. Sudden deaths (SD) and non-haemorrhagic strokes (NHS) are 'the end-stages' of different ECG abnormalities. The possible clinical consequences of these ECG abnormalities in HIV-positive persons have not been assessed.
Methods Centrally validated cases of SD and NHS were identified using standard case-definitions with cardiologist input. Person-years (PY) were calculated from entry in D:A:D to the first event, death, 6 months after last clinic visit or February 2009. The association between the combined endpoint and exposure to PIs was investigated using Poisson regression, adjusting for confounders (age, sex, body mass index, family and personal history of CVD).
Results Two hundred and fifty patients developed an event (79 SD and 171 NHS) over 234 818 PY (incidence: 1.06/1000 PY; rates of 1.23 and 0.92, respectively, for those exposed to PIs and those not exposed). The unadjusted rate ratio for exposure to PIs was 1.34 (95% confidence interval 1.04–1.71); this was diminished in adjusted analysis to 1.19 (0.92–1.52). Similar results were obtained when SD were considered alone [unadjusted rate ratio for PI use: 1.40 (0.90–2.19); adjusted rate ratio: 1.31 (0.84–2.04)].
Conclusions We have no evidence to suggest that PIs, as a class, increase the risk of SD/NHS. As SD/NHS are 'the end-stages' of different ECG abnormalities, any association with sudden deaths, if one does indeed exist, may have been diluted by the inclusion of NHS. However, the fact that several PIs have been reported to have an effect on the electric conductivity of the heart means that both outcomes are of relevance.
Keywords sudden death, HIV, protease inhibitors, non-haemorrhagic strokes