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Atrial Fibrillation Screening in Hong Kong – Where Are We Now?

NGAI-YIN CHAN

Deputy Chief-of-Service, Department of Medicine & Geriatrics, Princess Margaret Hospital, Hong Kong

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder and has become a global epidemic especially in the developed countries with aging population. Although the risk of AF-related stroke can be markedly reduced by 64-70% by oral anticoagulation therapy, a major challenge remains to be the evasive nature of the condition to be diagnosed early for effective treatment. Around a quarter of patients have silent or asymptomatic AF and up to 25% of patients with AF-related stroke have AF diagnosed only at the time of stroke.

According to the WHO criteria, a disease is suitable for screening when it is an important health problem with an accepted treatment, there are facilities for diagnosis and treatment, there is a latent and symptomatic stage, the natural history is understood, there is an agreed policy on whom to treat, the cost of finding is economically balanced with overall health, the case finding is a continuous process and the screening test is suitable and acceptable to the population. AF satisfies most of those criteria and currently the European Society of Cardiology recommends opportunistic screening for AF by pulse taking or electrocardiogram rhythm strip in patients over 65 years of age. Screening for AF in different settings and with different tools have been studied and in recent few years, researchers in Hong Kong have contributed significantly to the knowledge base in this area.

There were 2 large-scale community-based systematic screening programs carried out in Hong Kong in recent years. In both studies, Kardia mobile device, capable of producing a single-lead wireless smartphone electrocardiogram (sECG) for 30 seconds was used as the tool for screening. Chan et al reported a study aiming to assess the feasibility of community screening for AF using sECG and to generate epidemiological data on the prevalence and risk factors of AF in Hong Kong. All citizens aged 18 or above were eligible for participation. Among 13,122 (mean age 64.7) citizens, 101 (0.8%) had newly diagnosed AF with 66 (65.3%) being asymptomatic. The mean CHA2DS2-VASc score was 3.1 in patients with newly diagnosed AF. The number-needed-to-screen (NNS) for one newly diagnosed AF was 129. AF was detected with sECG in 239 (1.8%) citizens and it was likely persistent AF. Apart from those patients, 872 (6.6%) citizens self-reported history of AF without sECG showing it and this likely represents paroxysmal AF. The independent predictors of AF shown in this study included increasing age and height, history of heart failure, valvular heart disease, stroke, hyperlipidaemia, coronary artery disease, peripheral artery disease and cardiothoracic surgery. Chan et al further examined the effectiveness of another community-based AF screening program named the AFinder program, the results of which were recently presented in a late-breaking session of the European Society of Cardiology Congress 2017. The AFinder program was characterized by being initiated by a panel of cardiologists, led by the Hong Kong Council of Social Service which was a non-governmental organization, and carried out by a group of trained layperson volunteers. All citizens aged 50 or above were eligible for participation. Among 10,735 (mean age 78.6) citizens screened with interpretable sECG’s, 244 (2.3%) had AF and 74 (0.69%) had newly diagnosed AF. The...
mean CHA\textsubscript{2}DS\textsubscript{2}-VASc score was 3.9 in patients with newly diagnosed AF. The NNS for one newly diagnosed AF was 145. A nurse performed a 9-month phone follow-up on those patients with AF and assessed the health-seeking behavior of them and for those indicated, whether they were given oral anticoagulation and their compliance. Among 72 patients with newly diagnosed AF and indication for oral anticoagulation, only 47 (65\%) of them sought medical attention and more disappointingly, only 17 (24\%) of them were prescribed oral anticoagulation. Once they were given oral anticoagulation, most of them (16, 94\%) reported 100\% compliance to therapy. Compared with the NNS for one newly diagnosed AF, the NNS for one patient receiving appropriate oral anticoagulation for newly diagnosed AF increased 3.6-fold to 671. This seriously underscores the utmost importance of a more structured downstream management pathway being embedded in any AF screening program. The potential of Kardia mobile device for auto-screening for AF has also been assessed in this study. The sensitivity and specificity of the automated algorithm in diagnosing AF were 75\% and 98.2\% respectively. The positive predictive value and negative predictive value were 64.9\% and 99.5\% respectively. The suboptimal sensitivity of the current version of algorithm limits its application in auto-screening.

Screening for AF has also been studied in the primary care setting in Hong Kong and different tools have been used.\textsuperscript{11,12} Chan and Siu et al used a smartphone camera-based device capable of diagnosing AF by measuring photoplethysmographic pulse waveform for AF screening in a primary care setting.\textsuperscript{11} Patients with hypertension and/or diabetes mellitus or who were ≥65 years of age were screened. AF was found in 28 (2.76\%) of 1,013 participants and 5 (0.5\%) had newly diagnosed AF. The sensitivity and specificity of the automated algorithm of the device were 92.9\% and 97.7\% respectively. The positive and negative predictive value were 53.1\% and 99.8\% respectively. The same group of researchers reported the use of another device, an automated blood pressure measurement device which is capable of generating an irregularity index based on R-R intervals, for AF screening, again in the primary care setting.\textsuperscript{12} Similar to the study described above, they screened patients with hypertension and/or diabetes mellitus or who were ≥65 years of age. In 5,969 patients recruited, AF was diagnosed in 72 (1.2\%) of them. The proportion of patients with newly diagnosed AF was however not mentioned. The sensitivity and specificity of this device in diagnosing AF were 80.6\% and 98.7\% respectively. The positive and negative predictive value were 42.4\% and 99.8\% respectively. The overall diagnostic performance as determined by area under curve was 0.90.

AF screening program has also been carried out in specialist medical outpatient clinic in Hong Kong.\textsuperscript{13} Yan et al screened 9,046 (mean age 72.1) patients with the Kardia mobile device and identified 121 (1.5\%) patients with newly diagnosed AF, all of whom had CHA\textsubscript{2}DS\textsubscript{2}-VASc score ≥2. In addition, the overall prevalence of AF was 9.4\% (850/9,046) in this screened population.

Although increasing data has become available in AF screening in recent years, the questions on what the most appropriate setting is and what the best tool should be remain. Obviously, many of us are looking forward to large and appropriately-powered randomized outcome studies to answer the above questions and in addition, to confirm that systematic AF screening programs can indeed reduce the burden of stroke and the consequent mortality. In Hong Kong, different groups of researchers studied AF screening in different settings and with different tools. However, they have the same passion and vision of reducing the burden of stroke and the consequent disability and deaths in Hong Kong. For any AF screening program to be sustainable, it is essential, at some point in time, to seek support from the government. In Hong Kong, we are now probably at that critical juncture.

References


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SCIENTIFIC PROGRAMME (as of 25 October 2017)

11 NOVEMBER 2017 (SATURDAY)

08:30-09:00 Registration

09:00-09:30 Invited Lecture
Cardiovascular Manifestation in Systemic Inflammatory Disorders
Dr. Kelvin K.H. Yiu, The University of Hong Kong, HKSAR

09:30-10:30 Oral Presentations for Young Investigator Award (I)
Sponsored by Sun Chieh Yeh Heart Foundation

10:30-11:00 Coffee break, poster viewing and booth visit

11:00-12:40 Oral Presentations for Young Investigator Award (II)
Sponsored by Sun Chieh Yeh Heart Foundation

12:40-13:15 Lunch Symposium
Sponsored by AstraZeneca Hong Kong Limited

DAPT in MI Management - From ESC Guidelines to Clinical Practice
Dr. Frankie C.C. Tam, Queen Mary Hospital, HKSAR

13:15-14:00 Lunch

14:00-14:30 Opening Ceremony
Prof. Chak-sing Lau, President of the Hong Kong Academy of Medicine, & Associate Dean of the Faculty of Medicine, The University of Hong Kong, HKSAR
Prof. David C.W. Siu, The University of Hong Kong, HKSAR

14:30-15:30 Keynote Lectures

Managing Stable Chronic Heart Failure in Primary Care Setting
Prof. David C.W. Siu, The University of Hong Kong, HKSAR

Topic TBC
Dr. Michael P.H. Chan, The University of Hong Kong, HKSAR
15:30-16:00  Free Oral Communications

Randomized Controlled Trial of Phytosterols in a Once-Daily Soya Drink in Normocholesterolaemic Chinese  
Dr. Ching-lung Cheung, The University of Hong Kong, HKSAR

Chloride Channels are Involved in the Development of Atrial Fibrillation – A Transcriptomic and Proteomic Study  
Prof. Guo-wei He, TEDA International Cardiovascular Hospital, China

16:00-16:30  Coffee break, poster viewing and booth visit

16:30-17:30  Invited Lectures

Mechanosensitive TRP Channels in Cardiovascular System  
Prof. Xiao-qiang Yao, Chinese University of Hong Kong, HKSAR

Mature Cardiomyocytes from Human Pluripotent Stem Cells for Drug Screening and Disease Modelling  
Dr. Ellen N.Y. Poon, The University of Hong Kong, HKSAR

17:30-18:00  Closing Remarks and Young Investigator Award Ceremony  
Prof. Bernard M.Y. Cheung, The University of Hong Kong, HKSAR

18:00  Annual General Meeting
Abstracts for Invited Lectures:

II.1. CARDIOVASCULAR MANIFESTATION IN SYSTEMIC INFLAMMATORY DISORDERS

KH Yiu
Department of Medicine, The University of Hong Kong, Hong Kong

Systemic inflammatory diseases, including those of rheumatology and dermatology, are associated with increased cardiovascular events. Multiple evidences suggested that the chronic systemic inflammation may play a pivotal role in all stages of atherosclerotic plaque formation, from initiation of the fatty streak to plaque rupture and consequent acute coronary syndrome in those diseases. By using different cardiovascular imaging modalities, a number of studies have been completed to investigate the disease pattern, pathophysiology and clinical outcomes of cardiovascular manifestation in patients with systemic inflammatory disorders. By identifying those who had premature cardiovascular disease using advanced imaging technique may improve risk-stratification. Finally, future studies should focus on the relationship between the cumulative burden of inflammation and cardiovascular disease development, and the effects of aggressive treatment on the long-term cardiovascular outcome of these patients.

II.4. MECHANOSENSITIVE TRP CHANNELS IN CARDIOVASCULAR SYSTEM

XQ Yao
School of Biomedical Sciences and Li Ka Shing Institute of Health Science, The Chinese University of Hong Kong, Hong Kong

Accumulating amount of evidence suggests that transient receptor potential (TRP) channels may function as cellular sensors to perceive and respond to a variety of mechanical stimuli including stretch, hydrostatic pressure and fluid flow. In cardiovascular system, cardiomyocytes are constantly subjected to cyclic stretch due to heart contraction and relaxation during cardiac cycle. On the other hand, vascular endothelial cells lining the blood vessels are exposed to hemodynamic shear force generated by blood flow. In addition, arterial baroreceptors serve as a frontline pressure sensor to detect blood pressure in circulation system. Our group has been studying these mechanosensors in cardiovascular system. With the use of human embryonic stem cell-derived cardiomyocytes (hESC-CMs) as models, we studied the uniaxial cyclic stretch in human cardiomyocytes. TRPV4 was found to be expressed in these cardiomyocytes. 4α-phorbol 12,13-didecanoate (4α-PDD), a TRPV4 agonist, elicited a cytosolic Ca^2+ ([Ca^2+]_i) rise, the effect of which was abolished by TRPV4 inhibitors RN1734 and HC067047. Importantly, longitudinal stretch was found to induce a [Ca^2+]_i rise, the effect of which was inhibited by TRPV4 antagonists. These data strongly suggest endogenous TRPV4 channels as a mechanosensor for longitudinal stretch during cardiac cycle. We further found important roles of TRPV4 in mediating cyclic stretch-induced realignment of hESC-CMs and disease progression of dilated cardiomyopathy. We also explored the molecular identity of pressure sensor in arterial baroreceptor, which serves as a frontline sensor to detect blood pressure. We identified TRPC5 channels as one mechanical sensor in the aortic and carotid baroreceptor. TRPC5 knockout mice showed diminished pressure-induced action potential firing in the afferent nerve and baroreflex-mediated heart rate reduction upon blood pressure elevation. Telemetric measurement of the daily blood pressure demonstrated that TRPC5 knockout mice displayed phenotype of severe blood pressure fluctuation. These studies suggest that TRPC5 channels are a key pressure transducer in the baroreceptor and plays an important role in maintaining blood pressure stability. This study was supported by Hong Kong RGC Grants (Hong Kong RGC Grant T13-706/11, AoE/M-05/12, RGC-NSFC Joint Grant N_CUHK439/13 and National Science Foundation of China 14118516.
IL5.
MATURE CARDIOMYOCYTES FROM HUMAN PLURIPOTENT STEM CELLS FOR DRUG SCREENING AND DISEASE MODELLING

NY Poon
School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Differentiation of human pluripotent stem cells (hPSCs) to the cardiac lineage represents a potentially unlimited source of cardiomyocytes (CMs) for research and clinical applications. Limitations to their use include their immature, embryonic-like developmental state and their heterogeneity characterized by mixed population of cells and poorly defined function. Using a unique strategy for proteomics profiling, we identified proteins on the cell surface of hPSC-CMs. Our dataset revealed an association between the expression of late protein 1 (L1), a surface protein involved in metabolism, with a more advanced differentiation stage. Viable CMs positive for this developmental marker can be isolated by cell sorting and are more adult-like in their gene expression pattern, morphology and functions. Our work provides important proof-of-principle for the isolation and characterisation of mature and defined hPSC-CM subpopulations, and will greatly advance the use of hESC-derivatives for medical research, disease modelling and drug testing.
ABSTRACTS

Abstracts for Oral Presentation:

**OP1.**

**NETWORK META-ANALYSIS OF CARDIOVASCULAR OUTCOMES IN RANDOMISED CONTROLLED TRIALS OF NEW ANTIDIABETIC DRUGS**

Y Fei, MF Tsoi, CR Kumana, TT Cheung, BMY Cheung

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

**Objectives:** Evidence directly comparing the effect of new antidiabetic drugs on cardiovascular outcomes in patients with type 2 diabetes (T2D) in randomised controlled trials (RCTs) was limited. We therefore assessed cardiovascular safety of these drugs using network meta-analysis.

**Methods:** We searched MEDLINE, EMBASE, the Cochrane database, and ClinicalTrials.gov for RCTs involving glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Those reported rates of major adverse cardiovascular events (MACE) and deaths in T2D patients with established cardiovascular risks were eligible to be included. Data were analysed using R.

**Results:** Nine RCTs with altogether 72262 T2D patients were included for analysis. Compared to placebo, GLP-1 RAs and SGLT-2 inhibitors reduced MACE (OR 0.89, 95%CI 0.82-0.97 and OR 0.86, 95%CI 0.77-0.95, respectively), all-cause mortality (OR 0.89, 95%CI 0.80-0.99 and OR 0.78, 95%CI 0.69-0.88, respectively) and cardiovascular mortality (OR 0.85, 95%CI 0.73-0.99 and OR 0.76, 95%CI 0.65-0.88, respectively). SGLT-2 inhibitors were more beneficial than DPP-4 inhibitors in reducing MACE (OR 0.87, 95%CI 0.77-0.98) and cardiovascular mortality (OR 0.75, 95%CI 0.62-0.90). DPP-4 inhibitors, although were comparable to placebo, increased all-cause mortality when compared to GLP-1 RAs (OR 1.16, 95%CI 1.01-1.33) and SGLT-2 inhibitors (OR 1.31, 95%CI 1.13-1.53).

**Conclusions:** GLP-1 RAs and SGLT-2 inhibitors reduced the risk of MACE and death. DPP-4 inhibitors were inferior to these two drug classes. SGLT-2 inhibitors were the best in reducing cardiovascular events among the three drug classes, which can be considered as the prior second-line treatment for T2D patients at high cardiovascular risks after metformin.

**OP2.**

**EFFECTS OF AGE AND HYPERLIPIDEMIA ON PROSTACYCLIN RECEPTOR-MEDIATED RELAXATIONS**

YH Cheng, PM Vanhoutte, SWS Leung

Department of Pharmacology and Pharmac, Faculty of Medicine, The University of Hong Kong, Hong Kong

The role of prostacyclin receptors (IP) in the consequences of ageing and hyperlipidemia on vascular responsiveness was investigated in the aorta of apolipoprotein E knockout (ApoE−/−; a well-established hyperlipidemic animal model) mice and their wild-type counterparts (C57BL/6 mice). ApoE−/− mice and age-matched wild-type mice were fed a normal or a high-fat high-cholesterol diet for 29 weeks (starting at five weeks of age). Aortic rings were contracted with phenylephrine and relaxed with cumulative additions of increasing concentrations of iloprost (IP receptor agonist; 10⁻⁹-10⁻⁶ M), acetylcholine (muscarinic agonist; 10⁻¹⁰-10⁻⁵ M) or UK14304 (α₂-adrenergic agonist; 10⁻¹⁰-10⁻⁵ M). In young (five weeks old) wild-type mice, iloprost caused IP receptor-, endothelial nitric oxide (NO) synthase (eNOS)-, and soluble guanylyl cyclase (sGC)-dependent relaxations. Ageing (from five to 34 weeks) did not alter responses to iloprost but reduced relaxations to acetylcholine and UK14304 were inhibited; the greater iloprost-induced relaxations were not associated with changes in protein presence of IP and TP receptors. Deletion of ApoE also unmasked an L-NAME-resistant response to iloprost in the ageing group and prevented the impact of high fat diet on relaxations to IP receptor stimulation. The latter is likely through inhibition of TP receptor activation since the presence of IP receptors was not different between wild-type and ApoE−/− mice after 29 weeks of high-fat diet.
OP3.

EXERCISE AMELIORATES ENDOTHELIAL DYSFUNCTION IN TYPE2-DIABETIC MICE THROUGH INCREASING MicroRNA-181b LEVEL VIA AMPK PATHWAY

WB Shang, L Wang, JY Luo, XY Tian, Y Huang
School of Biomedical Sciences and Institute of Vascular Medicine, Chinese University of Hong Kong, Hong Kong

Background and Purpose: Endothelial dysfunction plays an essential role in the pathogenesis of diabetic vascular diseases. Our previous studies showed that exercise ameliorates endothelial dysfunction by inhibiting ER stress and increasing NO production. AMPK is one of the mediators for the beneficial effect of exercise in vasculature. MicroRNA 181b (miR-181b) was reported to improve glucose homeostasis and insulin sensitivity by regulating endothelial function. However, whether miR-181b is regulated by exercise and AMPK remains largely unclear. Therefore, we aim to investigate the regulation of miR-181b expression by exercise and AMPK and the role of miR-181b in mediating the beneficial effect of exercise.

Methods and Results: To investigate whether exercise upregulates miR-181b expression, db/db mice were subjected to treadmill exercise for 45 min per day for two months. Thereafter, mouse aorta was dissected for real-time PCR. The results show that exercise significantly increases miR-181b expression in mouse aorta compared to that from control mouse. To examine the impact of blood flow on miR-181b, human umbilical vein endothelial cells (HUVECs) exposed to laminar flow in a constant speed at 12 dyn/cm for 24 hours exhibited a dramatically increase of miR-181b expression. To understand the mechanism of miR-181b induction by laminar flow, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) used to treat HUVECs in three separate time points (2, 4, 8 h) significantly induces miR-181b expression and peaks at 8 h. To examine whether miR-181b has beneficial effect on endothelial function, we over-expressed the miR-181b with adenovirus. The result show miR-181b over-expression improves endothelial function in db/db mice accompanied with decreased vascular inflammation and increased eNOS expression in mouse arteries.

Conclusion: Exercise ameliorates endothelial dysfunction at least in part through increasing miR-181b level probably via AMPK pathway while miR-181b improves endothelial function in diabetic mice by inhibiting vascular inflammation and increasing eNOS expression. MiR-181b may serve as a therapeutic target for treatment of diabetic vasculopathy (supported by RGC-CRF and CUHK Direct Grant).

OP4.

DELETION OF RAP1 AGGRAVATES THE DEVELOPMENT OF ATHEROSCLEROSIS IN APOLIPOPROTEIN E-DEFICIENT MICE

XY Chen, EHC Tang
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Repressor activator protein 1 (Rap1) normally docks to the ends of telomeres and function to regulate telomere length and its structural integrity. However, it is now known that Rap1 is able to move onto the chromosome arms or into the cytoplasm and exert many other physiological functions. Recent data from our lab shows that Rap1 is highly expressed in human atherosclerotic lesions and Rap1 promotes the formation of macrophage foam cells. These findings suggest that Rap1 may play an important role in atherosclerosis development. We crossed Rap1 knockout mice with ApoE knockout mice to generate Rap1−/−ApoE−/− double knockout mice (DKO, on a C57BL/6 background) to unveil the importance of Rap1 in atherogenesis. DKO and ApoE−/− (control) mice were subjected to a high fat high cholesterol diet. After 10 weeks of feeding, the body weights of DKO mice were similar to that of control mice. However, plasma cholesterol and triglyceride levels were significantly increased in DKO mice as compared to control mice. When lesion formation was assessed in frozen section of aortic root using oil red O staining, significantly larger lesion area (control 19.8±0.7% vs. DKO 34.7±2.3%; n=5-6; P<0.001) and lipid deposition area (control 53.2±1.9% vs. DKO 78.3±1.8%; n=5-6; P<0.001) were observed in DKO mice. Similar conclusions were obtained when oil red O stained aortic arches and abdominal aortas were assessed. In summary, our data demonstrate that deletion of Rap1 promotes the development of atherosclerotic lesions in ApoE−/− mice by increasing the plasma lipid level and lipid retention, as well as plaque burden in aortic roots, aortic arches and abdominal aortas.
ABSTRACTS

Abstracts for Oral Presentation:

OP5.

PHARMACOLOGIC INHIBITION OF FOXO1 IMPROVES CARDIAC FUNCTION BY AMELIORATING EXCESSIVE MITOPHAGY IN TYPE 1 DIABETIC RATS

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Objective: Diabetic cardiomyopathy (DCM) is a heart muscle disorder with significant morbidity and mortality in diabetes. Forkhead transcriptional factor (FOXO1) is aberrantly active in Type2 Diabetic mice and triggers the development of DCM. Furthermore, endogenous FOXO1 has been suggested to exacerbate autophagy of mitochondria (mitophagy), which is a critical process for degradation of damaged mitochondria, and maintain cardiomyocyte health under normal condition. However, the role of excessive mitophagy in the pathogenesis of DCM is less studied and the link between FOXO1 over-activation and mitophagy in diabetic heart has not been investigated. Thus, we set out to investigate whether pharmacologic inhibition of FOXO1 can attenuate DCM in type 1 diabetic rats and the underlying mechanism.

Methods: Streptozotocin (STZ)-induced Type 1 diabetic rats (4 weeks after STZ injection) were administered with 10% hydroxypropyl-β-cyclodextrin with/without AS1842856 (FOXO1 selective inhibitor, 50 mg/kg) by oral gavage twice daily for one week. On the day of harvest, the left ventricular (LV) functions of the rats were assessed by Pressure-volume (PV) loop analysis and the heart tissue were collected for protein analysis, etc. We used western blot to detect FOXO1, P-FOXO1(S256), LC3 II/I ratio (index of autophagy), as well as mitophagy-related protein (pink1, parkin, BECLIN1, BNIP3), mitochondrial fusion-mediated protein (mitofusin1, mitofusin2), etc.

Results: PV loop analysis indicated that heart rate (bpm), LV ejection fraction (%), -dp/dt min (mm Hg/s) were all significantly reduced in diabetic (D) rats when compared with control (C) rats (all P<0.05). Biochemically, FOXO1 activity (decreased P-FOXO1/FOXO1 ratio, increased FOXO1 nuclear translocation), LC3 II/I ratio, pink1/parkin, BECLIN1, BNIP3, mitofusin1 and mitofusin2 all significantly increase whereas P62 was significantly reduced in D rats (all P<0.05, vs. C rats). The above results indicate mitophagy is excessively activated in D rats that is concomitant with cardiac diastolic dysfunction. Administration of FOXO1 inhibitor AS1842856 significantly inhibited FOXO1 activity (increased P-FOXO1/FOXO1 ratio, decreased FOXO1 nuclear translocation), improved cardiac function and reverted all the above mentioned diabetes-induced biochemical changes except the changes in BECLIN1 and BNIP3.

Conclusion: Pharmacologic inhibition of FOXO1 and the subsequent downregulation of pink1/parkin and mitigating mitophagy over-activation may represent major mechanism whereby inhibition of FOXO1 improves cardiac function in early stage of DCM in Type 1 diabetic rats and may provide a promising therapeutic target to treat the disease.

Conclusions: The present results suggest that serum exosomes inhibit NO production and impair endothelial function in mouse aorta. Serum exosomes also impair vascular integrity by altering the tight junction composition, which might contribute to diabetes-associated microvascular complications (supported by RGC-CRF and RGC-GRF).

OP6.

ROLE OF SERUM EXOSOMES IN REGULATING ENDOTHELIAL FUNCTION IN DIABETES

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Objectives: Exosomes are abundant in blood, and the various molecules contained in exosomes can be delivered to recipient cells via blood circulation. Vascular endothelial cells are constantly exposed to circulating substances. Therefore, we aim to investigate how endothelial cells respond to serum exosomes and its implication in diabetes-associated vascular dysfunction.

Methods: Aortas were dissected and isometric force was measured in wire myograph to test vascular function. To measure NO bioavailability, endothelial cells were stained with NO-sensitive fluorescent dye and NO production was detected by confocal microscopy. Expression of target genes were measured by RT-PCR.

Results: The present study shows endothelial cell is able to take up PKH67-labeled serum exosomes isolated from diabetic (db/db) mouse indicated by increased incorporation of fluorescence into aortic endothelial cells. db/db exosomes treatment reduced NO production in endothelial cells, and severely impaired NO-dependent vascular relaxation in non-diabetic (db/m+) mice. In addition, serum exosomes from db/db mouse and diabetic Zucker (fa/fa) rat induced proliferation in primary cultured mouse and rat endothelial cells. Yap target genes were activated in diabetic exosomes treated endothelial cells. Screening of the tight junction proteins transcription shows significant downregulation of Cldn1 and upregulation of Zo2 in diabetic exosomes treated endothelial cells.
OP7.
ASSOCIATION BETWEEN BLOOD LEAD LEVEL AND SYSTOLIC BLOOD PRESSURE: UNITED STATES NATIONAL HEALTH NUTRITION AND EXAMINATION SURVEY (NHANES) 1999-2014
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Introduction: Lead toxicity is an uncommon cause of hypertension. We recently reported that blood lead level has declined in America. Therefore, we examined if there is still an association between low blood lead level and systolic blood pressure (SBP).

Methods: We included participants who had blood lead level and blood pressure measurement in the National Health Nutrition and Examination Survey 1999-2014. Results were analysed using SPSS complex sample module version 22 with sample weight adjustment. We further analysed the association between blood lead level and SBP in people with blood lead level <5 µg/dL and in ethnic groups. We calculated regression coefficient and 95% confidence interval for every 2.72 times increase in blood lead level.

Results: 20596 participants were included in this analysis. Every 2.72 times increase in blood lead level was associated with increase of 4.98 [4.54-5.43] mmHg in SBP (p<0.0001). This remained significant after adjusting for age, gender, ethnicity and waist circumference (0.75 [0.30-1.20]; p=0.001). This significant association was also found in participants with blood lead level <5 µg/dL (5.59 [5.12-6.07]; p<0.0001) and in all ethnicities (Mexican Americans: 4.14 [3.45-4.83]; p<0.0001; Other Hispanics: 4.93 [3.56-6.30]; p<0.0001; 6.04 [5.40-6.67]; p<0.0001; Non-Hispanic Blacks: 5.82 [4.95-6.68]; p<0.0001; Other Races: 3.28 [1.51-5.04]; p<0.0001).

Conclusion: Blood lead level is associated with systolic blood pressure in the general population, most of whom do not have elevated blood lead level. Reducing lead in the environment not only benefits children but may also benefit adults.

OP8.
ROLE OF AMPK IN EDH-LIKE RELAXATIONS IN RAT SUPERIOR MESENTERIC ARTERIES
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Introduction and Objective: Adenosine monophosphate-activated protein kinase (AMPK) has beneficial effects on the vasculature, including facilitation of vasodilatation. Endothelium-derived hyperpolarization (EDH) is one of the major vasoactive signals generated by endothelial cells for the regulation of vascular tone, in particular in resistance arteries which contribute to arterial blood pressure regulation. Although the mechanism underlying EDH varies with species and blood vessel type, activation of intermediate- and small-conductance calcium-activated potassium channels (IKCa and SKCa, respectively) in the endothelium followed by stimulation of Na+/K+-ATPase and inwardly-rectifying potassium channels (Kir) in the underlying vascular smooth muscle, is a common characteristic of the EDH pathway. The present study aimed to examine whether or not AMPK affects EDH-mediated relaxations and, if so, to determine the mechanism(s) involved.

Methods: Male twelve-week-old Sprague Dawley (SD) rats were used. Superior mesenteric arterial rings were suspended in conventional organ chambers for isometric tension recording and were collected for measuring the activity of AMPK.

Results: AICAR (AMPK activator; 10^{-4} M) significantly reduced acetylcholine-induced EDH-like relaxations in superior mesenteric arteries of SD rats; the effect was restored by compound C (AMPK inhibitor; 10^{-4} M). AMPK activity assays confirmed that AICAR (10^{-4} M) caused AMPK activation in SD rat mesenteric arteries. Ouabain (inhibitor of Na+/K+-ATPase; 10^{-4} M), but not barium chloride (inhibitor of Kir; 3 x 10^{-5} M), significantly reduced acetylcholine-induced EDH-like relaxations. The inhibitory effects of ouabain and AICAR on EDH-like relaxations were not additive. Similar results were obtained with endothelium-dependent relaxations induced by SKA-31 (positive allosteric modulator of SKCa and IKCa channels; 10^{-5} M). In rings without endothelium, potassium chloride (5 x 10^{-3} M)-induced relaxations were abolished by ouabain but were not affected by AICAR.

Conclusions: Activation of AMPK reduces EDH-like relaxations in the rat superior mesenteric artery, likely by inhibiting, at the endothelial level, the IKCa-Na+/K+-ATPase signaling pathway.
ABSTRACTS
Abstracts for Oral Presentation:

OP9.
UNDERSTANDING THE VASOPROTECTIVE EFFECTS OF TETRAMETHYLPYRAZINE: NEW EVIDENCE FOR ANTI-ER STRESS-DEPENDENT PREVENTION OF BKCa CHANNEL DYSFUNCTION
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Aim: We previously demonstrated that BKCa channel inhibition by ER stress contributes to homocysteine-induced vascular dysfunction. In this study, we investigated whether tetramethylpyrazine (TMP), an active ingredient of the Chinese herb Chuanxiong, may protect BKCa channel function via an anti-ER stress mechanism.

Methods: Porcine small coronary arteries were used. Isometric force study was performed in endothelium-denuded arterial rings for the dilator function of BKCa channels. Primary culture of coronary arterial smooth muscle cells (PCASMCs) were used for determination of expressions of ER stress molecules, BKCa channel subunits, and ubiquitin ligases, as well as recording of BKCa channel currents.

Results: TMP showed significant inhibitory effect on ER stress in PCASMCs. In cells exposed to homocysteine or the chemical ER stress inducer tunicamycin, TMP significantly decreased expression of GRP78 and ATF6 and suppressed phosphorylation of PERK, eIF2α, and IRE1. Suppression of ER stress by TMP was observed to restore the BKCa β1 protein level and enhance the BKCa channel current in PCASMCs, with a subsequent improvement in BKCa channel-mediated dilatation of coronary arteries. The anti-ER stress-dependent restoration of BKCa β1 by TMP may be attributable to inhibition of FoxO3a-induced upregulation of ubiquitin ligases Murf-1 and atrogin-1.

Conclusions: This study revealed that TMP possesses anti-ER stress properties and inhibition of BKCa β1 degradation by alleviating ER stress is involved in the protective effects of TMP against homocysteine in the coronary vasculature.

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OP10.
CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR REGULATES PANNEXIN 1 CHANNEL OPENING FOR ACIDOSIS-INDUCED ATP RELEASE FROM CARDIOMYOCYTES
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ATP is released in the heart under a variety of conditions, including hypoxia, ischaemia and catecholamine stimulation. Under physiological conditions, extracellular ATP, and its breakdown product, adenosine, contribute to local vasodilation and regulation of coronary blood flow. We investigated the mechanism of ATP release in cardiomyocytes isolated from adult rat heart. Treatment with lactic acid produced pH depression and enhanced ATP release from cardiomyocytes. On the other hand, simulated ischaemia (metabolic inhibition plus anoxia) lowered ATP release. The acidosis-induced ATP release was abolished by the specific CFTR inhibitor, CFTRinh-172, CFTR pore blocker, GlyH-101, or CFTR siRNA, suggesting that CFTR was involved. Forskolin and IBMX, agents that activate CFTR by elevating the intracellular cAMP, also increased ATP release, confirming the role of CFTR. However, blockade of Pannexin1 channels by Fast Green FCF, Brilliant Blue FCF, or pannexin1 siRNA, attenuated the ATP release during acidosis or forskolin treatment, and further lowered the ATP release during simulated ischaemia, suggesting that Pannexin1 functions as the ATP release channel. Immunofluorescence imaging suggested that CFTR and Pannexin1 were not co-localized. An src tyrosine kinase inhibitor failed to modify the acidosis-induced ATP release, whereas forskolin- or lactic-acid-stimulated ATP release was abolished by a caspase inhibitor. We propose that the CFTR Cl channel opens during acidosis, allowing the movement of a signaling molecule into the cell, which indirectly modulates Pannexin1 gating by activation of caspase.
ABSTRACTS

Abstracts for Oral Presentation:

OP11.
NON-INVASIVE NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) SCORES AND CARDIOVASCULAR DISEASES (CVDs) IN THE UNITED STATES NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 1999-2014
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Objectives: Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in the Hong Kong population. Hence, it is important to identify the possible complications. Whether NAFLD is a risk factor for cardiovascular diseases (CVDs) is uncertain. We therefore analysed their association in this crosssectional study.

Methods: Data from the United States National Health and Nutrition Examination Survey (NHANES) 1999-2014 were analysed using the SPSS complex sample module. A total of 11,427 non-pregnant adults without viral hepatitis, self-reported insulin injection, prescription of anti-diabetic medications and missing data were included in this analysis. By applying binary logistic regression, four non-invasive NAFLD scores, fatty liver index (FLI), NAFLD liver fat score (LFS), hepatic steatosis index (HSI) and lipid accumulation product (LAP), were examined for association with CVD outcomes, namely, coronary heart disease (CHD), myocardial infarction (MI), heart failure (HF) and stroke.

Results: LFS was associated with increased risk of CHD (Odds ratio adjusted for age, gender, ethnicity and high-density lipoprotein (HDL) level [95% confidence interval]: 1.12 [1.06-1.17]), MI (1.09 [1.05-1.14]) and HF (1.09 [1.02-1.16]) with AUC of 0.595, 0.592, 0.590, respectively (p<0.0001 for these outcomes). FLI was associated with increased risk of MI (1.01 [1.00-1.01]) and HF (1.01 [1.00-1.02]) with AUC of 0.594 (p=0.013), 0.616 (p<0.0001) respectively. HSI was associated with increased risk of HF (1.03 [1.00-1.05]). LAP was not associated with these three outcomes (CHD: 1.00 [1.00-1.00]; MI: 1.00 [1.00-1.00]; HF: 1.00 [1.00-1.00]). None of the NAFLD scores were associated with stroke (FLI: 1.00 [1.00-1.01]; HSI: 1.01 [0.98-1.03]; LFS: 1.05 [0.99-1.11]; LAP: 1.00 [1.00-1.00]).

Conclusions: With a large study population, we could demonstrate a weak association of NAFLD with CHD, MI and HF. Despite its high prevalence, NAFLD is generally benign with only a slightly elevated risk for CVDs.

OP12.
NILOTINIB EXACERBATES DISTURBED FLOW-INDEUCED ATHEROSCLEROSIS THROUGH FOCAL TLR4 ACTIVATION
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Objectives: The use of nilotinib (Tasigna), a second-generation tyrosine kinase inhibitor for treating chronic myeloid leukemia, increases risk of atherosclerosis. We aim to investigate the role of nilotinib in endothelial function and atherosclerosis, and hope to identify a therapeutic strategy to alleviate the vascular adverse effects of nilotinib.

Methods: Partial carotid ligation was performed in ApoE— mice to generate disturbed flow and to induce atherogenesis in left common carotid in mice. Proximity ligation assay was used to detect interaction between target proteins in endothelial cells. HUVECs were transfected with TLR4 shRNA or non-target shRNA by lentiviral vector and cells with stable expression of shRNA were selected by puromycin.

Results: Here, we demonstrated that orally administered nilotinib profoundly accelerated atherosclerosis plaques formation in ApoE— mice receiving carotid partial ligation surgery. Co-administration of TLR4 inhibitor CLI-095 reversed the pro-atherosclerotic effect of nilotinib. This reversal was achieved by two TLR4-dependent mechanisms involved in endothelial inflammation. First, in endothelial cells, nilotinib-induced inflammatory molecules expression and monocyte attachment were inhibited by knockdown of TLR4 or CLI-095. Second, disturbed flow per se activated TLR4, leading to endothelial inflammation. Knockdown of TLR4 or CLI-095 administration suppressed the disturbed flow-induced inflammation.

Conclusions: Our findings suggest TLR4 inhibition as a therapeutic approach to address the vascular safety issue of nilotinib, with its efficacy double-secured by targeting both disturbed blood flow- and nilotinib-induced endothelial inflammation.

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OP13. EFFECTS OF OUABAIN ON ENDOTHELium-DEPENDent RESPONSE

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Ouabain is an inhibitor of sodium-potassium adenosine triphosphatase (Na+/K+-ATPase, also known as Na+ pumps). It is released by high sodium chloride concentration from hypothalamus and adrenals. Upon released in the circulation, it increases arterial constriction and hence blood pressure. Since high circulating levels of sodium chloride and ouabain are likely present concurrently, the present study aimed to examine whether or not sodium affected the vascular effects of ouabain locally. Aortae were isolated from male Sprague Dawley rats (8-12 weeks old) and incubated in the organ chambers with modified Krebs-Henseleit solutions containing normal (140 mM) or high (160 mM) sodium, in the absence or presence of different contractions of ouabain (10^-6, 10^-4, 2 x 10^-4, 5 x 10^-4 M). They were contracted with phenylephrine (10^-6 to 10^-5 M) and relaxed with increasing concentrations of endothelium-dependent and -independent vasodilators, acetylcholine (10^-9 to 10^-5 M) and DETA NONOate (10^-9 to 10^-3.5 M). Ouabain, at 5 x 10^-4 M, decreased the relaxation to acetylcholine in rat aorta with endothelium, and merely shifted the relaxation curve of DETA NONOate to the right in preparations without endothelium. Ouabain caused greater decrease in acetylcholine-induced relaxations under high sodium condition, and in aortae incubated in solutions containing mannitol (40 mM), which increased the osmolarity of the incubating solution to that similar to the increased sodium chloride level (from 140 to 160 mM). The increased sodium level or mannitol alone did not affect the relaxation to acetylcholine. The results, therefore, suggested that elevation of extracellular osmolarity [by high sodium concentration or mannitol] enhanced the inhibitory effect of ouabain. In order to elucidate the mechanism(s) through which ouabain affect relaxations, rat aortae were incubated without or with different concentrations of ouabain and relaxations to arachidonic acid (AA) were examined. Ouabain decreased AA-induced relaxation in aortae with endothelium, but not in those without endothelium. The inhibition by ouabain was not observed in the presence of indomethacin (cyclooxygenase inhibitor), L-NAME (nitric oxide synthase inhibitor) or ODQ (soluble guanylyl cyclase inhibitor). These findings suggested that ouabain likely inhibits endothelial cyclooxygenase or nitric oxide synthase to reduce relaxation.

OP14. CHLORIDE CHANNELS ARE INVOLVED IN THE DEVELOPMENT OF ATRIAL FIBRILLATION – A TRANSCRIPTOMIC AND PROTEOMIC STUDY

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Objectives: The exact pathogenic factors of atrial fibrillation (AF) are unknown. We investigated the AF-related pathogenic factors at the mRNA, protein, and structure levels by using multiple approaches.

Methods: Transcriptomic (RNA-Seq) and proteomic (iTRAQ) techniques were applied to investigate the left and right atrial tissue collected from 62 patients with rheumatic mitral valve disease in either persistent AF or sinus rhythm (SR) undergoing valve replacement procedures.

Results: The up-regulated expression of CLIC1, CLIC4, CLIC5 proteins was detected in AF patients (p<0.05), especially in the left atrial tissue. These were in accordance with the change of mRNA of these CLICs and were verified by western blot and qRT-PCR. The bioinformatic analysis suggested the involvement of CLICs in biological process, cell component, and molecular function in AF patients. Immunofluorescence staining disclosed that CLIC1, CLIC4, and CLIC5 were expressed on myocardial membrane and organelles. Combined with the results from immunohistochemistry and electron microscope analysis, the excess type IV collagen was deposited around myocytes and was upregulated in the left atrium tissue of the AF patients. In addition, by protein structure prediction and co-immunoprecipitation, there was a possible interaction between CLICs and type IV collagen.

Conclusions: These results for the first time indicate that CLICs play an important role in the development of AF and that CLICs and structural type IV collagen may interact on each other to promote the development of AF. These findings may lead to the new direction for mechanisms of AF and reveal new drug targets.
OP15.
RANDOMIZED CONTROLLED TRIAL OF PHYTOSTEROLS IN A ONCE-DAILY SOYA DRINK IN NORMOCHOLESTEROLAEMIC CHINESE
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Introduction: Phytosterols reduce intestinal cholesterol absorption and help to lower LDL-cholesterol (1). Many Chinese adults have lactose intolerance and cannot tolerate phytosterol added to cow’s milk. We therefore conducted a randomized double-blind controlled trial to assess the efficacy and tolerability of a phytosterol-fortified soya drink in lowering serum LDL-cholesterol.

Method: Two hundred and one normocholesterolaemic healthy adult participants (100 men and 101 women; age 19-79) were randomized to daily intake for three weeks of one pack of phytosterols-enriched soya drink that contained 2 g phytosterols per day (N=100) or a matched soya drink without phytosterols (N=101). The primary outcome variable was the serum LDL-cholesterol. Adverse events, withdrawal and compliance were documented. The study protocol received ethical approval and was registered (ClinicalTrials.gov identifier: NCT02881658; Date of registration: 14 Aug 2016). All participants gave written informed consent. Data management and intention-to-treat analysis were carried out by an accredited Clinical Trials Centre and an independent statistician respectively.

Results: Only seven participants did not complete the study. The compliance (mean±SD) was 99.6±6.9% and 99.2±6.3% in the treatment and control group respectively. Serum cholesterol decreased by 6.6%, from 2.9±0.96 to 2.71±0.83 mmol/L (mean±SD), in the treatment group; and by 1.6%, from 2.83±0.81 to 2.75±0.79 mmol/L, in the control group. Compared to control, phytosterols reduced serum LDL-cholesterol (mean±SE) by 0.13±0.06 mmol/L (p=0.02). There were no significant changes in body weight, waist circumference, blood pressure, blood glucose or other lipid parameters such as HDL and triglycerides. Ninety-five percent of the participants randomised to the fortified drink reported no adverse events at all. Of the six adverse events, five were intestinal symptoms. There were no serious adverse events. Conclusion: The phytosterol-fortified soya drink reduced LDL-cholesterol and was well-tolerated. This nonpharmaceutical way of lowering LDL-cholesterol is suitable for people in the general population who have not yet developed cardiovascular disease or cardiovascular risk factors.
GINKGO BILOBA EXTRACT PROTECTS AGAINST MYOCARDIAL INJURY THROUGH ATTENUATION ENDOPLASMIC RETICULUM STRESS IN STZ-INDUCED DIABETIC APOE−/− MICE

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Objectives: It is known that cardiomyocytes apoptosis, interstitial fibrosis, and intramyocardial inflammation are pathological characters of diabetic myocardial injury. Traditional medicine Ginkgo biloba leave extrat (GBE) exerts biological effects including scavenging free radical, lowering oxidative stress and anti-inflammation. Aim of the present study was to investigate the cardio-protection effects of GBE against diabetic myocardial injury.

Methods: High-fat fed ApoE−/− mice were rendered diabetes by low dose of streptozotocin (STZ) for 5 consecutive days. The diabetic ApoE−/− mice were treated with 200 mg/kg or 400 mg/kg GBE by daily gastric gavage for 12 weeks. The diabetic ApoE−/− mice received saline served as untreated diabetic group, and non-diabetic C57BL/6J mice served as control group. HE, MASSON and TUNEL staining were performed to analysis myocardial tissue morphological changes. Immunohistochemical staining for cleaved caspase-3 was used to analysis cardiomyocytes apoptosis. Collagen I and III mRNA contents were determined by real time PCR. NF-κB expression, TNF-α and IL-β mRNA contents were determined to analysis the intramyocardial inflammation. Hallmarks of endoplasmic reticulum stress (ERS)-related apoptosis pathways including phosphorylated c-Jun N-terminal kinase (p-JNK), CHOP, caspase-12 and cleaved caspase-3 were analysed by Western blot.

Results: Diabetic ApoE−/− myocardial injury was associated with increased cardiomyocytes apoptosis, intramyocardial inflammation and interstitial fibrosis. Immunohistochemical staining revealed increased expression of cleaved caspase-3 in untreated diabetic myocardium. Collagen I and III mRNA contents were significantly increased in untreated diabetic heart. NF-κB expression, TNF-α and IL-β mRNA contents which represent intramyocardial inflammation were increased in untreated diabetic ApoE−/− heart. Expression of hallmarks of ERS-related apoptosis pathways including p-JNK, CHOP, caspase-12 and cleaved caspase-3 were significantly elevated in untreated diabetic myocardial tissue compared to that in control group (P<0.05). GBE both at 200 mg/kg/d and 400 mg/kg/d significantly blunt the myocardial collagen deposition, cardiomyocytes apoptosis and intramyocardial inflammation within diabetic heart, associated with inhibition of p-JNK, CHOP and caspase-12 pathways, accompanied by decreased serum inflammation cytokines IL-6, IL-1β and TNF-α. Regulation effect of blood glucose and lipid profiles was also manifested in the present study.

Conclusion: Our data demonstrate that myocardial protection effects of GBE involves attenuation of ERS-related apoptosis under diabetic conditions, indicating that GBE treatment might be beneficial in diabetic myocardial injury.

EFFECTS OF AN AQUATIC PHYSIOTHERAPY PROGRAM ON CARDIOVASCULAR OUTCOMES AND FUNCTIONAL AEROBIC CAPACITY IN OLDER ADULTS WITH OSTEOARTHRITIS OF THE KNEE: A RANDOMISED CONTROLLED TRIAL

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Objectives: This study aimed to evaluate the efficacy of a novel aquatic exercise program on resting heart rate, resting blood pressure and functional aerobic capacity in a population with osteoarthritis (OA) of the knee.

Methods: This was a randomised, single-blinded, controlled trial. Eighty-three older adults with OA of the knee were randomly assigned to either an aquatic-exercise group (n=31; mean age±SD=56.2±9.8 years) or a control group (n=52; mean age±SD=61.4±10.7 years). The aquatic-exercise group received physiotherapist-designed aquatic exercise training 1-hour per week for 10 weeks along with advice on self-care. The control group received self-care advice only. Measurements were taken before and after the aquatic intervention. Primary outcomes were resting heart rate and blood pressure. Secondary outcome was total distance covered in a six-minute walk test.

Results: Intention-to-treat analysis revealed that resting heart rate increased in the aquatic-exercise group and decreased in the control group after training (p=0.030). In addition, the resting diastolic blood pressure decreased exclusively in the control group overtime (p=0.013). No significant group, time or group-by-time interaction effects were noted in all other outcomes.

Conclusions: The aquatic exercise program was not effective in improving cardiovascular outcomes and functional aerobic capacity of older adults with OA of the knee.

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ABSTRACTS

Abstracts for Posters:

P03.

ARTERIAL WALL STRESS INDUCES ATHEROSCLEROSIS IN VASCULAR REMODELLING BY ACTIVATING YAP/TAZ EXPRESSION

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The increasing wall stress or biomechanical stretch as it is experienced by arteries influence the initiation of atherosclerotic lesions. Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), effectors of the Hippo pathway, have been identified as mediators for mechanical stimuli. Herein, the purpose of this research is to investigate the functional role of YAP/TAZ in the stretch regulation programs HUASMCs to a proliferative phenotype and the consequential development of atherosclerotic lesions. We reported that the YAP/TAZ activation controls critical aspects of the VSMCs phenotype and is activated by biomechanical stretch. YAP/TAZ knockdown significantly attenuated the VSMCs proliferative and proinflammatory phenotypes in the regulation of biomechanica stretch. In addition, treatment with atorvastatin, an antiatherosclerotic drug, inhibited YAP/TAZ expression and nuclear traslocation. Then, we showed that stretch inhibits the Hippo pathway through activation of PI3-kinase (PI3K) and phosphoinositide-dependent kinase (PDK1), but independent of AKT activity. These findings show that an important activity of YAP/TAZ by biomechanical stretch promoting atheroprone phenotypes and atherosclerotic lesion development. Taken together, our results indicate that inhibition of YAP/TAZ activation holds promise antiatherogenesis therapeutic strategy.

P04.

KNOWDOWN OF TM9SF4 TRIGGERING ER STRESS EXERTS ANTI-GROWTH EFFECT ON DRUG-RESISTANT BREAST CANCER CELLS

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Introduction: Drug-resistance of chemotherapy is the leading cause of mortality in breast cancer patients. Understanding how drug-resistant cancer cell survival is of great importance for the breast cancer therapy. Here, we identified a key protein, TM9SF4, namely transmembrane 9 superfamily, isoform 4, which play vital role in drug-resistant breast cancer survival. TM9SF4 is significantly up-regulated in drug-resistant breast cancer cells (MCF-7/ADM) compared to its parental wildtype cell line MCF-7/WT. Knockdown of TM9SF4 using lenti-TM9SF4-shRNA dramatically decreased cell viability and induced cell death of MCF-7/ADM. Moreover, drug-resistant xenografts derived from animal model also showed a significantly reduced growth rate after the delivery of lenti-TM9SF4-shRNA. The underlying mechanism appeared to be related to the triggering of ER stress via altered ER Ca2+ content, leading to unfolded protein response, which will induce apoptosis/necrosis, causing cell death. Our study provides TM9SF4 as a promising target for the overcoming of drug-resistance in clinical breast cancer therapy.

Methods:
Cell culture: Wild-type MCF-7 (MCF-7/WT) (ATCC) and MCF-7/ADM cells were cultured. MCF-7/ADM cells were derived by exposing MCF-7 cells to stepwise increasing concentrations of adriamycin over 8 months.
Western blot: Measurements of the protein level
CYQUANT assay and Edu assay: Cell viability and proliferation rate analysis
Immunofluorescence: Detection of the expression and distribution of TM9SF4 and ER marker in breast cancer cells
Flow cytometry: Apoptosis/necrosis and aggresomes detection

Results: TM9SF4 expression level was up-regulated in drug-resistant MCF-7 cells (MCF-7/ADM). Knockdown of TM9SF4 reduced MCF-7/ADM cell proliferation rate and caused cell death. TM9SF4 could alter ER Ca2+ content. Knockdown of TM9SF4 increased ER stress and protein misfolding in MCF-7/ADM cells.

Conclusions: TM9SF4 is essential for drug-resistant breast cancer cell survival. The underlying mechanism may involve ER stress induced by altered ER Ca2+ content, which triggers unfolded protein response, inducing cell apoptosis/necrosis. Our study provides TM9SF4 as a promising target in drug-resistant breast cancer therapy.

Objectives: To explore the underlying molecular and cellular mechanisms of how TM9SF4 knockdown could reduce cell population growth of chemoresistant MCF-7/ADM breast cancer cells.
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