FREE PAPER SESSION 1

Oriole Room, 08:15h, 6th April 2019

08:15 – 08:25 **Community Sourced Discovery of Genetic Variants in Statin Metabolism**

Wei Loong Sherman Yee*[1] ; Chester Drum[1]
[1]Medicine/ National University of Singapore/ Singapore

08:25 – 08:35 **Global Single Cell Sequencing Reveals Extensive Cell-Cell Crosstalk and Specific Regulation of Macrophage Inflammatory Polarisation by Cardiac Fibroblasts Following Myocardial Injury**

Matthew Ackers-Johnson*[1 2] ; Motakis Efthymios[1 2] ; Justus Stenzig[3] ; Rongrong Zhao[1 2] ; Zenia Tiang[2] ; Wilson Tan[2] ; Tuan Luu[1] ; Peter Li[1] ; Roger Foo[1 2]
[1]Cardiovascular Research Institute/ National University of Singapore/ Singapore, [2]Human Genetics/ Genome Institute of Singapore/ Singapore, [3]Institut für Experimentelle Pharmakologie und Toxikologie/ Universitätsklinikum Hamburg-Eppendorf/ Germany (Deutschland)

08:35 – 08:45 **The Effects of Blood Pressure and Flow on Non-invasive Fractional Flow Reserve**

Junmei Zhang*[1 2] ; Gaurav Chandola[1] ; Ris Low[1] ; Ru San Tan[1 2] ; Aaron Sung Lung Wong[1 2] ; Jack Wei Chieh Tan[1 2] ; Khung Keong Yeo[1 2] ; Ping Chai[3] ; Lynette LS Teo[3] ; Ching Ching Ong[3] ; Adrian F Low3 ; Lohendran Baskaran[1] ; Terrance Siang Jin Chua[1 2] ; Tian Hai Koh[1 2] ; Swee Yaw Tan[1 2] ; Soo Teik Lim[1 2] ; Liang Zhong[1 2]
[1]National Heart Research Institute Singapore/ National Heart Center Singapore/ Singapore, [2]SingHealth Duke-NUS Cardiovascular Sciences ACP/ Duke-NUS Medical School/ Singapore, [3]Cardiology/ National University Hospital Singapore/ Singapore

08:45 – 08:55 **Non-Obstructive Coronary Artery Disease is an Independent Predictor of Death**

Alfred YIP*[1] ; Vijay Ramadoss[1] ; Andie Djohan[1] ; Ting Wei Teo[1] ; Ting Ting Low[1] ; Yoke Ching Lim1
[1]Internal Medicine/ National University Health Systems/ Singapore

08:55 – 09:05 **A Clinical and Echocardiographic Comparative Study of Patients with Asymptomatic Moderate and Severe Bicuspid and Tricuspid Aortic Valve Stenosis**

Joe Jia-Liang Chua*[1] ; Ching-Hui Sia[2] ; Benjamin Yong-Qiang Tan[3] ; Nicholas Jinghao Ngiam[3] ; Hui-Wen Sim[2] ; Tiong-Cheng Yeo[1 2] ; William Kok-Fai Kong[1 2] ; Kian-Keong Poh[1 2]
[1]Yong Loo Lin School of Medicine/ National University of Singapore/ Singapore, [2]Department of Cardiology/ National University Heart Centre/ Singapore, [3]Department of Medicine/ National University Health System/ Singapore

09:05 – 09:15 **Correlation of Quantitative Flow Ratio Assessment Against Instantaneous Wave-Free Ratio in Hemodynamic Evaluation of Coronary Lesions**

Ki Fung Cliff Li*[1] ; Paul Ong[1] ; Jason Chuang[1]
[1]Cardiology/ Tan Tock Seng Hospital/ Singapore

Topic: Heart Failure / Cardiovascular Rehabilitation & Preventive Cardiology
Abstract No: 10256

Community Sourced Discovery of Genetic Variants in Statin Metabolism

Wei Loong Sherman Yee*[1] ; Chester Drum[1]
[1]*Medicine/ National University of Singapore/ Singapore*

Objective(s)

1) Evaluate the inter-individual variability in statin drug metabolism using statin drug and drug metabolite concentrations obtained during late elimination phase in the Singapore population

2) Assess the association between clinical and pharmacogenetic variables and statin drug and metabolite concentrations in subjects

Material and Method

1500 subjects on atorvastatin and simvastatin will be prospectively recruited at two outpatient heart clinics, with each clinic contributing half of the study population. Two blood draws, three hours apart, are done per patient per visit via venipuncture. Blood drawn is used for genomic analysis then spun down to plasma for clinical biomarker measurements via COBAS c111 and drug and metabolite measurements via LC-MS/MS.

Result(s)

The first 100 atorvastatin subjects were analyzed. Intra-individual variation of drug and metabolite concentrations ranged from 8% to 30% while inter-individual variation ranged from 70% to 100% for different metabolites. Non-parametric tests were used to test for significant differences between categories. There were significant differences ($p<0.05$) in drug concentrations found between different orally administered doses, with higher doses showing higher plasma concentrations. This was true for atorvastatin metabolites as well. In addition, there was a significant difference ($p<0.05$) in atorvastatin concentration between the SLCO1B1 *rs4149046* genotypes. No difference was observed for other atorvastatin metabolite concentrations. Spearman rank correlation was used to analyze associations between quantitative variables. Significant correlations ($p<0.05$) were seen between urea, creatine kinase and triglycerides with atorvastatin and metabolite concentrations. Significant correlations were also seen between hsCRP and the metabolite:parent drug ratios. Simple linear regression was used to judge the contribution of genetic variables to statin drug and metabolite concentration.

Conclusion

Statin drug and drug metabolite levels obtained during the late elimination phase have been found to be significantly associated with known pharmacogenomic variants of statin metabolism. They were also significantly correlated with other clinical biomarkers.

Keywords: Statin; Pharmacogenomics; Pharmacokinetics; Biomarkers; Metabolism

Topic: Basic Science
Abstract No: 10364

Global Single Cell Sequencing Reveals Extensive Cell-Cell Crosstalk and Specific Regulation Of Macrophage Inflammatory Polarisation by Cardiac Fibroblasts Following Myocardial Injury

Matthew Ackers-Johnson*[1 2] ; Motakis Efthymios[1 2] ; Justus Stenzig[3] ; Rongrong Zhao[1 2] ; Zenia Tiang[2] ; Wilson Tan[2] ; Tuan Luu[1] ; Peter Li[1] ; Roger Foo[1 2]

[1]Cardiovascular Research Institute/ National University of Singapore/ Singapore, [2]Human Genetics/ Genome Institute of Singapore/ Singapore, [3]Institut für Experimentelle Pharmakologie und Toxikologie/ Universitätsklinikum Hamburg-Eppendorf/ Germany (Deutschland)

Objective(s)
Cardiac function and injury responses depend upon complex interactions between multiple specialised cell types of various origin, including infiltrating inflammatory immune cells, which are increasingly understood to have critical roles in disease. Research is however limited by inherent difficulties in identifying, isolating and characterising relevant cellular populations. We sought to apply an unbiased transcriptomic approach to characterise global cardiac non-myocyte populations and map intercellular cross-talk, in order to identify novel disease-associated cell markers and interactions, which could represent targets for future therapies.

Material and Method
A flow cytometry single-cell RNA sequencing "FACS-seq" approach was developed to characterise non-myocyte populations from murine myocardium. Over 2000 cells were collected one week after surgically induced myocardial infarction (disease group) or sham surgery (control group). Single cell transcriptomic profiles were generated, and integrated with published datasets to create global cardiac intercellular interaction maps. Validation was performed using mouse and human histological sections and cardiac primary cell culture models.

Result(s)
All major cardiac cell types were identified at relative proportions in line with recent reports, and new putative cell-type and disease-associated marker genes were revealed and validated. Global interaction maps revealed a striking increase in specific cross-talk between resident cardiac fibroblasts and macrophages in the disease environment. A unique regulatory function for cardiac fibroblasts in suppressing pro-inflammatory macrophage activation and driving macrophages towards an M2, anti-inflammatory polarised phenotype, was confirmed using in-vitro mouse and human cell culture models.

Conclusion
We have developed a FACS-Seq procedure to enable unbiased, marker-independent analysis of myocardial cell populations. This technique revealed extensive cell-cell crosstalk and specific regulation of macrophage inflammatory polarisation by cardiac fibroblasts following cardiac injury. We anticipate that further investigation into this immunomodulatory mechanism will lead to the elucidation of new targets for therapeutic intervention.

Keywords: single-cell; fibroblast; macrophage; cross-talk; inflammation

Topic: Basic Science
Abstract No: 10361

The Effects of Blood Pressure and Flow on Non-invasive Fractional Flow Reserve

Junmei Zhang*[1 2] ; Gaurav Chandola[1] ; Ris Low[1] ; Ru San Tan[1 2] ; Aaron Sung Lung Wong[1 2] ; Jack Wei Chieh Tan[1 2] ; Khung Keong Yeo[1 2] ; Ping Chai[3] ; Lynette LS Teo[3] ; Ching Ching Ong[3] ; Adrian F Low[3] ; Lohendran Baskaran[1] ; Terrance Siang Jin Chua[1 2] ; Tian Hai Koh[1 2] ; Swee Yaw Tan[1 2] ; Soo Teik Lim[1 2] ; Liang Zhong[1 2]
[1]National Heart Research Institute Singapore/ National Heart Center Singapore/ Singapore, [2]SingHealth Duke-NUS Cardiovascular Sciences ACP/ Duke-NUS Medical School/ Singapore, [3]Cardiology/ National University Hospital Singapore/ Singapore

Objective(s)
From computed tomography coronary angiography (CTCA), we developed a methodology for non-invasive fractional flow reserve (FFR_B) assessment using computational fluid dynamics (CFD), which has demonstrated good discrimination for coronary ischemic lesions. In this study, we aimed to assess the effects on FFR_B of (1) blood pressure (BP); and (2) total coronary blood flow (CBF).

Material and Method

All subjects underwent both CTCA and invasive FFR measurement. Ischemia was defined as invasive FFR ≤0.8. Using our developed reduced-order CFD algorithm, FFR_B was computed with inputs of (1) BP measured before CTCA; and (2) estimated total CBF, which is conventionally calculated from left ventricular mass (LVM) assessed on CTCA. To evaluate the effects of BP and CBF, FFR_B was also computed at graded levels of simulated BPs (70%BP, 80% BP, 90%BP, 110%BP, 120%BP, and 130%BP) and CBF (70%CBF, 80%CBF, 90%CBF, 110%CBF, 120%CBF, and 130%CBF) for each patient-specific CTCA-derived 3D coronary model. Correlation and agreement between FFR_B and invasive FFR were assessed by the Pearson test and Bland-Altman analysis, respectively.

Result(s)

9 patients with 10 coronary lesions were studied. Mean invasive FFR and FFR_B (derived using measured BP and estimated CBF values) were 0.787±0.0998 and 0.792±0.100, respectively. Correlation between FFR_B and FFR was excellent (FFR_B=0.9431FFR+0.0499, R=0.937, $p<0.05$, FFR-FFR_B=-0.00514±0.0354). FFR_B increased with the increasing magnitude of simulated BP, but decreased as simulated CBF increased. At simulated 70%BP, 80% BP, 90%BP, 110%BP, 120%BP, and 130%BP, the mean FFR_B were 0.715±0.134, 0.747±0.119, 0.773±0.108, 0.810±0.092, 0.823±0.085, and 0.835±0.080, respectively. At simulated 70%CBF, 80%CBF, 90%CBF, 110%CBF, 120%CBF, and 130%CBF), mean FFR_B were 0.817±0.088, 0.809±0.092, 0.801±0.095, 0.784±0.104, 0.775±0.109, and 0.767±0.113, respectively.

Conclusion

Use of measured BP before CTCA procedure and CBF calculated from CTCA-estimated LVM are obligatory for accurate noninvasive FFR_B assessment. BP and CBF variations have directionally opposite effects on FFR_B calculation, and inaccurate assumptions can misclassify physiologic significance in borderline coronary lesions.

Keywords: Coronary artery disease; fractional flow reserve (FFR); computed tomography coronary angiography (CTCA); computational fluid dynamics (CFD); non-invasive

Topic: Basic Science
Abstract No: 10459

Non-Obstructive Coronary Artery Disease is an Independent Predictor of Death

Alfred YIP*[1] ; Vijay Ramadoss[1] ; Andie Djohan[1] ; Ting Wei Teo[1] ; Ting Ting Low[1] ; Yoke Ching Lim[1]
[1]Internal Medicine/ National University Hospital Systems/ Singapore

Objective(s)

Non-obstructive coronary artery disease (NOCAD) is a poorly understood entity, but there is emerging evidence that this condition is more threatening than it seems. Our study aims to examine the clinical significance of NOCAD in a local population.

Material and Method

In this retrospective study, we included 1542 consecutive patients with <50% epicardial coronary stenosis on index coronary angiogram from January 2005 to December 2011. The patients had follow-up data available till 31 December 2017 from our audit database, from the hospital medical records. We compared 2 groups of patients, NOCAD which was defined as presence of coronary stenosis that was <50% versus absent CAD which was defined as 0% coronary stenosis. Baseline characteristics, survival and major adverse cardiac events (MACE) were analysed, using multivariate analysis and the cox regression model.

Result(s)

Out of 1542 patients, 379 patients had NOCAD, while 1163 patients had absent CAD. The mean age was 53.9 and 37.4% were female. Racial distribution was consistent with our population census. NOCAD patients were more likely to have hypertension (56.4% vs 41.5%, p-value 0.000), diabetes (26.4% vs 19.6%, p-value 0.005) and hyperlipidaemia (54.1% vs 40.6%, p-value 0.000) than patients with absent CAD. All-cause mortality was higher in the NOCAD group (HR 2.38) but there was no difference in hospitalizations or MACE. NOCAD was found to be an independent predictor of all-cause mortality (p-value 0.032). Other independent predictors of mortality were age (p-value 0.000), previous acute coronary syndrome (p-value 0.000) and diabetes mellitus (p-value 0.013).

Conclusion

In this retrospective review of a multi-ethnic Asian population, NOCAD is associated with decreased survival and deserves attention as an important cardiovascular risk. Prospective studies with longer follow-up are indicated to investigate the effect of NOCAD on other major clinical events as well as treatment options.

Keywords: NOCAD,Coronary Artery disease,local population, CAD, Racial

Topic: Non-Invasive Cardiac Imaging, Echocardiography, Nuclear Cardiology / Adult Congenital Heart Disease / Cardiac Surgery
Abstract No: 10301

A Clinical and Echocardiographic Comparative Study of Patients with Asymptomatic Moderate and Severe Bicuspid and Tricuspid Aortic Valve Stenosis

Joe Jia-Liang Chua*[1] ; Ching-Hui Sia[2] ; Benjamin Yong-Qiang Tan[3] ; Nicholas Jinghao Ngiam[3] ; Hui-Wen Sim[2] ; Tiong-Cheng Yeo[1 2] ; William Kok-Fai Kong[1 2] ; Kian-Keong Poh[1 2]
[1]Yong Loo Lin School of Medicine/ National University of Singapore/ Singapore, [2]Department of Cardiology/ National University Heart Centre/ Singapore, [3]Department of Medicine/ National University Health System/ Singapore

Objective(s)

To guide the management of asymptomatic moderate and severe bicuspid (BAV) and tricuspid (TAV) aortic valve patients prior to aortic valve replacement (AVR), we aimed to describe and compare differences in clinical and echocardiographic parameters between the 2 groups.

Material and Method

We performed a retrospective cohort study in a tertiary academic centre. 554 consecutive cases of asymptomatic aortic stenosis (512 TAV, 42 BAV) were identified from our echocardiographic database from 7thSeptember 2011 to 31stDecember 2015. Demographics, symptoms, aortic stenosis and aortic dimension parameters, left ventricular geometry and systolic/diastolic function were analysed. The outcomes (time-to-event analysis) were admission for congestive cardiac failure (CCF), AVR, all-cause mortality, and a composite endpoint of AVR and all-cause mortality.

Result(s)

Patients with TAV, compared with BAV, were about 2 decades older (76.4 vs 53.6 years, p<0.001) and more likely to be female (58.6% vs 40.5%, p=0.023). TAV patients had a higher prevalence of hypertension (81.2% vs 54.8%, p<0.001), diabetes (42.8% vs 14.3%, p<0.001) and chronic kidney disease (20.2% vs 4.8%, p=0.014). TAV patients had less severe aortic valve disease (aortic valve index 0.7cm^2/m^{2}vs 0.6cm^2/m^2, p=0.005) and smaller aortic dimensions (p<0.001). TAV patients also had more diastolic dysfunction with a lower septal S' (6 vs 13cm/s, p=0.001), higher septal E/e' (19 vs 15cm/s, p=0.039), and larger left atrial diameters (42 vs 39mm, p=0.004). Left ventricular parameters and geometry were similar. On multivariate Cox regression for the composite of AVR and all-cause mortality, significant predictors included prior CCF (HR 1.86, 95% CI 1.09–3.15) and aortic sinus diameter (HR 1.02, 95% CI 1.002–1.04) but not aortic valve severity or morphology.

Conclusion

Asymptomatic moderate and severe aortic stenosis patients with BAV and TAV demonstrate different clinical and echocardiographic findings. Treatment of comorbidities and regular valve surveillance may be helpful.

Keywords: aortic stenosis; bicuspid aortic valve

Topic: Invasive Diagnostic & Interventional Cardiology
Abstract No: 10366

Correlation of Quantitative Flow Ratio assessment against instantaneous wave-free ratio in hemodynamic evaluation of coronary lesions

Ki Fung Cliff Li*[1] ; Paul Ong[1] ; Jason Chuang[1]
[1]*Cardiology/ Tan Tock Seng Hospital/ Singapore*

Objective(s)

Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are tools to assess hemodynamic significance of coronary lesions (CL). The angiographic 3D Quantitative Flow Ratio (QFR) assessment has been compared with FFR with good correlation. This is the first report on QFR benchmarked against iFR in South East Asian patients.

Material and Method

Our study included 26 coronary vessels with iFR done (69% LAD; 7% Diagonal branch; 7% LCx; RCA 15%) from 23 patients (aged 59±9; 69% male; 39% diabetes; 73% hypertension; 87% hyperlipidemia; 13% smoker), of which 39% presented with acute coronary syndrome (55% was done for non-culprit vessels in STEMI, 22% NSTEMI). QFR of these vessels were analysed offline after anonymisation and in a blinded manner with QAngio XA 3D software (Medis Medical Imaging).

Result(s)

Comparison between iFR and fQFR was done via Pearsons bivariate analysis, and correlation coefficient of 0.627 was statistically significant, $p = 0.001$. The results were plotted on a scatter plot with a general linear relationship. There was only 1 outlier on scatterplot. When the cut-off for QFR was set at <0.80 and iFR ≤ 0.89, there were 3 results that were positive for iFR but negative for QFR. However, when the QFR threshold was set at <0.85 instead, there was no CL with positive iFR.

Conclusion

From our results, QFR has a good correlation with iFR. It is effective as a "gatekeeper" for further invasive pressure wire assessment with iFR, with a high negative predictive value when QFR threshold is set at 0.85. This is in line with the study by Yazaki et al which showed wide variation in agreement between QFR and FFR when QFR is approximately 0.80. We thus propose a hybrid approach in CL assessment, performing iFR only when QFR ≤ 0.85 . This might be a cost-effective way to assess CL in resource poor countries.