Suomen Kardiologinen Seura

Finnish Cardiac Society

44th Progress Report Meeting

April 11, 2018

Helsinki

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44th Progress Report Meeting Programme

44th 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 Helsingissä 11.–13.4.2018. Abstraktien lähetysaika päättyy su 18.2.2018.

Kilpasarjojen voittajat palkitaan Boehringer Ingelheim Finlandin lahjoittamilla 2300 euron matka-apurahoilla. Lisätietoja kilpailusta Suomen Kardiologisen Seuran nettisivuilta www.fincardio.fi/tutkimus/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

The occurrence of postpericardiotomy syndrome: association with operation type and post-operative mortality after open-heart operations

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Jarmo Gunn, Heart Centre, Turku University Hospital and University of Turku, Turku, Finland,
Juhani Airaksinen, Heart Centre, Turku University Hospital and University of Turku, Turku, Finland,
Ville Kytö, Heart Centre, Turku University Hospital and University of Turku, Turku, Finland

Background

Postpericardiotomy syndrome (PPS) is a common complication after cardiac surgery. However, large-scale epidemiological studies concerning the effect of procedure type on the occurrence of PPS and mortality of PPS patients have not yet been performed.

Table. Predictors for postpericardiotomy syndrome admissions.

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Age class		<0.0001		0.0059
18–40 years vs. ≥71 years	2.509 (1.559–4.035)	0.0001	1.606 (0.976–2.643)	0.0621
41–50 years vs. ≥71 years	1.929 (1.382–2.693)	0.0001	1.765 (1.249–2.495)	0.0013
51–70 years vs. ≥71 years	1.217 (1.000–1.481)	0.0495	1.266 (1.031–1.554)	0.0240
Female sex	1.060 (0.869–1.294)	0.566	1.035 (0.842–1.273)	0.744
Charlson Comorbidity Index (CCI)		0.739		0.833
Mild risk (CCI 1) vs. low risk (CCI 0)	0.996 (0.817–1.214)	0.965	0.926 (0.747–1.143)	0.698
Moderate risk (CCI 2) vs. low risk (CCI 0)	0.855 (0.632–1.156)	0.308	0.893 (0.655–1.211)	0.618
High risk (CCI ≥ 3) vs. low risk (CCI 0)	0.910 (0.626–1.322)	0.620	0.998 (0.684–1.458)	0.992
AVR (± CABG) vs. CABG	1.909 (1.542–2.363)	<0.0001	1.968 (1.576–2.456)	<0.0001
MVR (± CABG) vs. CABG	1.757 (1.332–2.315)	<0.0001	1.619 (1.218–2.151)	0.0009
Aortic surgery (± AVR or CABG) vs. CABG	3.493 (2.634–4.632)	<0.0001	3.055 (2.244–4.161)	<0.0001
Urgent or emergency procedure	1.544 (1.161–2.054)	0.0028	1.355 (1.004–1.829)	0.0471
Resternotomy	1.368 (0.915–2.045)	0.1272	1.244 (0.824–1.876)	0.2992

HR: hazard ratio; CI: confidence interval; AVR: aortic valve replacement; CABG: coronary artery bypass graft; MVR: mitral valve replacement.

Methods

We studied the association of PPS occurrence with operation type and post-operative mortality in a nationwide follow-up analysis of 28761 consecutive patients entering CABG, aortic valve replacement (AVR), mitral valve replacement (MVR) or ascending aortic procedure. Only PPS episodes severe enough to result in hospital admission (99.4% of included PPS cases) or to contribute as a cause of death (0.6%) were included. Data were collected from mandatory Finnish national registries including data on all cardiovascular hospital admissions in 29 hospitals and causes of death between 2005 and 2014.

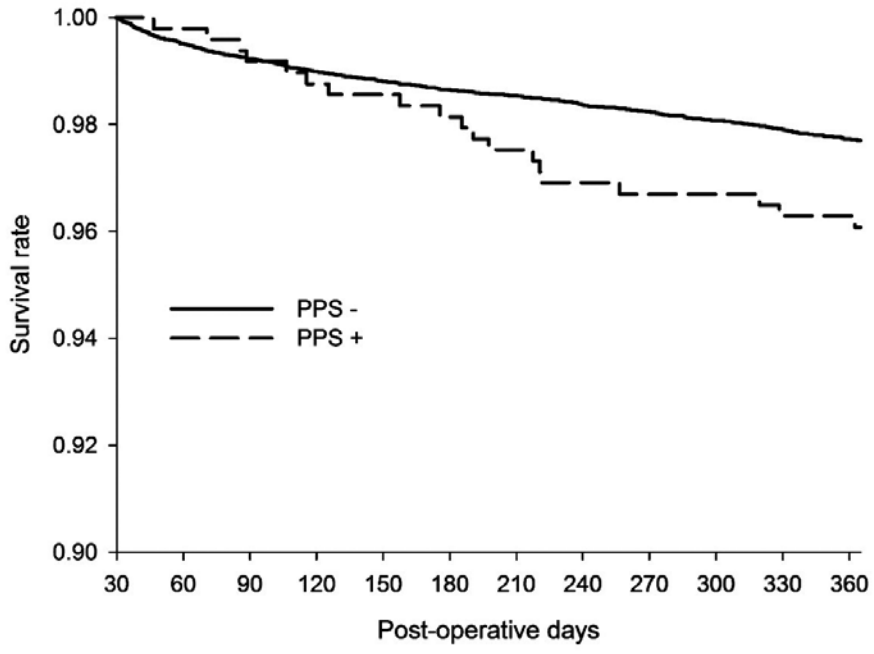
Results

Of all the patients included, 493 developed PPS during the study period. The occurrence of PPS was significantly higher in AVR (HR 1.97, 95% CI 1.58–2.46, p<0.0001), MVR (HR 1.62, 95% CI 1.22–2.15, p=0.0009) and aortic procedure (HR 3.06, 95% CI 2.24–4.16, p<0.0001), when compared to CABG procedure in both univariable and multivariable analyses. Urgent or emergency procedure was an independent predictor of PPS (HR 1.36, 95% CI 1.00–1.83, p=0.047). Occurrence of PPS decreased significantly with aging (p<0.0001). Occurrence of PPS was associated with an increased risk of mortality within the first year after the surgery (adjusted HR 1.78, 95% CI 1.12–2.81, p=0.014).

Conclusions

The occurrence of PPS was higher after AVR, MVR and aortic surgery when compared to CABG procedure. Aging decreased the risk of PPS. Development of PPS was associated with higher mortality within the first year after cardiac or ascending aortic surgery.

Figure. Survival after cardiac and ascending aortic surgery and occurrence of PPS. Including patients alive 30 days after the surgery.



Novel biomarkers predict congestive heart failure in 10,106 Finnish men

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Aim

Predicting heart failure (HF) remains an important challenge in health care. We applied metabolomics to identify biomarkers predicting HF in the large prospective population-based METSIM study.

Methods

Serum metabolites and lipoprotein lipids were determined by a high-throughput serum nuclear magnetic resonance (NMR) platform in 10,106 men of the METSIM study who did not have HF at baseline. Incident HF cases during the 6.9-year follow-up were identified from the medical records of the university hospital, which is the only hospital and cardiology outpatient clinic in the living area of the study subjects. Cox regression analysis was applied to identify biomarkers predicting incident HF. Principal components analysis was used to analyse the clustering of baseline variables.

Results

Of the 10,106 men (age 57.6 ± 7.1 years, body mass index 27.3 ± 4.1 kg/m2), a total of 172 (1.7%) developed incident HF during the mean follow-up of 6.9 years. Of those who had incident heart failure, a total of 36 (20.9%) had suffered a myocardial infarction prior to the baseline study, and 65 (37.8%) had reimbursement for hypertension. Subjects with incident HF had higher baseline concentrations of plasma adiponectin, IL-1 receptor antagonist, glycoprotein acetyls, glycerol and pyruvate compared to those without incident HF. In Cox regression analysis, adiponectin (9.08 ± 6.09 µg/ml vs 7.81 ± 4.32 µg/ml, HR 1.19 (1.10-1.26), P = 1.7E-06) and pyruvate (0.081 ± 0.027 mmol/l vs 0.067 ± 0.023 mmol/l, HR 1.38 (1.28-1.50), P = 9.4E-08) predicted HF. There was a J-shaped distribution of incident cases of HF across the quintiles of adiponectin. In principal components analysis, we identified a novel cluster of biomarkers, consisting of alanine, glycoprotein acetyls, pyruvate, glycerol and phenylalanine, which predicted HF independently of other clusters of baseline variables (OR 1.39 (1.20-1.60), P = 9.0E-06).

Conclusions

Plasma adiponectin and pyruvate predicted HF during the 6.9-year follow-up of the METSIM study. In addition, we identified a novel cluster of biomarkers independently predicting heart failure. New biomarkers might help to identify subjects at high risk of heart failure.

Disheet Shah (MSc) 12.35–12.50
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Modeling dilated cardiomyopathy due to Lamin A/C gene mutation using human induced pluripotent stem cell derived cardiomyocytes

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Aim

Dilated cardiomyopathy (DCM) is a leading cause of heart failure and heart transplantation. A part of familial DCM is due to mutation in the genes encoding the nuclear envelope proteins Lamin A and C. The role of Lamin A/C is to provide mechanical support and shape to the nucleus and they are involved in many biological processes. Mutations in the Lamin A/C gene (LMNA) cause a group of inherited diseases known as laminopathies with DCM being the most common laminopathy. People with this mutation have a poor survival outcome. Aim of the current study is to model this disease using induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM) to understand the pathophysiology of the mutation.

Methods

In this study, we have created a model of this disease using hiPSC-CMs from skin biopsies from one healthy control and from two patients carrying the mutation S143P in the rod domain of the LMNA gene. The structure and function of the CMs was assessed using confocal imaging, western blot, microelectrode array, calcium imaging and patch clamp at baseline conditions and under stress of adrenaline and hypoxia.

Results

Cardiomyocytes derived from hiPSC lines harboring the mutations reproduced pathophysiological hallmarks of the disease and results were in line with data obtained from expression systems. This is the first hiPSC-CM model for S143P mutation affecting several DCM families. Morphologically, confocal imaging revealed that the DCM hiPSC-CMs (labelled Patient 1 and 2) displayed more nucleoplasmic Lamin A compared to the control; Figure 1(a) left panel. The fluorescence intensities ratios of the

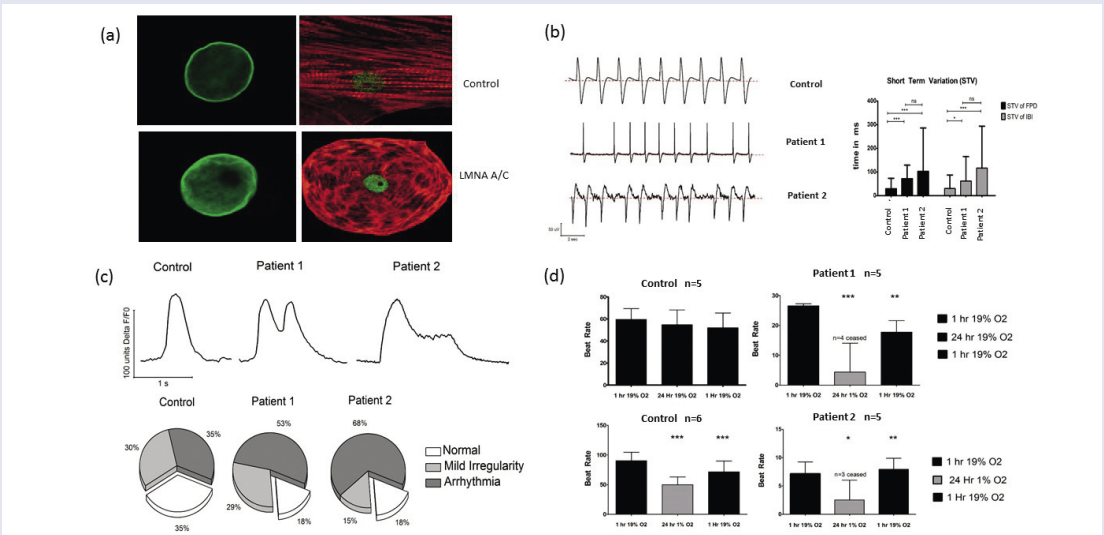

Figure 1.

lamina to nucleoplasm significantly more in Control compared to DCM; Figure 1(a). Sarcomeres showed increased disorganization in the DCM; Figure1 (a) right panel. Electrophysiologically, the DCM model displayed bradycardia and increased arrhythmias characterized by increased beating rate variation at multi cellular level by MEA; Figure 1(b) and at single cell level by calcium imaging both at baseline; Figure 1(c) and under adrenaline and at baseline by patch clamp. Calcium imaging revealed significantly altered calcium decay characteristics in the DCM model. Induction of stress on cardiac aggregates using hypoxic conditions displayed an exaggerated effect on the DCM patient cardiomyocytes; Figure 1(d).

Conclusions

Our model does not only recapitulate major phenotype characteristics as observed in DCM patients but also is a proof of concept that this model can be used to study the disease mechanisms further and can serve as a platform for pharmacological screenings.

Electrocardiogram as a predictor of survival without appropriate shocks in primary prophylactic ICD patients: A retrospective multi-center study

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Background

Abnormalities in standard 12-lead electrocardiogram (ECG) can predict cardiovascular events, including sudden cardiac death in various populations. We tested the hypothesis that ECG might provide useful information on guiding primary prevention implantable cardioverter defibrillator (ICD) therapy to individuals with impaired left ventricular ejection fraction (LVEF) who would benefit from the device.

Methods

Retrospective data of primary prevention ICD implantations from 14 European centers were gathered. The compiled registry included 5,111 subjects of whom 2,041 had a pre-implantation ECG available. The final analytic cohort consisted of 1,686 patients with an interpretable ECG (80.7% male, 62.3±12.0 years). Primary outcome was survival without appropriate ICD shocks; secondary outcome was the first appropriate ICD shock. A low-risk ECG was defined as a combination of ECG variables that were associated with the primary outcome.

Results

A total of 1,261 (74.8%) patients survived the follow-up (2.0±1.2 years) without an ICD shock, while 234 (13.9%) received an appropriate shock and 243 (14.4%) died. Low-risk ECG criteria, such as QRS duration <120 ms, corrected QTcB interval <500 ms, sinus rhythm and absence of R-wave fragmentation, were met by 435 patients (25.8%). Survival rate without appropriate shocks was higher in the low-risk ECG group (86.9% vs. 70.6%; $p<0.001$). Similarly, the occurrence of the first appropriate shock was lower in the low-risk ECG group (9.0% vs. 15.7%; $p<0.001$), but ECG predicted the appropriate shock only in patients with ischemic heart disease ($p<0.001$) but not in those with non-ischemic cardiomyopathy (NS).

Conclusion

Standard 12-lead ECG provides information about survival without appropriate ICD shocks and might become an additional tool in selecting patients to primary prevention ICD therapy.

Displaced aortic flow and increased circumferential wall shear stress associate to ascending aortic dilatation. Results from a prospective clinical study

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S. Petteri Kauhanen: Oiva Vaittinen will grant, Rättimäen KardioVaskulaarinen seura

Aim

Aim of this study was to find predictive parameters for ascending aortic (AA) dilatation by using modern 4D flow MRI.

Methods

4D flow, 2D flow and anatomic imaging were performed at 1.5T (Siemens Aera) to 20 patients with dilated AA (age; 62.8±15.1 years, AA maximum diameter ≥ 42 mm) and to 20 healthy controls (age; 58.5±6.3 years, AA maximum diameter < 42 mm) in Kuopio University Hospital between 7/2017-11/2017. The main analyzed parameters were: wall shear stress (WSS) and flow displacement (FD). Thoracic aorta was divided for 10 planes and each plane for 6 segments (Fig.); 0°-point was located into the inner curvature of aorta and the first segment (60°) was set anticlockwise and so on.

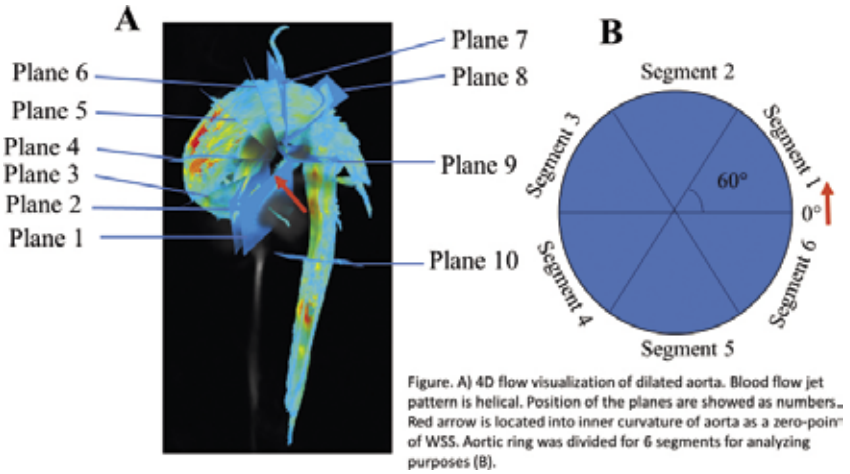

Figure. A) 4D flow visualization of dilated aorta. Blood flow jet pattern is helical. Position of the planes are showed as numbers.. Red arrow is located into inner curvature of aorta as a zero-point of WSS. Aortic ring was divided for 6 segments for analyzing purposes (B).

Table: Medians of FD given as percentage with ranges for all dilated AA, dilated AA without bicuspid aortic valve (BAV) patients and non-dilated groups. Statistical differences between all dilated AA and dilated AA without BAV groups with non-dilated AA group (*p<0.05, **p<0.01, ***p<0.001, Mann-Whitney –test).

Plane	All dilated AA n=20	Dilated AA without BAV patients n=17	Non-dilated AA n=20
Plane 1	3.0 % [2.0–5.0 %]	3.0 % [2.0–5.0 %]	3.0 % [2.0–4.0 %]
Plane 2	3.5 % [2.0–6.0 %] **	4.0 % [2.0–6.0 %] **	2.0 % [1.3–3.0 %]
Plane 3	5.5 % [3.0–11.8 %] ***	5.0 % [3.0–11.0] ***	2.0 % [1.0–3.0 %]
Plane 4	4.5 % [3.0–8.0 %] *	4.0 % [3.0–6.5 %]	3.0 % [2.0–4.0 %]
Plane 5	2.0 % [2.0–3.8 %]	2.0 % [2.0–3.0 %]	3.0 % [2.0–3.8 %]

Results

Aortic flow was displaced from the center line of aorta in the whole dilated part of AA. FD was greatest in the proximal part of AA and was higher in dilated AA compared to non-dilated AA (5.5 % [3.0–11.8 %] vs. 2.0 % [1.0–3.0 %], respectively, p<0.001). Three patients with AA dilatation had bicuspid aortic valve. Flow was displaced in dilated AA regardless the number of aortic cusps (Table). Total WSSs were 1.5±0.6-times higher (p=0.001) on displaced side than on non-displaced side. Wall shear stress circumferential (WSSc) ratio to total WSS (WSSt) was greater in the dilated AA in segments 1 and 6 on planes 1–4 and in segments 3–5 on plane 5. WSSc / WSSt values were greater in dilated AA (46.4 %) compared to non-dilated AA (29.8 %, p<0.01).

Conclusions

Aortic flow is displaced in dilated AAs despite of the number of valve cusps. Flow displacement increases wall shear stress on the side of displacement. WSSc / WSSt ratio was greater in dilated AAs compared to non-dilated AAs. Thus, flow displacement and increased WSSc / WSSt ratio might be used as signs of a risk for aortic dilatation. In future, 4D flow MRI may provide prognostic new information in patients with aortic dilatation.

Glucagon-like peptide-1 receptor expression after myocardial infarction: Imaging study using 68Ga-NODAGA-exendin-4 positron emission tomography

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Aim

Therapies activating glucagon-like peptide-1 receptor (GLP-1R) signalling have cardioprotective effects. However, cardiac GLP-1R expression during healing of myocardial infarction (MI) and left ventricle remodelling remains unknown. 68Ga-NODAGA-exendin-4 is a novel positron emission tomography (PET) tracer developed for imaging of GLP-1R expression in pancreatic β-cells and insulinomas. The aim of the study was to evaluate 68Ga-NODAGA-exendin-4 PET in new indication, for assessment of GLP-1R expression after MI in rats.

Methods

Rats were studied at 3 days, 1 week and 12 weeks after permanent coronary ligation or a sham-operation. Rats were injected with 68Ga-NODAGA-exendin-4 and scanned with PET and contrast-enhanced computed tomography (CT) followed by digital autoradiography and histology of left ventricle tissue sections.

Results

68Ga-NODAGA-exendin-4 PET/CT showed focally increased tracer uptake in the infarcted regions peaking at 3 days and continuing at 1 week after MI. Pre-treatment with an unlabelled exendin-4 peptide significantly reduced 68Ga-NODAGA-exendin-4 uptake ($p=0.007$). By autoradiography, 68Ga-NODAGA-exendin-4 uptake was 8.6-fold higher in the infarcted region ($p<0.0001$) and slightly increased also in the remote, non-infarcted myocardium at 1 week and 12 weeks post-MI ($p<0.05$) compared with sham. Uptake of 68Ga-NODAGA-exendin-4 correlated with the amount of CD68-positive macrophages in the infarcted area ($r=0.70$, $p<0.001$) and myofibroblasts in the remote myocardium ($r=0.56$, $p=0.04$).

Conclusions

68Ga-NODAGA-exendin-4 PET detects up-regulation of cardiac GLP-1R expression during healing of MI in rats. Imaging of GLP-1R has translational relevance studying the therapeutic potential of GLP-1 in the heart, and may enable monitoring of activated repair mechanisms after ischemic myocardial injury.

Differences in the risk of stroke, bleeds, and mortality between female and male patients with atrial fibrillation during warfarin therapy

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Aim

Female patients with atrial fibrillation (AF) have been suggested to carry a higher risk for thromboembolic events than males. The FinWAF study was designed to evaluate the risks of stroke, bleeding events, cardiovascular and all-cause mortality in relation to the quality of warfarin therapy in patients with AF. Here we compared the residual risk of clinical endpoints among anticoagulated AF patients according to their gender.

Methods

In the FinWAF study data from several nationwide registries and laboratory databases in Finland were linked. We included a total of 54568 AF patients with their INR data on the quality of warfarin treatment (time in therapeutic range, TTR) prior to the events. Gender differences in the endpoints were reported for the whole population, in pre-specified age groups (< 65 years, 65-74 years, and ≥ 75 years), and different TTR groups (< 40 %, 40-50 %, 50-60 %, 60-70 %, 70-80 %, and > 80 %). Adjusted Cox proportional hazard models were tested for different outcomes.

Results

During the 3.2 ± 1.6 years follow-up there were no gender differences in the adjusted risk of stroke (HR 0.97, 95 % CI 0.91 - 1.03, p=0.304) in the whole or any age-specified study populations. On the other hand, the risk of cardiovascular mortality (HR 0.82, 95 % CI 0.78 - 0.88, p<0.001), and all-cause mortality (HR 0.79, 95 % CI 0.75 - 0.83, p<0.001) were lower in women compared with men, also in all age groups. In the TTR groups, except for those with TTR < 50 %, there were no differences in the risk of stroke, cardiovascular mortality, and all-cause mortality between the sexes. Bleeding events were less frequent in females (HR 0.52, 95 % CI 0.49 - 0.56, p<0.001).

Conclusions

Despite lower risk of cardiovascular mortality and all-cause mortality in women there were no gender differences in the risk of stroke among AF patients taking warfarin. The risk of bleeding events was lower in females in all pre-specified age and TTR subgroups. Our observations clearly imply, that female gender should not be considered as a risk factor for adverse outcomes in anticoagulated AF patients.

Susceptibility of LDL particles to aggregate depends on particle lipidome, is modifiable, and associates with future cardiovascular deaths

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Aims

LDL particles cause atherosclerotic cardiovascular disease through their retention and modification within the arterial intima. High plasma concentrations of LDL drive this disease, but LDL quality may also contribute. Here, we focused on the intrinsic propensity of LDL to aggregate upon modification. We examined whether inter-individual differences in this quality are linked with LDL lipid composition and coronary artery disease (CAD) death, and basic mechanisms for plaque growth and destabilization.

Methods and Results

We developed a novel, reproducible method to assess the susceptibility of LDL particles to aggregate during lipolysis induced ex vivo by human recombinant secretory sphingomyelinase (hrSMase). Among patients with established CAD, we found that the presence of aggregation-prone LDL was predictive of future cardiovascular deaths, independently of conventional risk factors. Aggregation-prone LDL contained more sphingolipids and less phosphatidylcholines than did aggregation-resistant LDL. Three interventions in animal models to rationally alter LDL composition lowered its susceptibility to aggregate and slowed atherosclerosis. Similar compositional changes induced in humans by PCSK9 inhibition or healthy diet also lowered LDL aggregation susceptibility. Aggregated LDL in vitro activated macrophages and T-cells, two key cell types involved in plaque progression and rupture. Remarkably, we identified a single specific motif in the C-terminus of apolipoprotein B-100 that becomes exposed upon digestion of LDL with hrSMase and is necessary for particle aggregation.

Conclusions

Our results identify the susceptibility of LDL to aggregate as a novel measurable and modifiable factor in the progression of human atherosclerotic cardiovascular disease.

Drug-eluting balloon for the treatment of de novo coronary artery lesions in patients with high bleeding risk, a randomized controlled single-blind multicenter trial (DEBUT)

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Optimal PCI technique in patients with bleeding risk is not known. DAPT may be kept short (usually 1 month) after PCI using DEB as no metallic material is left in the vessel. Only little data exist regarding PCI using DEB for de novo coronary artery lesions.

We randomly assigned 208 patients with known bleeding risk, presenting stable angina or ACS to PCI using DEB (n=103) or bare-metal stent (BMS, n=105) in five centers in Finland. For inclusion patient had to have an ischemic de novo lesion in a coronary artery or bypass graft that could be treated with DEB-PCI (2.5-4.0 mm in diameter) and at least one risk factor for bleeding, for example oral anticoagulation or anemia. The exclusion criteria were ST-elevation myocardial infarction, cardiogenic shock or resuscitation before PCI, bifurcation lesion needing two stent-technique, restenosis, life-expectancy less than one year, left main intervention, chronic total occlusion and flow-limiting dissection or significant recoil (>30%) of the target lesion after predilatation. Primary endpoint was the composite of cardiovascular mortality, non-fatal myocardial infarction or target-lesion revascularization (TLR) at 9 months. Secondary endpoint was TLR at 9 months. The duration of DAPT was 1 month in stable angina and 6 months after ACS in both groups.

Mean age of the patients was 77 years and 46% of patients had ACS. At 9 months, the primary end point (MACE) had occurred in 2 patients (1.9%) in the DEB group and in 13 patients (12.4%) in the BMS group (risk difference, -10.4 percentage points; 95% confidence interval [CI], -3.6% to -17.3%; risk ratio, 0.15; 95% CI, 0.04 to 0.68; P<0.001 for noninferiority and P=0.004 for superiority). At 9 months, the secondary endpoint (TLR) had occurred in 0 patients (0%) in the DEB group and in 5 patients (4.8%) in the BMS group (risk difference, -4.8 percentage points; 95% confidence interval [CI], -0.3% to -9.1%; risk ratio, 0.09; 95% CI, 0.01 to 1.65; P<0.001 for noninferiority and P=0.06 for superiority). There were two definitive stent thrombosis events in the BMS group but no vessel closures in the DEB group. The risk for significant bleeding did not differ between the groups.

DEB was superior to BMS with lower MACE rate in patients with bleeding risk with no TLR or acute vessel closure at 9 months. DEBUT trial is the first randomized controlled trial investigating the efficacy of DEB in de novo coronary artery lesions.

The role of genetics in apparently acquired non-ischemic cardiomyopathies leading to sudden cardiac death

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Aim

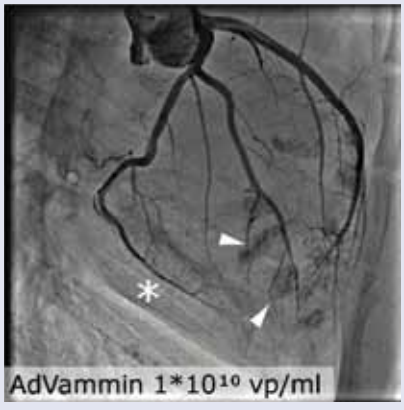
Non-ischemic causes of sudden cardiac death (SCD) comprise substantial and increasing proportion of SCDs. Most of the SCDs are thought to be result of acquired cardiomyopathies in the presence of cardiovascular risk factors and compatible structural heart disease at autopsy. However, genetic background of these cardiomyopathies is unknown as post-mortem genetic testing is currently primarily focused on autopsy-negative SCD cases and those with signs of inherited cardiac disease. Our aim was to clarify the potential role of genetic factors in apparently acquired non-ischemic cardiomyopathies leading to SCD.

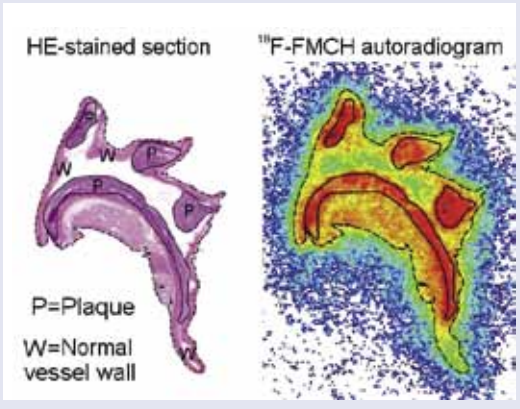
Methods

We performed targeted next generation sequencing of a panel of 174 myocardial structure and function related genes using NextSeq550 platform (Illumina) for 120 autopsy confirmed non-ischemic SCD victims (median age 51, 78% male) as a part of the Fingesture study. 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 consensus guidelines.

Results

Obesity cardiomyopathy (OCMP) (n=58) and hypertensive cardiomyopathy (HCMP) (n=45) were the most common causes of death in death certificates based on autopsy findings and medical history of the subjects. Dilated cardiomyopathy (DCM) (n=9), sudden arrhythmic death (n=3), hypertrophic cardiomyopathy (HCM) (n=3) and arrhythmogenic right ventricular cardiomyopathy (ARVC) (n=2) were less frequent. In total, we observed 53 variants in 47 subjects (39%). Thirteen were pathogenic/likely pathogenic variants in 14 subjects (12%) and 40 were variants of uncertain significance (VUS) in 38 subjects (32%). Likely disease causing mutations were mainly either in HCM (CSRP3, MYH7, MYH6, LAMP2, TCAP), in ARVC (PKP2, DSP, DSG2) or in DCM (TTN, LDB3, RBM20) related genes. Additionally, two unrelated subjects with HCMP and OCMP shared the same likely disease causing variant in CAV3-gene. We found no rare variants in ion channel coding genes.





Conclusions

Likely disease causing mutations and VUSs are surprisingly common among non-ischemic SCD victims with cardiovascular risk factors and compatible structural heart disease at autopsy, especially obesity and hypertension. Inherited structural heart diseases, such as HCM, ARVC and DCM, seem to be relatively common in victims of non-ischemic SCD and remain undiagnosed without genetic testing.