Suomen Kardiologinen Seura

Finnish Cardiac Society

45th Progress Report Meeting

June 10, 2019

Helsinki

Contents

45th PROGRESS REPORT MEETING - Young Investigators Award Competition

Monday, June 10, 2019

Organized in conjunction of the 27th Nordic-Baltic Congress of Cardiology
June 10-12, 2019 Helsinki, Finland

Scientific Program

10.00-10.25	Power break: Coffee and fruits at 1st floor (outside Terrace open)

10.25-12.00 45th PROGRESS REPORT YIAC, PART I

Terrace Hall — Chairperson Matti Niemelä (FI)

10.25-10.30	Opening remarks. Matti Niemelä (FI)
10.30 - 10.45	Genome-wide association analysis on coronary artery disease in type 1 diabetes confirms CDKN2B Antisense RNA 1 and suggests beta-defensin 127 as a novel risk locus. Anni Antikainen (MSc. Tech), Folkhälsan Institute of Genetics, Folkhälsan Research Center
10.45 - 11.00	Wrist band photoplethysmography pulse morphology analysis enables atrial fibrillation detection without the need of pulse detection. Eemu-Samuli Väliaho (BM, BHC), University of Eastern Finland, Doctoral School
11.00 - 11.15	Lymphatic insufficiency increases cardiac edema after myocardial infarction as assessed by novel magnetic resonance TRAFFn and T2 relaxation times. Elias Ylä-Herttuala (MSc), A.I. Virtanen Institute, Biomedial Imaging Unit
11.15 - 11.30	Coronary CT angiography with selective PET perfusion imaging guides referral to invasive coronary angiography and revascularization. Iida Stenström (MD), Turku PET Centre
11.30 - 11.45	The ablation of VEGFR-1 signaling promotes angiotensin II induced cardiac dysfunction and sudden death. Annakaisa Tirronen (MSc), A.I. Virtanen Institute, Molecular medicine group
11.45 - 12.00	Silent myocardial infarction and sudden cardiac death. Juha Vähätalo (BM), University of Oulu, Department of Internal Medicine
12.00-12.30	Snack lunch at 1st floor

12.30-13.30 45th PROGRESS REPORT YIAC, PART II

Terrace Hall — Chairperson Matti Niemelä (FI)

12.30 - 12.45	Sudden cardiac death in women: causes of death, autopsy findings and electrocardiographic risk markers. Anette Haukilahti (BM), Medical Research Center Oulu, University of Oulu, Research Unit of Internal Medicine
12.45 - 13.00	Current European Society of Cardiology guidelines for normal ascending aortic diameter: prevalence of aortic dilatation increases to 23 % in a coronary computed tomography population. S. Petteri Kauhanen (BM), Kuopio University Hospital, Clinical Radiology
13.00 - 13.15	miR-1468-3p Regulates Development of Cardiac Fibrosis. Ruizhu Lin (PhD student), Research Unit of Biomedicine, Department of Pharmacology and Toxicology
13.15 - 13.30	Single centre experience on percutaneous left atrial appendage closure in patients with atrial fibrillation and contraindications to oral anticoagulation. Jussi-Pekka Pouru (B.M.), University of Turku, Department of Internal Medicine
13.30-14.00	Networking break: coffee, exhibition and posters at 2nd floor YCC at 3rd floor

Meeting is supported by unrestricted educational grant from Boehringer Ingelheim

Progress Report -kilpailu tulee,

miksi nuoren tutkijan kannattaa osallistua?

Vastaajana kardiologi, Suomen Kardiologisen Seuran varapuheenjohtaja Matti Niemelä.

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 27th Nordic-Baltic Congress of Cardiology -kokouksen yhteydessä Helsingissä 10.–12.6.2019.

Kilpasarjojen voittajat palkitaan Boehringer Ingelheim Finlandin lahjoittamilla 2300 euron matka-apurahoilla. Lisätietoja kilpailusta Suomen Kardiologisen Seuran netti sivuilta
www.fincardio.fi/apurahat/progress_report_yiac/

Boehringer Ingelheim

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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
2017	Tarja Alakoski	Samuli Jaakkola
2018	Maija Ruuth	Tero Penttilä

10.30–10.45 Anni Antikainen (MSc. Tech)
Folkhälsan Institute of Genetics, Folkhälsan Research Center

Genome-wide association analysis on coronary artery disease in type 1 diabetes confirms CDKN2B Antisense RNA 1 and suggests beta-defensin 127 as a novel risk locus

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David-Alexandre Trëgouet, INSERM, Paris, France, Romain Charmet, INSERM, Paris, France,
Amy Jayne McKnight, Centre for Public Health, Belfast, United Kingdom,
Tarunveer Ahluwalia, Steno Diabetes Center Copenhagen, Gentofte, Denmark,
Anna Syreeni, Folkhälsan Institute of Genetics, Helsinki, Finland,
Erkka Valo, Folkhälsan Institute of Genetics, Helsinki, Finland,
Carol Forsblom, Folkhälsan Institute of Genetics, Helsinki, Finland,
Daniel Gordin, Folkhälsan Institute of Genetics, Helsinki, Finland,
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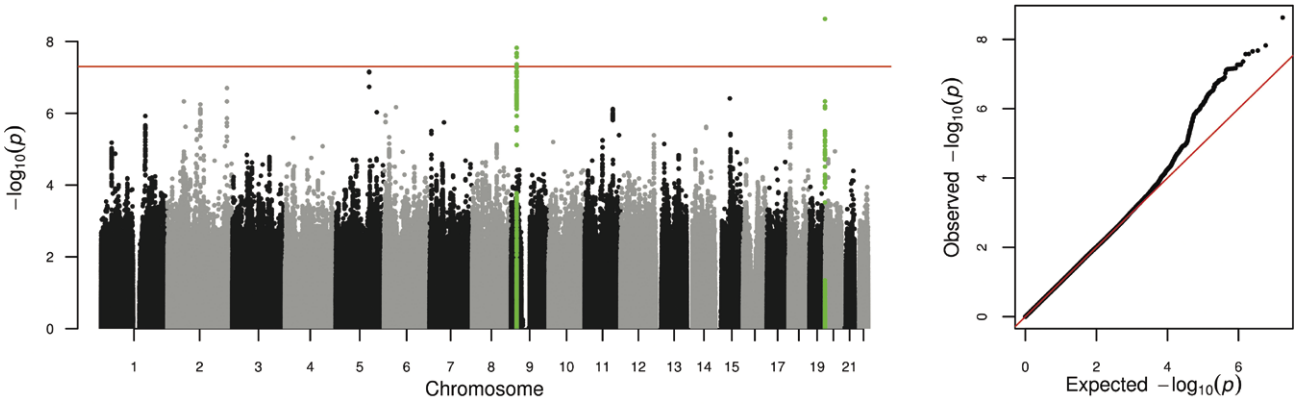
Aim

Type 1 diabetes (T1D) is a known risk factor for coronary artery disease (CAD). However, the genetics of CAD have not been extensively studied in T1D. Whether the genetic background is similar to the general population, or loci specific to T1D exist, is not established. We aimed to search for loci specific to T1D, describe their role in the pathogenesis and assess the effects of known CAD risk variants.

Methods

A genome-wide association study was performed with RVTEST for 8,744,746 variants on 4869 individuals with T1D (cases/controls: 941/3928). Genotyping of the individuals recruited through the Finnish Diabetic Nephropathy Study and the National Institute of Health and Welfare had been performed with Illumina HumanCoreExome chips at the University of Virginia in addition to imputation with Minimac3 using the 1000 Genomes Phase 3 reference panel. Replication was attempted as a GWAS



look-up (434/3123). We evaluated function of the discoveries with a cardio-phenome-wide analysis and assessed the role of the known variants with genetic risk scores (GRS).

Results

Two loci reached genome-wide significance: rs1970112 (EAF=0.41, OR=1.32) on a known risk locus CDKN2B-AS1 and rs6055069 (EAF=0.98, OR=0.24) near DEFB127. Replication was successful only for CDKN2B-AS1. Nevertheless, the novel DEFB127 discovery provides an interesting link to inflammation, since ß-defensins are involved in the immune system. We discovered eight suggestive loci ($p<1\times10\text{-}6$) out of which for instance rs1344228 was also associated with atherosclerosis markers. GRSs suggested that the known risk variants modestly increase CAD risk also in T1D ($p=4.21\times10\text{-}7$).

Conclusions

We confirmed the CDKN2B-AS1 and suggested a DEFB127 association with CAD in T1D. Our results provide evidence for shared genetic variants with the general population and variants specific to T1D.

Wrist band photoplethysmography pulse morphology analysis enables atrial fibrillation detection without the need of pulse detection

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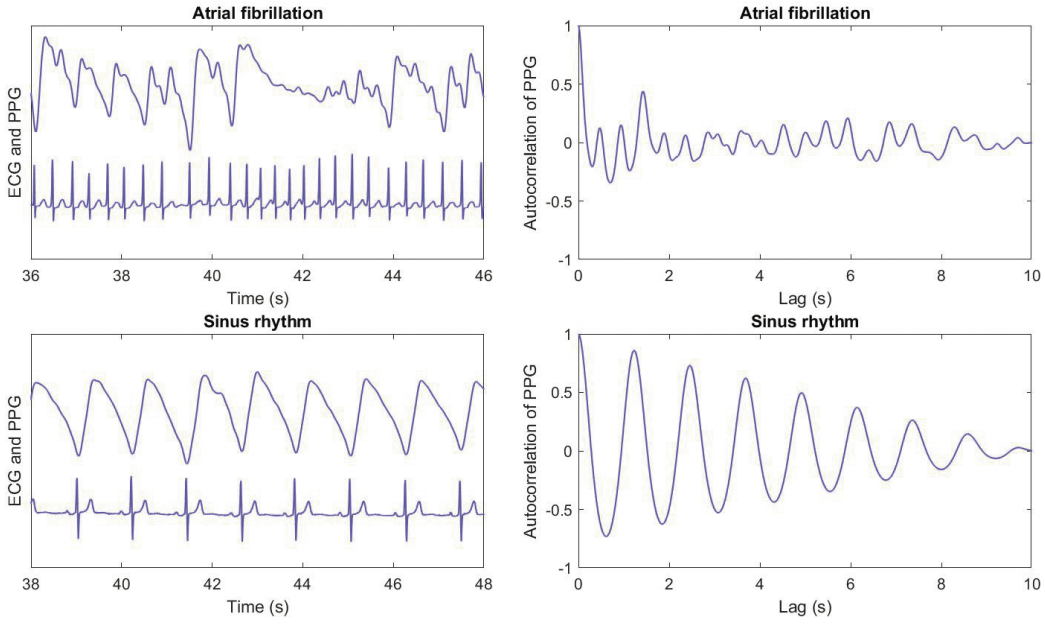
Aim

Atrial fibrillation (AF) is often asymptomatic and intermittent making its detection a major clinical challenge. A photoplethysmography (PPG) wrist band with algorithm-based detection of AF provides a promising solution for screening of AF. However, the shapes of individual pulse waveforms vary in AF decreasing pulse detection accuracy. We evaluated the utility of PPG wrist band pulse morphology in detection of AF.



Methods

A 5-minute PPG was recorded with a PPG wrist band from patients with AF or sinus rhythm. A simultaneously registered ECG served as the golden standard for the rhythm analysis and was interpreted by two cardiologists. In addition to using the inter-beat-interval (IBI) based AFEvidence algorithm in comparison, we extracted a feature straight from the PPG signal, without the need of pulse detection. This feature was calculated as the average of absolute autocorrelation values over different lags. The feature describes the regularity of the PPG signal and is decreased if the shape and periodicity of pulse waves vary. The performance of this PPG morphology-based method in detection of AF was evaluated and compared to the AFEvidence.

Results

The study population consisted of 213 patients (106 AF, 107 sinus rhythm). The sensitivity and specificity of PPG morphology-based autocorrelation AF detection method were 98.1% and 94.4%. For AFEvidence, the sensitivity and specificity were 96.2% and 98.1%, respectively (p=.146 between the methods, McNemar test).

Conclusions

The PPG morphology-based autocorrelation method detects AF with good accuracy without the need of pulse detection. The method seems promising in detection of AF and should be studied further.

Elias Ylä-Herttuala (MSc)
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Lymphatic insufficiency increases cardiac edema after myocardial infarction as assessed by novel magnetic resonance TRAFFn and T2 relaxation times

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Introduction

The role of cardiac lymphatic system in myocardial infarction (MI) is still unclear. A new method to characterize MI without contrast agent is a relaxation along a fictitious field in nth rotating frame (RAFFn). RAFFn takes advantage of the fictitious magnetic field, which is produced by a fast sweep of an effective radio frequency field, to increase a spin locking field strength without increasing SAR. MI is detected as increased RAFFn relaxation times and cardiac edema by an increased T2 relaxation time.

Purpose

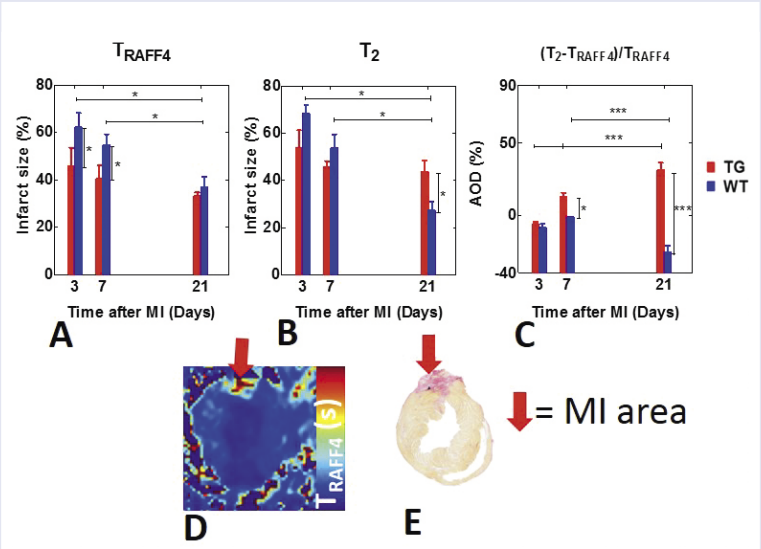
Study the effects of the lack of cardiac lymphatic system on MI and cardiac edema in mouse model.

Methods

Transgenic (TG) mice expressing soluble decoy VEGF receptor 3 (sVEGFR3), blocking lymphatic vessel formation in the heart, and wild type (WT) were used. MI was induced in TG (n=11) and WT (n=14) mice by ligating the LAD coronary artery. The RAFFn (TRAFF2 and TRAFF4), T1ρ and a T2 relaxation times were acquired at time points 0, 3, 7 and 21 days after the MI at 9.4 T. Histological sections were stained with Sirius Red to assess cellularity and MI area. Area of difference (AOD) was determined by subtracting MI areas based on TRAFF2, TRAFF4 and T1ρ maps from MI area based on T2 map.

Results

MI size based on the TRAFF4 and T2 relaxation time maps were larger at early time points 3 and 7 days post MI in the WT group compared to the TG group (Figure A-B). However, the MI size was significantly larger in the T2 relaxation time map in the TG group compared to the WT group at the last time point (Figure A-B). The AOD values increased in the TG group (Figure C). TRAFF2, TRAFF4 (Figure D), T1ρ and T2 relaxation times increased significantly (˜50 %) after MI. In the WT group, the lymphatic vessel network is fully functional and removes edema efficiently between days 3 and 21 after the MI, while in the TG group the MI area in T2 map is relative stable indicating insufficient edema removal. Sirius Red stained histology verified MI area (Figure E).



Conclusion

Lymphatic deficiency increases cardiac edema (AOD values) 7-21 days after MI as compared to the WT group. Results support the importance of cardiac lymphatic vessels for healing after MI. Effects of the lymphatics on MI can be detected based on the MI size difference based on the TRAFFn and the T2 relaxation times.

Coronary CT angiography with selective PET perfusion imaging guides referral to invasive coronary angiography and revascularization

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Aim

Hybrid imaging combining coronary computed tomography angiography (CCTA) and myocardial perfusion imaging enables detection of coronary stenoses and evaluation of their hemodynamic consequences non-invasively. In order to address the impact of hybrid imaging on patient management, we studied the referral rates to invasive coronary angiography (ICA) and revascularization in patients with suspected obstructive coronary artery disease (CAD) after hybrid imaging with selective ischemia-testing by positron emission tomography (PET) perfusion imaging if obstructive lesions were suspected based on coronary CT angiography (CCTA).

Methods

We retrospectively evaluated 672 symptomatic patients in whom CCTA was clinically indicated due to suspected obstructive CAD. PET perfusion imaging with 15O-water during adenosine stress was performed during the same visit if obstructive stenosis was suspected based on CCTA. Frequencies and indications of ICA and revascularization during six months, as well as rates of cardiovascular death and non-fatal myocardial infarction (MI) during a median follow-up of 5.2 years, were recorded.

Results

Based on CCTA alone, there was no obstructive CAD in 417 (62%) patients. Of the 255 (38%) patients with suspected obstructive CAD on CCTA, PET perfusion imaging showed ischemia in 141 (55%). The frequency of ICA was significantly lower (1%) in the absence of obstructive CAD by CCTA as compared to non-ischemic PET (5%, $p=0.016$) and significantly higher (55%) after ischemic PET compared to non-ischemic PET ($p<0.001$) within 6 months after PET/CCTA. The rate of revascularization was equally low after CCTA alone or non-ischemic PET (0 and 1%, $p=0.215$), but higher after ischemic PET (31%, $p<0.001$). During follow-up, 8 cardiovascular deaths and 12 MIs occurred. Ischemic PET was associated with a higher annual risk of an adverse event (1.5% vs. 0.28%, $p<0.001$).

Conclusions

Selective ischemia-testing based on CCTA effectively guides referral to ICA in patients with suspected obstructive CAD, and potentially reduces the number of ICAs not leading to revascularization.

The ablation of VEGFR-1 signaling promotes angiotensin II induced cardiac dysfunction and sudden death

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Aim

Concentric left ventricular hypertrophy (LVH) and diastolic dysfunction develops as an adaptive response to pressure overload. Eventually this may lead to decompensated hypertrophy characterised by interstitial fibrosis, contractile dysfunction as well as changes in metabolism and electrophysiology, consequentially triggering heart failure. The molecular mechanisms involved in cardiac remodelling are not fully understood but maladaptive angiogenesis could promote the transition from adaptive LVH to decompensated heart failure. Angiogenesis is mediated by vascular endothelial growth factors but their role in LVH has remained unresolved. In this study, we wanted to investigate whether vascular endothelial growth factor receptor 1 (VEGFR-1) signaling has a role in the progression of LVH and development of heart failure.

Methods

We used wild type littermate controls and domain specific knock out mouse lacking the intracellular VEGFR-1 tyrosine kinase domain (VEGFR-1 TK-/-) and induced pathological hypertrophy with subcutaneous angiotensin II infusion. We examined the cardiac function with echocardiography and acquired surface ECG signal during the development of LVH. Mice were followed up for 14 days before sacrification and sample collection. Cross-sectional cardiac samples were stained with Masson's trichrome to assess the level of fibrosis and immunostained for lectin to determine capillary area. Additionally, we performed a CD31 whole mount staining to visualise capillary 3D network. To analyse changes in gene expression levels, we performed RT-qPCR measurements.

Results

VEGFR-1 TK deficiency led to increased mortality (33.3%) and lack of adaptive LVH. Whereas wild type mice responded to angiotensin II infusion with a significant increase in ejection fraction (55.5% to 69.9%) within the first 6 days, VEGFR-1 TK-/- mice displayed a 5.2% decrease and without adaptive thickening of the LV anterior wall. The most striking difference was seen in LV volume, where wild type mice displayed a 63.3% reduction but in VEGFR-1 TK-/- mice it remained unaltered after angiotensin II infusion. Histological analysis showed that VEGFR-1 TK-/- mice displayed significant cardiomyocyte hypertrophy combined with ventricular dilatation but without changes in fibrosis or angiogenesis. ECG analysis revealed that VEGFR-1 TK-/- mice exhibited widening of the QRS complex, similar to human LVH, and this was accompanied by increased ANP/BNP levels.

Conclusions

In this study, we show that the ablation of VEGFR-1 TK signaling has an unexpected role in pressure overload inducing mortality. VEGFR-1 TK-/- mice displayed dilated LVH and a protracted response to angiotensin II infusion, suggesting that VEGFR-1 signaling is required for the adaptive response and concentric hypertrophy of the myocardium.

Silent myocardial infarction and sudden cardiac death

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Aim

Myocardial infarction (MI) that occurs with unrecognized symptoms are characterized as silent (SMI). The prevalence of SMI among sudden cardiac death (SCD) victims has not previously been described. The aim was to determine the prevalence of autopsy verified SMI in SCD victims without a prior diagnosis of coronary artery disease (CAD) and to detect ECG abnormalities related with SMI.

Methods

The Fingesture study consists of a large series of consecutive victims of autopsy-verified SCD in Northern Finland between the years 1998-2017 (n=5,869, 78.9% males, mean age 64.9 ± 12.4 years). The autopsies routinely included histological examinations, and a toxicology investigation was carried out if needed. SMI was defined as focal scar in the distribution of a stenotic or occluded coronary artery. Pre-mortem clinical history was obtained from medical records, previously recorded ECGs, and a standardized questionnaire provided to the next of kin.

Results

Coronary artery disease was determined to be the cause of SCD in 4,392 victims (74.8%), among whom 3,122 had no history of CAD prior to death. This represents 53.2% of all SCDs, and 71.1% of CAD-associated SCDs. CAD with silent MI was detected in 42.4% victims without a clinical history of CAD. The SMI subjects were older than subjects without MI scar (67±11 years versus 66±12 years, $p<0.001$) and were more often men (83% versus 76%, $p<0.001$). Heart weight was higher in SMI subjects (483±109 g vs. 438±106 g, $p<0.001$). In SMI subjects, SCD occurred more often during physical activity (19% versus 13%, $p<0.001$) and outdoors (21% versus 15%, $p<0.001$). Overall ECG abnormalities were more common in the SMI than non-SMI group (67% vs. 55%, $p=0.018$). Inverted T-waves were observed in 17%, pathologic Q-waves in 13%, and fragmented QRS complex in 54% in the SMI group.

Conclusions

Many SCD victims with associated CAD had a previously undetected MI at autopsy. Previous SMI was associated with myocardial hypertrophy and SCD during physical activity. Pre-mortem ECG was abnormal in two thirds of the SCD victims with SMI.

Anette Haukilahti (BM)
Medical Research Center Oulu, University of Oulu,
Research Unit of Internal Medicine

Sudden cardiac death in women: causes of death, autopsy findings and electrocardiographic risk markers

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Tikkanen Jani, Research Unit of Internal Medicine, Medical Research Center Oulu, University of Oulu, Oulu, Finland,
Lasse Pakanen, Forensic Medicine Unit, National Institute for Health and Welfare, Oulu, Oulu, Finland,
Marja-Leena Kortelainen, Department of Forensic Medicine, Medical Research Center Oulu, University of Oulu, Oulu, Finland,
Juha Perkiömäki, Research Unit of Internal Medicine, Medical Research Center Oulu, University of Oulu, Oulu, Finland,
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Aim

Among women the incidence of sudden cardiac death (SCD) is significant, but lower than in men. The mechanisms and risk markers of SCD are not as well defined for women as they are for men possible due to difference in population burden. The aim of this study was to determine the autopsy findings and causes of death among women in a large SCD population. Additionally, we sought to classify prior electrocardiographic characteristics in male and female SCD victims.

Methods

The Fingesture study has systematically collected clinical and autopsy data from SCD victims in Northern Finland between 1998 and 2017. The cohort consists of 5,869 SCD victims. Previously recorded electrocardiograms (ECG) were available and analyzed in 1,101 subjects.

Results

Female SCD victims were significantly older than men: 70.1±13.1 yrs. vs. 63.5±11.8 yrs. ($P<0.001$). The most frequently identified cause of death was ischemic heart disease in both sexes: 71.7% in women vs. 75.7% in men, $P=0.005$. In contrast, women were more likely to have non-ischemic cause of SCD than men (28.3% vs. 24.3%, $P=0.005$). The prevalence of primary myocardial fibrosis was higher among women (5.2%, N=64) than in men (2.6%, N=120; $P<0.001$). Female SCD victims were more likely to have normal prior ECG tracings (22.2% vs. 15.3%, $P<0.001$). A normal ECG was even more common among non-ischemic female SCD victims (27.8% vs. 16.2%, $P=0.009$). However, ECG markers of left ventricular hypertrophy (LVH), with or without repolarization abnormalities, were more common among women (8.2%; 17.9%) than in men (4.9%; 10.6%, $P= 0.036$; $P<0.001$).

Conclusions

Women were considerably older at the time of SCD and more commonly had non-ischemic causes. Women were also more likely to have a prior normal ECG than men, but an increased marker for SCD risk based upon ECG criteria for LVH with and without repolarization abnormalities was more commonly observed in women.

Current European Society of Cardiology guidelines for normal ascending aortic diameter: prevalence of aortic dilatation increases to 23% in a coronary computed tomography population

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Aim

Epidemiological studies on the prevalence of ascending aortic (AA) dilatation are scanty. Aim was to clarify prevalence of AA dilatation according to ESC 2014 guidelines and to study its risk factors.

Methods

This retrospective study included 1000 consecutive patients scheduled for diagnostic coronary artery computer tomography angiography (CCTA) with low to moderate pretest probability for coronary artery disease (CAD). AA diameter was measured at 3 planes; sinus valsalva, sinotubular junction and tubular part. Threshold for AA dilatation was set to >40 mm (ESC 2014). Traditional risk factors for AA dilatation were collected from medical records. Aortic size index (ASI) was used as a comparative measurement. ASI is defined as the ratio between aortic diameter and body surface area (BSA). The threshold for AA dilatation was set to upper limit of normal distribution exceeding two standard deviations (95%). Heart-aorta angle (HAA, Figure) was measured as one suggestive risk factor.

Results

Patients' mean age was 52.9±9.8 years, 66.5% were women. The prevalence of AA dilatation in the whole study population was 23% according to ESC 2014 guidelines. When patients with hypertension (n=445) or coronary calcifications or stenosis in CCTA (n=375) were excluded, the prevalence of AA dilatation was 15.1% in the population of normotensive patients without CAD (n=380).

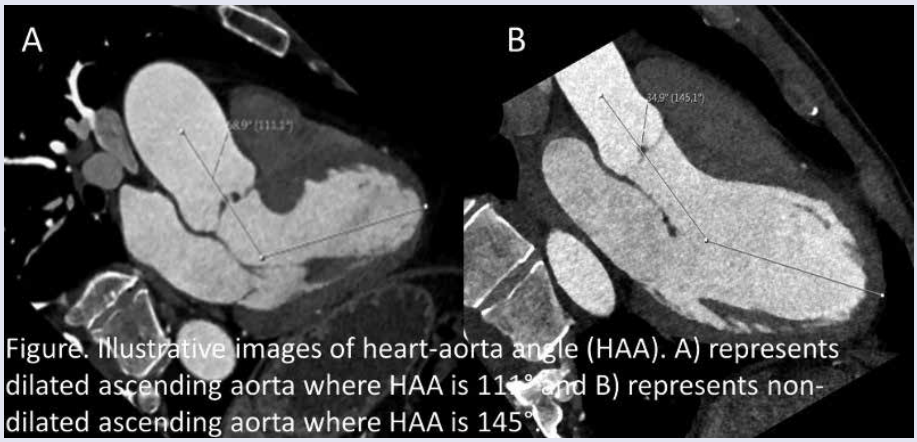

Figure. Illustrative images of heart-aorta angle (HAA). A) represents dilated ascending aorta where HAA is 111° and B) represents non-dilated ascending aorta where HAA is 145°.

According to the normal-distributed ASI values the threshold for normal dimension of sinus valsalva was defined as 23.5 mm/m^2 and for tubular part 22.7 mm/m^2 for normotensive patients without CAD. Using these thresholds, the prevalence of AA dilatation was 14.5% in the whole population. Smaller HAA was associated to AA dilatation. Median HAA was 125.6° (range: 119.2–131.5°) in patients with dilated AA and 130.1° (123.–136.4°) in patients with non-dilated AA ($p<0.001$). Higher BSA was associated to larger AA dimensions. Risk factors for AA dilatation (according to ESC criteria) were male gender, BAV, hypertension and smoking ($p<0.01$).

Conclusions

The prevalence of AA dilatation proved to be relatively high in this consecutive CCTA population when using ESC 2014 guidelines. Body size is associated to AA dimensions; thus, it seems reasonable to include BSA in the definition of AA dilatation.

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13.00–13.15

miR-1468-3p Regulates Development of Cardiac Fibrosis

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Aims

Accumulation of extracellular matrix disturbs the electrical conduction and stiffens myocardium, leading to higher risk for arrhythmias and diastolic dysfunction. MicroRNAs (miRNAs) function in post-translational gene regulation, and aberrant alteration of miRNAs level has been implicated in cardiac pathologies. However, the role and mechanism of miRNAs in cardiac fibrosis is unclear. To date, there are no reports on the role of miR-1468-3p in human cardiac fibrosis. Here, we aim to study 1) if miR-1468-3p was implicated in cardiac fibrosis and 2) how miR-1468-3p regulates fibroblast function.

Methods

RNA sequencing of cardiac samples of sudden cardiac death (SCD) victims with idiopathic myocardial fibrosis (IMF) were used for identifying miRNAs potentially involved in cardiac fibrosis. Gain- and loss-of-function approaches were performed respectively with synthetic mimic or inhibitor (antimiR) of miR-1468-3p to study the role of miR-1468-3p in modulating fibroblast function in human cardiac fibroblasts (hCFs). Quantitative real-time polymerase chain reaction (qPCR) was used for determining gene and miRNA expression levels. Western blot analysis was used for monitoring fibrotic and signal protein expression level. A two-dye Sirius Red/Fast Green staining (Chondrex) was used for determination of total collagen level. Statistical analysis was performed with IBM SPSS Statistics software (IBM, Armonk, NY). Normally distributed data was analyzed with two-way ANOVA followed by Tukey's post hoc test. When two groups were compared, Student's t-test was used.

Results

RNA sequencing of RNA samples of SCD victims with IMF for differentially expressed miRNAs identified miR-1468-3p. qPCR analysis validated that miR-1468-3p expression is upregulated in hearts of SCD victims with IMF comparing to control subjects. Overexpressing miR-1468-3p in hCFs increased several fibrotic genes expression compared with hCFs transfected with control mimic. Western blot analysis showed that miR-1468-3p mimic was sufficient to drive expression of collagen I and CTGF protein expression. Treatment of hCFs with miR-1468-3p antimiR did not alter expression of fibrosis-related gene at basal level, whereas miR-1468-3p inhibition significantly attenuated TGF-β1-induced collagen I and CTGF expression. Treatment of hCFs with miR-1468-3p antimiR blunted TGF-β1-induced collagen I and CTGF protein expression, but not TGF-β1-induced αSMA expression. With total collagen staining, we validated that depletion of miR-1468-3p antagonized both TGF-β1-triggered collagen deposition. Finally, we found that miR-1468-3p antimiR downregulated TGF-β1-induced collagen expression partially through the interference of TGF-β1/MAPK signals.

Conclusions

Our data indicate a pro-fibrotic role of miR-1468-3p in modulating cardiac fibrosis, and manipulating the expression of miR-1468-3p may provide a therapeutic strategy for treatment of cardiac fibrosis.

Single centre experience on percutaneous left atrial appendage closure in patients with atrial fibrillation and contraindications to oral anticoagulation

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Aim

There is limited evidence available on percutaneous left atrial appendage closure (LAAC) in patients with atrial fibrillation (AF), high thromboembolic risk and either high bleeding risk or prior major bleeding. We aimed to study periprocedural and late events after LAAC in AF patients with contraindications to oral anticoagulation (OAC) therapy.

Methods

Data were collected into a prospective registry from all consenting AF patients who underwent LAAC from February 2009 to August 2018. Follow-up data was gathered through scheduled clinical visits, annual phone calls and electronic patient records. For the present analysis only AF patients with contraindications to OAC were included.

Results

LAAC using mainly Amplatzer Cardiac Plugs (98.2%) was attempted in a total of 172 patients (mean age 74 years; 112 men). The mean CHA2DS2-VASc score was 3.8 ± 1.5 and HAS-BLED score 4.0 ± 1.0. Contraindications to OAC were prior intracranial haemorrhage in 112 (65.1%), other major bleeding in 33 (19.2%) and high bleeding risk in 27 patients (15.7%). The implantation procedure was successful in 166 (96.5%) patients. Eleven patients (6.4%) had clinically significant in-hospital complications: two patients (1.2%) had cardiac tamponade, fatal in one case (0.6%). There was one device embolization and eight (4.7%) clinically significant access-site bleedings, but no thromboembolic complications. After implantation, 152 patients (91.6%) were discharged on aspirin, 30 (18.1%) on dual antiplatelet therapy and 8 patients (4.8%) received no antiplatelet therapy. The length of initial antiplatelet therapy ranged from 0.5 to 12 months. Long-term antiplatelet therapy was prescribed in 53 patients (31.9%). After 453.3 patient-years of follow-up, all-cause mortality rate was 6.4 per 100 patient-years. Thromboembolic event, ischaemic stroke and major bleeding rates were 3.7, 2.5 and 4.3 per 100 patient-years, respectively. Thromboembolic complications consisted of 11 strokes (6.6%) and 5 transient ischaemic attacks (3.0%). At the time of thromboembolic event, 10 patients (62.5%) were on antithrombotic therapy. Intracranial haemorrhage occurred in 7 patients (4.2%) and 6 of them (85.7%) were on antithrombotic therapy at the time of events. Most thromboembolic events (68.8%) and intracranial bleedings (57.1%) occurred after one year of follow-up. One (0.6%) asymptomatic device embolization was detected at 3-month control visit. No predictive factors for thromboembolic or major bleeding events were identified.

Conclusions

The early outcome of this patient group is acceptable following LAAC. However, thromboembolic and major bleeding events are not uncommon during later follow-up.