ABSTRACTS

Abstracts for Posters:

P01.

VASODILATING EFFECTS OF ADTM, A NOVEL DERIVATIVE OF DANSHENSU AND TETRAMETHYLPYRAZINE

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Danshen (Radix *salviae miltiorrhizae*) and ChuanXiong *(Ligusticum wallichii)* are two herbal medicines which are widely used in treating cardiovascular diseases. The active components in Danshen is Danshensu (DSS) while that in ChuanXiong is tetramethylpyrazine (TMP). Recently, we have synthesized a novel chemical called ADTM, which is a synthetic dimer of TMP and DSS, in which the hydroxyl groups on DSS are acetylated for enhancing its chemical stability. In this study, the effect of ADTM on the dilation of rat mesenteric arteries was investigated.

The results showed that the rat mesenteric arteries were dilated by ADTM in a dose-dependent manner, with an IC_{50} value of 133±1.3 μM. The vasodilating effect of ADTM was more potent than DSS, TMP and the combination of DSS and TMP. The ADTM-induced vasodilation was not affected upon the removal of endothelium. Moreover, the vasodilating effect of ADTM was not reduced by L-NAME (a nitric oxide synthase inhibitor) and ODQ (a soluble guanylyl cyclase inhibitor). In addition, the vasodilating effect of ADTM was not reduced by SQ 22536 (an adenylate cyclise inhibitor), indicating that adenylate cyclase/cAMP-dependent pathway was not involved. The ADTM-induced vasodilation was not linked to potassium channels since the effect of ADTM was not reduced by iberiotoxin (a big conductance Ca^{2+}-activated K^+ channel blocker), glibencalmide (a ATP-sensitive K^+ channel blocker), 4-aminopyridine (a voltage-activated K^+ channel blocker), barium chloride (an inward rectifier K^+ channel blocker) and tetraethylammonium (a non-specific K^+ channel blocker). In contrast, the potassium chloride-induced and calcium chloride-induced contractions were attenuated by 65.6±4.0% and 43.4±4.1%, respectively, by 100 μM ADTM, reflecting that the vasodilating effect of ADTM might be the result of blockade of Ca^{2+} channels in the vascular smooth muscle cells.

In summary, our study demonstrated that ADTM is a novel vasodilator, which probably works by blocking the voltage-dependet Ca^{2+} channels in the vascular smooth muscle cells. The vasodilating effect of ADTM is stronger than its parent compounds DSS and TMP.

P02.

A SINGLE NUCLEOTIDE POLYMORPHISM OF INTERLEUKIN-6 GENE IS RELATED TO PLASMA ADRENOMEDULLIN LEVELS

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Objective: Plasma adrenomedullin (ADM) level is elevated in inflammation and is associated with cardiovascular diseases. Single nucleotide polymorphisms (SNPs) in the *ADM* gene have been found to be associated with ADM level. The 5'-flanking region of *ADM* is known to contain a consensus sequence of the binding site for the nuclear factor for interleukin-6 (*IL-6*). Therefore, we investigated if plasma ADM level is related to SNPs in the *IL6* gene.
Methods: Plasma ADM level was measured in 476 subjects (236 men, 240 women; mean age 50.9±10.8 years) in the Hong Kong Cardiovascular Risk Factor Prevalence Study-2 (CRISP2). The subjects were genotyped for three tagging SNPs in the *IL-6* gene.
Results: The minor allele frequencies of the *IL-6* SNPs rs17147230, rs1800796 and rs2069837 were 41.8%, 20.0% and 15.4% respectively. The SNP rs17147230, was associated with plasma ADM level after adjusting for age and sex (β=-0.096, P=0.034). The association was significant in women (β=-0.115, P=0.021) but not in men. Amongst all subjects, plasma ADM level decreased with an increasing number of minor alleles of rs17147230 in multivariate analysis (P=0.034). Compared to subjects with AA genotype, subjects with TT genotype had a plasma ADM level 12.8% lower (95% CI: 0.6%-23.5%, P=0.041).
Conclusion: Plasma ADM level is related to the SNP rs17147230 in *IL-6* gene, and the association appears stronger in women. The effect of the polymorphism on inflammation and cardiovascular disease remains to be determined.

ABSTRACTS

Abstracts for Posters:

P03.

UPREGULATED TRPM2 AND ITS POTENTIAL ROLE IN NEOINTIMAL HYPERPLASIA

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A hallmark in atherosclerosis is progressive intimal thickening, which leads to occlusive vascular disease such as myocardial infarction and stroke. A causation of neointimal hyperplasia is the migration and proliferation of smooth muscle cells, in which reactive oxygen species (ROS) play an important role. This study was designed to investigate the involvement of TRPM2, a member of the transient receptor potential superfamily, in neointimal hyperplasia. Neointimal hyperplasia of rat femoral artery was induced by cuff placement. The TRPM2 expression and ROS generation were detected. The effect of TRPM2 inhibitors on neointimal hyperplasia of cultured human saphenous veins, and on proliferation and migration of primary rat aortic smooth muscle cells was further examined. It was found that arteries with cuff placement for 14 days showed distinct intimal thickening. The neointima area displayed an enhanced cell cycle activity and upregulated TRPM2 expression. ROS generation was dramatically increased in the neointima and media layer of arteries after cuff placement. After culture for 14 days, the human saphenous veins clearly showed neointimal hyperplasia, which was markedly reduced by *in vitro* treatment with TM2E3, a specific TRPM2-blocking antibody, or 2-aminoethoxydiphenyl borate, a chemical blocker. Both TM2E3 and 2-aminoethoxydiphenyl borate inhibited hydrogen peroxide-induced proliferation and wound-induced migration in primary rat aortic smooth muscle cells. These results suggest that TRPM2 is involved in neointimal hyperplasia and that blocking TRPM2 could be a way to prevent vascular wall thickening.

P04.

ENDOTHELIUM-DEPENDENT AND DIRECT RELAXATION INDUCED BY TOTAL FLAVONOIDS OF ELSHOLTZIA SPLENDENS IN RAT THORACIC AORTA

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Objective: To explore the vasoactive effects of total flavonoids of Elsholtzia splendens (TFES) and its underlying mechanisms on the rat thoracic aorta.
Methods: The tension in isolated ring preparations of thoracic aortas from Sprague-Dawley rats was measured isometrically. The NO synthase (NOS) activity of isolated ring preparations was measured by NOS kits.
Results: TFES (5-200 μg/ml) caused a concentration-dependent relaxation on endothelium-intact rings precontracted by phenylephrine (PE, 10^{-6} M) or a high level of K^+ (6×10^{-2} M). This vasorelaxation was not abolished but reduced significantly by removal of endothelium. N^{ω}-nitro-L-arginine methyl ester hydrochloride (L-NAME) (10^{-4} M), 1H-[1,2,4] oxadiazolo[4,2-α] quinoxalin-1-one (ODQ) (5×10^{-4} M) significantly inhibited the effect of TFES. Meanwhile, aortic NOS activity in TFES group was markedly elevated versus the control. However, indomethacin did not alter TFES effect. Tetraethylammonium, $BaCl_2$ and 4-aminopyridine also did not alter the vascular effect of TFES, but glibenclamide significantly attenuated its vasodilation. TFES reduced PE-induced transient contraction in Ca^{2+}-free Krebs-Henseleit solution, and the accumulative Ca^{2+}-induced contraction.
Conclusion: It is concluded that TFES induces both endothelium-dependent and independent relaxation in rat thoracic aorta. NO/cGMP-mediated pathway is likely involved in the endothelium-dependent relaxation, whereas inhibition of voltage-dependent Ca^{2+} channel, receptor-operated Ca^{2+} channel, intracellular Ca^{2+} release and activation of K_{ATP} contribute in part to the endothelium-independent relaxation.
Acknowledgement: This study was supported by grants from the Department of Science and Technology of Zhejiang Province, China (2011C23105, 2012C33088).

ABSTRACTS

Abstracts for Posters:

P05.

EFFECTS OF HYPOOSMOLARITY ON CANONICAL TRANSIENT RECEPTOR POTENTIAL 5 ACTIVITY IN RAT AORTIC ARCH BARORECEPTOR NEURONS

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Aortic arch baroreceptor is a major arterial baroreceptor which plays an essential role in regulation of arterial blood pressure. Yet the molecular identity of the aortic arch baroreceptor sensor remains unclear. Canonical Transient Receptor Potential 5 (TRPC5) is a member of the seven mammalian TRPC cationic channels respond to mechanical stress including hypoosmolarity. It was found that TPRC5 is expressed in aortic arch baroreceptor neurons. We examined the hypothesis that TPRC5 was involved in pressure sensing in baroreceptor neurons. Whole-cell patch clamping study was performed on the cultured rat nodose baroreceptor neurons isolated from the left nodose ganglion. Gadolinium ion (Gd^{3+}, 20 µM) was included in the bath solution to potentiates TRPC5 activity and to block other cation channels. A whole-cell cationic current was substantially increased in hypotonic condition (240 mOsm) when compared with isotonic condition (300 mOsm). Pretreatment of anti-TRPC5 blocking antibody T5E3 (15 µg/ml) abolished the hypoosmolarity-activated current, whereas perimmmune IgG (15 µg/ml) had no effect. To further verify the mechanosensitivity of TRPC5, the nodose ganglion neurons were transiently tranfected with TPRC5 (6 mg/ml) by electroporation. Hypoosmolarity stimulated a whole-cell cation current in TRPC5-overexpressing neurons. Pretreatment of TRPC5 inhibitor 2-aminoethoxydiphenyl borate (2APB, 100 µM, 10 min) markedly reduced this whole cell current. Taken together, these results suggest that TRPC5 is involved in mechanosensing at the aortic arch baroreceptor.

P06.

THE FUNCTIONAL ROLE OF TRPM2 CHANNELS IN H_2O_2-INDUCED CA^{2+} INFLUX AND CELL APOPTOSIS IN H5V ENDOTHELIAL CELLS

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Melastatin-like transient receptor potential channel 2 (TRPM2) is an oxidant-sensitive cationic non-selective channel that is expressed in mammalian vascular endothelium. I used murine heart microvessel endothelial cell line H5V to investigate the role of TRPM2 channels in H_2O_2-induced Ca^{2+} responses and apoptosis. A TRPM2 blocking antibody channel (TM2E3), which targets the E3 region near the ion permeation pore of TRPM2, was developed. Treatment of H5V cells with TM2E3 reduced the Ca^{2+} responses to H_2O_2. Suppressing TRPM2 expression using TRPM2-specific short hairpin RNA (shRNA) had similar inhibitory effect in H_2O_2-induced Ca^{2+} responses. H_2O_2-induced apoptotic cell death in H5V cells was examined using MTT assay, DNA ladder formation analysis, and DAPI-based nuclear DNA condensation assay. Based on these assays, TM2E3 and TRPM2-specific shRNA both showed protective effect on H_2O_2-induced apoptotic cell death. In contrast, overexpression of TRPM2 in H5V cells increased the Ca^{2+} responses to H_2O_2 and aggravated the apoptotic cell death in response to H_2O_2. These findings strongly suggest that the TRPM2 channel mediates Ca^{2+} overload in response to H_2O_2 and contributes to oxidant-induced apoptotic cell death in vascular endothelial cells. I also examined the downstream cascades of TRPM2 activation and explored whether caspase-3, -8 and -9 were involved in this process. My data indicates that H_2O_2-induced cell apoptosis through both intrinsic and extrinsic apoptotic pathways, leading to activation of caspases-3. Furthermore, TRPM2 played an essential role in the process. Together, my data suggest that TRPM2 mediates H_2O_2-induces endothelial cell death and that down-regulating endogenous TRPM2 could be a means to protect the vascular endothelial cells from apoptotic cell death.

ABSTRACTS

Abstracts for Posters:

P07.

FUNCTIONAL ROLE OF VANILLOID TRANSIENT RECEPTOR POTENTIAL 2 CHANNEL IN HUMAN INDUCED PLURIPOTENT STEM-CELL MODEL OF HUTCHINSON GILFORED PROGERIA SYNDROME

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Hutchinson-Gilford Progeria syndrome (HGPS) is a severe genetic disorder characterized by premature aging including skin, musculoskeletal cardiovascular systems. However, the pathogenesis of HGPS is unknown. Vanilloid transient receptor potential channels (TRPV) are calcium-permeable non-selective cation channels that act as cellular sensor respond to osmolarity, membrane stretch which thought to be related to cardiovascular diseases. The aim of our present study is to examine the expression and functional role of TRPV channels in Induced pluripotent stem cells derived endothelial-like cells (iPSC-ECs) from HGPS patient. Semi-quantitative RT-PCR revealed that the relative expression of TRPV2 in HGPS-iPSC ECs was significantly higher than that in control IMR90-iPSC ECs. We then examined the possible functional role of TRPV2. Then we applied the hypotonic osmotic solution to iPSC-ECs while measuring intracellular calcium ($[Ca^{2+}]_i$). Perfusion of hypotonic solution caused transient $[Ca^{2+}]_i$ elevation in both groups and $[Ca^{2+}]_i$ rise was sustained in HGPS-iPSC ECs. General cation channel blocker ruthenium red (20 μM) and specific TRPV2 channel inhibitor Transilast (100 μM) markedly attenuated hyptonicity-induced $[Ca^{2+}]_i$ elevation in HGPS-iPSC ECs. Taken together, these results suggested that up-regulated TRPV2 in HGPS-iPSC ECs is involved in elevation of $[Ca^{2+}]_i$ by osmotic pressure changes.

P08.

EFFECTS OF VITAMINS K_2 AND D_3 ON BONE MATRIX MINERALIZATION OF OSTEOBLASTS OF OBESE/ DIABETIC (*db*$^+$/*db*$^+$) MICE

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Background and Objective: Patients with Type 1 and Type 2 diabetes mellitus (DM) have a higher risk of bone fractures, particularly at the hip. Previous studies suggested that both altered leptin level and calcium homeostasis are responsible for type 2 DM-associated osteoporosis. This study was designed to assess the effects, *in vitro*, of vitamin K_2 and vitamin D_3, applied alone or in combination, on osteoblasts (bone building cells).
Methods: C57BL/KsJ (female; 4-6 months old) lean/control (*db*$^+$/*m*$^+$) and obese/diabetic (*db*$^+$/*db*$^+$) (leptin receptor-deficient) mice were used. Osteoblasts harvested from the iliac crests (both left and right) were cultured and randomly assigned into control (drug-free) and drug treated groups (vitamin K_2 and vitamin D_3 (1 and 10 nM), alone or in combination, for 7, 14 and 21 days) for the determination of osteoblasts differentiation and mineralization (alkaline phosphatase activity and calcium-sensing receptor (CaSR) levels).
Results: ALP activity and protein expression of CaSR were significantly lower in osteoblasts of *db*$^+$/*db*$^+$ mice compared to *db*$^+$/*m*$^+$ mice. Vitamin K_2 and vitamin D_3 caused a concentration- and time-dependent increase of CaSR levels and ALP activities, with a greater magnitude of increase was detected when both vitamins were applied in combination, in osteoblasts of both strains of mice.
Conclusion: Our results indicate that ALP activity and CaSR expression were lower in osteoblasts of *db*$^+$/*db*$^+$ mice compared to *db*$^+$/*m*$^+$ mice. More importantly, vitamin K_2 and vitamin D_3, when applied in combination, enhanced mineralization of osteoblasts of both strains of mice with a greater magnitude of increase was observed in *db*$^+$/*db*$^+$ mice.
Acknowledgement: Provision of post-graduate studentship to Miss CCW Poon by the School of Biomedical Sciences (The Chinese University of Hong Kong) is acknowledged.

ABSTRACTS

Abstracts for Posters:

P09.

FLUOXETINE-INDUCED CARDIAC DEPRESSION IN ISOLATED PERFUSED RAT HEART

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Introduction: Fluoxetine is a widely used antidepressant compound and its action is primarily attributed to selective serotonin reuptake inhibitor (SSRI) in the central nervous system. SSRI drugs had been believed to cause fewer cardiovascular side effects. However, there are an increasing number of case reports on dysrhythmias, such as atrial fibrillation or bradycardia. Since an intracellular Mg^{2+} concentration ([Mg^{2+}]i) should be maintained within a relatively narrow concentration range in order to ensure the proper functioning of the heart, Mg^{2+} is often lost from cardiac cells during the development of heart disease, which may exacerbate the damage caused by disease. Our objective was to investigate an effect of fluoxetine on cardiac functions and to investigate alteration of Mg^{2+} homeostasis.
Materials and Methods: Left ventricular development pressure (LVDP), maximum velocity of the change in pressure (dP/dtmax), minimum velocity of the change in pressure (dP/dtmin), heart rate (HR) and Mg^{2+} efflux ([Mg^{2+}]e) were measured simultaneously in isolated rat hearts with Langendorff's perfusion system. [Mg^{2+}]i was measured using Mag-fura 2 AM in H9c2 cell. The activation of ERK 1/2 was analyzed by Western blot. Electrocardiogram in anesthetic rats was recorded using a BIOPAC® system.
Results: Fluoxetine produced reversible dose-dependent decreases in the LVDP, dP/dtmax and dP/dtmin in the perfused hearts of rat. After wash out, [Mg^{2+}]e was significantly increased, accompanied by decreases in HR. In H9c2 cells, fluoxetine produced significant activation of ERK 1/2 and a dose-dependent increase in the [Mg^{2+}]i, which were inhibited by pretreatment of PD98059, an ERK 1/2 inhibitor. Phosphorylated-ERK 1/2 in isolated hearts were increased by treatment of fluoxetine. Fluoxetine caused change of ECG including prolongation of PR, R-R and QT interval.
Conclusions: Fluoxetine can produce cardiac depression partly through an increase in [Mg^{2+}]i and [Mg^{2+}]e accompanied by the activation of ERK 1/2.

P10.

RELATION OF HYPOTHERMIA AND MAGNESIUM IN HEART

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Introduction: Deep hypothermia (4°C) is widely used in conjunction with cardioplegia to minimize neurologic and cardiac damage during cardiac surgery. However, during the subsequent rewarming and reperfusion many destructive processes result in inevitable post-ischemic myocardial injuries due to Ca^{2+} overload. Mild hypothermia (core temperature 30-35°C) has been shown to protect the beating rabbit heart against infarction and donor hearts from pig kept in a beating state under mild hypothermia (32-34°C) showed improved recovery of metabolic and mechanical functions compared with traditional cold storage. To ensure the proper function of the heart, intracellular Mg^{2+} concentrations ([Mg^{2+}]i) should be maintained within a relatively narrow concentration range because Mg^{2+} plays a vital role in the mechanical and electrical properties of the heart. Our aim was to investigate Mg^{2+} regulation in heart during mild hypothermia (30°C to 35°C).
Materials and Methods: [Mg^{2+}]i, intracellular Na^{+} concentration ([Na^{+}]i), total Mg efflux ([Mg]e) and extracellular signal-regulated kinases 1/2 (ERK 1/2) were measured in isolated papillary muscle, cardiac cell and perfused heart from guinea-pig during mild hypothermia.
Results: In beating papillary muscle of the guinea pig, [Mg^{2+}]i was significantly increased by hypothermia (34°C and 30°C), accompanied by an increase in [Na^{+}]i, a large positive inotropic effect, depolarization of membrane potential and prolongation of action potential duration. In addition, mild hypothermia enhanced the increase in [Mg^{2+}]i induced by high extracellular Mg^{2+} concentration ([Mg^{2+}]o). The rate of [Mg]e in perfused heart was significantly attenuated by hypothermia. Free [Mg^{2+}]o provoked the activation of ERK1/2 in cardiac cells, which was attenuated at 30°C compared to that at 37°C.
Conclusions: These results suggested that the mild hypothermia could produce an increase in [Mg^{2+}]i in guinea-pig heart by stimulation of Mg^{2+} influx and attenuation of Mg^{2+} efflux, accompanied by attenuation of ERK1/2 activation.
(Mun-Young Lee, Sei-Jin Lee equally contributed to this study.)

ABSTRACTS

Abstracts for Posters:

P11.

EFFECT OF BLOOD MAGNESIUM AND CALCIUM BY FORCED HYPER- AND HYPO-VENTILATION

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Introduction: It was well-known that respiratory change alters blood pH, $PaCO_2$, HCO_3, and many ions level including phosphorus, potassium and calcium. Although some researches had investigated total magnesium during hyperventilation or hypoventilation, magnesium ion (Mg^{2+}) has been given little attention compared with potassium and calcium ion. Magnesium exists in biological fluids in the ionized and nonionized form, of which only former has physiological activity. In the present study, we attempted to determine the values of blood ionized Ca^{2+} (iCa^{2+}), Mg^{2+} (iMg^{2+}), and the ratio of iCa^{2+}/iMg^{2+} during the change of respiration in anesthetized rats.

Materials and Methods: Hyperventilation induced by increase 2 times in tidal volume and respiratory rate during 10 min in anesthetized rats (male Sprague-Dawley, 200-250 g). Hypoventilation induced by decrease 1/2 times in tidal volume and respiratory rate during 10 min in anesthetized rats. Blood samples were obtained before and after operation and were analyzed whole blood ions using Nova Stat Profile 8 CRT (NOVA Biomedical Corp, Waltham, MA, USA) including the blood pH, blood gas compositions and the concentrations of ionized Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+} and lactate. Hematocrit (Hct) was measured by conductivity. The concentration of HCO_3^- was calculated using the Henderson-Hasselbach equation. The anion gap values were calculated by the formula; [Na^+-(Cl^-+HCO_3^-)].

Results: After hyperventilation, the blood pH, glucose, lactate, partial O_2 tension (PO_2), O_2 saturation (O_2sat; $P<0.05$), alveolar O_2 (A), partial O_2 tension/fraction of inspired O_2 (PO_2/FI), iCa^{2+}, and iMg^{2+} were significantly increased ($P<0.01$, n=11, paired *t*-test). The blood partial CO_2 tension (PCO_2), total CO_2 (TCO_2), HCO_3^-, base excess of extracellular fluid (BE-ECF), base excess of blood (BE-B), and iCa^{2+}/iMg^{2+} were significantly decreased ($P<0.01$), although the blood osmolarity (Osm), Hct, hemoglobin (Hb), O_2 content (O_2ct), arterial alveolar O_2 tension ratio (a/A), Na^+, and K^+ were not significantly changed. After hypoventilation, the blood pH, lactate, PO_2, O_2ct, O_2sat, A, a/A, and iCa^{2+}/iMg^{2+} were significantly decreased ($P<0.01$, n=12). The blood glucose, PCO_2, TCO_2, HCO_3^- ($P<0.05$), and iMg^{2+} were significantly increased ($P<0.01$), although the blood Osm, Hct, Hb, Na^+, K^+, and iCa^{2+} were not significantly changed.

Conclusions: These data suggest that the change of respiration could alter blood iMg^{2+}, iCa^{2+} and the ratio of iCa^{2+}/iMg^{2+} and both hyperventilation and hypoventilation increased in iMg^{2+} accompanied with decreasing in the ratio of iCa^{2+}/iMg^{2+}.

(Mun-Young Lee, Sei-Jin Lee equally contributed to this study.)

P12.

SODIUM-RESTRICTED DIET FOR HEART FAILURE PATIENTS: AN UPDATE

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Introduction: Heart failure is a common cardiovascular disease with high morbidity and mortality rates. In Hong Kong, the number of deaths due to heart failure was 817 in year 2010. Also, heart failure remains one of the primary reasons for hospital admission and readmission. The American Heart Association recommends sodium-restricted diet for health failure patients and research supported that sodium-restricted diet prevents worsening of the heart failure condition. The objective of this study is to provide an update on the effects of sodium-restricted diet on heart failure patients.

Methods: Search of literature was conducted with multiple databases. Literature related to the effects of sodium-restricted diet on heart failure patients were reviewed and summarized.

Results: Research supported that patients who consumed sodium-restricted diets (less than 3 g/day) showed lower symptoms burdens related to the disease such as shortness of breath, swelling of legs or ankles, and difficulty in sleeping. With the compliance of diet recommendation, heart failure patients demonstrated a decreased rate of hospital admission and readmission, and a longer cardiac event-free survival than those who did not follow the diet recommendation. Nevertheless, sodium-restricted diet improved the severity of sleep apnea caused by fluid retention among heart failure patients.

Conclusion: Sodium-restricted diet is recognized to be positively associated with clinical health outcomes in heart failure patients. Thus, the therapeutic importance of sodium-restricted diet in heart failure patients is supported.

ABSTRACTS

Abstracts for Posters:

P13.

NITRIC OXIDE INHIBITS 11,12-EET INDUCED PORCINE CORONARY ARTERIAL HYPERPOLARIZATION AND RELAXATION

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Objective: The vascular endothelial cells synthesize and release vasodilators such as Nitric oxide (NO) and epoxyeicosatrienoic acids (EETs). In normal physiological state, NO inhibits EETs-mediated vascular relaxation. In this study, we examined the molecular target of EETs and explored the mechanism of NO inhibition on EETs in isolated porcine small coronary arterial segments without endothelium.

Methods and Results: Co-immunoprecipitation and immunohistochemistry studies demonstrated that TRPV4 (vanilloid transient receptor potential channel 4), TRPC1 (canonical transient receptor potential channel 1), and BK_{Ca} (large conductance Ca^{2+}-activated K^+ channels) physically interact with each other to form TRPV4-C1-BK_{Ca} tri-complex. Isometric force measurement and sharp microelectrode methods showed that 11,12-EET induced relaxation and membrane hyperpolarization in porcine small coronary artery, which were markedly reduced by treatments that inhibit the activity of TRPV4, TRPC1, or BK_{Ca}. 11,12-EET-induced relaxation and membrane hyperpolarization were inhibited by 8-Br-cGMP and NO donor S-nitroso-N-acetylpenicillamine (SNAP). This action was markedly reduced by treatments that suppress the protein kinase G phosphorylation on TRPC1.

Conclusion: This study uncovers a novel mechanism by which NO inhibits the action of EETs. We found that 11,12-EET acts on TRPV4-C1-BK_{Ca} complex to induce VSMC hyperpolarization and vascular relaxation in porcine small coronary artery, and that NO-cGMP-PKG inhibits 11,12-EET-induced membrane hyperpolarization by acting on TRPC1 component within the TRPV4-C1-BK_{Ca} complex.

P14.

A LOW AST-TO-ALT RATIO PREDICTS NEW-ONSET DIABETES IN PATIENTS TREATED WITH ATORVASTATIN: RESULTS FROM THE TREATING TO NEW TARGETS [TNT] TRIAL)

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Introduction: Features of the metabolic syndrome such as baseline fasting glucose, body mass index, hypertension, and fasting triglycerides, are independent risk factors for new-onset diabetes (NOD) in patients with statin therapy. As non-alcoholic fatty liver disease has been recognized as the hepatic manifestation of the metabolic syndrome, this study investigated whether hepatic markers can predict NOD in patients with statin therapy.

Methods: A total of 7,595 patients without prevalent diabetes at baseline from the Treating to New Targets (TNT) study were included in this analysis. In TNT, patients were randomized to atorvastatin 10 or 80 mg/day and followed for a median of 4.9 years. The associations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and AST/ALT ratio at baseline with NOD were investigated.

Results: Among 7,595 patients, 659 developed NOD during the follow-up. Patients with NOD had significantly higher ALT level (17.14±6.69 vs 15.78±5.94 U/l, $P<0.001$) and lower AST/ALT ratio (0.94±0.25 vs 1.02±0.28, $P<0.001$) at baseline than those without NOD. In multivariate analysis, a lower AST/ALT ratio was an independent predictor of NOD, in addition to higher fasting glucose, higher body mass index, higher white blood cell count, and hypertension. The hazard ratios (95% CI) were 0.82 (0.67-0.99), 0.75 (0.60-0.93), and 0.75 (0.59-0.96), respectively, in patients with AST/ALT ratio in quartiles 2, 3, and 4, compared to those in quartile 1.

Conclusion: AST/ALT ratio at baseline is predictive of NOD in patients with statin therapy. Further studies are needed to investigate whether this ratio can be used as a biomarker to monitor the NOD risk in patients taking statin therapy.