YOUNG INVESTIGATOR AWARD

FINALISTS' PRESENTATIONS

Grand Ballroom, 1000h, 6th April 2019

10:00 – 10:15 **Left Atrial Function Predicts Clinical Outcomes in Patients Following ST Elevation Myocardial Infarction: A Study with Rapid Semi-Automated Strain Derived from Cardiovascular Magnetic Resonance**

Shuang Leng*[1] ; Heng Ge[2] ; Jie He[2] ; Lingcong Kong[2] ; Ru-San Tan[1 3] ; Xiaodan Zhao[1] ; Derek Hausenloy[1 4] ; Liang Zhong[1 4]
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10:15 – 10:30 **Disease and Phenotype Relevant Genetic Variants Identified from Histone Acetylomes in Human Hearts**

Lek Wen Tan*[1 2] ; Eleanor Wong[1 2] ; Chukwuemeka George Anene-Nzelu[1 2] ; Thomas P. Cappola[3] ; Marie Loh[2 4 5] ; John Chambers[4 5] ; Shyam Prabhakar[1] ; Roger Foo[1 2]
[1]Human Genetics 3/ Genome Institute of Singapore/ Singapore, [2]Medicine/ National University of Singapore/ Singapore, [3]Perlman School of Medicine/ University of Pennsylvania / United States, [4]Epidemiology and Biostatistics/ Imperial College London/ United Kingdom, [5]Lee Kong Chian School of Medicine/ Nanyang Technological University/ Singapore

10:30 – 10:45 **Artificial Circular Mirna Sponges as A Novel Mirna Interference Technology**

Annadoray Lavenniah*[1 2] ; Matthew Ackers-Johnson[1 2] ; Yiqing Li[1 2] ; Tuan Luu Danh Anh[1 2] ; Tingsen Benson Lim[1 2] ; Roger Foo[1 2]
[1]Human Genetics 3/ Genome Institute of Singapore/ Singapore, [2]Cardiovascular Research Institute/ National University of Singapore/ Singapore

10:45 – 11:00 **An Evaluation of Recurrent Heart Failure Patients' Adherence to Medications in Changi General Hospital**

Daniel Fletcher*[1] ; Chun Yan Ong[1] ; Sherry Goh[1] ; Weng Leong Woo[1] ; Michael Macdonald[2]
[1]Pharmacy/ Changi General Hospital/ Singapore [2]Cardiology/ Changi General Hospital/ Singapore

11:00 – 11:15 **Sleep Apnoea and Cardiovascular Events after Coronary Artery Bypass Grafting**

Chieh Yang Koo*[1] ; On behalf of the SABOT study investigators[1]
[1]Cardiology/ National University Heart Centre/ Singapore

11:15 – 11:30 **Statin and Antiplatelet Initiation in Patients with a Normal Stress Single Photon Emission Computed Tomographic Myocardial Perfusion Imaging and Elevated Coronary Artery Calcium Score**

Yi Hui To*[1] ; Xi Min Tan[1] ; Cher-Lyn Low[1] ; Htet Htet Min[2] ; Min Sen Yew[3]
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Topic: Basic Science
Abstract No: 10297

LEFT ATRIAL FUNCTION PREDICTS CLINICAL OUTCOMES IN PATIENTS FOLLOWING ST ELEVATION MYOCARDIAL INFARCTION: A STUDY WITH RAPID SEMI-AUTOMATED STRAIN DERIVED FROM CARDIOVASCULAR MAGNETIC RESONANCE

Shuang Leng[*1] ; Heng Ge[2] ; Jie He[2] ; Lingcong Kong[2] ; Ru-San Tan[1 3] ; Xiaodan Zhao[1] ; Derek Hausenloy[1 4] ; Liang Zhong[1 4]

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Objective(s)
The left atrium (LA) modulates left ventricular (LV) filling and cardiac performance in a complex manner that comprises discrete reservoir, conduit and booster pump phases. Routine clinical assessment of LA function is limited to simple measurements of maximal LA volume, area or maximal diameter, belying the complex phasic LA-LV interactions, and may thus be inadequate for characterizing LA phasic function comprehensively and fail to glean the full diagnostic and prognostic potentials. We have developed novel semi-automated image post-processing software to measure LA phasic strain parameters from cine standard cardiovascular magnetic resonance (CMR). The aim of the present study is to evaluate the prognostic importance of LA phasic strain parameters in patients after ST elevation myocardial infarction (STEMI).

Material and Method
In 321 patients, CMR scans were performed 3 to 7 days after STEMI. LA phasic strains and strain rates were analyzed using in-house software to post-process standard cine 4- and 2-chamber CMR images. The incidence of the primary endpoint, a composite of death, re-infarction, stroke and heart failure was censored during the follow-up [median: 3.7 years (inter-quartile range: 2.7 – 4.8 years)].

Result(s)
Reduced LA reservoir and conduit strains were significantly associated with larger infarct size expressed as a percentage of LV mass (r = -0.36 and -0.33, respectively, both $P < 0.0001$). A total of 77 patients (24%) met the primary endpoint. In Cox regression analysis adjusting for known risk factors (including infarct size), LA reservoir strain [adjusted hazard ratio (HR): 0.89; 95% confidence interval (CI): 0.85 – 0.94; $P < 0.0001$] and conduit strain [adjusted HR: 0.83; 95% CI: 0.76 – 0.91; $P < 0.0001$] remained independently associated with the primary outcome.

Conclusion
In STEMI patients, impaired LA strains were associated with larger infarct size, and were independent predictors of adverse clinical outcome, and therefore should be considered as a useful adjunct to established markers.

Topic: Basic Science
Abstract No: 10400

Disease and phenotype relevant genetic variants identified from histone acetylomes in human hearts

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Objective(s)

Identifying genetic markers for heterogeneous complex diseases such as heart failure has been challenging, and may require prohibitively large cohort sizes in genome-wide association studies (GWAS) in order to meet genome-wide statistical significance. On the other hand, chromatin quantitative trait loci (QTL), elucidated by direct epigenetic profiling of specific human tissues, may contribute towards prioritising sub-threshold variants for disease-association.

Material and Method

We captured non-coding genetic variants by performing enhancer H3K27ac chromatin immunoprecipitation sequencing (ChIP-seq) in 70 human control and end-stage failing hearts.

Result(s)

We mapped out a comprehensive catalogue of 47,321 putative human heart enhancers. 3,897 differential acetylation peaks (FDR 5%) pointed to pathways altered in heart failure (HF). To identify cardiac histone acetylation QTLs (haQTLs), we regressed out confounding factors including HF disease status, and employed the G-SCI test to call out 1,680 haQTLs (FDR 10%). RNA-seq performed on the same heart samples proved a subset of haQTLs to have significant association also to gene expression (expression QTLs), either in *cis* (180), or through long range interactions (81), identified by Hi-C and Hi-ChIP performed on a subset of hearts. Finally, 62 unique loci were identified by colocalisation of haQTLs with heart-related GWAS datasets.

Conclusion

Population genetic variants at noncoding enhancer loci may indeed have functional value for disease and phenotype if they perturb transcription factor binding motifs, leading to chromatin and gene expression differences. The haQTL dataset here should now prove useful for prioritising more genetic variants from other heart-related GWAS. The approach of chromatin QTL and 3D connectome analyses in disease-relevant tissue promises not just to resolve the identity of functional genetic variants, but target genes with correlated expression changes may be implicated to represent important pathways for new disease therapy.

Keywords: Histone; Acetylome; Heart; GWAS; QTL; RNA-seq; ChIP-seq; SNP; DNA;

Topic: Basic Science
Abstract No: 10289

ARTIFICIAL CIRCULAR MIRNA SPONGES AS A NOVEL MIRNA INTERFERENCE TECHNOLOGY

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Objective(s)

Circular RNAs (circRNAs) are an emerging class of noncoding RNAs with a circular structure that confers nucleolytic resistance. Recently, circRNAs have been discovered to sequester microRNAs (miRs) and repress their activity. We hypothesise that artificial circRNA sponges (circmiRs) can be constructed to target miRs therapeutically, with low dosage requirement and extended half-lives compared to current alternatives.

Material and Method

CircmiRs were expressed using plasmid vectors in which inverted repeats flanked a linear miR sponge sequence. *In vitro* testing of circmiRs was performed using luciferase rescue, RNA pull-down and stability assays. Adeno-associated viral vectors were used to deliver circmiRs to cardiomyocytes *in vivo* in a transverse aortic constriction (TAC) mouse pressure overload model. Cardiac function was monitored by echocardiography. T7 *in vitro* transcription was used to synthesise exogenous circmiRs for comparison with antagomiRs.

Result(s)

A circmiR sponge was constructed and optimised to target known pro-hypertrophic miRs-132 and -212. CircmiR expression competitively inhibited miR-132 and -212 activity in luciferase rescue assays. circmiRs were more stable than linear miR sponges. Direct sequestration of target miR-132 and -212 was confirmed by RNA pull down. *In vivo,* circmiR delivery preserved cardiac function and suppressed induction of stress genes up to 4 weeks post-TAC. Finally, artificial circmiRs were successfully synthesised at high yields and showed greater efficacy than antagomiRs in inhibiting miR function.

Conclusion

circmiRs were successfully expressed and showed inhibition of target miR-132 and -212 activity *in vitro.* Delivery into a TAC mouse model attenuated hypertrophic characteristics suggesting the potential efficacy of circmiR as a novel therapeutic tool *in vivo*. Follow-up studies are ongoing to validate the molecular inhibition of miR-132 and -212 *in vivo*, and to confirm the *in vivo* efficacy of *in vitro* synthesised circmiRs in comparison to current linear miRNA interference technologies.

Keywords: circRNA;miRNA;hypertrophy;therapy

Topic: Heart Failure / Cardiovascular Rehabilitation & Preventive Cardiology
Abstract No: 10302

AN EVALUATION OF RECURRENT HEART FAILURE PATIENTS' ADHERENCE TO MEDICATIONS IN CHANGI GENERAL HOSPITAL

Daniel Fletcher*[1] ; Chun Yan Ong[1] ; Sherry Goh[1] ; Weng Leong Woo[1] ; Michael Macdonald[2]
[1]Pharmacy/ Changi General Hospital/ Singapore [2]Cardiology/ Changi General Hospital/ Singapore

Objective(s)
Poor adherence to medications often leads to aggravation of heart failure (HF) symptoms, leading to re-hospitalisations. Hence, there is a need to understand the rate of and reasons for non-adherence. This study was thus undertaken to (1) assess patients' adherence to prescribed HF medications and knowledge of HF and (2) examine the factors underlying non-adherence.

Material and Method
This is a cross-sectional study conducted at Changi General Hospital. HF patients who were readmitted from November 2015 to March 2016 were recruited for this study. Eligible patients who agreed to be enrolled in this study were asked a series of questions. This includes a (1) dichotomous questions on comprehension of instructions on medication use, (2) open-ended questions on adherence to medications, (3) eight-item Morisky Medication Adherence Scale (MMAS-8) and (4) Dutch HF Knowledge Scale (DHFKS) was administered. Results were tabulated and analyzed using the Statistical Package for Social Sciences (SPSS) v.21.0 Fisher's exact test for statistical significance.

Result(s)
Fifty patients were recruited whereby 80% could understand the instructions on medication use, especially when aided by caregivers. However, 67% of the patients had inadequate HF knowledge, by scoring 9 or less on the DHFKS. Questions on HF general knowledge gathered the lowest score of 32%. Patients with at least secondary school education scored better for DHFKS than their counterparts, with an average score of 9.2 versus 6.9 out of 15 (p=0.04). Nevertheless, their adherence as indicated by MMAS-8 scores were not significantly better (p=0.25). Apart from poor knowledge on medication use (61%), forgetfulness (26%) and low health literacy rates (9%) are among the top few reasons considered by patients as barriers for adherence.

Conclusion
These findings provide interesting insights into the rates of and reasons for non-adherence, which in turn may assist healthcare professionals in devising strategies to address frequent re-hospitalizations due to poor medication adherence.

Keywords: heart failure readmission; adherence; medication compliance; MMAS-8; DHFKS

Topic: Non-Invasive Cardiac Imaging, Echocardiography, Nuclear Cardiology / Adult Congenital Heart Disease / Cardiac Surgery
Abstract No: 10294

Sleep Apnoea and Cardiovascular Events after Coronary Artery Bypass Grafting

Chieh Yang Koo*[1] ; On behalf of the SABOT study investigators [1]
[1]*Cardiology/ National University Heart Center/ Singapore*

Objective(s)

Sleep apnoea (SA) is prevalent and independently associated with adverse cardiovascular events after percutaneous coronary intervention. Patients with complex and high-risk features are often referred for coronary artery bypass grafting surgery (CABG) and it remains unknown if SA is a risk marker. We evaluated the association between SA and major adverse cardiac and cerebrovascular events (MACCE) in patients undergoing non-urgent CABG.

Material and Method

This was a prospective cohort study conducted between November 2013 and December 2018. Patients from 3 public hospitals referred to a tertiary cardiac centre for non-urgent CABG were recruited for an overnight sleep study prior to CABG. The mean follow-up duration was 2.1 years.

Result(s)

Among the 1007 patients who completed the study, SA (defined as apnoea-hypopnoea index ≥15 events per hour) was diagnosed in 513 patients (50.9%). Most of the patients underwent on-pump CABG (96.7%) and received a left internal mammary artery graft (95.2%). MACCE, a composite of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke and unplanned revascularisation, occurred in 123 patients (12.2%). The crude incidence of MACCE was higher in the SA than the non-SA group (15.0% versus 9.5%, p=0.003). Likewise, the crude incidence of all-cause mortality (7.2% versus 4.3%, p=0.028), sudden cardiac death (3.9% versus 1.6%, p=0.028) and heart failure hospitalisations (10.9% versus 5.3%, p=0.001) was higher in the SA than the non-SA group. Multivariate Cox regression analysis demonstrated that SA was predictive of MACCE with an adjusted hazard ratio of 1.54 (95% confidence interval, 1.06-2.22; p=0.023), after adjusting for the effects of age, gender, body mass index, left ventricular ejection fraction, hypertension and chronic kidney disease.

Conclusion

Sleep apnoea is independently associated with increased MACCE in patients undergoing CABG. Further evaluation regarding the efficacy of treatment of sleep apnoea in patients undergoing CABG surgery is warranted.

Keywords: Sleep apnea; coronary artery bypass graft; surgery; revascularisation; peri-operative

Topic: Non-Invasive Cardiac Imaging, Echocardiography, Nuclear Cardiology / Adult Congenital Heart Disease / Cardiac Surgery
Abstract No: 10234

Statin and antiplatelet initiation in patients with a normal stress single photon emission computed tomographic myocardial perfusion imaging and elevated coronary artery calcium score

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Objective(s)
Coronary artery calcium (CAC) scoring gives additional prognostic information over stress Single Photon Emission Computed Tomographic (SPECT) Myocardial Perfusion Imaging (MPI). High CAC is associated with increased major adverse cardiac and cerebrovascular events (MACCE) despite normal stress MPI (nsMPI). Moderate-high intensity statins (MHIS) and antiplatelets are recommended for high CAC. We aim to assess the practices and impact of statin/antiplatelet initiation in patients with nsMPI and elevated CAC.

Material and Method
Retrospective review of nsMPIs performed between 1 March 2016 – 31 January 2017 with simultaneously measured CAC score >300. Cases with post-stress left ventricular ejection fraction <50% were excluded. Clinical data including statin/antiplatelet prescriptions and MACCE at 24 months (cardiac death, acute coronary syndrome, ischaemic stroke) were traced using electronic records.

Result(s)
There were 311 nsMPIs meeting inclusion criteria (56.3% male, 50.1% diabetic). Median age was 71 (49 - 97) years. There were 215 (69.1%) on statins at baseline, of which 69.3% were MHIS. Post MPI, 52.1% of statin-naïve patients were started on statins (all MHIS) and 2/66 (3.0%) were escalated from low intensity statins (LIS) to MHIS. Antiplatelet/anticoagulation was used by 46.9% at baseline, with a further 56/165 (33.9%) initiated post-MPI. Reasons for not starting antiplatelet were documented in 10.1%, of which anaemia/bleeding risk (54.6%) and patient refusal (36.4%) were most common. MACCE within 24 months was significantly lower in patients taking MHIS compared to LIS or no statins post-MPI (3.5% vs 6.4% vs 13.0%, p=0.034). There was no significant difference in MACCE between patients with or without antiplatelets/anticoagulation post-MPI (2.5% vs 7.3%, p=0.070).

Conclusion
A substantial proportion of patients with nsMPI and high CAC do not receive MHIS/antiplatelets. Post-MPI MHIS use is associated with lower 24-month MACCE. There is a need to promote greater awareness of the importance of aggressive medical therapy for high CAC despite a nsMPI.

Keywords: Coronary calcium score; Myocardial Perfusion Imaging; Statins; Antiplatelets