

**Journal of the Hong Kong College of**  
**CARDIOLOGY**



Including Abstracts of  
Seventeenth Annual Scientific Meeting  
Institute of Cardiovascular Science and Medicine  
23 November 2013  
Hong Kong

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# Journal of the Hong Kong College of Cardiology



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The Journal of the Hong Kong College of Cardiology publishes peer-reviewed articles on all aspects of cardiovascular disease, including original clinical studies, review articles and experimental investigations. As official journal of the Hong Kong College of Cardiology, the journal publishes abstracts of reports to be presented at the Scientific Sessions of the College as well as reports of the College-sponsored conferences.

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- Standard abbreviations should be used for all measurements (SI units).

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- The text should follow the abstract and begin on a new page, as should References, Tables, and Legends.
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### Books (edited by other authors of article)

2. Furman S. Pacemaker follow-up. In Barold SS, (eds): *Modern Cardiac Pacing*. Mount Kisco, New York, Futura Publishing Company, 1985, pp. 889-958.

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3. Chung EK. *Principles of Cardiac Arrhythmias*. Baltimore, MD, Williams & Wilkins, 1977, pp. 97-188.

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Tel: (852) 2899 2035, Fax: (852) 2899 2045

E-mail: [enquiry@hkccchk.com](mailto:enquiry@hkccchk.com)

# A Coronary Rupture in the Left Anterior Descending Artery at Second Diagonal Artery Bifurcation Level in an Intervention with a Tryton Side Branch Stent

MUHAMMED HAKAN TAŞ, ZIYA SIMSEK, YAVUZER KOZA, ZAKIR LAZOGLU, EDNAN BAYRAM, HUSEYIN SENOCAK

From Department of Cardiology, Faculty of Medicine, Ataturk University, Erzurum, Turkey

**HAKAN TAŞ ET AL.: A Coronary Rupture in the Left Anterior Descending Artery at Second Diagonal Artery Bifurcation Level in an Intervention with a Tryton Side Branch Stent.** Percutaneous coronary intervention (PCI) for bifurcation lesions (BLs) is considered high risk due to increased procedural adverse events when compared to non-bifurcation lesion. Dedicated bifurcation stents, specifically designed to allow minimally traumatic implantation in the main vessel and/or side branch while providing adequate scaffolding of the side branch ostium may offer an advantage over utilization of conventional stents. Coronary perforation as a complication of PCI is a rare but potentially lethal complication that is associated with a high rate of morbidity. Coronary artery perforation during PCI has been reported repeatedly. To our best knowledge perforation in a BL, PCI with the Tryton Side-Branch Stent has not been reported. This case highlights that the Tryton to be an easy-to-use device in BLs, also operator should be careful, not too aggressive, their potential risks should be born in mind and a graft stent must be available in catheterization laboratory for emergencies. (*J HK Coll Cardiol 2013;21:51-56*)

*Bifurcation lesion, Coronary rupture, Dedicated stent, Graft stent*

## 摘要

經皮冠狀動脈介入治療 (PCI) 分叉病變 (BLs) 是具有高風險的，因為與非分叉病變治療相比其增加了程式的不良事件。專用分叉支架因為其植入主要血管和／或分支時創傷最小，同時又給分支口提供足夠的支撐作用，故比傳統支架可能更具優勢。冠狀動脈穿孔是PCI術中一種罕見但具有潛在致死性的併發症。PCI術中冠狀動脈穿孔已多次報導。據我們所知，運用Tryton側枝支架進行PCI治療時冠狀動脈穿孔尚未見報導。這一案例強調Tryton側枝支架對於分叉病變更易於操作，同時操作者也需小心謹慎，切忌冒進，要時刻謹記其潛在風險，應在導管室備有移植支架以防緊急情況。

關鍵詞：分叉病變，冠狀動脈破裂，專用支架，移植支架

## Introduction

Bifurcation lesions (BLs) accounts for 15 to 20% of percutaneous coronary interventions (PCI).<sup>1,2</sup> PCI for BLs is considered high risk due to increased

procedural adverse events when compared to non-bifurcation lesions. Dedicated bifurcation stents, specifically designed to allow minimally traumatic implantation in the main vessel and/or sidebranch while providing adequate scaffolding of the sidebranch ostium may offer an advantage over utilization of conventional stents. Previous Tryton registry studies have been reported good clinical outcomes, but these studies are limited by the small sample size and the relative short follow-up period (6 months). In straight lesions, these stents have been shown to provide good early and long term results.<sup>3,4</sup> Acute coronary artery perforation is a rare but

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Address for reprints: Prof. Muhammed Hakan Taş  
Department of Cardiology, Faculty of Medicine, Ataturk University,  
Erzurum, Turkey

Email: mhakantas@gmail.com

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challenging complication of PCI with hazardous potential for the patient. It has been reported to occur in 0.1 to 3.0% of patients undergoing PCI procedures.<sup>5</sup> Coronary artery perforation during PCI has been reported repeatedly. To our best knowledge perforation in a BL with the Tryton Side-Branch Stent (Tryton Medical, Inc., Newton, MA, USA) after kissing balloon has not been reported.

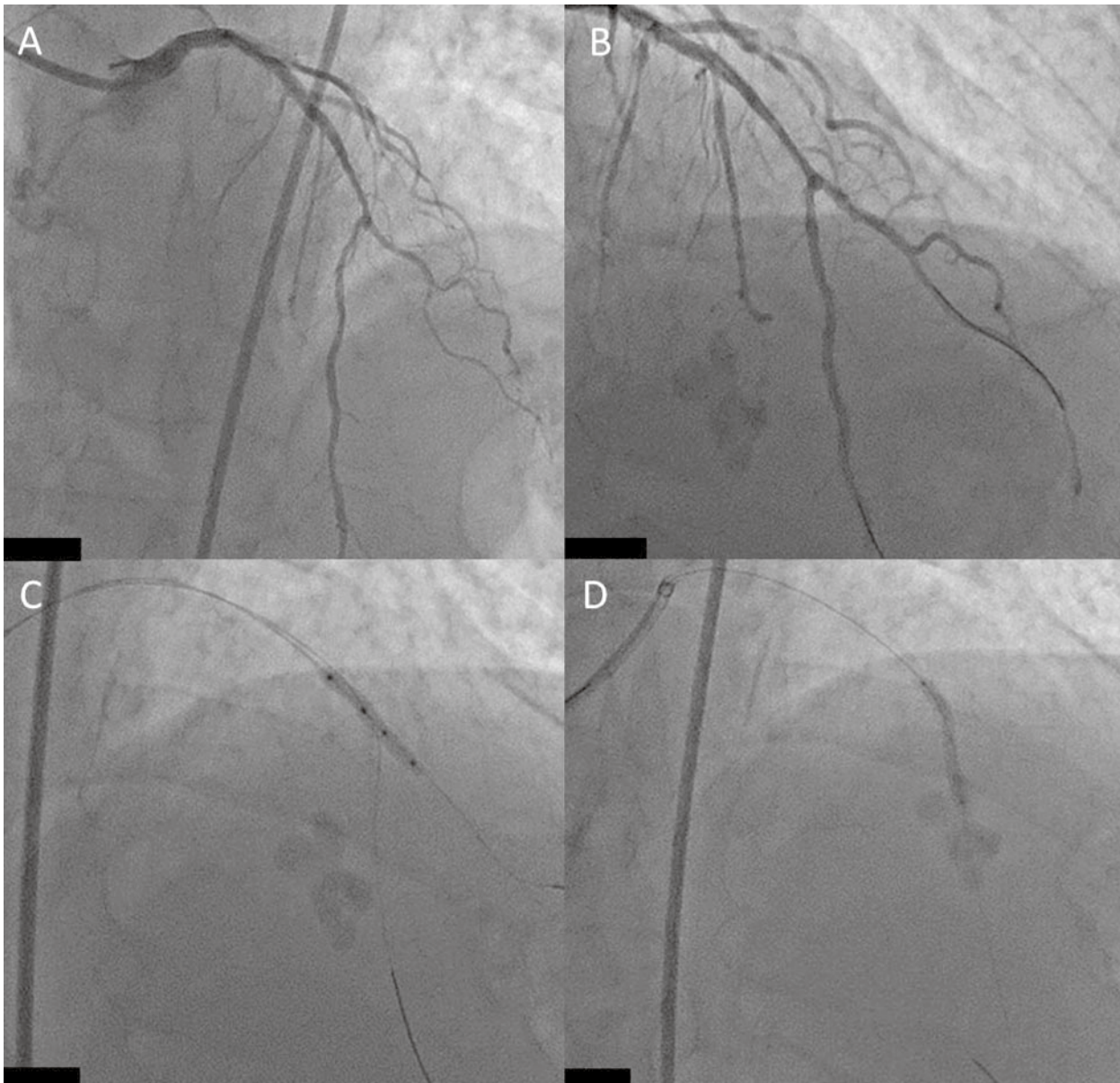
### Case

A 73-year-old male was admitted to our hospital with recurrent angina with a period of four weeks. He was an ex-smoker, hypertensive and dyslipidemic patient under treatment with aspirin, clopidogrel,  $\beta$ -blocker, angiotensin-converting-enzyme inhibitor and statin. Two months ago a bare metal stent had implanted to right coronary artery (RCA) because of inferior myocardial infarction. On physical examination blood pressure was 140/80 mmHg and pulse rate was 66 beats per minute. He also had normal laboratory tests besides elevated lipoprotein levels (predominantly high low-density lipoprotein). Patient underwent control coronary angiography via right femoral artery which yielded critical BL at the second diagonal level of the left anterior descending artery (LAD) and 20% restenosis in the stent of RCA (Figure 1A). We decided to implant a Tryton stent to the BL. Patient informed consent was taken. The LAD and second diagonal branch were wired with Asahi Prowater (0.014 inch) and Asahi Sion blue (0.014 inch), respectively (Figure 1B). A Tryton side branch stent 3.0 x 2.5 mm was deployed in the second diagonal artery at 10 atm pressure and another drug-eluting stent (DES) (Abbott Xience V 2.75 x 23 mm; Abbott Vascular Company, CA, USA) was deployed main branch to the LAD at 10 atm pressure (Figures 1C-D). Kissing dilatation was performed at 12 atm pressure with 2.5 x 25 mm Quqlimed Pyxis-C balloon to the LAD and 2.5 x 15 mm Blue Medical Protege balloon to the second diagonal branch (Figure 2A). This led to the LAD perforation at the main branch zone of the Tryton stent with contrast medium leaking into the pericardial cavity (Figure 2B). Type C coronary rupture

was visualized. Pericardiocentesis was not performed because there was no evidence of cardiac tamponade. The patient was still asymptomatic and hemodynamically stable. A 2.75 x 23 mm Direct Stent-Graft (InSitu Technologies, Minnesota, USA) was implanted at the bifurcation level of LAD at 12 atm pressure (Figure 2C). After dye injection there was no contrast medium leaking into the pericardium (Figure 2D). After 15 minutes the patient complained from severe angina. An acute thrombosis was seen in the graft stent (Figure 3A). Tirofiban infusion with high dose bolus regimen was started for 24 hours and than control angiography was performed. The stents were patent (Figure 3B). At first day echocardiographic controls were made at every one hour. The patient was hospitalized for six days and discharged with medication.

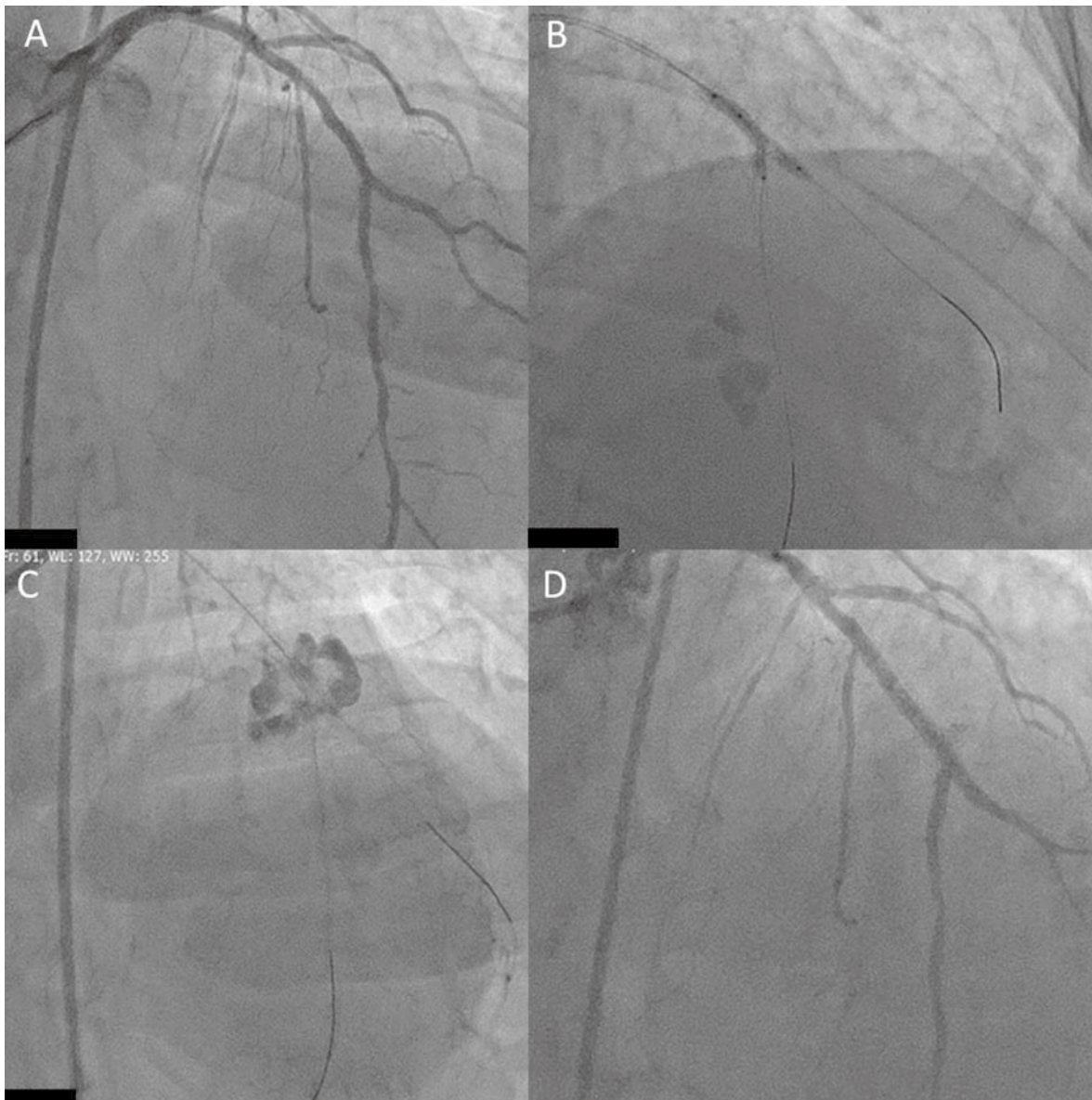
### Discussion

We report the successful management of a perforation of the LAD because of BL stenting with Tryton side branch stent. Coronary perforation as a complication of PCI is a rare but lethal complication that is associated with a high rate of morbidity. According to the published reports, coronary perforation occurs in 0.1-3.0% of all PCI cases and is associated with a mortality rate of approximately 10% or higher. Nevertheless, even if a provisional single-stent approach is used, PCI of a BL is still associated with poorer clinical outcomes when compared with PCI of a non-BL. Therefore, several dedicated bifurcation stents have been developed to improve clinical outcomes of BLs after PCI. One of these devices is the Tryton Side-Branch Stent (Tryton Medical, Inc., Newton, MA, USA) which is used in combination with a conventional DES in the main branch. The Tryton stent is a 5 or 6 Fr-compatible balloon expendable cobalt-chromium slotted-tube bare-metal stent. The stent consists of three zones: a distal side branch zone, a transition zone at the carina and a main branch zone. The distal side branch zone has a design similar to a regular stent, scaffolding the side branch. The central transition zone has specific

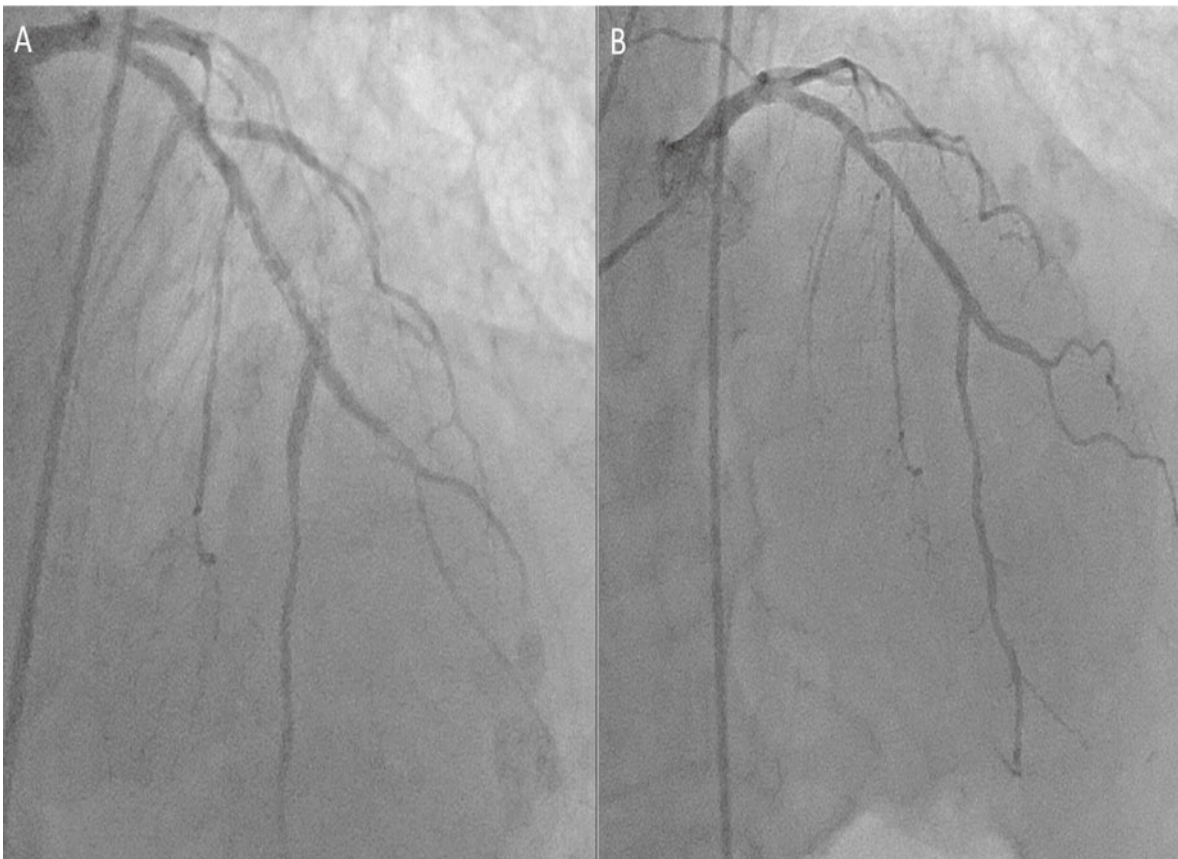


**Figure 1.** Angiographic images of (A) Critical lesion at the LAD and second diagonal branch bifurcation. (B) LAD and second diagonal branch were wired with Asahi Prowater and Asahi Sion blue. (C) Deployed Tryton side branch stent in to the second diagonal artery (D) Deployed drug-eluting stent in the main branch to the LAD.





**Figure 2.** Angiographic images of (A) After Tryton stent deployment; (B) Kissing dilatation; (C) Perforated segment of LAD and the contrast medium leaking into the pericardial cavity; (D) Graft stent emplacement at the bifurcation level of LAD and seal of the rupture and the absence of contrast medium leaking into the pericardium.



**Figure 3.** Angiographic images of A: Acute thrombosis in graft stent. B: After tirofiban infusion patency of the stents.

geometry of three elements which can be independently deformed to accommodate the wide range of carinal anatomy. The proximal main branch zone ('the collar') consists of two wedding bands and has a minimal amount of metal allowing easy delivery of a standard work-horse DES. The stent delivery system has four markers for optimal positioning of the stent.

In coronary perforation patient-related predictors of increased risk include previous interventions of the target vessel, prior myocardial infarction, female gender, and advanced patient age.<sup>6</sup> As anatomic and procedure-related predictors of increased risk include severe vessel calcification or pronounced vessel tortuosity, low lumen diameter of the target vessel, a balloon-to-artery ratio >1.3, and the use of atheroablative interventional devices.<sup>5,6</sup> The use of oversized balloons is a very important mechanism in the development of perforation. Achievement of a greater luminal diameter after the

intervention is associated with a lower restenosis rate, but carries a higher risk for perforation. In our case patient's advanced age, mismatch between balloon diameter and coronary artery diameter and the calcified lesion structure were the reasons of the perforation. We used 2.5 x 25 mm and 2.5 x 15 mm balloons for kissing balloon dilatation the balloon to artery ratio was approximately 1.9 and higher than the 1.3. The proximal main branch zone of the stent was the point of the rupture. At this zone has a minimal amount of metal so protective effect of stent for rupture was minimal.

There is no consensus on the optimal treatment of patients with coronary perforation.<sup>6,7</sup> Non-surgical prolonged balloon inflation to induce intracoronary thrombosis, implantation of (membrane-covered) stents, coil embolisation, injection of polyvinyl alcohol, and intracoronary administration of autologous blood have been reported as treatment modalities.<sup>6-8</sup> Although the

use of graft stents is associated with good immediate success rates, long-term results are disappointing due to the high incidence of restenosis and/or late thrombotic occlusions.<sup>7</sup> In our case stent-graft used for treatment of the coronary dissection but an acute thrombosis occurred 15 minutes after stenting. This might be due to excessive metal overload in the proximal portion of the left anterior descending artery. Intracoronary imaging with intravascular ultrasound or optical coherence tomography would be useful but we could not perform due to technical incompetence. Fortunately, this problem resolved with a tirofiban infusion of high bolus dose .

This case highlights that the Tryton to be an easy-to-use device in BLs, also operator should be careful, not too aggressive; potential risks of PCI to BLs should be borne in mind and a graft stent must be available in catheterization laboratory for emergencies.

### Disclosure statement

The authors declare that they have no financial relationships or conflicts of interest regarding the content herein.

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## SCIENTIFIC PROGRAMME

23 NOVEMBER 2013 (SATURDAY)

- 08:30-09:00 **Registration**
- 09:00-10:30 **Oral Presentations for Young Investigator Award**  
*Sponsored by Sun Chieh Yeh Heart Foundation*  
*Chairmen: Dr. Carmen Chan, Queen Mary Hospital, Hong Kong*  
*Dr. K.H. Yiu, The University of Hong Kong*
- 10:30-11:00 Coffee Break, Poster Viewing and Booth Visit
- 11:00-11:20 **Invited Lecture**  
*Chairmen: Professor Y. Huang, Chinese University of Hong Kong*  
*Dr. Katherine Fan, Grantham Hospital, Hong Kong*
- 22.q11.21 Deletion Associated with Sporadic Tetralogy of Fallot in Han Chinese  
*Professor G.W. He, Nankai University, China*
- 11:20-12:30 **Poster Presentations for Young Investigator Award**  
*Sponsored by Sun Chieh Yeh Heart Foundation*  
*Chairmen: Dr. George Leung, The University of Hong Kong*  
*Professor Sookja K. Chung, The University of Hong Kong*  
*Dr. S.Q. Yang, Chinese University of Hong Kong*
- 12:30-14:00 **Lunch**  
*Courtesy of Astra Zeneca Hong Kong Ltd*
- 14:00-14:30 **Opening Ceremony**  
*Professor Sophia Chan, Under Secretary for Food and Health, Government of the Hong Kong Special Administrative Region*  
*Professor C.S. Lau, Acting Dean, Li Ka Shing Faculty of Medicine, The University of Hong Kong*  
*Professor Bernard M.Y. Cheung, Director, Institute of Cardiovascular Science and Medicine, The University of Hong Kong*
- 14:30-16:00 **Symposium I : New Approaches in Treating Cardiovascular Disease**  
*Chairmen: Dr. Chris Wong, Hong Kong College of Cardiology*  
*Professor H.F. Tse, The University of Hong Kong*  
*Professor Brian Tomlinson, Chinese University of Hong Kong*
- Astra Zeneca Keynote Lecture**  
Personalized Medicine for Cardiovascular Diseases  
*Professor H.F. Tse, The University of Hong Kong*
- Novartis Keynote Lecture**  
Advances in Hypertension Management and New Guideline Update  
*Dr. N.Y. Chan, Princess Margaret Hospital, Hong Kong*
- Institute of Vascular Medicine Keynote Lecture**  
Recent Advances in the Management of Heart Failure  
*Professor C.M. Yu, Chinese University of Hong Kong*

- 16:00-16:30 Coffee Break, Poster Viewing and Booth Visit
- 16:30-17:50 **Symposium II: New Mechanisms and Potential Targets in Cardiovascular Disease**  
*Chairmen: Professor Richard Y.H. Yu, Hong Kong College of Physicians*  
*Professor Ronald A. Li, The University of Hong Kong*  
*Dr. Victor Yan, Specialist in Cardiology*
- Takeda Keynote Lecture**  
Bidirectional Nature of Cardiovascular and Kidney Disease  
*Dr. Koichi Shimizu, Nangai Clinic and Saitama Medical School, Japan*
- MSD Keynote Lecture**  
TRPC3 in Coronary Endothelial Function: Role of Hypoxia-Reoxygenation and Hyperkalemia  
*Dr. S.Q. Yang, Chinese University of Hong Kong*
- Human Cardiac Tissue Fabricated from Human Embryonic Stem Cells (hESCs): Present Status and Potential Applications  
*Dr. C.W. Kong, The University of Hong Kong*
- A-FABP is a Potential Mediator of Diabetic Cardiomyopathy and Ischemic Reperfusion Induced Cardiac Injury  
*Dr. Ruby Hoo, The University of Hong Kong*
- 17:50-18:00 **Young Investigator Award Ceremony and Closing Remarks**  
*Professor C.P. Lau, Sun Chieh Yeh Heart Foundation*  
*Professor Bernard M.Y. Cheung, The University of Hong Kong*
- 18:00 **Annual General Meeting**

**ABSTRACTS**

Abstracts for Invited Lectures:

**IL1.**

**22q11.21 DELETION ASSOCIATED WITH SPORADIC TETRALOGY OF FALLOT IN HAN CHINESE**

GW He,<sup>1,2,3</sup> CL Maslen,<sup>3</sup> XY Bai,<sup>1</sup> XC Liu,<sup>1</sup> ZG Liu,<sup>1</sup> Q Yang<sup>1,4</sup>

<sup>1</sup>TEDA International Cardiovascular Hospital, Tianjin, China; <sup>2</sup>The Affiliated Hospital, Hangzhou Normal University, Hangzhou, China; <sup>3</sup>Heart Research Center, Oregon Health & Science University, Portland, Oregon, 97239, USA; <sup>4</sup>Department of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong

**Purpose:** Tetralogy of Fallot (TOF) is a congenital cardiac malformation that consists of an interventricular communication, also known as a ventricular septal defect, obstruction of the right ventricular outflow tract, override of the ventricular septum by the aortic root, and right ventricular hypertrophy. Overall it is the most common cause of cyanotic cardiac disease in infants. In the United States TOF occurs in approximately one in 3,000 live births and accounts for 10% of all serious congenital heart disease. However, studies suggest that the incidence in TOF is substantially higher in China. This study was designed to investigate the genetic basis of TOF in Han Chinese.

**Methods:** Genomic DNA was extracted from peripheral blood for each index patient and control subject. Affymetrix genome-wide human SNP array 6.0 was used. Each array has 1,800,000 genetic markers, including more than 906,600 single nucleotide polymorphisms (SNPs) and more than 946,000 probes for the detecting copy number variations (CNVs). DNA was extracted, amplified and hybridized to an Affymetrix Genome-Wide human SNP array 6.0. Copy number was calculated based on probe hybridization signal intensity data relative to the signal of disease-free normal controls. To determine CNV status on each sample we performed real-time PCR. TaqMan™ probes designed by the manufacturer (Applied Biosystems, Foster City, CA) were used to target each of the specific region. The *RNase P* was chosen as the reference gene.

**Results:** Deletion of 22q11.21 was seen in 8/60 (13.3%) cases. However, the deletion was seen in different patterns in those patients, shown by different starting and ending loci and involving genes. Parents of TOF probands with a disease-associated CNV provided with ability to determine if any of the CNVs were inherited or *de novo*. The CNVs were *de novo* mutations for all these cases.

**Conclusions:** 22q11.21 deletion is associated with sporadic tetralogy of Fallot in Han Chinese involving a large number of genes and the related individual genes warrant further detailed investigations.

**IL3.**

**ADVANCES IN HYPERTENSION MANAGEMENT AND NEW GUIDELINES UPDATE**

NY Chan

Princess Margaret Hospital, Hong Kong

Hypertension is a prevalent disease worldwide with an estimated prevalence of 30-45% in the European countries. In a recent community survey involving 803 Hong Kong citizens, the prevalence of hypertension was 32%, with a 28% rise compared to similar surveys performed in 2011 and 2012. Apart from the high disease burden, the high prevalence of organ damage in patients with hypertension calls for extra attention. In a recently performed study involving 55 hypertensive patients followed up in Princess Margaret Hospital in Hong Kong, 66% of patients had a carotid intima media thickness  $\geq$ 75th percentile and 26% of patients had carotid plaques respectively. There have been new evidence on several diagnostic and therapeutic aspects of hypertension and consequently, the recently released management guidelines on hypertension differ in many aspects from the previous one. The new management guidelines will be discussed in details with special emphasis on (1) asymptomatic organ damage and its prognostic significance; (2) initiation of antihypertensive treatment for high normal blood pressure; (3) treatment target for patients with different cardiovascular risk; (4) choice of monotherapy, combination therapy and fixed-dose single-pill combination; (5) treatment in elderly patients and (6) new therapeutic options for drug-refractory hypertension.

**ABSTRACTS**

Abstracts for Invited Lectures:

**IL4.**

**RECENT ADVANCES IN THE MANAGEMENT OF HEART FAILURE**

CM Yu

Faculty of Medicine, Chinese University of Hong Kong, Hong Kong

Management of heart failure has gained significant success in the last 2 decades. There has been significant progress in medical therapy exemplified by the cocktail of neurohormonal blockers and device therapy. In managing heart failure, device therapy had been at the forefront of non-pharmacological therapy. It starts with the introduction of cardiac resynchronization therapy (CRT), a pacing therapy that includes a left ventricular lead to improve synchronous contraction of the heart. The therapy was initially targeting NYHA Class III and IV patients with EF<35% and with a wide QRS complex. With the evolution of this therapy from clinical evidence, this therapy now also extended to NYHA class II patients. Although patient with a narrow QRS complex (<120 ms) was demonstrated to have systolic dyssynchrony, in a recent multicenter trial, CRT did not result in improvement of heart failure event in this population. For medical therapy, our current study focuses on the prediction of lack of favorable medical therapy in heart failure patients with systolic dysfunction. This includes the potential role of biomarkers which are linked to the pathophysiologic changes of heart failure. Furthermore, activation or suppression of certain microRNAs might also play a role in heart failure progression, such as adverse histopathological changes, which was being explored in our recent study program. Lastly, the incorporation of echocardiographic imaging may add further strength in the prediction of heart failure treatment response. These findings may hope to triage patient therapy and design effective treatment program. In prevention of HF, optimal control of cardiovascular risk factors

has been advocated in the guideline (e.g. hypertension and other risk factors for atherosclerosis). Medical therapy for asymptomatic left ventricular dysfunction has also been advocated. However, there is another phenomenon which had drawn attention recently, which is the electromechanical delay caused by pacing related-induced LBBB. This phenomenon commonly happened in patients received right ventricular apical pacing. We had conducted the first randomized, controlled, multicentre trial which showed that CRT is able to prevent adverse remodeling of the left ventricle induced by right ventricular apical pacing. Currently, long-term follow up study is underway to determine if this therapy will prevent heart failure development.

**IL5.**

**BIDIRECTIONAL NATURE OF CARDIOVASCULAR AND KIDNEY DISEASE**

K Shimizu

Cardiovascular Division, Nangai Clinic, National Medical Center, Saitama Medical School, Japan

Cardiovascular disease (CVD) is the principal cause of morbidity and mortality in patients with chronic kidney disease (CKD). CKD promotes hypertension and dyslipidemia. Hypertension and diabetes causes nephrosclerosis and diabetic nephropathy, leading to the progression of renal failure. These traditional cardiovascular risk factors can promote CVD development. In addition, inflammatory mediators such as cytokines, chemokines, adhesion molecules, fibroblast growth factor 23, homocysteine, or reactive oxygen species are often elevated and the renin-angiotensin system, endothelin, and the sympathetic nervous system are frequently activated in patients with CKD, accelerating atherosclerosis and/or left ventricular hypertrophy. Mineral dysregulation accompanied by reduction of vitamin D, hyperphosphatemia, and hyperparathyroidism in CKD patients promotes vascular calcification associated with end-stage renal disease. Accelerated atherosclerosis then leads to increased prevalence of coronary artery disease, peripheral arterial disease, arterial stiffness, left ventricular hypertrophy, and cerebrovascular disease. On the other hand, renal dysfunction can result from diminished renal perfusion secondary to low cardiac output in left ventricular failure, peripheral arterial disease, and atherosclerosis and increased renal vasoconstriction mediated by neurohormonal and autonomic activation. Thus, traditional and non-traditional cardiovascular risk factors serve as cardiovascular and kidney risk factors. Consequently, kidney and cardiovascular dysfunction bidirectionally promote chronic renal failure and

congestive heart failure. Whether differences in CVD in CKD patients suggest preventative or therapeutic strategies unique to this population remains unclear. Randomized controlled clinical trials must confirm the effectiveness of current pharmacological and interventional therapies modifying traditional and novel cardiovascular risk factors in patients at each stage of CKD, with or without unique co-morbidities.



**ABSTRACTS**

Abstracts for Invited Lectures:

**IL6.**

**TRPC3 IN CORONARY ENDOTHELIAL FUNCTION: ROLE OF HYPOXIA-REOXYGENATION AND HYPERKALEMIA**

Q Yang, JH Huang, XQ Yao, CM Yu

Division of Cardiology, Department of Medicine and Therapeutics & Institute of Vascular Medicine, Chinese University of Hong Kong, Hong Kong

Canonical transient receptor potential channels (TRPCs) have been considered as the most important Ca<sup>2+</sup>-permeable cation channels in vascular endothelium physiology. Our previous studies in porcine coronary arteries have demonstrated that exposure to hypoxia-reoxygenation (H-R) or hyperkalemic cardioplegic solutions impair endothelial function. eNOS-NO dysfunction and compromised EDHF responses are mechanisms underlying the impairment. Recently, we studied the role of TRPC3 in endothelial NO production and EDHF responses with further investigations of the effects of H-R and hyperkalemic/hyperkalemic cardioplegic solutions on this channel. Our results showed that Ca<sup>2+</sup> influx via TRPC3 significantly contributes to NO release. The reduction of NO during H-R is associated with the suppression of TRPC3 activity and the inhibition of TRPC3-mediated Ca<sup>2+</sup> influx in coronary endothelial cells. TRPC3 is also involved in EDHF response. Hyperkalemic exposure reduced TRPC3-mediated Ca<sup>2+</sup> influx in a concentration-dependent manner. Hyperkalemic cardioplegic solutions that are commonly used in clinical practice such as St. Thomas Hospital (ST), Histidine-Tryptophan-Ketoglutarate (HTK), and University of Wisconsin (UW) solutions also reduced Ca<sup>2+</sup> influx in coronary endothelial cells. Activation of TRPC prevented the reduction of Ca<sup>2+</sup> influx in cells exposed to solutions containing mild to moderate high concentration of K<sup>+</sup>. Furthermore, the EDHF response compromised by hyperkalemic or

hyperkalemic cardioplegic solutions was restored by addition of TRPC activator in the solution. These data suggests that inhibition of TRPC3 by high concentration of K<sup>+</sup> is a mechanism underlying the detrimental effect of hyperkalemia on EDHF-mediated endothelial function. Taken together, TRPC3 may represent a potential target for endothelial protection in hypoxic/ischemic-related cardiovascular diseases and in open heart surgery. (Supported by grants from Research Grant Council of Hong Kong (GRF CUHK4774/12M) and National Natural Science Foundation of China (81200123)).

**IL7.**

**HUMAN CARDIAC TISSUE FABRICATED FROM HUMAN EMBRYONIC STEM CELLS (hESCs): PRESENT STATUS AND POTENTIAL APPLICATIONS**

CW Kong

Stem Cell & Regenerative Medicine Consortium (SCRMC) and Department of Physiology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

Impairment and loss of cardiomyocytes (CMs) due to aging or pathophysiological conditions (e.g., myocardial infarction and chronic hypertension) are generally considered irreversible, and can lead to conditions from cardiac arrhythmias to heart failure. Human pluripotent stem cells (hPSCs), including the embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC), can self-renew while maintaining their pluripotency to differentiate into all cell types, including CMs. Indeed, various directed differentiation protocols are available and dishes of hPSC-CMs are now readily available from laboratories around the world. The lack of appropriate human heart model to more closely simulate the normal and pathophysiology of our native human heart is, however, a major roadblock for further advancement. Novel bio-engineering and bio-nanofabrication approaches to construct 3D human heart tissue and chambers as more sensitive, accurate and high-throughput tools for disease modelling, drug discovery and cardiotoxicity screening as well as transplantable bio-devices and prototypes investigating currently will be discussed.

## ABSTRACTS

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Abstracts for Invited Lectures:

### IL8.

#### **A-FABP IS A POTENTIAL MEDIATOR OF DIABETIC CARDIOMYOPATHY AND ISCHEMIC REPERFUSION INDUCED CARDIAC INJURY**

RLC Hoo

Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong

Diabetes increases the risk of heart dysfunction by inducing cardiomyopathy. We have demonstrated that serum levels of adipocyte fatty acid-binding protein (A-FABP), a fat-derived adipokine, increased significantly in patients with heart failure and are independently associated with the deterioration of heart function. We here describe the role of A-FABP in the pathogenesis of diabetic cardiomyopathy and myocardial ischaemia/reperfusion (MI/R) induced cardiac injury. A-FABP knockout (KO) mice and their wild-type (WT) littermates were employed in this study. The mRNA abundance and protein expression levels of A-FABP in heart tissue were markedly elevated after MI/R injury and streptozocin (STZ)-induced diabetes in WT mice. After MI/R, myocardial infarct size, apoptotic index and superoxide production were alleviated in A-FABP KO mice which accompanied by improved left ventricular function compared with WT mice in either non-diabetic or diabetic groups. Immunofluorescence staining showed that A-FABP was co-localized with endothelial marker CD31. eNOS phosphorylation and NO production in the heart tissue were significantly decreased in WT mice after MI/R while elevated in that of A-FABP KO mice after MI/R injury and STZ-induced diabetes. Diabetes-induced myocardial hypertrophy and fibrosis were also significantly alleviated in A-FABP KO mice. In conclusion, A-FABP protects mice against diabetic cardiomyopathy and myocardial ischemia/reperfusion induced cardiac injury, which may through inducing eNOS phosphorylation and NO production in the heart tissue.

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**ABSTRACTS**

## Abstracts for Oral Presentation:

**OPI.****TRPM2 CONTRIBUTES TO NEOINTIMAL HYPERPLASIA IN VASCULAR WALLS**X Ru,<sup>1</sup> Y Huang,<sup>1</sup> Y Mori,<sup>2</sup> X Yao<sup>1</sup><sup>1</sup>Li Ka Shing Institute of Health Science and School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong; <sup>2</sup>Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, Japan

A hallmark of atherosclerosis is progressive intimal thickening (or neointimal hyperplasia). Over-production of reactive oxygen species and alteration of Ca<sup>2+</sup> signaling are among the key factors contributing to the progression of neointimal hyperplasia. In the present study, we investigated the role of TRPM2, a ROS-sensitive Ca<sup>2+</sup> entry channel, in neointimal hyperplasia. Perivascular cuffs were used to induce neointimal hyperplasia in rodent arteries. Immunostaining showed numerous TRPM2-positive smooth muscle cells (SMCs) in neointimal regions. The neointimal hyperplasia was reduced in *Trpm2* knockout mice compared to wild-type mice. In cultured rodent aortic SMCs, H<sub>2</sub>O<sub>2</sub> treatment stimulated SMC proliferation and migration. The effect of H<sub>2</sub>O<sub>2</sub> was reduced by TRPM2-specific blocking antibody TM2E3, 2-aminoethoxydiphenyl borate and *Trpm2* knockout. These data suggest a key functional role of TRPM2 in neointimal hyperplasia.

**OP2.****BONE MORPHOGENIC PROTEIN 4 SUPPRESSION PROTECTS ENDOTHELIAL FUNCTION IN TYPE 2 DIABETIC MICE**

Y Zhang, J Liu, XY Tian, L Wang, JY Luo, WT Wong, Y Huang

Institute of Vascular Medicine, Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, Hong Kong

**Objective:** Bone morphogenic protein 4 (BMP4) is involved in the progression of vascular dysfunction in hypertension. Yet, its role in endothelial dysfunction in type 2 diabetes remains unknown. This study aims to investigate whether suppression of BMP4 can protect endothelial function in type 2 diabetic mice, and to study the mechanism underlying BMP4-induced oxidative stress in diabetes.

**Methods:** Type 2 diabetic *db/db* mice were utilized as animal model. In *in vivo* experiments, the level of BMP4 in the arteries was inhibited by noggin via osmotic pump infusion (1 µg·h<sup>-1</sup>·kg<sup>-1</sup>, 2 weeks) and also by BMP4 silencing with BMP4-shRNA adenovirus (Ad-BMP4 shRNA) transduction via tail vein injection (10<sup>9</sup> pfu/mouse). In *ex vivo* experiments, isolated mouse aortic rings were cultured in medium containing BMP4 inhibitors, Ad-BMP4 shRNA and BMP receptor 1a (BMPR1a) shRNA lentiviral particles. Vasoreactivity was examined on wire myograph and pressure myograph. Reactive oxidative species (ROS) in aortic endothelium and in cultured endothelial cells were measured by dihydroethidium (DHE) staining, CM-H<sub>2</sub>DCFDA fluorescence and chemiluminescence. Protein expression was determined by Western blotting.

**Results:** Noggin treatment and Ad-BMP4 shRNA transduction improved impaired endothelium-dependent relaxations (EDRs) in aortae and mesenteric arteries of *db/db* diabetic mice in both *in vivo* and *ex vivo* experiments. Suppression of BMP4 reduced the over-production of ROS in *db/db* mouse aortae, in *ex vivo* cultured C57BL/6 mouse aortae and primary mouse aortic endothelial cells (MAECs) treated with high glucose (30 mmol/L). BMPR1a silencing improved EDRs in *db/db* mouse aortae, and inhibited ROS production in the endothelial layer. The suppression of BMP4-BMPR1a signaling diminished BMP4 over-generation under hyperglycemic condition. **Conclusion:** Inhibition of BMP4/BMPR1a axis restored endothelial function in diabetic mice through reducing oxidative stress in the endothelium. Attenuation of BMP4 signaling could be a potential therapeutic strategy against diabetic vascular dysfunction. (Supported Hong Kong RGC-CRF grant)

**ABSTRACTS**

Abstracts for Oral Presentation:

**OP3.**

**OXIDATIVE STRESS INDUCED BY INTERMITTENT HYPOXIA EXACERBATES LIPID ACCUMULATION AND INFLAMMATION IN A CELL MODEL OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)**

JF Pan,<sup>1</sup> R Guo,<sup>2</sup> EC Liang,<sup>2</sup> GL Tipoe,<sup>2</sup> ML Fung<sup>1</sup>

Departments of <sup>1</sup>Physiology and <sup>2</sup>Anatomy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

**Background/Aims:** The prevalence of obstructive sleep apnea (OSA) is high in patients with non-alcoholic fatty liver disease (NAFLD) and NASH is a progressive hallmark of the pathogenesis of NAFLD. Chronic intermittent hypoxia is associated with recurrent episodes of oxygen desaturation and reoxygenation in OSA patients, leading to excessive production of reactive oxygen species (ROS). The causal link between OSA and NAFLD is not known and the mechanistic effect of intermittent hypoxia (IH) on the pathogenesis of NAFLD remains elusive. Here we tested the hypothesis that IH-induced oxidative stress aggravates lipid accumulation and inflammation induced by sodium palmitate in HepG2 cells.

**Materials and Methods:** HepG2 cells were treated with sodium palmitate or vehicle under normoxia (Nx) or IH condition for 72 hours in the presence or absence of a ROS scavenger MnTBAP. Cell viability was detected by MTT assay and intracellular lipid deposit was examined by oil red staining. Lipid peroxidation was measured by malondialdehyde (MDA) assay and levels of reactive oxygen species (ROS) were detected by CM-H2DCFDA staining. The expressions of pro-inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , IL-6), fatty acid uptake-associated genes (caveolin-1 and FATP5), fatty acid synthesis genes (SREBP1 and ACC1) and fatty acid  $\beta$ -oxidation gene ACOX were determined by real-time PCR.

**Results:** Results showed that sodium palmitate increased lipid deposit in the cells and it also decreased cell viability. The effect of sodium palmitate was more prominent in the group co-treated with hypoxia. Levels of MDA and ROS and the expressions of IL-1 $\beta$ , TNF- $\alpha$ , IL-6 and caveolin-1, but not FATP5, were significantly increased in the palmitate- or hypoxia-treated group and were remarkably elevated in the co-treated group. These effects were abolished by MnTBAP treatment. In addition, levels of the expression of ACOX, SREBP1 and ACC1 were significantly lowered in the cells treated with palmitate or hypoxia and the expressions were much less in the co-treated group. Treatment of MnTBAP prevented the decreased expression of ACOX but had no effect on the SREBP1 and ACC1 expression.

**Conclusion:** IH-induced oxidative stress exacerbates lipid accumulation and inflammation induced by sodium palmitate in HepG2 cells, probably mediated by an increase in lipid uptake and a decrease in the fatty acid  $\beta$ -oxidation.

**OP4.**

**ROLE OF PROSTAGLANDIN E RECEPTOR SUBTYPE 4 (EP4) IN THE REGULATION OF TRIGLYCERIDE METABOLISM**

Y Cai, PM Vanhoutte, EHC Tang

Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

**Objectives:** Hypertriglyceridemia is strongly associated with future risk of insulin resistance, diabetes and cardiovascular disease. Interestingly, it has been recently demonstrated that mice lacking cyclic AMP-responsive element-binding protein H (CREB-H) showed higher plasma triglyceride concentrations compared to wild-type mice. As an upstream stimulating factor of CREB-H, prostaglandin E receptor subtype 4 (EP4) may participate in the regulation of triglyceride metabolism. Thus, we tested whether or not deletion of EP4 influences triglyceride metabolism, and if so, to explore the underlying mechanisms.

**Methods:** EP4 wild-type and knockout mice were put on a high-fat diet (HFD) for thirty weeks and changes in plasma triglycerides were monitored. The impact of EP4 deletion on the ability to synthesize hepatic very low density lipoprotein (VLDL)-triglyceride (TG) and intestinal chylomicron (CM)-TG, as well as the ability to clear TG during HFD was examined. Lipoprotein lipase (LPL) activity and mRNA expression of LPL and CD36 in brown adipose tissue (BAT) were determined by fluorometric assay kit and quantitative polymerase chain reaction (Q-PCR), respectively.

**Results:** After thirty weeks of high-fat diet, EP4 knockout mice had a higher plasma TG level than wild-type mice. The deletion of EP4 did not influence hepatic VLDL-TG production or intestinal CM-TG synthesis but impaired

TG clearance rate. EP4 knockout mice had a decreased mRNA expression and activity of LPL in their BAT, suggesting impaired hydrolysis and uptake of triglycerides in this tissue. Moreover, EP4 knockout mice had a reduced expression of CD36 in BAT, which may indicate that the uptake of fatty acids is impaired.

**Conclusions:** Deletion of EP4 in high-fat fed mice resulted in hypertriglyceridemia. The hypertriglyceridemia that accompanies EP4 deficiency is the result of impaired TG clearance, attributed to reduced mRNA expression of LPL and CD36, and impaired LPL activity in BAT. The results indicate that EP4 plays a critical role in systemic lipid homeostasis.

**ABSTRACTS**

Abstracts for Oral Presentation:

**OP5.**

**CIGARETTE SMOKING INDUCED OXIDATIVE STRESS IN RAT HEART**

YM Liang,<sup>1</sup> MSM Ip,<sup>1,3</sup> JCW Mak<sup>1,2,3</sup>

Departments of <sup>1</sup>Medicine and <sup>2</sup>Pharmacology & Pharmacy; <sup>3</sup>Research Centre of Heart, Brain, Hormone and Healthy Aging, The University of Hong Kong, Hong Kong

**Objectives:** Cigarette smoking is known to be one of the important risk factors for the development of cardiovascular disease. Despite the suggestion that cigarette smoke (CS), a complex mixture of chemicals including more than 4,000 components, affects several known pathophysiological pathways, such as oxidative stress, inflammation, and endothelial dysfunction, leading to the development of athero-thrombosis; however, little is known about the underlying mechanisms. To investigate the role of CS as a risk factor for cardiovascular disease, we assessed the changes in oxidative stress markers in heart tissues after CS exposure.

**Methods:** Male Sprague-Dawley rats (aged 6-7 weeks) were randomly divided into two groups, as sham air (SA) group (n=8) and CS group (n=8) respectively. The CS group was exposed to 4% CS for 1h each day for 56 days in ventilated smoking chambers, while the SA group was exposed to fresh air. Animals were sacrificed 24 h after the last exposure and heart tissues were collected. Heart homogenates were prepared for the determination of level of advanced oxidation protein products (AOPP, a protein oxidation marker) by spectrophotometric detection method and enzyme activity of superoxide dismutase (SOD) by using commercial assay kit. The expression of endothelial nitric oxide synthase (eNOS) was also determined by Western blot analysis.

**Results:** CS exposure caused significant elevation of cardiac AOPP level ( $p < 0.05$ ), suggesting the presence of protein oxidation in CS-induced oxidative damage in rat heart. In addition, cardiac SOD activity was significantly reduced after exposure to CS ( $p < 0.01$ ), indicating the imbalance between oxidants and anti-oxidants in the heart. We also found CS-induced inhibition of eNOS phosphorylation in heart homogenates.

**Conclusions:** All these data provide evidences for the potential contribution of CS to endothelial dysfunction and thus to cardiovascular disease due to the existence of oxidative stress in the heart of CS-exposed rat.

*(This study is supported by Hong Kong RGC General Research Fund (HKU 774410M)).*

**OP6.**

**SIRT1 PROTECTS AGAINST OBESITY AND AGEING INDUCED ENDOTHELIAL DYSFUNCTION VIA ENHANCING BROWN-REMODELING OF PERIVASCULAR ADIPOSE TISSUE (PVAT)**

HXY Hui, P Gu, A Xu

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

**Background and objective:** SIRT1 is a key molecule controlling adipose tissue browning. Our previous study has demonstrated that perivascular adipose tissue (PVAT) plays a pivotal role in determining endothelial function. However, the exact function of SIRT1 in PVAT is unknown. The aim of the present study is to investigate whether SIRT1 elicits a protective role toward obesity and ageing-associated endothelial dysfunction.

**Methods:** Adipose-specific SIRT1 knockout mice (AKO) were generated by crossing SIRT1 flox mice with a-fabp-Cre mice. The SIRT1 flox mice were used as the wild type control (WT). The mice were fed with either standard chow for 1 year or high fat high cholesterol diet for 12 weeks followed by exposure to 4°C for 6 days. The aortic rings with or without PVAT were subjected to wire myograph to examine the acetylcholine induced vascular relaxation. The adiponectin level was measured by qPCR or immunohistochemistry.

**Results:** The WT and AKO mice exhibited similar endothelial function under obese and ageing conditions. However, in the presence of PVAT, acetylcholine induced relaxation was impaired in obese and ageing AKO mice, suggesting that SIRT1 within PVAT plays an essential role in antagonizing against obesity and ageing-associated vascular dysfunction.

Moreover, PVAT displayed a switch from brown toward white phenotype upon obese and ageing conditions. To further establish a correlation between brown phenotype in PVAT with its vascular-modulating function, WT and AKO mice were acclimated to cold temperature for 6 days before the aortic relaxation was examined. The results showed in WT mice, the brown phenotype in PVAT was readily enhanced by cold exposure. Meanwhile, cold acclimation led to improved vascular function in the presence of PVAT. In contrast, AKO mice were resistant to cold-induced brown remodeling and improvement of vascular function. Additionally we found cold exposure increased adiponectin expression in WT mice, but not in AKO mice.

**Conclusion:** The brown phenotype in PVAT is related to a protective function of PVAT under obese and ageing conditions and SIRT1 was a key factor in controlling brown phenotype in PVAT. Adiponectin represents the possible link between PVAT browning and its function.

**ABSTRACTS**

Abstracts for Oral Presentation:

**OP7.**

**CONNEXIN-HEMICHANNELS ARE INVOLVED IN ACIDOSIS-INDUCED ATP RELEASE FROM SKELETAL MYOCYTES**

L Lu, J Tu, HJ Ballard

Department of Physiology, The University of Hong Kong, Hong Kong

ATP is an important extracellular signalling molecule which contributes to exercise vasodilation. We have previously shown that the cystic fibrosis transmembrane conductance regulator (CFTR) is involved in acidosis-induced ATP release from skeletal muscle. However, it is still unknown whether ATP is released through CFTR itself or whether CFTR regulates a separate ATP-release channel. So we investigated: (1) the pathway responsible for CFTR activation in myocytes at low pH; (2) whether connexin (Cx) hemichannels were involved in the acidosis-induced ATP release from skeletal muscle. Lactic acid (10 mM) increased the intracellular cAMP and the extracellular ATP in L6 skeletal myocytes. Similarly, the cAMP-elevating agent, forskolin, increased extracellular ATP. The phosphodiesterase inhibitor, IBMX, increased extracellular ATP in the absence or presence of lactic acid. CFTR phosphorylation was increased by the addition of forskolin alone, and further increased by forskolin plus dibutyryl-cAMP and IBMX, but the forskolin-induced increase in CFTR phosphorylation was inhibited by the PKA inhibitor, KT5720. Whereas KT5720 inhibited acidosis-induced ATP release from myocytes. These data suggest that skeletal muscle CFTR is activated through the cAMP/PKA pathway at low pH. RT-PCR indicated that cultured rat L6 skeletal myocytes expressed mRNA for both Cx40 and Cx43, but Cx40 was expressed only weakly in western blot, whereas Cx43 was strongly expressed. Co-immunoprecipitation results showed that CFTR and Cx43 were associated with each other in the cell membrane. A Cx43 over-expression model was

created by transfecting myocytes with a Cx43 plasmid: Cx43 over-expression was confirmed using western blot. Cx43 over-expressing myocytes released significantly more ATP than control myocytes at pH 6.8, suggesting that Cx43 may be involved in acidosis-induced ATP release, whereas silencing Cx43 expression using siRNA inhibited the acidosis-induced ATP release. Over-expression of CFTR alone did not alter ATP release from myocytes, whereas co-over-expression of CFTR with Cx43 increased ATP release significantly more than over-expression of Cx43 alone. These data suggest that Cx43 co-localises with CFTR in the myocyte membrane, and that it may be involved in ATP release during acidosis; further investigation is required to determine whether and how CFTR interacts with Cx43 to induce ATP release.

**OP8.**

**COMPARISONS OF MEASURED AND SELF-REPORTED ANTHROPOMETRIC VARIABLES AND BLOOD PRESSURE IN A SAMPLE OF HONG KONG ADULT WOMEN**

YJ Xie,<sup>1</sup> S Chan Ho<sup>2</sup>

<sup>1</sup>Division of Epidemiology and Biostatistics, School of Public Health, The University of Hong Kong; <sup>2</sup>Division of Epidemiology, The Jockey Club School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

**Objectives:** To assess the validity of self-reported weight, height, waist circumference and blood pressure by comparison with measured values in a sample of Hong Kong adult women, and to determine the extent of misclassification of body mass index (BMI) arising from differences between self-reported and measured values.

**Methods:** This pilot study was integrated in a life course study named "Hong Kong Women's Health Study" in 1253 Hong Kong female nurses aged from 35 to 65 years. A mailed self-administered questionnaire was used to collect data. The validity of self-reported weight, height, waist circumference and blood pressure was examined by inviting 144 (11.5%) participants to have their body measurements at the research centre according to the standard measurement protocol. The measured values were compared with their self-reported values to assess the validity.

**Results:** On average, there was a high correlation between the self-reported and measured anthropometric and blood pressure values (correlation coefficients ranged from 0.72 to 0.96). No significant differences were found between self-reported and measured weight and blood pressure values (all  $P > 0.05$ ). However, women tended to overestimate their height (mean

difference between self-reported and measured height: 0.42 cm,  $P < 0.05$ ) and underestimate their waist circumference (mean difference between self-reported and measured: 1.61 cm,  $P < 0.05$ ). The Kappa consistency tests all showed good consistency between the categories of the self-reported and measured BMI, waist circumference and blood pressure values, percentage of overall agreement ranging from 60% to 100%. The use of self-reported weight and height resulted in the correct classification of weight status in 85% of women.

**Conclusion:** We suggest that the self-reported height, weight, waist circumference and blood pressure measures were generally reliable in this population of Hong Kong female nurses. However it is still important to carefully consider potential biases in the interpretation of data when using self-reported indicators in epidemiological studies.

**ABSTRACTS**

Abstracts for Chaired Posters:

**CP1.**

**PPAR $\delta$  INVOLVES IN THE VASCULAR BENEFITS OF METFORMIN IN OBESE MICE**

WS Cheang, XY Tian, WT Wong, Y Huang

Li Ka Shing Institute of Health Sciences and School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong

**Objectives:** Anti-diabetic drug metformin is known to activate AMP-activated protein kinase (AMPK) which forms a transcriptional complex with PPAR $\delta$  and synergistically induces gene expression. The present study investigated whether PPAR $\delta$  is a critical mediator for metformin in ameliorating endothelial dysfunction in diet-induced obese (DIO) mice.

**Methods:** Aortae from C57BL/6J mice were cultured with endoplasmic reticulum (ER) stress inducer tunicamycin, metformin, PPAR $\delta$  antagonist GSK0660, PPAR $\delta$  agonist GW1516 or AMPK inhibitor compound C. Male PPAR $\delta$  wild-type and knockout mice were fed with high-fat diet for 3 months to induce obesity, followed by oral administration with metformin for one week. Vascular reactivity and protein levels were determined by wire myograph and Western blotting respectively. Levels of reactive oxygen species (ROS) and nitric oxide (NO) were measured by fluorescence imaging.

**Results:** Tunicamycin impaired endothelium-dependent relaxations (EDR) in response to acetylcholine, and increased the levels of ROS and ER stress markers, such as phosphorylated eIF2 $\alpha$ , ATF6 and ATF3 in mouse aortae. These harmful effects of tunicamycin were reversed by co-treatment with metformin while such benefits of metformin were abolished by GSK0660. GW1516 exerted similar beneficial effects as metformin but the benefits were unaffected by compound C. Chronic metformin treatment alleviated

EDR and reduced the levels of ROS and above-described ER stress markers in DIO PPAR $\delta$  wild-type but not in PPAR $\delta$  knockout mice. NO production in endothelial cells was also enhanced by metformin.

**Conclusions:** The present study provides novel evidence that PPAR $\delta$  is a crucial mediator in the vascular benefits of chronic metformin treatment in restoring the impaired endothelial function and curtailing ER and oxidative stress in obese mice (under revision for publication in *Atherosclerosis, Thrombosis, and Vascular Biology*).

**CP2.**

**INTERLEUKIN-6 IMPAIRS ENDOTHELIUM-DEPENDENT DILATATIONS IN MOUSE ARTERIES THROUGH INCREASING OXIDATIVE STRESS**

D Qu, J Liu, CW Lau, Y Huang

Institute of Vascular Medicine and Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, Hong Kong

**Objective:** Interleukin-6 (IL-6) is one of major pro-inflammatory cytokines involved in chronic inflammation, hence contributing to the pathogenesis of diabetes, atherosclerosis and other cardiovascular diseases. The plasma level of IL-6 rises in response to infection, vascular injury, and exercise as well. IL-6 secretion is not restricted to cells of the immune system, but also occurs in many other types of cells, including endothelial cells and vascular smooth muscle cells. Nevertheless, whether IL-6 is beneficial or deleterious in the vascular system remains debated. The present study investigates how IL-6 impacts on endothelial function in both conduit and resistance mouse arteries and its relevance in vascular pathogenesis.

**Methods and results:** Both DHE staining of mouse aortic endothelial cells and *en face* imaging of mouse aortae show that IL-6 (1 ng/ml) stimulates the production of reactive oxygen species (ROS) which reaches its maximum at 1 hour, and can be diminished by ROS scavengers, vitamin E and tempol. The ROS generation is also confirmed by chemiluminescence assay. The acute effect of IL-6 on vasoreactivity of aortae and small mesenteric arteries from C57BL/6 mice was examined. Arterial rings were suspended in wire myograph or pressure myograph for measurement of isometric force or vessel diameter. One-hour acute treatment with IL-6 (1 ng/ml) attenuates acetylcholine-

induced endothelium-dependent relaxations in aortas, and impairs flow-mediated dilatation of 2nd-order resistance mesenteric arteries. Such impairment can be reversed by ROS scavengers. Moreover, IL-6 stimulates ROS increase through NADPH oxidases. Finally, IL-6 treatment reduces nitric oxide production stimulated in primary mouse aortic endothelial cells.

**Conclusion:** IL-6 acutely impairs endothelial function in mice likely through stimulating ROS generation and thus reducing the NO bioavailability. (Supported Hong Kong GRF and CRF)

**ABSTRACTS**

Abstracts for Chaired Posters:

**CP3.**

**MECHANISTIC EFFECTS OF *LYCIUM BARBARUM* POLYSACCHARIDES AGAINST RAT HIPPOCAMPAL INJURIES INDUCED BY CHRONIC INTERMITTENT HYPOXIA**

CS Lam,<sup>1</sup> GL Tipoe,<sup>2</sup> RCC Chang,<sup>2</sup> KF So,<sup>2</sup> KH Cheung,<sup>1</sup> ML Fung<sup>1</sup>  
Departments of <sup>1</sup>Physiology and <sup>2</sup>Anatomy, The University of Hong Kong, Hong Kong

**Background:** Chronic intermittent hypoxia (CIH), highlighting clinical manifestations of obstructive sleeping apnea (OSA), induces oxidative stress, inflammation, endoplasmic reticulum (ER) stress and apoptosis in hippocampus in which regenerative mechanism is subsequently activated for repairing damages. *Lycium barbarum* polysaccharides (LBP), bioactive fraction of traditional Chinese herbal medicine Goji, are demonstrated to possess anti-oxidative and anti-inflammatory properties, and promote hippocampal neurogenesis inhibited by corticosterone.

**Objectives:** Our study aims to elucidate the mechanistic effects of LBP in CIH rats. We hypothesize that LBP attenuate oxidative stress, inflammation, endoplasmic reticulum stress, apoptosis, and facilitate hippocampal regeneration in rat exposed to CIH.

**Methods:** Adult Sprague-Dawley rats (180-200 g) were exposed to air as normoxic control (Nx) or to intermittent hypoxic treatment (IH) with normobaric oxygen content alternating between 5 to 21% 8 hr/day for 1 week. Rats were orally fed LBP solution (1 mg/kg body weight) or vehicle 2 hours prior to hypoxic treatment. Lipid peroxidation extent was measured by MDA assay. Western blot was employed to examine the expressions level of antioxidant enzymes (SOD-1, SOD-2, GPx-1); inflammatory mediators (IL-1 $\beta$ , TNF $\alpha$ , COX-2); redox sensitive transcriptional factor Nuclear factor

kappa B (NF $\kappa$ B) p65 and p50; negative regulator of NF $\kappa$ B (I $\kappa$ B $\alpha$ ); ER stress markers (GRP78/Bip, PERK and CHOP); caspase-dependent extrinsic (FADD, caspase 8, Bid) and intrinsic apoptotic (Bax, Bcl2, cytochrome C) cell death (cleaved caspase 3) cascades; endogenous cell cycles markers (PCNA); phosphorylation of survival molecule Akt (p-Akt(Ser 473)). In situ cell death staining (TUNEL) was utilized to reveal the apoptotic situation of hippocampal subfields (DG, CA1 and CA3). PCNA and BrdU DAB immunostaining were performed to demonstrate cellular proliferation in subgranular zone (SGZ) of dentate gyrus in hippocampus.

**Results:** LBP administration significantly decreased and restored, respectively, the elevated MDA level and depleted antioxidant enzymes in the hypoxic treated group. Besides, degradation of I $\kappa$ B $\alpha$ , activation and translocation of NF $\kappa$ B p65 and p50 were observed in hypoxic treated groups but were significantly inhibited by LBP pre-treatment. Additionally, LBP pre-treatment markedly attenuated ER stress sensors activated in hypoxic treated groups. The number of TUNEL positive labelled cells was found significantly increased when compared with that of controls but dramatically reduced by LBP pre-treatment. Importantly, LBP antagonized CIH-induced hippocampal cell death through mitigation of caspase mediated intrinsic and extrinsic cascades. On the other hand, the numbers of PCNA- and BrdU-positive labelled cells were elevated in hypoxic groups and were further augmented by LBP administration. Consistently, protein levels of PCNA and phosphorylated Akt were increased in the hypoxic group, which were further enhanced by LBP pre-treatment.

**Conclusion:** The anti-oxidant, anti-apoptotic and pro-regenerative properties of LBP could explain its protective effects against neurocognitive deficit induced by severe OSA conditions.

**CP4.**

**EFFECTS OF ADVANCED GLYCATION ENDPRODUCTS ON ADRENOMEDULLIN GENE EXPRESSION IN MACROPHAGES**

HK Wong, RYH Leung, BMY Cheung

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

**Objectives:** Oxidative stress can stimulate adrenomedullin (ADM) secretion and mRNA expression. One source of oxidative stress comes from the formation of advanced glycation endproducts (AGEs) from glycation reaction stimulated by hyperglycemia. This study aims to investigate whether AGEs affect ADM expression in rat macrophage cells.

**Methods:** Rat macrophage NR8383 cells were grown to confluence before experiments. The cells were stimulated by AGEs, bovine serum albumin (BSA), AGEs plus exogenous ADM or saline. The dose response and time response of AGEs treatment was investigated. Cells were harvested and RNA was extracted for measurement and analysis of *ADM* gene expression.

**Results:** *ADM* gene expression increased by an average of 16.5% after 6 hours, but the increase was independent of AGEs doses (P=0.715). Within 4 hours of AGEs treatment there was a significant trend of gene expression increase with time (P<0.01). The increase was the greatest upon 1-hour treatment by 67.8%. However the changes in *ADM* gene expression were not significantly different from those found with control treatments.

**Conclusions:** AGEs has no significant effect on *ADM* gene expression in this model, therefore the relationship between AGEs on ADM expression is yet to be proven.



**ABSTRACTS**

Abstracts for Chaired Posters:

**CP5.**

**INVOLVEMENT OF AUTOPHAGY IN THE EFFECT OF EXERCISE ON LEFT VENTRICULAR HYPERTROPHY INDUCED BY HIGH FAT DIET IN RATS**

F Wu,<sup>1</sup> R Guo,<sup>2</sup> JF Pan,<sup>1</sup> GL Tipoe,<sup>2</sup> ML Fung<sup>1</sup>

Departments of <sup>1</sup>Physiology and <sup>2</sup>Anatomy, The University of Hong Kong, Hong Kong

**Objectives:** Left ventricular hypertrophy (LVH) associated with obesity increases the morbidity and mortality of cardiovascular disease, which could be attenuated by exercise in overweight and hypertensive patients. The lysosomal degradation pathway – autophagy is reportedly mediated the beneficial effect of exercise on glucose and lipid homeostasis. The present study aimed to investigate the involvement of autophagy in the effect of exercise on LVH induced by high fat diet in rats.

**Methods:** Female adult SD rats were divided into 4 groups namely: (i) high fat diet (HFD), (ii) HFD+exercise, (iii) exercise, (iv) control. Rats in the HFD groups were orally fed with high-fat chow (30% fat) daily for 12 weeks, and rats in the exercise groups had exercise with a motorized wheel in the last 4 weeks. Noninvasive measures of systolic pressure and fat composition were assessed, respectively by tail cuff and MRI. The expression of markers for cardiac hypertrophy and the protein expression in autophagic pathway were determined by quantitative real time-PCR and western blot, respectively. Statistical significance was at  $p < 0.05$  with ANOVA analysis followed by post-hoc tests.

**Results:** Rats fed with HFD had LVH (increased heart weight and LV/RV+septum ratio) with higher levels of body weight, arterial pressures and fat composition than that of the control rat. In addition, the QTc interval and

the diameter and disarray of ventricular myocytes were significantly increased in the HFD group, supported by elevated levels of the expression of hypertrophic markers (ANP, BNP,  $\beta$ -MHC). These parameters were attenuated by exercise in the HFD-fed rats. Moreover, we found elevated levels of LC3II in the HFD heart, which were also attenuated by exercise, suggesting an involvement of autophagy in the beneficial effect of exercise. Furthermore, the expression level of AMPK $\alpha$  was also increased in the exercise groups.

**Conclusion:** We demonstrated that exercise lowers the body weight and attenuates the HFD-induced LVH in rats, which probably involves autophagy. Future studies will focus on the role of autophagy in the pathogenesis.

**CP6.**

**THE FUNCTIONAL ROLE OF TRPV4 CHANNELS IN BARORECEPTOR SENSITIVITY**

EOC Lau, CY Lo, Y Huang, X Yao

School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong

There are two major arterial baroreceptors that can detect blood pressure change in the arteries. They are the aortic (arch) baroreceptor and carotid (sinus) baroreceptors. Aortic baroreceptor detects blood pressure in the aorta. Carotid baroreceptor detects blood pressure in carotid artery, which carries the blood to the brain. Reports suggest that there are differences between these two baroreceptors in terms of their pressure sensitivity and functional role. But the results are controversial. In the present study, the properties of the two baroreceptors were investigated. It was found that aortic baroreceptor neurons were more sensitive to pressure change than carotid baroreceptor neurons. Electrophysiology studies showed that, compared to the carotid baroreceptor neurons, a higher percentage of aortic baroreceptor neurons were stretch-sensitive. Furthermore, the pressure threshold that can initiate action potential firing was found to be lower in the aortic baroreceptor neurons than in the carotid baroreceptor neurons. Uniaxial stretch-induced  $[Ca^{2+}]_i$  rise was compared between aortic and carotid baroreceptor neurons. Again, the aortic baroreceptor neurons were found to be more sensitive to stretch than the carotid baroreceptor neurons. Immunostaining experiments revealed that, compared to carotid baroreceptor neurons, a much higher percentage of aortic baroreceptor neurons were TRPV4-positive.

Consistently, the stretch-induced  $[Ca^{2+}]_i$  rise could be inhibited by RN1734, which is a potent TRPV4 channels blocker. Taken together, these results suggest that the difference in pressure sensitivity between the aortic and carotid baroreceptor neurons was probably brought about by TRPV4 channels, which are stretch-activated channels.

**ABSTRACTS**

Abstracts for Chaired Posters:

**CP7.**

**SALVIANOLIC ACID B IMPROVED ENDOTHELIUM-DEPENDENT RELAXATIONS IN DIABETIC DB/DB MICE AORTAS**

J Liu,<sup>1</sup> J Han,<sup>2</sup> HN Zhang,<sup>1</sup> Y Huang<sup>1</sup>

<sup>1</sup>School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong; <sup>2</sup>Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China

**Objective:** Diabetes is a world-wide health problem and cardiovascular disease is the leading cause of death and disability in diabetic patients. Danshen Dripping pills is widely used in China for the treatment of cardiac angina, coronary artery disease and other vascular events. But the underlying mechanism is still unclear. The major ingredients of Danshen Dripping Pills are found to be Salvianolic acid B (SAB) danshensu and protocatechuic aldehyde, among which SAB is believed to account for a substantial part of the vascular benefit. However how SAB improves vascular function remains poorly understood. The present study aims at examining the effect of SAB against diabetic vasculopathy and the possible cellular mechanism involved. **Methods:** Twelve-week old *db/db* diabetic mice were orally administrated with SAB for one week and then sacrificed. The aortae were dissected out for both functional and molecular studies.

**Results:** Acetylcholine-induced endothelium-dependent relaxations were impaired in *db/db* mice compared with non-diabetic *db/m<sup>+</sup>* mice. SAB treatment improved the impaired endothelial function in *db/db* mice and this improvement was accompanied with suppressed C-jun N-terminal kinase phosphorylation.

**Conclusion:** Both in *vivo* and *ex vivo* treatment with SAB alleviate diabetic endothelial dysfunction in *db/db* mice and this finding highlights the therapeutic potentials of SAB-containing herbs against diabetic vasculopathy.

**CP9.**

**PERIVASCULAR ADIPOSE TISSUE (PVAT) INDUCES ENDOTHELIAL DYSFUNCTION VIA PRODUCTION OF SUPEROXIDE**

P Gu, HXY Hui, A Xu

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

**Background and objective:** Perivascular adipose tissue (PVAT) has been shown to produce vasoactive substances and regulate vascular tone. The aim of this study is to investigate whether obesity induces endothelial dysfunction via PVAT and elucidate the underlying mechanisms.

**Methods:** Six-week-old C57BL/6J mice were fed with either standard chow or high fat, high cholesterol diet for 12 weeks. The obese mice were exposed to cold environment (4°C) for 6 days. The aortic rings either without or with PVAT were isolated and the endothelial-dependent relaxation (EDR) of aorta in response to acetylcholine was measured by wire myograph. The superoxide production of PVAT was determined by DHE staining and lucigenin assay.

**Results:** The EDH was reduced in the presence of PVAT, demonstrating that PVAT elicits an anti-relaxation effect to blood vessel. Following that, we sought to investigate whether this anti-relaxation activity was changed under obese condition. The EDR of aorta without PVAT were not different between lean and obese mice. However, in the presence of PVAT, the relaxation was significantly impaired in aortic artery from obese mice, suggesting obesity was accompanied by a more prominent anti-relaxation activity in PVAT. PVAT from obese mice showed increased superoxide production while the superoxide scavenger Tiron partially recovered impaired

**CP8.**

**ANTI-INFLAMMATORY EFFECT OF miR-17-3P VIA NF-κB PATHWAY IN HUMAN ENDOTHELIAL CELLS**

Y Zhang, SWS Leung, RYK Man

Department of Pharmacology & Pharmacy, The University of Hong Kong, Hong Kong

**Objective:** MicroRNAs (miRNAs) are a class of small, noncoding RNAs of ≈22 nucleotides that negatively regulate gene expression. They appear to play a role in the development/progression of many disorders, including inflammation, cardiovascular diseases and endothelial dysfunction. This study examines the role of miR-17-3p in vascular inflammation.

**Methods:** Human umbilical vein endothelial cells (HUVECs) were transfected with miR-17-3p agomir (miR-17-3p mimic) or its negative control using lipofectamine 2000. They were incubated with lipopolysaccharide (LPS, 10 ng/ml) for 16 hours to induce inflammatory reactions. The level of miR-17-3p and the expressions of IκBα, p65 and phosphorylated p65 (p-p65) were measured by qPCR and Western blotting. The amount of interleukin-8 (IL-8) and tumor necrosis factor (TNF)-α released in the culture medium was detected with ELISA kit.

**Results:** The levels of miR-17-3p, IL-8, TNF-α and p-p65 were increased following LPS stimulation. While the expression of p65 was not changed, the expression of IκBα was reduced. LPS-induced increase in IL-8 level and decrease in IκBα expression were smaller in HUVECs transfected with miR-17-3p agomir than in those transfected with the negative control.

endothelial function induced by DIO. After 6 days exposure to 4°C, DIO mice showed decreased superoxide production within PVAT and the EDR was also improved in aorta with PVAT.

**Conclusion:** PVAT has anti-relaxation effect to aorta and this effect is further enhanced in obesity which in turn induces endothelial dysfunction via increased production of superoxide.

**ABSTRACTS**

## Abstracts for Chaired Posters:

**CP10.****DO UNSATURATED FATTY ACIDS HAVE BENEFICIAL EFFECT ON REDUCTION OF STROKE RISK IN HYPERTENSIVE POPULATION?**

H Peng,<sup>1</sup> XQ Cai,<sup>2</sup> TK Tsang,<sup>3</sup> HS Shen,<sup>4</sup> XH Wu,<sup>2</sup> YB Zhou,<sup>2</sup> C Li,<sup>5</sup> BMY Cheung<sup>5</sup>

<sup>1</sup>Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou, China; <sup>2</sup>Department of Laboratory Medicine;

<sup>3</sup>Department of Surgical Oncology, Kunshan Affiliated Hospital of Nanjing University of Traditional Chinese Medicine, Suzhou, China; <sup>4</sup>School of Public Health; <sup>5</sup>Department of Medicine, The University of Hong Kong, Hong Kong

**Background:** It has been suggested that monospecific unsaturated fatty acids have potential effect on protection against stroke. Studies on the effect of different categories of fatty acids are lacking. The stroke incidence is high in hypertensive patients. Therefore, we studied the relationship between serum level of 6 categories of fatty acids and stroke incidence in hypertensive patients. **Methods:** 89 pairs including 100 men and 78 women matched by sex and age were recruited and analyzed in this study. We allowed age discrepancy within 5 years in each pair. All the patients aged from 34 to 85 years old were diagnosed with hypertension or had an average (mean of 3) blood pressure  $\geq 140/90$  mm Hg. The fatty acids used for internal standard solution were obtained from Sigma, US. All the patient serum fatty acids were methylated before concentration determination. Each concentration determination was repeated twice and percent recovery was estimated. Univariate analysis was used to identify potential confounders in the relationship between serum levels unsaturated fatty acids and stroke incidence. Conditional logistic regression for matched pair data was used to adjust for potential confounders and classical risk factors for stroke.

**Results:** Comparing participants with or without history of stroke, there were differences in educational level ( $P=0.002$ ) and occupation ( $P<0.001$ ). Participants without history of stroke had higher levels of total cholesterol ( $P<0.001$ ), triglyceride ( $P=0.041$ ), LDL ( $P=0.048$ ) and HDL ( $P=0.001$ ) compared with those with history of stroke. All the levels of 6 fatty acids were higher in participants without history of stroke compared with those with history of stroke ( $P=0.017$  for palmitoleic acid, 0.001 for palmitic acid,  $<0.001$  for linoleic acid,  $<0.001$  for behenic acid,  $<0.001$  for nervonic acid and 0.002 for lignoceric acid). Before adjustment, the stroke incidence was inversely associated with the levels of fatty acids except lignoceric acid ( $P=0.160$ ). After adjustment for education and occupation, the levels of palmitoleic acid ( $P=0.102$ ) and palmitic acid ( $P=0.094$ ) were no longer inversely associated with the stroke incidence. After further adjustment for systolic blood pressure, smoking, drinking, total cholesterol and triglyceride, the inverse associations of linoleic acid (OR=0.965, 95%CI=0.942-0.990,  $P=0.005$ ), behenic acid (OR=0.778, 95%CI=0.664-0.939,  $P=0.009$ ), nervonic acid (OR=0.323, 95%CI=0.121-0.860,  $P=0.024$ ) with stroke incidence were still highly significant.

**Conclusion:** In this cross-sectional study, the levels of all the fatty acids except lignoceric acid were inversely associated with the stroke incidence. Our results raise the possibility that unsaturated fatty acids may have beneficial effect on reduction of stroke risk in hypertensive population.

**CP11.****VITAMIN D PROTECTS VASCULAR FUNCTION IN DIET-INDUCED OBESE MICE**

Z Gao, HN Zhang, J Liu, WS Cheang, L Wang, Y Huang

Institute of Vascular Medicine and School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong

The health benefits of vitamin D are increasingly recognized. Vitamin D protects the cardiovascular function although the detailed cellular mechanisms remain largely unclear. Our previous study demonstrates an endothelial cell protective benefit of calcitriol, an active form of vitamin D in arteries from hypertensive rats and humans and in estrogen-deficient rats.

**Objectives:** This study aims at investigating the potential beneficial effects of calcitriol in high fat diet-induced obese mice.

**Methods:** Glucose metabolism and insulin sensitivity were tested by oral glucose and insulin tolerance test. Acetylcholine-induced endothelium-dependent relaxation (EDR) in aortae were measured by wire myograph, flow-dependent vasodilatations in resistance mesenteric arteries were measured by pressure myograph. Fluorescence imaging determined the levels of reactive oxygen species (ROS) in human umbilical vein endothelial cell (HUVEC) under confocal microscope.

**Results:** After four-month feeding on high fat diet, mice became obese with impaired metabolic and vascular function. Four-week treatment with calcitriol via intraperitoneal injection improves glucose metabolism and insulin sensitivity, restores the impaired EDR in response to acetylcholine in aortas and flow-dependent vasodilatations in resistance mesenteric arteries of obese mice. This benefit is accompanied by marked reduction in the level of reactive oxygen species (ROS) in the vascular wall and in endothelial

cells. Ex vivo study demonstrates that calcitriol can reverse ROS production induced by endoplasmic reticulum (ER) stress inducer and high glucose (30 mM) in HUVEC and this effect is antagonized by selective human vitamin D receptor antagonist, TEI-9647. Calcitriol also rescues the endothelial function that is impaired by ER stress inducer.

**Conclusions:** We thus provide the first line of evidence that calcitriol is effective in restoring both metabolic and vascular functions in obese mice, adding additional health benefit of vitamin D.

**ABSTRACTS**

Abstracts for Posters:

**P01.**

**BMP4 UPREGULATES PDGF-AA EXPRESSION: RELEVANCE TO ENDOTHELIAL DYSFUNCTION**

WN Hu, JY Luo, L Wang, CW Lau, Y Huang

Institute of Vascular Medicine and Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, Hong Kong

Bone morphogenetic protein 4 (BMP4) stimulates superoxide anion production and exerts pro-inflammatory effects in blood vessels. However, the underlying mechanisms by which BMP4 mediates endothelial dysfunction, hypertension and diabetes remain partly understood. The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are major angiogenic regulators and are involved in arteriosclerosis, hypertension and diabetes, although their relations to BMP4 signaling are unclear. The present study shows that BMP4 treatment up-regulates the expression of PDGF-AA and PDGFR $\alpha$  in human umbilical vein endothelial cells, which was reversed by the BMP4 antagonist noggin and ROS scavenger, tiron plus DETCA. Furthermore, PDGF-AA can stimulate ROS generation in endothelial cells and in mouse arteries as measured by DHE fluorescence imaging and lucigenin fluorescence assay. Functional studies show that treatment with PDGF-AA attenuates acetylcholine-induced endothelium-dependent relaxations in mouse aortas and exaggerates endothelium-dependent contractions in L-NAME-treated rat renal arteries. Pharmacological inhibition with COX-2 and ROS ameliorates PDGF-induced impairment of the relaxations. The present results indicate that ROS probably mediates PDGF-induced harmful effects on endothelial function and PDGF may be involved in BMP4-induced endothelial dysfunction. Since BMP4 is one of the important common initiators of vascular dysfunction in hypertension and diabetes, inhibiting PDGF-mediated actions in blood vessels might be effective in helping control vascular events in hypertension and diabetes (Supported by Hong Kong GRF and CRF).

**P03.**

**cGMP AND PROTEIN KINASE G REGULATE HYPERTROPHY OF HUMAN EMBRYONIC STEM CELL-DERIVED CARDIOMYOCYTES – POSSIBLE ROLE OF ORAI1?**

Y Wang, XQ Yao

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

Cardiac hypertrophy is initially compensatory, but it ultimately leads to heart failure. An increasing amount of evidence suggests that cyclic guanosine 3', 5'-monophosphate (cGMP) and its effector kinase, protein kinase G (PKG), play an important role in modulating cardiac hypertrophy and remodeling and exert cardioprotective effect through the regulation of calcium handling upstream. Store-operated calcium entry (SOCE) can be induced in cardiomyocytes and is a potential mechanism that is involved in cardiac hypertrophy. ORAI1 is the pore-forming subunit of the calcium release-activated calcium (CRAC) channel. This prompts us to study the cGMP/PKG regulation of SOCE/ORAI1 activity with respect to cardiac hypertrophy. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) have great promise for tissue repair and as a potential human-based in vitro cardiomyocyte model system for studying cardiac physiology and pathophysiology. The majority of hESC-CM initially resembles immature human cardiomyocytes. However, the signaling pathways involved in their growth have not yet been fully characterized. In this study, we will expose hESC-CMs to hypertrophic stimuli such as phenylephrine (PE) to build up a novel in vitro test system and focus on hypertrophic response of hESC-CMs.

**P02.**

**NITRIC OXIDE AND PROTEIN KINASE G ACTS ON TRPV4-TRPC1-K<sub>Ca</sub>1.1 COMPLEX TO INHIBIT 11,12-EET-INDUCED VASCULAR VASCULAR RELAXATION**

P Zhang, Y Ma, X Ma, XQ Yao

School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong

**Objective:** To explore the mechanism of nitric oxide (NO) inhibition on epoxyeicosatrienoic acids (EETs)-induced smooth muscle hyperpolarization and relaxation.

**Approach and Results:** Co-immunoprecipitation studies demonstrated that TRPV4 (vanilloid transient receptor potential channel 4), TRPC1 (canonical transient receptor potential channel 1), and K<sub>Ca</sub>1.1 (large conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels) physically interact with each other to form a TRPV4-TRPC1-K<sub>Ca</sub>1.1 complex in porcine coronary artery smooth muscle cells. Arterial tension measurement and sharp microelectrode methods showed that 11,12-EET-induced membrane hyperpolarization and vascular relaxation were markedly reduced by treatments that inhibit the activity of K<sub>Ca</sub>1.1, TRPV4, or TRPC1. S-nitroso-N-acetylpenicillamine (SNAP) and 8-Br-cGMP exert an inhibitory influence on the 11,12-EET-induced membrane hyperpolarization and vascular relaxation. The inhibitory action of SNAP and 8-Br-cGMP was markedly reduced by treatments that suppress the protein kinase G (PKG) phosphorylation on TRPC1. Similar results were also obtained in human embryonic kidney 293 (HEK293) cells that over-expressed with TRPV4, TRPC1 and K<sub>Ca</sub>1.1.

**Conclusions:** This study uncovers a novel mechanism by which NO inhibits the action of EETs. We found that NO-cGMP-PKG inhibits the 11,12-EET-induced smooth muscle cell hyperpolarization and vascular relaxation by acting on the TRPC1 component within the TRPV4-TRPC1-K<sub>Ca</sub>1.1 complex.

**P04.**

**THE USE OF HEALTH BELIEF MODEL IN PROMOTING CARDIOVASCULAR HEALTH**

SY Yau,<sup>1</sup> PL Fung,<sup>1</sup> YL Cheung<sup>2</sup>

<sup>1</sup>Open University of Hong Kong, <sup>2</sup>Tuen Mun Hospital, Hong Kong

**Background:** Medical models have been dominated in the treatment of cardiovascular diseases. However, the application of medical models limited the intertwining of various components of health such as socio-cultural factors. Health Belief Model (HBM) has been widely applied as a conceptual framework to study health behavior. It is a well-known model and has been tested in many different situations. HBM is supported to explain the change and maintenance of health behaviors. The objective of this study is to explore the current literature in applying HBM in promoting cardiovascular health.

**Methods:** A systematic search on multiple databases was conducted using keywords "health belief model", "cardiovascular", "heart", "cardiac". The results were reviewed and summarized.

**Results:** The review of studies suggested that limited studies had applied HBM in studying health behavior in promoting cardiovascular health. Majority of the studies focused on promoting self-care of heart failure patients, knowledge among individuals on cardiovascular health, medication adherence of patients with cardiovascular diseases, the relationship between demographic features and cardiovascular health, and preventive behavior among individuals.

**Conclusion:** Although HBM is supported to be widely applicable in health behavior studies. The result of this study addressed the limited use of HBM in promoting cardiovascular health. In order to promote cardiovascular health, the use of HBM as conceptual framework in further studies is suggested.

**ABSTRACTS**

Abstracts for Posters:

**P05.**

**EMP4 – A POTENTIAL POTASSIUM ION CHANNEL?**

L Sun, YW Tjong, XQ Yao

Li Ka Shing Institute of Health Sciences and School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong

Nonspanins are characterized by a large N-terminal extracellular domain and nine putative transmembrane domains. This evolutionarily conserved family comprised four members in mammals. Human EMP4 protein, which belongs to the superfamily member 4, has been found to be expressed in human metastatic melanoma cells, where EMP4 play an important role in tumour cannibal activity. EMP4 are also required for phagocytosis in *S2 Drosophila* cells. However, it is not clear which ion can pass through this channel and its functional role in mammalian cells. To answer these questions, we firstly examined the subcellular localization of human EMP4 protein in HEK293 cells and tissue distribution in rat. Then, whole-cell patch clamp was applied to investigate its electrophysiological properties. Here, we report some preliminary data. (1) Raising polyclonal antibodies against human EMP4 derived from rabbit. (2) We found that EMP4 is abundantly expressed in rat heart, kidney, liver and aorta tissues using western blot and immunohistochemistry. (3) EMP4 is mainly localized in the late endosome and Golgi body and a small part localized in early endosome in HEK293 cells by immunostaining. (4) Whole-cell currents were recorded in HEK293 cells. The results demonstrated that the over-expression of EMP4 resulted in an electrical current, which was inhibited by a broad-spectrum K<sup>+</sup> channel inhibitor Ba<sup>2+</sup>, but could not blocked by chloride channel blocker SITS, suggesting that EMP4 could be a potential K<sup>+</sup>-selective ion channels. (5) In

order to visualize compartmentalized EMP4 activity in plasma membrane microdomains, we targeted EMP4 to plasma membrane using different lipid modification domains for further functional study. Overall, our data indicates that EMP4 could be a potential potassium selective channel which mainly localized in the late endosome and Golgi body in HEK293 cells and abundance expression in kidney and heart. Further investigation needs to do to explore its function.

**P06.**

**INVOLVEMENT OF CALCIUM/CALMODULIN-DEPENDENT KINASE II IN THE REGULATION OF VASCULAR TONE IN PORCINE CORONARY ARTERIES**

DKY Yeung, Q Pu, RYK Man, SWS Leung

Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

**Objectives:** Inhibition of calcium/calmodulin-dependent kinase II (CaMKII) has been shown to reduce vascular contraction and relaxation. The present study examined the role of CaMKII in the different signaling pathways involved in the regulation of vascular tone.

**Methods:** Isolated porcine coronary arteries were incubated in organ chamber for the measurement of isometric tension. They were contracted with cumulative additions of contracting agents, potassium chloride and the thromboxane A<sub>2</sub> analogue, U46619, or contracted with U46619 (30 nM) followed by cumulative additions of different relaxing agents, in the presence or absence of the CaMKII inhibitor, KN-93.

**Results:** Inhibition of CaMKII by KN-93 (30 μM) significantly inhibited contractions to potassium chloride (10-70 mM) and U46619 (0.1 nM-1 μM) in porcine coronary arteries without endothelium. While endothelium-dependent nitric oxide (NO)-mediated relaxations to bradykinin (0.1 nM-1 μM) were significantly inhibited by KN-93, endothelium-dependent hyperpolarization (EDH)-mediated relaxations were not affected. On the other hand, KN-93 inhibited endothelium-independent relaxations to levromakalim (adenosine triphosphate-sensitive potassium channel opener; 0.1 nM-100 μM), but not those to sodium nitroprusside (NO donor; 0.1 nM-100 μM).

**Conclusions:** Our data suggested that CaMKII in both the endothelium and smooth muscle of porcine coronary arteries plays a role in the regulation of vascular tone. In the smooth muscle, CaMKII contributes to contraction likely via mechanisms downstream of increases in intracellular calcium concentration. It is also involved in the activation of adenosine triphosphate-sensitive potassium channels leading to vascular relaxation. In the endothelium, CaMKII appears to play a role in the release of NO, but not the induction of EDH, for relaxation. (This study was supported by the Small Project Funding of the University of Hong Kong Research Grant).

**ABSTRACTS**

Abstracts for Posters:

**P07.**

**THE EFFECT OF ASTRAGALUS MEMBRANACEUS ON PATHOLOGICAL ANGIOGENESIS**

WY Liu,<sup>1</sup> KKW Auyeung,<sup>2</sup> JKS Ko,<sup>2</sup> RYK Man,<sup>1</sup> SWS Leung<sup>1</sup>

<sup>1</sup>Department of Pharmacology and Pharmacy, Faculty of Medicine, The University of Hong Kong; <sup>2</sup>Center for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong

Abnormality of angiogenesis can contribute to several pathologic processes including atherosclerosis and cancer. Different bioactive components of *astragalus membranaceus* (huangqi), a commonly used herb in traditional Chinese medicine, exert different effects on the angiogenesis of human cancer cells and endothelial cells. Therefore, the effect of *astragalus membranaceus* and its active components on angiogenesis under different pathological conditions were investigated. Human umbilical endothelial cells (HUVECs) and human colon cancer cell HCT 116 were used for *in vitro* studies. The effect of *astragalus membranaceus* on proliferation were examined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The results indicated that the viabilities of HUVECs treated with astragalus saponin (0.1 to 25 µg/ml), astragaloside IV (0.01 to 100 µM) and calycosin (1 to 200 µM) for 24-72 hours were not significantly different from the control group (without any treatment). Astragalus saponin and astragaloside IV, at the same concentrations as used in HUVECs, also did not affect the viability of HCT 116 cells, while the highest concentration of calycosin (200 µM) inhibited the growth of HCT 116 cells. The angiogenic potential of these components of *astragalus membranaceus* are examined in both

HUVECs [under the stimulation of phorbol myristate acetate (PMA), a protein kinase C activator] and HCT 116 cells by wound healing migration assay and tube formation assay, in order to identify the influence of *astragalus membranaceus* and its components on pathological angiogenesis.

**P08.**

**IDENTIFICATION OF ALTERED PLASMA PROTEINS BY PROTEOMIC STUDY IN VALVULAR HEART DISEASES AND THE POTENTIAL CLINICAL SIGNIFICANCE**

G Gao,<sup>1</sup> C Xuan,<sup>2</sup> Q Yang,<sup>1,3</sup> XC Liu,<sup>2</sup> ZG Liu,<sup>2</sup> GW He<sup>1,4</sup>

<sup>1</sup>TEDA International Cardiovascular Hospital & The Affiliated Hospital, Hangzhou Normal University, Tianjin & Hangzhou, China; <sup>2</sup>TEDA International Cardiovascular Hospital, Tianjin, China; <sup>3</sup>Department of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong; <sup>4</sup>Department of Surgery, Oregon Health and Science University, Portland, Oregon, U.S.A.

**Objectives:** Little is known about genetic basis and proteomics in valvular heart disease (VHD) including rheumatic (RVD) and degenerative (DVD) valvular disease. The present proteomic study examined the hypothesis that certain proteins may be associated with the pathological changes in the plasma of VHD patients.

**Methods and Results:** Differential protein analysis in the plasma identified 18 differentially expressed protein spots and 14 corresponding proteins or polypeptides by two-dimensional electrophoresis and mass spectrometry in 120 subjects. Two up-regulated (complement C4A and carbonic anhydrase 1) and three down-regulated proteins (serotransferrin, alpha-1-antichymotrypsin, and vitronectin) were validated by ELISA in enlarging samples. The plasma levels (n=40 for each) of complement C4A in RVD (715.8±35.6 vs. 594.7±28.2 ng/ml, P=0.009) and carbonic anhydrase 1 (237.70±15.7 vs. 184.7±10.8 U/L, P=0.007) in DVD patients were significantly higher and that of serotransferrin (2.36±0.20 vs. 2.93±0.16 mg/ml, P=0.025) and alpha-1-antichymotrypsin (370.0±13.7 vs. 413.0±11.6 µg/ml, P=0.019) in RVD

patients were significantly lower than those in controls. The plasma vitronectin level in both RVD (281.3±11.0 vs. 323.2±10.0 µg/ml, P=0.006) and DVD (283.6±11.4 vs. 323.2±10.0 µg/ml, P=0.011) was significantly lower than those in normal controls.

**Conclusions:** We have for the first time identified alterations of 14 differential proteins or polypeptides in the plasma of patients with various VHD. The elevation of plasma complement C4A in RVD and carbonic anhydrase 1 in DVD and the decrease of serotransferrin and alpha-1-antichymotrypsin in RVD patients may be useful biomarkers for these valvular diseases. The decreased plasma level of vitronectin – a protein related to the formation of valvular structure – in both RVD and DVD patients might indicate the possible genetic deficiency in these patients.

## **List of Reviewers 2013**

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