Suomen Kardiologinen Seura

Finnish Cardiac Society

43rd Progress Report Meeting

March 29, 2017

Kuopio

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43rd Progress Report Meeting

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Meeting is supported by unrestricted educational grant from Boehringer Ingelheim

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Progress Report -kilpailu tulee,

miksi nuoren tutkijan kannattaa osallistua?

Vastaajana kardiologi, Suomen Kardiologisen Seuran ed. puheenjohtaja Mikko Pietilä.

1 Miksi Suomen Kardiologisen Seuran Progress Report -kilpailuperinne on tärkeä?

Kilpailu on nuorelle tutkijalle paraatipaikka esitellä omia tutkimustuloksia suomalaiselle kardiologikunnalle. Tilaisuus on kannustava, mutta toisaalta siinä on riittävästi painetta antamaan esimakua siitä, millaista on esittää tuloksia ulkomaisilla areenoilla. Kilpailu mittaa paitsi tutkimuksen tasoa myös esiintymistaitoa. On erittäin tärkeää osata tuoda tutkimustuloksia esille sujuvassa muodossa.

Kilpailu on myös eräänlainen ponnahduslauta suuremmille areenoille. Aika moni nykyisistä professoreista ja ylilääkäreistä on sijoittunut hyvin näissä kilpailuissa.

2 Miksi nuoren tutkijan kannattaa osallistua kisaan?

Kilpailu on hyvä tilaisuus saada itsensä suomalaisen kardiologikunnan tietoisuuteen ja kouliintua esiintymistaidoissa. Omasta kokemuksestani tiedän, että esimerkiksi amerikkalaiskokouksissa vastaanotto saattaa olla kylmää ja aggressiivistakin. Kun on harjoitellut esiintymistä, ei jää sanattomaksi tiukkojen kommenttien ja kysymysten edessä. Lisäksi saman abstraktin voi lähettää vaikka ESC:n kokoukseen, jonka lähetysaika päättyy samoihin aikoihin. Parhaimmillaan pääsee harjoittelemaan siellä pidettävää esitystä hyvissä ajoin!

Kisa on myös tilaisuus saada palautetta oman tutkimusryhmän ulkopuolelta meritoituneilta suomalaistutkijoilta. Tämä voi avata uusia näkemyksiä omaan tutkimusalueeseen.

3 Mikä rooli Progress Report -kilpailulla on Suomen Kardiologisen Seuran toiminnassa?

Seuran jäsenyys ei ole osallistumisen edellytys. Seuran tärkeimpiä tehtäviä on viedä suomalaista tutkimusta eteenpäin, ja kilpailu palvelee tätä tarkoitusta. Kilpailu on toisaalta yksi tapa tehdä seuraa tutuksi uudelle kardiologipolvelle. Millään yhdistyksellä ei ole tulevaisuutta ilman nuoria.

4 Olet itsekin osallistunut kisaan, millainen kokemus se oli?

Osallistuin kisaan kahdesti 1990-luvun jälkipuoliskolla väitöskirjatyöhöni liittyneillä, sydämen vajaatoimintaa käsitelleillä tutkimuksilla. Kun ensimmäisellä kerralla esittelin työni tuloksia, se oli kohtuullisen jännittävä tilanne. Toisella kerralla sitä suhtautui jo vapautuneemmin. Itselläni osallistuminen lievitti myös turhaa jännitystä siitä, osaanko esittää tuloksiani kansainvälisillä areenoilla.

Vaikken sijoittunut kahden parhaan joukkoon, kokemus oli silti hyvä. Jo esikarsinnasta esiintymään pääseminen tuntui saavutukselta. Erityisen positiivista osallistumisessa oli, että moni kollega oli silloin kilpailemassa. Se lujitti meidän samanikäisten wannabe-kardiologien yhteishenkeä.

Suomen Kardiologisen Seuran nuorten tutkijoiden Progress Report -kilpailu järjestetään seuran kevätkokouksen yhteydessä Kuopiossa 29.-31.3.2017 Abstraktien lähetysaika päättyy su 12.2.2017. Kilpasarjojen voittajat palkitaan Boehringer Ingelheim Finlandin lahjoittamilla 2300 euron matka-apurahoilla.

Lisätietoja kilpailusta Suomen Kardiologisen Seuran nettisivuilta
www.fincardio.fi/apurahat/progress_report_yiac/

Boehringer Ingelheim

P94/20112015

History of the Progress Report Meetings

Progress Report Meeting is organized by Finnish Cardiac Society to present opportunity for young investigators to report results of their studies. An important point is also training in presenting scientific papers to criticism of senior colleagues.

Boehringer Ingelheim has supported organizing the meeting from the beginning, 1975 by helping in practical matters and presenting grants to the best of speakers.

Winners of the Boehringer Ingelheim grants

From year 2007 onwards the competition has had two categories instead of 1st and 2nd prize. However, if less than three eligible abstracts has been received to either category, the organizers reserve the right to combine the categories.

Year	1st Prize	2nd Prize
1975	Erkki Pesonen	–
1976	Heikki Karppanen	Markku S. Nieminen
1977	Matti Halinen	Ulla Korhonen
1978	Ilkka Torstila	Markku S. Nieminen
1979	Olli Meretoja	Aila Rissanen
1980	Jorma Viikari	Jouko Jalonen
1981	Markku Kupari	Irma Koivula
1982	Heikki Huikuri	Markku Kupari
1983	Seppo Hietakorpi	Kari Niemelä
1984	Markku Laakso	Heikki Huikuri
1985	Jukka Räisänen	Kari Niemelä
1986	Pekka Koskinen	Juha Mustonen
1987	Kimmo Mattila	Silja Majahalme
1988	Heikki Tikkanen	Paula Rämö
1989	Hannu Näveri	Keijo Peuhkurinen
1990	Markku Mäkijärvi	Juhani Valkama
1991	Eero Mervaala	Paavo Uusimaa
1992	Eero Mervaala	Anne Remes
1993	Juha Hartikainen	Helena Kovanen
1994	Kai Kiilavuori	Juha Perkiömäki
1995	Sirkku Pikkujämsä	Pasi Tavi
1996	Jorma Kokkonen	Timo Mäkikallio
1997	Pekka Raatikainen	Marja Laitinen
1998	Marja Laitinen	Antti Ylitalo, 3rd Prize Timo Mäkikallio
1999	Mika Laine	Timo Mäkikallio
2000	Saila Vikman	Antti Kivelä
2001	Jari Tapanainen	Pertti Jääskeläinen
2002	Tuomas Rissanen	Markku Pentikäinen
2003	Juhani Junttila	Markus Leskinen
2004	Jere Paavola	Tuomas Rissanen
2005	Mikko Mäyränpää	Satu Helske
2006	Olli Tenhunen	Johan Lassus

Year	Basic Science category	Clinical Research category
2007	Satu Helske	Ville Kytö
2008	Mirella Hietaniemi	Minna Kylmälä
2009	Johanna Lähteenvuo o.s. Markkanen	Annukka Marjamaa
2010	1st Prize Jani Tikkanen 2nd Prize Riina Kandolin	the categories were combined
2011	Markku Lähteenvuo	Aapo Aro
2012	1st Prize Kirsi Kujala 2nd Prize Maija Bry	the categories were combined
2013	Suvi Syväranta	Toni Grönberg
2014	1st Prize Leena Kaikkonen 2nd Prize Heli Tolppanen	the categories were combined
2015	1st Prize Aissa Bah 1st Prize Markus Räsänen	the categories were combined
2016	1st Prize Heli Tolppanen 1st Prize Kaj Ekström	the categories were combined

ST-segment elevation in baseline electrocardiogram predicts mortality in cardiogenic shock

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Aim

The most common aetiology of cardiogenic shock (CS) is acute coronary syndrome (ACS), but 20% of CS is caused by other disorders. ST-segment deviations in electrocardiogram (ECG) have previously been investigated in patients with CS caused by ACS but not in those with other CS aetiologies. The aim was to explore the prevalence of different ST-segment patterns and their association with the aetiology and 90-day mortality in CS.

Methods

We analysed the baseline ECG of 196 patients who were included in a multinational prospective cohort study of CS. The patients were divided into three groups according to their ECG: 1) ST-segment elevation (STE): ST-segment elevation at the J point in two contiguous leads with following cut-points: ≥0.1 mV in all leads other than leads V2–V3 where the following cut points apply: ≥0.2 mV in men ≥40 years; ≥0,25mV in men <40 years, or ≥0.15 mV in women. 2) ST-segment depression (STDEP): horizontal or down-sloping ST-depression ≥0.05 mV in two contiguous leads. 3) No ST-segment deviation or ST-segment impossible to analyse (NSTED). The multivariable model was adjusted for age, gender, left ventricular ejection fraction and comorbidities.

Results

Mean age was 66 years, 74% were men, and 81% had ACS as CS aetiology. The prevalence of any ST-segment deviation was 80% (n=157). Half of the patients had STE (n=105, 54%), one fourth had STDEP (n=52, 27%) and remaining 20% (n=39) NSTED. The prevalence of ACS aetiology was higher in patients with STE (93%) in comparison with STDEP (71%, p<0.01) and NSTED (59%, p<0.01). Overall, 90-day mortality was 41%; in STE group 46%, STDEP 37% and NSTED 33% (p=0.19). In multivariable analysis, STE was an independent predictor of mortality (adjusted HR 2.15, 95% CI 1.33-3.48) along with increasing age, previous ischaemic heart disease, renal insufficiency and decreasing left ventricular ejection fraction (Figure).

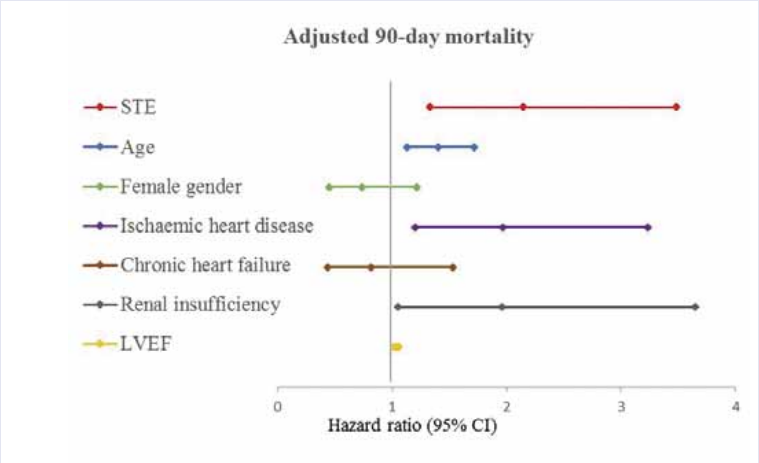

Figure.

Conclusions

Most CS patients have ST-segment deviations in baseline ECG. STE is strongly associated with ACS aetiology. Interestingly, CS aetiology was other than ACS in one third of patients with STDEP. Furthermore, CS was caused by ACS in over half of the NSTED patients. Importantly, STE is an independent predictor of 90-day mortality.

Prognostic significance of different patterns and amplitude of QRS fragmentation in patients with implantable defibrillator in primary prevention

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Aim

Fragmented QRS (fQRS) in standard 12-lead electrocardiogram (ECG) is considered to represent myocardial conduction delay due to myocardial scar, and it has been associated with mortality and sudden cardiac death in previous studies. The aim of this study was to assess the prognostic value of different fQRS phenotypes and fQRS amplitude in patients with implantable cardioverter-defibrillator (ICD) in primary prevention.

Methods

ECGs acquired prior to the implantation of ICD device were analyzed in 728 patients (81% male, age 58.6±13.0 years, QRS duration <120ms) from a retrospective multi-center study (EU-CERT-ICD). Fragmentations were categorized according to their timing into Q-, R- and S-wave fragmentations, and R-wave fragmentations were further divided into two groups: notched R and a group containing various RSR patterns. The degree of fragmentation was measured with custom-made software to ensure the highest accuracy of amplitude measurement. In addition the territory of the fQRS was defined as inferior (II, III, aVF), lateral (I, aVL, V4 to V6) or anterior (V1 to V3).

Results

During the follow-up (3.4±2.4 years), a total of 85 deaths (12%) and 94 appropriate shocks (13%) occurred. In competing risk regression, notched R in inferior leads was the only fQRS morphology to predict mortality during the follow-up with 1.6-fold risk (95% confidence interval: 1.0 – 2.4; $p<0.042$). Similarly, notched R in any location was the only fQRS morphology to predict the first appropriate shock with 2.2-fold risk (95% CI: 1.3 – 3.7; $p<0.004$). Fragmentation of any size (>0mV) in two lateral leads was associated with 1.7-fold risk for mortality during the follow-up (95% CI: 1.2-2.8, $p<0.008$). Single fragmented lateral lead with ≥0.05mV fragmentation was also predictive of mortality during the follow-up with 1.8-fold risk (95% CI: 1.1-2.7, $p<0.014$).

Conclusions

These results indicate that even the smallest fragmentations convey prognostic value in ICD patients. However, it seems that the risk for death is increased even with one fragmented lead, if the fragmentation is ≥0.05mV. Notched R in inferior leads is associated with mortality in primary prophylactic ICD recipients, whereas notched R in any location is associated with first appropriate ICD shock in these patients.

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Models for VEGF-B induced physiological and pathological cardiac hypertrophy

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Cardiovascular diseases are the leading causes of mortality world-wide and they have become the single most important and largest cause of non-communicable diseases. Heart failure among them forms a huge and growing burden to dozens of millions of patients around the world. – We have previously reported that mice expressing a cardiomyocyte-specific aMHC-VEGF-B transgene show impressive expansion of the coronary vasculature and cardiac hypertrophy without significant changes in heart function, rather mimicking physiological "athlete-like" cardiac hypertrophy. We

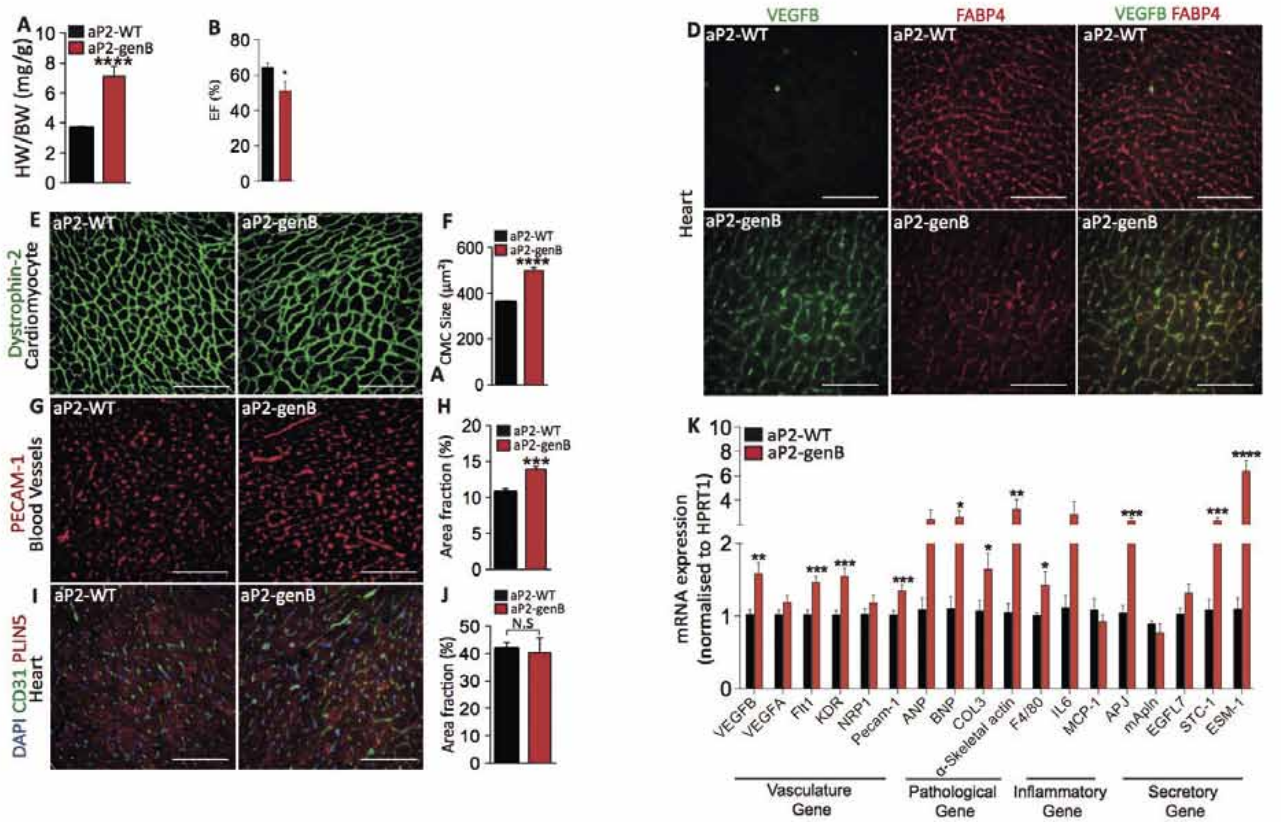

Figure 1: Transgenic overexpression of VEGFB in endothelial cells induce different phenotype than overexpression in cardiomyocytes. (A-B) Graphical representation of heart and kidney weight normalised to body weight (mg/g), **(C)** Quantification of VEGFR2 expression in heart lysate by WB, **(D)** VEGFB expression by immunofluroscent staining in the capillaries and co-stained with FAPB4, **(E)** IF staining of cardiomyocyte with Dystrophin-2, **(F)** Quantification of cardiomyocytes size **(G)** IF staining of blood vessels in the heart, **(H)** Quantification of PECAM-1 positive blood vessels in heart, **(I)** IF staining of lipids in the heart, **(J)** Quantification of PLIN5 in the heart, **(K)** mRNA expression of vasculature, pathological, inflammatoryand secretory gene normalised to HPRT1. 40X images scaled as 100µm.

believe, these changes are caused by "angiocrine" signaling between the cardiomyocytes and the endothelium, whereby CMCs secrete VEGF-B and the vascular endothelium responds by sending as yet unknown factor(s) to the CMCs.

We therefore wanted to study, how the phenotype and its mechanisms differ, if VEGF-B is expressed specifically in the endothelium instead of the cardiomyocytes. We created a novel model, where the mouse VEGF-B genomic sequence (genB) was inserted downstream of the promoter sequence of adipocyte protein 2 (aP2/Fabp4). Both the endogenous Fabp4 gene and the resulting aP2-VEGF-B transgene were found to be highly expressed in cardiac endothelial cells. Interestingly, these transgenic hearts were observed to be massively larger than in the wildtype mice or in mice that overexpress VEGF-B in the cardiomyocytes (aMHC-VEGF-B). The aP2-VEGF-B mice die prematurely and their cardiac function (EF) is clearly impaired. aP2-VEGF-B transgenic mice also had significantly bigger cardiomyocytes and increased vessel density, when compared to the littermate control mice.

Unlike in the aMHC-VEGF-B model, in the aP2-VEGF-B model, we observed increased expression of pathological cardiac markers suggestive of cardiac maladaptation. We also studied, how the pathological cardiac hypertrophy evolves during embryogenesis and first postnatal weeks. In the transgenic embryos aP2-genB did not provoke any obvious phenotype, suggesting that the actual pathological changes appear during the first postnatal weeks, consistently with the previous data that aP2 expression in vascular endothelial cells starts between postnatal days 3 and 7.

The new aP2-VEGF-B cardiac hypertrophy model and its precise characterization and comparison with the "athlete-like" hypertrophy of the aMHC-VEGF-B hearts could provide valuable information for the understanding of the differences between physiological and pathological cardiac hypertrophy in patients, and possibly hints for new druggable targets in the heart.

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Relationships between electrical and mechanical dyssynchrony in patients with left bundle branch block

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Aim

In left bundle branch block (LBBB) patients, abnormal pattern of electrical activation may result in dyssynchronous ventricular contraction. Recent electrophysiological findings have demonstrated that LBBB is a heterogeneous electrical disease. Therefore, its effect on mechanical contraction may be diverse. The aim of this study was to characterize electrical and mechanical dyssynchrony and to analyze their relationships in LBBB patients.

Methods

We retrospectively analyzed data of 994 patients who underwent myocardial perfusion imaging (MPI) SPECT/CT between April 2009 and May 2011. Forty-three patients fulfilled Strauss criteria for LBBB. Twenty-four healthy controls formed a reference group. The 12-lead-ECG recorded along with MPI protocol was reanalyzed using vectorcardiography (VCG) to characterize features of electrical dyssynchrony. Left ventricular (LV) mechanical dyssynchrony was described with

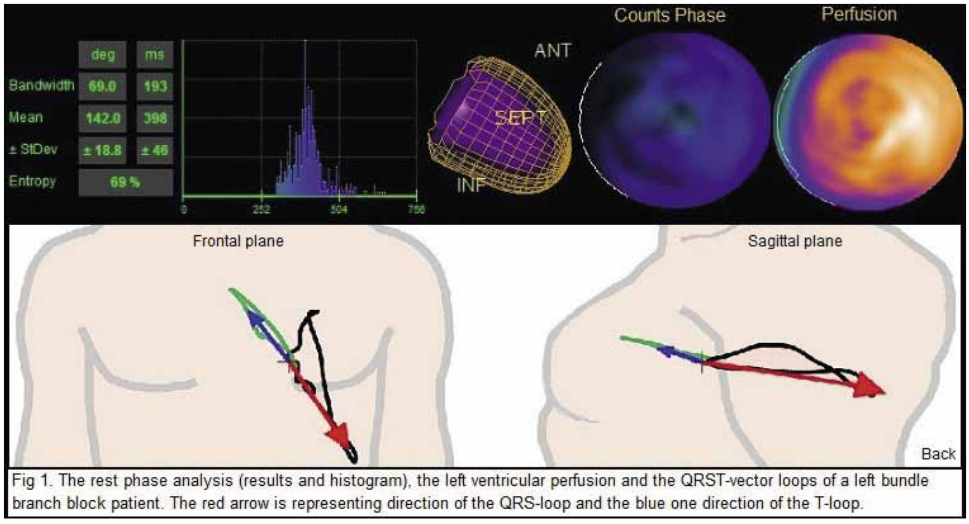

Fig 1. The rest phase analysis (results and histogram), the left ventricular perfusion and the QRST-vector loops of a left bundle branch block patient. The red arrow is representing direction of the QRS-loop and the blue one direction of the T-loop.

MPI phase histogram bandwidth (PHBW) or standard deviation values above limit of the highest normal. Univariate and multivariate regression analyses were performed to find out associations between features representing electrical alterations and synchronism of mechanical contraction. We determined receiver operating curves to evaluate diagnostic performance for potential predictors of mechanical dyssynchrony and to define optimal cut-off values.

Results

In addition to QRS prolongation, the main VCG features of LBBB were elongated, narrowed, downward and posteriorly pointing QRS-loop and signs of LV-hypertrophy. Sixty percent of LBBB patients had mechanical dyssynchrony. QRS duration (QRSd; $r=0.70$, $p<0.001$), magnitude of QRS-vector ($r=0.41$, $p<0.001$), QRS-angle in horizontal plane ($r=0.54$, $p<0.001$), QRST-angle ($r=0.46$, $p<0.001$) and Cornell voltage (CorV; $r=0.56$, $p<0.001$)) correlated significantly with PHBW. QRSd ($\beta=0.91$, $p<0.001$), QRST-angle ($\beta=-0.52$, $p=0.002$) and CorV ($\beta=0.31$, $p=0.01$) were independently associated with PHBW. The cut-off value predicting mechanical dyssynchrony was for QRSd 142 ms, for QRST-angle 166° and for CorV 4.9 mV yielding a sensitivity/specificity 82%/72%, 57/85% and 57/90%, respectively.

Conclusions

Despite obvious conduction abnormality, LBBB is not always accompanied by LV-mechanical dyssynchrony. Based on results of this study mechanical dyssynchrony can be predicted with various ECG/VCG-parameters.

Incidence and predictors of excessive warfarin anticoagulation in patients with atrial fibrillation. The EWA Study.

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Aim

Vitamin K antagonist warfarin is widely used in clinical practice and excessive anticoagulation is a well-known complication of this therapy. Little is known about permanent and temporary predictors for severe overanticoagulation. The aim of this study was to investigate the occurrence and predicting factors for episodes with very high (≥9) international normalized ratio (INR) values in warfarin treated patients with atrial fibrillation (AF).

Methods

Excessive Warfarin Anticoagulation (EWA) study screened all patients (n=13618) in the Turku University Hospital region with an INR ≥2 between years 2003-2015. Patients using warfarin anticoagulation for AF with very high (≥9) INR values (EWA Group) were identified (n=412 patients) and their characteristics were compared to a control group (n=405) of AF patients with stable INR during long-term follow-up.

Results

Over 20% (n=92) of the EWA patients had more than one event of very high INR and in 105 (25.5%) patients EWA led to a bleeding event. Of the several temporary and permanent EWA risk factors observed, strongest were excessive alcohol consumption in 9.6% of patients (OR 24.4, 95% CI 9.9-50.4, p<0.0001) and reduced renal function (OR 15.2, 95% CI 5.67-40.7, p<0.0001). Recent antibiotic or antifungal medication, recent hospitalization or outpatient clinic visit and the first 6 months of warfarin use were the most significant temporary risk factors for EWA. The 30-day mortality was 20.4% (n=84) in the EWA Group and 0.2% (n=1) in the Control Group. The survival advantage of patients without EWA persisted in long-term follow-up (median 23 months) (Figure 1).

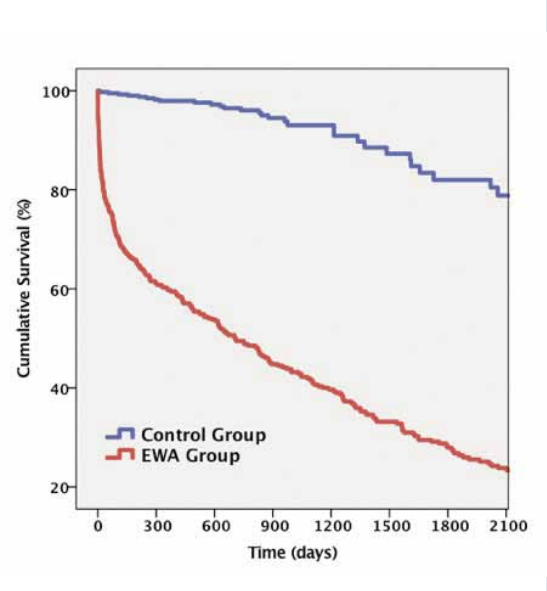

Figure 1.

Conclusions

The rare but dangerous event of excessive warfarin anticoagulation can be predicted with several permanent and temporary clinical risk factors, many of which are modifiable.

Apelin Modulates PGC-1a and Development of Heart Failure

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Background

Prior data implicates that apelin = apelin receptor system is involved in development of cardiac hypertrophy and heart failure. Both plasma apelin levels and myocardial apelin levels are reduced in patients with advanced heart failure. Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) plays a central role in the regulation of fuel selection, mitochondrial ATP generating capacity, and energy production in the heart.

Methods

Apelin knock-out (KO) and wild type (WT) mice were subjected to transverse aortic constriction (TAC) model to induce pathological cardiac hypertrophy and high intensity interval training (HIIT) treadmill running exercise model to achieve physiological cardiac hypertrophy.

Results

In response to treadmill HIIT, the WT mice showed modest increase in left ventricular wall thickness and cardiomyocyte size, whereas the hearts of apelin KO mice were identical to the baseline. Treadmill training resulted in a 20% increase in muscle cross-sectional area in WT mice, whereas no increase was observed in the muscles from apelin KO mice. qPCR analysis of samples from cardiac tissues revealed comparable increase in total PGC-1α, PGC-1α2 and PGC-1α3 levels in WT and apelin KO mice subjected to treadmill training. qPCR analysis of samples from skeletal muscle showed a modest increase in total PGC-1α mRNA levels in both WT and apelin KO mice, whereas mRNA levels of PGC-1α1 mRNA were decreased only in WT mice.

Hemodynamic overload by TAC induced cardiac hypertrophy in both WT and KO animals accompanied by decreased left ventricular systolic function. Apelin KO mice displayed more advanced heart failure as evidenced by increased left ventricular mass. TAC induced comparable increase in ANP, BNP and β-myosin heavy chain (β-MHC) mRNA levels in WT and apelin KO mice, whereas levels of α-MHC were significantly lower in the KO mice. Expression of all PGC-1α isoforms was downregulated in response to TAC in the hearts of WT mice and further decreased in the hearts of apelin KO mice.

Conclusions

Apelin modulates PGC-1α isoform expression in skeletal muscle in response to exercise training and in the myocardium in response to pathologic cardiac stress. Enhancing apelin signaling may be beneficial in restoring mitochondrial function and energy production in the failing myocardium.

Genetic background of sudden cardiac death caused by idiopathic myocardial fibrosis

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Aim

Idiopathic myocardial fibrosis (IMF) at autopsy has been recently found to be a common cause of sudden cardiac death (SCD) among young SCD victims. The etiology and causes of IMF are largely unknown. Our aim was to assess the genetic background of SCD caused by IMF.

Methods

We have collected autopsy findings and tissue samples (formalin fixed, paraffin embedded samples) from 4,031 SCD victims since 1998 in Northern Finland as a part of the Fingesture study. IMF was the cause of SCD in 145 subjects and the most common cause of SCD among the subjects under the age of 40 years. Most of the cases with IMF had no prior symptoms before the death. We performed targeted next generation sequencing of a panel of 174 myocardial structure related genes in 96 SCD victims with IMF who had the best quality of DNA for the analysis (median age 52, 67% males) using NextSeq550 platform (Illumina). All variants with effect on protein and with minor allele frequency under 0.01 in dbSNP and ExAC exome database were assessed further based on 1) data deposited in ClinVar database and The Human Gene Mutation Database, 2) recurrence in the analyzed data set and 3) for mutations without previous knowledge on disease association and observed only single patient, PolyPhen and SIFT predictions were taken into account.

Results

We detected 13 probably pathogenic mutations (literary and database search) in 15 subjects and 17 possibly pathogenic mutations (software and database search) in 19 subjects. From the probably pathogenic mutations, three were observed in two genes associated with arrhythmogenic right ventricular dysplasia (ARVD) (two in DSP, one in PKP2). Additionally, ARVD related genes were found also in possibly pathogenic mutations list (two in DSP, one in DSG2). Also, six mutations were found in hypertrophic cardiomyopathy (HCM) related genes (MYH7, MYBPC3, TPM1). Several of mutated genes have also been associated with dilated cardiomyopathy (DCM) and two particular mutations have previously been described only in DCM subjects (in CRYAB and CTF1 genes). In total, mutations were present in 31 subjects (32%) and 21/30 mutations were novel.

Conclusion

A relatively high number of SCD victims with IMF at autopsy have myocardial structure encoding gene mutations. Mutations in ARVD, DCM and HCM related genes are evident in IMF even without classical autopsy findings of ARVD, DCM or HCM suggesting overlapping genetic background in these pathologies.

Antiarrhythmic effects of carvedilol and flecainide in catecholaminergic polymorphic ventricular tachycardia patient specific induced pluripotent stem cell derived cardiomyocytes

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Aim

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac disorder characterized by stress-induced ventricular tachycardia and risk of sudden cardiac death in structurally normal hearts. Mutations in the cardiac ryanodine receptor (RYR2) is the leading cause for CPVT. During beta-adrenergic stimulation, CPVT patients experience arrhythmias caused by a leakage of calcium ions through RYR2. In this study we evaluated the efficacy of carvedilol, a non-selective beta blocker, and flecainide, a class Ic antiarrhythmic agent, in abolishing calcium abnormalities in CPVT patient specific induced pluripotent stem cell (iPSC) derived cardiomyocytes carrying different mutations in RYR2.

Methods

iPSC derived cardiomyocytes were generated from skin biopsies of three CPVT patients carrying the exon 3 deletion, L4115 or V4653F mutation in RyR2 and from one healthy control individual. Calcium kinetics of cardiomyocytes were studied by fluorescent imaging of Fluo-4 AM calcium indicator. Cardiomyocytes were stimulated with 1µM adrenaline after which 0.25µM carvedilol or 10µM flecainide were applied along with 1µM adrenaline. Calcium kinetics and drug responses were analyzed in the iPSC derived cardiomyocytes.

Results

Carvedilol abolished calcium abnormalities in 31% of L4115F, 36% of V4653F and 46% of exon 3 deletion carrying CPVT cell lines and Flecainide 33%, 30% and 52% respectively. Both drugs lowered the intracellular calcium and beating rate of the cardiomyocytes significantly. The CPVT cell line carrying the exon 3 deletion was the most sensitive to treatment with both drugs, although the incidence of the most severe type of calcium abnormalities before drug treatment was the highest in that line. Moreover, in control cells, flecainide caused abnormal calcium transient prolongation in 61% whereas carvedilol in only 26% of the cells.

Conclusions

Flecainide and carvedilol were equally effective treating arrhythmias in CPVT specific iPSC derived cardiomyocytes. However, the proarrhythmic risk of flecainide should be recognized as it induced arrhythmias in control cells. Even though the CPVT cell line carrying exon 3 deletion had the most severe calcium abnormalities it had the best response to the drug therapy. Both of these drugs are used in the clinics for the treatment of CPVT. However, according to this study, the arrhythmia abolishing effect of these drugs is not optimal. iPSC derived cardiomyocytes provide a unique platform for testing new potential drugs for CPVT.

Antiarrhythmic drug therapy among patients presenting to emergency department with symptomatic atrial fibrillation, The FinFib2 study

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Aim

Atrial fibrillation (AF) is a common arrhythmia that causes numerous visits to emergency departments (ED). The aim of the FinFib2 study was to evaluate whether treatment of patients with AF in ED is consistent with the contemporary management guidelines.

Methods

All patients within the two-week study period whose primary reason for the ED visit was symptomatic AF were included into this prospective multicentre study. Comprehensive data on factors contributing to the treatment of AF were collected.

Results

The study population consisted of 1013 consecutive patients (mean age 70 ± 13 years, 47.6 % female). The mean EHRA symptom score was 2.2 ± 0.8. Rhythm control strategy was opt for 498 (63.8 %) and 140 (64.5 %) patients with previously and newly diagnosed AF, respectively. In patients with previously diagnosed AF the most frequently used AAD was a beta blocker (80.9%). Prior use of class I (11.4%) and III AADs (9.1%) as well as start or adjustment of their dosage (7.4%) were uncommon. Most of the patients with newly diagnosed AF were prescribed a beta blocker (71.0%) or a calcium channel antagonist (24.0%), and only two of them received class I or class III AADs.

Conclusions

Our data demonstrated that despite guideline recommendations the use of class I and class III AADs in patients presenting to the ED with recurrent symptomatic AF was rare. It is possible that early adaptation of a more aggressive rhythm control strategy might alleviate the ED burden associated with AF.

Inhibition of cardiomyocyte Sprouty1 protects from ischemia-reperfusion injury

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Aim

The extracellular signal –regulated kinase (ERK) cascade is a nodal cardioprotective signaling cascade in the myocardium. Increased ERK activity is associated with protection from cardiac ischemia-reperfusion (I/R) injury, whereas inhibition of ERK exaggerates ischemic cardiomyocyte death. While the role of ERK in cardiomyocyte biology is rather well characterized, there is only little information of Sprouty1 (Spry1), one of the major negative modulators of ERK signaling cascade. This study aims to determine the role of Spry1 in regulating cardiomyocyte viability following ischemic stress.

Methods

Adult cardiomyocyte-specific tamoxifen-inducible Spry1 knockout (Spry1 cKO) and control mice were subjected to I/R injury by ligation of the left anterior descending artery and releasing the slipknot after 30 minutes to allow reperfusion of the myocardium for 6 or 24 hours. For in vitro studies, Spry1 was silenced by RNAi in neonatal rat primary cardiomyocytes, and the cells were subjected to hypoxia/reperfusion injury by using hypoxia chamber mimicking ischemic conditions in vivo.

Results

Following I/R injury, Spry1 cKO mice showed significantly smaller infarct size and attenuated increase in plasma cardiac troponin I levels compared to the control mice. Western blot analysis showed robust increase in ERK phosphorylation both in ischemic and non-ischemic areas of Spry1 cKO hearts. Spry1 knockdown in vitro substantially reduced I/R induced cardiomyocyte death as assessed by adenylate kinase release. Analysis for mitochondrial membrane potential showed that Spry1 knockdown significantly inhibited the collapse in mitochondrial membrane potential following hypoxia. Analysis for activated ERK revealed marked increase in phosphorylation of ERK in mitochondria of hypoxic Spry1 silenced cardiomyocytes compared to control cells. In addition, mitochondria of Spry1 silenced cells showed increased phosphorylation of GSK3β, indicating decreased GSK3β activity. Overexpression of constitutively active GSK-3β, but not wild type GSK3β, fully abrogated the protective effect of Spry1 silencing in cardiomyocytes.

Conclusions

Inhibition of Spry1 in cardiomyocytes protects from cardiac ischemia-reperfusion injury by phosphorylating (inhibiting) GSK3β and preserving mitochondrial membrane potential. Spry1 may serve as a novel therapeutic target to alleviate cardiac ischemia-reperfusion injury.