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PLENARY LECTURES

1.

DIABETES MELLITUS IS ASSOCIATED WITH HYPERREACTIVITY OF SMOOTH MUSCLE CELLS DUE TO ALTERED SUBCELLULAR CA^{2+} DISTRIBUTION IN THE HUMAN UTERINE ARTERY

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Alterations of vascular smooth muscle function have been implicated in the development of vascular complications and circulatory dysfunction in diabetes mellitus. However, little is known on changes in smooth muscle contractility and the intracellular mechanisms contributing to such altered responsiveness in blood vessels from diabetic patients. Thus, smooth muscle reactivity to increased K^+, norepinephrine (NE) and phenylephrine (PE) and acetylcholine-induced endothelium-dependent relaxation were assessed in uterine arteries from control individuals (CI) and diabetic patients (DM). Smooth muscle sensitivity to K^+, NE and PE was enhanced by 1.4-, 2.3- and 9.7-fold and relaxation was reduced by 64% in vessels from DM. In addition, in freshly isolated smooth muscle cells from DM an increased perinuclear Ca^{2+} signaling to K^+ (30 mmol/l: +73%; 30 mmol/l: +68%) and NE (300 nmol/l +86%; 10 µmol/l +67%) was found, which promotes smooth muscle contraction. In contrast, subplasmalemmal Ca^{2+} response, which favors smooth muscle relaxation due to activation of Ca^{2+}-activated K^+ channels, was reduced by 38% in DM, indicating a significant change in the subcellular Ca^{2+} distribution in vascular smooth muscle cells during diabetes. In contrast to the altered Ca^{2+} signaling found in freshly isolated cells from DM, in cultured smooth muscle cells isolated from CI and DM no further difference in the Ca^{2+} signaling to stimulation with either K^+ or NE was found. Hence, production of superoxide anions ($ïO^{2-}$) in intact and endothelium-denuded arteries from DM was increased by 150 and 136%, respectively. Incubation of freshly isolated smooth muscle cells from CI with the $ïO^{2-}$ generating system xanthine oxidase/ hypoxanthine mimicked the effect of DM on subcellular Ca^{2+} distribution in a SOD-sensitive manner. From these findings, we conclude that during diabetes mellitus, smooth muscle reactivity is increased due to changes in subcellular Ca^{2+} distribution upon cell activation. Increased $ïO^{2-}$ production seems to play a crucial role in the alteration of smooth muscle function.

2.

THE PROBLEMS IN THE USE OF HERBAL AND NATURAL SUSTANCES, WITH SPECIFIC EXAMPLE CONCERNING THE CARDIOVASCULAR SYSTEM

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Cardiovascular medicine is a fast moving field. During the last few decades, advances in our understanding of the physiology, pathology and pharmacology of the cardiac and vascular systems have been both stunning and overwhelming. In the meanwhile, the use of drugs in the treatment of cardiovascular diseases has experienced exponential growth. The awareness of side effects of synthetic drugs has led to the exploration of the use of natural or traditional medicine. What is needed is to bring together modern medicine and natural or traditional medicine. This presentation attempts to provide an example of how natural medicine can play a role in a new development in cardiovascular science. PHF, parathyroid hypercytocalcic factor, is a newly discovered hormone closely related to low-renin salt-sensitive hypertension. Our recent studies discovered a natural substance preparation which acts as a natural PHF antagonist. However, the use of natural medicine is currently experiencing a creditability problem. This presentation will also describe solutions to the problematic issues in natural medicine.

PLENARY LECTURES

3.

HEART VALVE REPLACEMENT SURGERY: PAST, PRESENT AND FUTURE

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This abstract summarizes a 40 year evolution of heart valve replacement surgery. In the late 1950s, the only surgery performed on a valve was a closed mitral valvotomy. The first successful valve replacements with the Starr-Edwards caged ball valve in 1960 were a milestone in the advancement of heart surgery. Operative mortality for the first mitral series decreased steadily from 50% in 1960 to near 0 within 5 years. Regression analysis showed that long-term survival was related to intrinsic patient preoperative characteristics. Other milestones in the advancement of heart surgery were the development of the aortic homograft, the Bjork-Shiley valve, the Hancock porcine valve, the St. Jude valve, pericardial and stentless valves. Porcine valves show a wide variation in structural failure among series, ranging from 55% to 90% and 50% to 80% at 10 years in the aortic and mitral positions, respectively. Increased patient age has an important effect on failure rates. Thromboembolism rates among series with a particular valve type vary greatly due to non valve-related factors. Valvular thrombosis is a relatively rare complication, and the majority of biological valve series have none, especially in the aortic position. Infection rates for most series are below l% per year, for both positions and classes of valves. There has been significant progress in diminishing operative mortality and enhancing long-term survival over the past 4 decades. Late complication rates are approximately similar with all valve types. The future will require more durable tissue valves and safer anticoagulation for mechanical valves, and perhaps less invasive surgery.

4.

A NEW STRATEGY IN THE TREATMENT OF HEART FAILURE - RESULTS FROM THE MERIT-HF TRIAL

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It has been well known for many years that betablockers exert antiischemic, antiarrhythmic effects and reduce sudden death in ischemic heart disease. Nevertheless cardiologists have been reluctant to use betablockers in patients with congestive heart failure mainly for two reasons: Inotropic stimluation was thought to be a more rational treatment in heart failure and there was widespread fear that betablocker treatment might harm the patient. Hesitance persisted despite several reports on improvement of myocardial function in heart failure both from idiopathic dilated cardiomyopathy and ischemic heart disease. The only way to overcome the sceptic attitude was to perform large scale placebo-controlled trials with emphasis on both mortality, morbidity and tolerability. Until 1999 no such study had enough statistical power to prove effect on survival although metanalysis of the smaller studies indicates a marked reduction in both mortality and morbidity. A study in dilated cardiomyopathy with metoprolol showed that heart transplantation was prevented. The rationale for betablocker treatment is thought to be reduction in energy demand in combination with increased blood supply due to lengthening of diastolic phase. This may lead to reduction in hibernation and stunning resulting in functional recovery of myocardium and reversed remodeling as shown in most studies. Additionally antiproliferative, antioxidant and antiapoptic effects may prevent ongoing deterioration due to celldeath. The first large survival trial with betablockers, the CIBIS II trial, with a mixed population of ischemic and nonischemic patients NYHA class II and IV showed a 34 % reduction in all cause mortality and 44 % reduction in sudden cardiac death. The study did not achieve enough power to show reduction in death due to congestive heart failure. The MERIT-HF trial included 3991 patients from 14 different countries in two continents, with approximately 50 % more patients than the CIBIS II trial. MERIT-HF trial also included NYHA class II patients. The target dose was 200 mg metoprolol per day in addition to baseline therapy with ACE-inhibitors. An average dose of 159 mg metoprolol was reached. Overall mortality was reduced by 34 %, cardiovascular mortality by 38, sudden death by 41 % and death due to congestive heart failure by 49 %. The treatment effect was consistent in pre-defined subgroups such as males and females, elderly compared to younger, ischemics versus nonischemics, diabetics versus nondiabetics, low versus high ejection fraction, low versus high blood presssure and low versus high heart rate and different NYHA classes. Sudden death was the dominating cause of death in NYHA class II and III. There was a 25 % ($p = 0.08$) reduction in number of patients withdrawn from study due to heart failure and fewer patients developed heart failure. Ten percent fewer patients were withdrawn from the metoprolol group compared to placebo (NS). All cause mortality and hospitalisation due to heart failure was reduced by 31 %. There was a significant improvement in NYHA class and quality of life score. **In conclusion:** The MERIT-HF trial confirmed that metoprolol reduces morbidity and mortality significantly with an excellent tolerability. Combination therapy with betablockers and ACE-inhibitors, and in more severe heart failure also spirolactone, should therefore be mandatory in modern heart failure treatment.

ABSTRACTS

1.

INHIBITION OF STRESS-ACTIVATED PROTEIN KINASE BY MAGNESIUM TANSHINOATE (MTB) IN ISOLATED RAT HEART

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Heart disease is the second leading cause of death in Hong Kong and Mainland China. The activation of stress-activated protein (SAP) kinase has been observed in myocardial ischemia/reperfusion. Extracts or purified compounds from Radix Salviae Miltiorrhiza (RSM) have been used to treat heart disease. Magnesium tanshinoate B (MTB) is an active ingredient isolated from RSM. The objective of this study is to elucidate the mechanism by which MTB regulates SAP kinase activity. The Langendorff isolated rat heart used as a model system for study. When isolated hearts were subjected to global ischemia and reperfusion, SAP kinase activity was increased by 50-70% when compared to nonischemic control. Maximum elevation in kinase activity was achieved when subjected to 30 minutes ischemia. In contrast, perfusion with 1.4μM MTB prior to ischemia/reperfusion completely abolished the elevation in SAP kinase activity. It was further determined that MTB directly inhibited the phosphotransferase activity of SAP kinase. A 50% inhibition of SAP kinase activity was obtained in the presence of 1.4μM MTB. At this concentration, there was no effect on p38 MAP kinase activity that was also activated by ischemia/reperfusion. In summary, the results indicate that MTB has a direct inhibitory effect on SAP kinase and this effect may be specific.

2.

NITRIC OXIDE INHIBITS VASODILATION CAUSED BY cAMP-DEPENDENT AGONISTS OR MUSCLE CONTRACTIONS IN THE DOG SKELETAL MUSCLE CIRCULATION

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The role of nitric oxide in the control of the skeletal muscle circulation was investigated using the vascularly-isolated, constant-flow-perfused gracilis muscle of the anaesthetised dog. Vascular responses were compared in the absence or presence of L-NAME, an inhibitor of NO synthase, with or without an excess of L-arginine. L-NAME infusion increased the muscle arterial perfusion pressure by about 50%, and simultaneous infusion of excess L-arginine returned the perfusion pressure to a value similar to the precontrol. The vasodilator response to gracilis muscle contractions was significantly enhanced in the presence of L-NAME. The degree of enhancement was similar whether the muscle contracted at a low (0.5 Hz) or high (2 Hz) frequency, and whether the muscle was perfused at low (100% resting) or high (200% resting) blood flow. These data suggest that endogenous nitric oxide release helps to maintain the resting blood flow, but inhibits the vasodilator response during muscle contractions, and that the effects of nitric oxide are unrelated to the oxygen supply-to-demand ratio in the muscle. We hypothesised that nitric oxide inhibits the portion of the exercise vasodilation that is mediated by cAMP-dependent vasodilators such as adenosine, since cGMP (which would be formed in the presence of nitric oxide) can activate some forms of phosphodiesterase. We compared the effects of L-NAME on some cAMP-dependent and some cAMP-independent agonists. The responses to the cAMP-independent vasodilators, papaverine or sodium nitroprusside, were not significantly different in the presence or absence of L-NAME infusion. However, the responses to the cAMP-dependent vasodilators, isoproterenol or adenosine, were significantly enhanced in the presence of L-NAME, and that enhancement was abolished by the simultaneous infusion of an excess of L-arginine. These data support the suggestion that nitric oxide limits the vasodilator response to muscle contractions by inhibition of the actions of cAMP-dependent vasodilators.

3.

THE ROLE OF PROTEIN KINASE C AND PHOSPHODIETERASE ON CYCLIC AMP ACCUMULATION UPON κ-OPIOID RECEPTOR STIMULATION IN RAT VENTRICULAR MYOCYTES

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The present study attempted to determine the role of protein kinase C (PKC) on cyclic AMP (cAMP) accumulation upon κ-opioid receptor (OR) stimulation in rat ventricular myocytes. U50,488H, a selective κ-OR agonist, decreased forskolin-stimulated cAMP accumulation dose-dependently, effects which PMA, a PKC agonist, mimicked. The effects of the agonist, that were blocked by nor-binaltorphimine, a selective κ-OR antagonist, were significantly antagonized by PKC inhibitors, staurosporine and chelerythrine. To determine the role of phosphodiesterase (PDE), the effects of U50,488H and PMA on cAMP production and PDE activity upon blockade of PDE were studied. The inhibitory effects of U50,488H and PMA on cAMP production were significantly attenuated by 1 mM IBMX, a PDE inhibitor. U50,488H also stimulated PDE activity, which was abolished by a specific PKC antagonist, 1 mM chelerythrine or 1 mM IBMX. The observations suggest that PKC may enhance cAMP degradation through activating PDE upon κ-OR stimulation. To further identify the PDE isozyme mediating the effect of PKC upon κ-OR stimulation, the effect of U50,488H and PMA on cAMP production and/or PDE activity were observed in the presence of MIBMX, a selective PDE-I inhibitor, or rolipram, a selective PDE-IV inhibitor. 10 mM rolipram abolished, while 100 mM MIBMX did not affect, the inhibitory effects of U50,488H and PMA. Moreover, 10 mM rolipram also significantly attenuated the stimulatory effects on PDE activity upon κ-OR and PKC activation. The results indicate that PDE-IV may mediate the action of PKC upon κ-OR stimulation (Supported by a RGC grant).

4.

INHIBITORY EFFECTS OF 17β-ESTRADIOL ON VASOCONSTRICTION

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Estrogen has profound beneficial effects on the cardiovascular system in women, reducing the risk of hypertension, coronary heart disease and stroke. Estrogen has been also found to have a direct relaxant effect on vasculature. The present study aimed to examine the role of endothelium and other factors in 17 β-estradiol-induced relaxation in both rat aorta and mesenteric arteries. The contractile force was measured by force transducers. It was found that 17 β-estradiol induced an endothelium-independent relaxation in rat mesenteric arteries while it caused both endothelium-dependent and -independent relaxation in rat aorta contracted with phenylephrine or with U46619. NG--Nitro-L-arginine (L-NAME; 100 μM) and methylene blue (3-10 μM), attenuated 17 β-estradiol-induced relaxation in aortic rings. The effect of L-NAME was partially reduced by pretreatment of 3 μM L-arginine, the nitric oxide precursor. Pretreatment of tissues with putative K^+ channel blockers such as tetrapentylammonium ions (3 μM) or iberiotoxin (100 nM) also reduced the estrogen-induced relaxation. Tamoxifen (10 μM), a partial antagonist, inhibited 17 β-estradiol-induced relaxation in aortic tissues. In addition, 17 β-estradiol also inhibited the contractile response to high K^+ (30 mM) or to activation of protein kinase C with active phorbol ester in the absence of extracellular Ca^{2+}. These results indicate that there may exist a differential distribution of functional estrogen receptors in conduit and small-sized arteries. Nitric oxide appears to be partially involved in 17 β-estradiol-induced aortic relaxation. Besides, 17 β-estradiol may interfere with Ca^{2+} influx and protein kinase C-mediated cellular pathway to cause vasodilatation (supported by HKRGC).

5.

EFFECTS OF TRILINOLEIN ON SUPEROXIDE DISMUTASE ACTIVITY AND MRNA IN CULTURED AORTIC SMOOTH MUSCLE CELLS

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Background: Oxygen free radicals are considered to be intimately involved in the development of atherosclerosis, and antioxidants may help to protect against this kind of damage. We tried to use a lipophilic antioxidant, trilinolein, to evaluate the effects on superoxide dismutase (SOD) activity and mRNA in cultured aortic smooth muscle cells (SMC). **Methods and Results:** Trilinolein, a triglyceride purified from the traditional Chinese medicinal plant *Panax pseudoginseng*, is a lipophilic antioxidant. The effects of trilinolein on the activity and gene expression of SOD in cultured SMC (A7r5) were evaluated. Different concentrations (1, 0.5, 1.0 μM) of trilinolein were incubated with A7r5 for short-term (2 days) and long-term (7 days) evaluation, and the mRNA level of SOD was measured by Northern blotting. The activity of SOD and SOD-mRNA levels were increased in rat A7r5 after two days of incubation with 0.1 μM trilinolein.. However, these levels were not affected by higher concentrations of trilinolein (1 uM). In contrast, both the activity of SOD and SOD-mRNA levels were reduced in a dose-dependent manner after seven days of incubation. **Conclusions:** The present study emphasized the importance of optimal dosage in supplementation with antioxidant, trilinolein, and it could be a scavenger of oxygen free radicals in A7r5.

6.

EFFECTS OF β_3-ADRENOCEPTOR ACTIVATION IN ISOLATED PULMONARY ARTERY AND AORTA OF SPONTANEOUSLY HYPERTENSIVE AND WISTAR-KYOTO RATS

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Adult pulmonary circulation is a low-resistance, low-pressure system. The autonomic nervous system may modify pulmonary blood flow under physiological conditions and may be involved in the pathophysiology of pulmonary vascular diseases. Based on the pharmacological and molecular biology techniques, four subtypes of β-adrenoceptors (β-AR) (β_1-, β_2-, β_3- and β_4-AR) have been identified in various tissue preparations. In this study, we examined the effects of a range of selective β_3-AR agonists on isolated pulmonary artery (PA) and thoracic aorta (A) of spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats (male, age: 14-18 wks). Isometric tension changes of endothelium-intact PA (resting tension (RT) = 10 ± 1 mN) and A (RT = 15 ± 1 mN), pre-contracted with 1 μM phenylephrine (plus 1 μM indomethacin), in response to individual β_3-AR agonists was recorded and compared. Cumulative application of β_3-AR agonist to PA and A of WKY rats produced a concentration-dependent (10 nM to 0.1 mM) relaxation with the relative order of the inhibitory potency of BRL 37344 > (±)-pindolol ≥ (±)-CGP 12177A >> CL 316243 (n = 5-7). A significantly smaller degree of vasorelaxation elicited by BRL 37344, (±)-pindolol and (±)-CGP 12177A was observed in PA and A of SHR whereas CL 316243 failed to produce relaxation in PA. β_3-AR agonist-mediated relaxation of PA and A (both SHR and WKY) was abolished in the presence of SR 59230A (0.3 μM, a selective β_3-AR antagonist). On the other hand, the presence of glibenclamide (3 μM), an ATP-sensitive K^+ channel blocker, significantly attenuated the β_3-AR agonist-mediated vasorelaxation of PA and A. In conclusion, these results suggested that β_3-ARs are present in PA and A and we have demonstrated, for the first time, that β_3-AR-mediated vasorelaxation involved the activation of ATP-sensitive K^+ channels and could be modified by the hypertensive state of the vasculatures. **Acknowledgements:** A gift of CGP 12177A from Dr. B. Willi (Novartis, Switzerland), CL316243 from Dr. A.P. Rifkind (American Home Products Corp., U.S.A.), SR 59230A from Dr. L. Manara (Sanofi, Italy) and the assistance from Ms. K.Y. Tam & M.Y. Tse & Mr.Y.H. Man & T.L. Ko are acknowledged.

7.

VASODILATING EFFECTS OF PRANIDIPINE ON ISOLATED PULMONARY ARTERY AND AORTA OF SPONTANEOUSLY HYPERTENSIVE AND WISTAR-KYOTO RATS

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The aim of pharmacological therapy for pulmonary hypertension is to induce pulmonary vasodilatation, thereby elevating systemic blood flow, and to reduce the workload of the right ventricle. However, most of the currently used Ca^{2+} antagonists have not been demonstrated to successfully achieve this goal. In this study, we evaluated the vasodilating effect of pranidipine (OPC-13340), a newly-developed 1,4 dihydropyridine Ca^{2+} channel antagonist in isolated pulmonary artery (PA) and thoracic aorta (A) of spontaneously hypertensive (SHR) and Wistar-Kyoto normotensive (WKY) rats (female, age: 22-26 wks). Isometric tension changes of endothelium-intacted PA (resting tension (RT) = 10 ± 1 mN) and A (RT = 15 ± 1 mN), pre-contracted with 1 μM phenylephrine (plus 1 μM indomethacin), in respond to pranidipine was recorded. For comparison, two other Ca^{2+} channel antagonists verapamil and nifedipine were also examined. Cumulative application of pranidipine elicited a concentration-dependent relaxation of pre-contracted PA (IC_{20} = 3.57 ± 1.71 μM, maximum response = 32 ± 4.5 %) (n = 6) and A (IC_{20} = 0.09 ± 0.07 μM, maximum response = 56 ± 2.2 %) (n = 3) of WKY rats. In SHR, pranidipine caused a significant greater vasodilating effect plus a decrease in the IC_{20} (PA; IC_{50} = 0.17 ± 0.1 μM, maximum response = 53 ± 5.4 %, n = 3; A; IC_{20} = 0.02 ± 0.01 μM, maximum response = 98 ± 3.7 %, n = 3). A similar enhancement of the vasodilating effect was observed in PA and A of SHR in the presence of verapamil. When endothelium was removed, the vasorelaxing effects of pranidipine and verapamil observed in SHR and WKY were not significantly different from each other. In contrast, the hypertensive state and endothelium denudation had no apparent effect on nifedipine-mediated vasorelaxation in both PA and A preparations. **Acknowledgements:** A gift of pranidipine from Dr. K. Toide (Otsuka Pharmaceuticals Co., Japan) and the assistance from Ms. K.Y. Tam & M.Y. Tse & Mr.Y.H. Man & T.L. Ko (candidates of Work Attachment for Sixth Formers 99, CUHK) are acknowledged.

8.

LONG TERM EFFECTS OF CARDIAC REHABILITATION PROGRAMME ON THE QUALITY OF LIFE OF PATIENTS AFTER MYOCARDIAL INFARCTION OR CORONARY ANGIOPLASTY

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Objective: This study is to evaluate the long term effects of cardiac rehabilitation programme (CRP) on the quality of life (QOL) of post-myocardial infarction (MI) or percutaneous transluminal coronary angioplasty (PTCA) patients. **Methods:** 276 patients (210 males; mean age = 65 ± 11) were randomly assigned to receive either an intensive exercise and educational programme at cardiac rehabilitation centre (by a multidisciplinary approach of 5 hrs/week for 8 weeks) (CRP group) or conventional therapy (Control group) at a ratio of 2:1. Serial assessments on QOL were performed for all patients at baseline, immediate after exercise (phase 2), 6 months after exercise (phase 3) and 18 months after exercise (phase 4). **Results:** The two groups were similar with respect to age and gender distributions. In the CRP group, significant improvements in the 7 out of 8 SF-36 parameters, including physical functioning ($p < 0.001$) and role ($p < 0.001$), bodily pain ($p = 0.016$), vitality ($p < 0.001$), social functioning ($p < 0.001$), emotional role ($p = 0.001$) and mental health ($p = 0.004$), were observed at the end of phase 2. For psychological symptoms, they were less anxious ($p = 0.003$), less depressed ($p = 0.039$) and more friendly ($p = 0.010$). The impact of the illness to their life appeared to be less ($p = 0.032$) as there were less frequent ($p = 0.003$) and less severe ($p = 0.001$) cardiovascular symptoms reported in the study group. For the control group, there were only improvements in SF-36 (4 out of 8 areas) in phase 2. At the end of 18 months after CRP, the improvements in the CRP group were largely maintained while the control group also had improvements in most of the QOL parameters, except on psychological status. **Conclusions:** Cardiac rehabilitation programme improves QOL of patients with AMI or PTCA greater and much faster than conventional therapy. These benefits are maintained at least 18 months after the programme. Therefore exercise and educational programme should be recommended for these patients.

9.

EXPRESSION AND CLONING OF CNG1 CHANNEL IN VASCULAR ENDOTHELIAL CELLS

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Ca^{++} entry in vascular endothelium is a key signal triggering the formation of NO, which subsequently acts on neighboring smooth muscle cells and causes vasorelaxation and a decrease in blood pressure. Entry of Ca^{++} in vascular endothelium is mediated by Ca^{++}-permeable nonselective cation channels (NSC). However, the molecular identities of these nonselective cation channels in vascular cells are not known. The aim of this study is to examine whether rod-type nucleotide-gated nonselective cation channel (CNGl), a channel which has been molecularly cloned, is related to the nonselective cation channels in vascular cells. Our RT-PCR results indicate that the CNGl mRNA is expressed in vascular endothelial cells. Northern blot analysis demonstrated abundant presence of CNGl mRNA in cultured endothelial cells. In situ hybridization was performed to further explore the cellular localization of CNGl mRNA in mesenteric arteries with internal diameter ranging from 100μm to lmm. The antisense CNGl probe yielded strong labeling in the endothelium layer but no labeling in tunica media layer which is composed of many smooth muscles and fibroblasts. Since CNGl mRNA is a a Ca^{++}-permeable nonselective cation channels, the abundant presence of CNGl mRNA implicates a possible involvement of CNGl protein in a Ca^{++} influx in vascular endothelium. An attempt was made to clone CNGl channel by PCR-cloning. Eight PCR fragments covering the full coding region of CNGl gene were successfully amplified. Comparison of one amplified PCR product with known human CNGl gene revealed a region containing 7 amino acid difference, suggesting the existence of an alternative spicing form of CNG1 in endothelial cells.

10.

FREQUENCY OF ANGIOTENSIN-CONVERTING ENZYME GENOTYPES IN HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

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Objective: Hypertension, left ventricular hypertrophy (LVH) and angiotensin-converting enzyme homozygous deletional (DD) genotype are all cardiovascular risk factors which, if present together, may confer especially high risk. We and others previously reported a decrease with age in the prevalence of the DD genotype in hypertensive patients, which may be due to decreased survival. In this study, we hypothesise that there might be fewer patients with the DD genotype among patients with hypertensive LVH. **Design and Methods:** 102 normal healthy controls and 70 hypertensive patients were studied. LVH was determined by echocardiography in hypertensive patients. DNA was extracted from peripheral leucocytes and amplified by PCR using specific primers. Insertion (I) or deletion (D) alleles were identified after electrophoresis of PCR products.

n	DD	ID	II	D	I	
Normal controls	102	22%	32%	46%	0.38	0.62
Hypertensives	70	14%	37%	49%	0.33	0.67
without LVH	33	24%	36%	39%	0.42	0.58
with LVH	37	5%*	38%	57%	0.24**	0.76

*$\chi^2 = 4.4$, $p = 0.04$ **$\chi^2 = 5.2$, $p = 0.02$

Results: The left ventricular mass index (LVMI) in hypertensive patients with DD, ID and II genotypes were (mean + SE) 111 ± 6, 115 + 5 and 136 ± 8 g/m2 respectively ($p = 0.03$). **Conclusion:** The lower prevalence of the DD genotype in hypertensive patients with LVH and the lower LVMI in hypertensive DD patients may be due to increased cardiovascular mortality in patients with hypertension, LVH and DD genotype.

11.

RANDOMISED PLACEBO-CONTROLLED TRIAL OF THE EFFECT OF FOSINOPRIL ON LEFT VENTRICULAR MASS IN UNTREATED HYPERTENSIVE PATIENTS

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Objective: Left ventricular hypertrophy is a powerful predictor of cardiovascular morbidity and mortality. We tested the hypothesis that fosinopril, an angiotensin-converting enzyme inhibitor, reduces left ventricular mass in hypertensive patients. **Design and Methods:** 54 patients (M:F, 34: 20; age 48 ± 14 yrs) with untreated mild essential hypertension were randomised to treatment with oral fosinopril (l0mg-20mg daily) or placebo for 12 weeks. No additional drugs were allowed. The primary outcome measure was the change in left ventricular mass index determined by echocardiography. **Results:** Diastolic blood pressure changed from 97.2 ± 1.8 mmHg at baseline to 98.1 ±2.3 mmHg at the final visit in control patients and changed from 99.2 ± 2.0 mmHg to 96.0 ± 2.5 mmHg in patients treated with fosinopril ($p = 0.05$). Systolic blood pressure changed from 147.9 ± 2.6 mmHg at baseline to 151.1 ± 3.4 mmHg at the final visit in control patients and changed from 159.2 ± 4.2 mmHg to 149.1 ± 4.5 mmHg in patients treated with fosinopril ($p = 0.01$). The left ventricular mass index changed from 110.3 ± 6.1 g/m^2 to 114.3 ± 8.7 g/m^2 in control patients and changed from 133.4 ± 9.2 g/m^2 to 127.1 ± 11.0 g/m^2 in patients treated with fosinopril ($p = 0.03$). There was no significant change in the left ventricular systolic or diastolic function, nor were there any significant changes in plasma electrolytes and renal function. **Conclusion:** Treatment with fosinopril as monotherapy for 12 weeks reduces left ventricular mass in hypertensive patients.

12.

INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE EXPRESSION IN ENDOTHELIAL CELLS BY EGb AND ITS METABOLITES

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Excessive production of nitric oxide (NO) may have cytotoxic effects through the formation of peroxynitrite with superoxide. The extract isolated from ginkgo biloba leaves (EGb) has been used for treating cardiovascular and cerebrovascular diseases. It has been demonstrated *in vitro* that EGb is a potent scavenger of free radicals. However, its effect on nitric oxide production in endothelial cells is unknown. The objective of this study was to elucidate the mechanism by which EGb affected the NO production in human endothelial cell line (ECV304). Various concentrations of EGb were added to culture media and incubated with endothelial cells. After the incubation, the amount of NO released was determined. EGb at the concentration of 50 μg/ml inhibited the release of NO to about 70% of the control. Furthermore, EGb inhibited the NO synthase (NOS) activity in cultured cells. Our results suggest that EGb may affect the release of NO by endothelial cells by inhibiting the NOS in these cells. Such effect may prevent the further formation of strong oxidant ions in diseased status (This study was supported by the CRCG of The University of Hong Kong).

13.

FETAL GROWTH AND EARLY POSTNATAL GROWTH ARE RELATED TO BLOOD PRESSURE IN ADULTS

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This study examined the association between fetal growth, early postnatal growth, and blood pressure in Chinese adults. One hundred and twenty-two subjects born in Hong Kong in 1967 were followed from birth to age 30 years. Multiple linear regression was used to analyse the association between size at birth, postnatal changes in body size, and systolic and diastolic blood pressure at age 30 years. Having adjusted for potential confounders and each other explanatory variable, it is found that birth length standard deviation score (SDS; regression coefficient or beta= -2.7), ponderal index at birth (beta= -2.2), postnatal changes in ponderal index from birth to age 6 months (beta= -1.4) and from age 6 months to 18 months (beta= -2.2) were inversely associated with systolic blood pressure (each $P<0.05$). Postnatal changes in length SDS were not significantly associated with systolic blood pressure. Birth length SDS was inversely associated with diastolic blood pressure at age 30 years (beta= -2.4; $P<0.05$). Ponderal index at birth, postnatal changes in ponderal index and length SDS were not associated with diastolic blood pressure. The results support the hypotheses that both fetal growth and early postnatal growth may have a long-term impact on blood pressure in adults.

14.

OCCLUSION OF NATIVE AND RESIDUAL ARTERIAL DUCTS BY DIFFERENT TYPES OF COILS

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Background: While various types of coils have been used to occlude persistent arterial ducts, no comparative studies have been performed and as yet no consensus opinion on the ideal types of coils to be selected is available. This study aims to compare the efficacy and safety of three different types of coils for the occlusion of native and residual arterial ducts. **Method:** Sixty-six patients underwent transcatheter occlusion of persistent arterial ducts between April l995 and March 1998, of which 45 had native and 21 had residual ducts. Their mean age and weight were 5.3 ± 3.5 years and 17.3 ± 7.8 kg, respectively. We reviewed the results and complications of ductal occlusion by 3 types of coils: Gianturco coils, Cook detachable coils and Duct Occlud devices. Kaplan-Meier analysis was used to assess the decrease in prevalence of residual shunting with time and multiple regression analysis was used to identify the risk factors for persistent residual shunting. **Results:** Coil occlusion of native and residual arterial ducts, measuring 2.3 ± 0.9 mm, was feasible in 61/66 (92%) patients. All the coils were implanted via the antegrade transvenous route. Gianturco coils were used in 33, Duct Occlud devices in 17, Cook detachable coils in 9 and combinations in 2 patients. A single coil was implanted in 35, 2 coils in 24 and 3 coils in 2 patients. The prevalence of residual leak at 24 hours, 3 and 6 months were respectively 42%, 28% and 24% for native ducts and 48%, 24% and 18% for residual ducts ($p = 0.88$). Coil embolization occurred in 3/66 (4.5%) procedures while intravascular haemolysis in 2/51 (3%) patients There was no significant relation between the coil types and the risk of embolization or haemolysis. The decrease in prevalence of residual shunting with time did not differ amongst the 3 types of coils ($p = 0.58$). The significant factor for persistent residual shunting was ductal size ($p = 0.04$). **Conclusion:** Transcatheter coil occlusion is safe and effective for both native and residual arterial ducts. Gianturco coils, Cook detachable coils and Duct Occlud devices have similar efficacy with none having excessive complications over the others. The findings are in favour of the relatively inexpensive Gianturco coils for occluding small arterial ducts of 3 mm or less.

15.

A STRUCTURE-ACTIVITY RELATIONSHIP STUDY OF TETRAMETHYLPYRAZINE ANALOGUES ON RENAL AND MESENTERIC ARTERIES OF SHR AND WKY RATS

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2,3,5,6-Tetramethylpyrazine (2,3,5,6-MP), a symmetrical methylated pyrazine compound, is an active principle of certain plants that was previously found to have a vasodilatory effect on blood vessels both *in vitro* and *in vivo*. In this study, the structure-activity relationship of the vasodilatory effect of pyrazine analogues was examined in isolated renal (RA) and mesenteric arteries (MA) of Wistar rats (female, 22-26 wks). The pyrazine analogues were: 2-methyl-pyrazine (2-MP), 2,3-dimethylpyrazine (2,3-MP), 2,5-methylpyrazine (2,5-MP), 2,3,5-trimethyl-pyrazine (2,3,5-MP), 2,3,5,6-tetramethylpyrazine (2,3,5,6-MP) and ethylpyrazine (EP). Isometric tension changes of isolated RA (resting tension (RT) = 5 mN) and MA (RT = 5 mN), pre-contracted with 1 μM phenylephrine (plus 1 μM indomethacin), in response to TMP analogues were examined and compared. Cumulative application of TMP analogues elicited a concentration-dependent relaxation of the pre-contracted RA and MA. In RA, the relative inhibitory potency (response measured at 1 mM) of the TMP was: 2-MP ≤ EP < 2,3-MP ≤ 2,5-MP < 2,3,5-MP ≤ 2,3,5,6-MP. The maximum relaxation recorded in the presence of 2,3,5,6-MP was 93.9 ± 4.3 %. A similar trend of the relative inhibitory potency was observed in isolated MA. Moreover, the relative vasodilatory effect of all MP analogues tested correlated fairly well with the log octanol/water partition coefficient. A linear relationship with a correlation coefficient of 0.76 and 0.79 was obtained in RA and MA, respectively. In conclusion, these results suggest that an enhanced vasodilatory activity of pyrazine analogues was associated with an increase in the number of alkyl groups as well as the length of alkyl group present on the pyrazine ring. Moreover, an increase in lipophilicity enhanced the vasodilatory properties of pyrazine compounds in isolated RA and MA. **Acknowledgements:** Data analysis performed by Ms. K.Y. Tam & M.Y. Tse and Mr. Y.H. Man & T.L. Ko (candidates of Work Attachment for Sixth Formers 99, CUHK) is acknowledged.

16.

EFFECT OF CHRONIC HYPOXIA ON ENDOTHELIN RECEPTORS OF ISOLATED PULMONARY ARTERIES OF RATS

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Circulating levels of endothelin (ET) are raised in babies with pulmonary hypertension of the newborn. Chronic exposure to hypobaric hypoxia causes pulmonary hypertension in rats, which similarly results in abnormalities in the pulmonary arterial structure. Therefore, we studied the effect of chronic hypoxia on the ET receptors of isolated pulmonary arteries from the rat. Treatment of arteries from normoxic rats with ET-1 produced net vasoconstriction, which was significantly inhibited by the ETA receptor antagonist, BQ610, suggesting that constriction was mainly mediated by ETA receptors in this preparation. Stimulation of ETB receptors resulted in a transient vasodilation, followed by a small net vasoconstriction. It has been reported that the transient vasodilation is mediated by endothelial ETB receptors, whereas the vasoconstriction is mediated by ETB receptors on the vascular smooth muscle. Treatment with the ETB receptor antagonist, BQ 788, abolished the initial vasodilation, confirming the presence of ETB dilator receptors in the normoxic pulmonary artery preparation. The constrictor response to a high dose of ET-1 (5×10^{-8}M) was significantly lower in hypoxic rats compared to normoxic rats. In the presence of the ETB receptor antagonist, BQ788, the constrictor responses to low doses of ET-1 (10^{-9} - 5×10^{-9}M) were also significantly less in hypoxic than in normoxic vessels, suggesting that ETA-receptor-mediated vasoconstriction was diminished in chronic hypoxia. In the presence of the ETA receptor antagonist, BQ610, there was significantly more constriction from hypoxic than from normoxic vessels in response to 10^{-8}M ET-1, but no difference between the responses to 10^{-7}M ET-1, suggesting that ETB-mediated dilation was also diminished in chronic hypoxia. Thus, at low ET concentrations, there was no net change in the response to ET in hypoxic vessels, but at high ET concentrations, the ETB dilator receptors were saturated and decreased ETA-mediated constriction became apparent.

17.

HOW TO MAKE USE OF MIDCAB, AND OFF AND ON PUMP CABG ON THE BEATING HEART

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Background: It is still difficult to decide what methods to use for CABG on the beating heart. I make it a rule to select one out of 3 choices. The first choice is MIDCAB, second On pump beating CABG with median sternotomy and third Off pump beating CABG with median sternotomy. **Results:** From December 1997 until September 1999, I performed MIDCAB, and Off and On pump CABG on the beating heart in 37 patients to treat coronary disease. Thirty patients underwent MIDCAB, 4 On pump beating CABG and 3 Off pump beating CABG. **Conclusion:** Principally, MIDCAB is to be performed for single vessel disease. It has the greatest merit not only to avoid cardiac arrest, but also CPB, and uses only a small incision. But in high risk patients or those with multivessel disease, On pump beating CABG has a greater merit for performing coronary artery reconstruction without any stress. Off pump beating CABG is economical, but sometimes puts a little stress on the surgeons. By using a combination of these three approaches, we can propose further indications for the various cardiovascular operations and predict an earlier discharge.

18.

REDUCED EDHF-MEDIATED RELAXATION OF THE CORONARY MICROARTERIES IN CORONARY ARTERY DISEASE

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Background & Objective: Disturbance in vasomotor at plaque site by atherosclerosis has been implicated in pathogenesis of coronary artery disease. Whether such effect exists at non-plaque site of downstream vessels is controversial. Additionally, the effect of atherosclerosis on individual endothelium-derived relaxing factors has not been studied. This study therefore investigated endothelium-derived hyperpolarizing factor (EDHF)-mediated relaxation in the human coronary micro-arteries. **Methods:** Intramyocardial arterioles (diameter at the pressure of 100 mmHg: 385 ± 11 μm) were isolated from the explanted human hearts with coronary atherosclerosis (atherosclerotic group) or without coronary artery disease (control group) during heart transplantation. Isometric force of the rings was measured in a wire myograph. In the rings precontracted by U_{46619}, EDHF-mediated relaxation was elicited by bradykinin in the presence of indomethacin and N^G-nitro-L-arginine. **Results:** U_{46619}-induced contraction force was elevated in atherosclerotic group (4.9 ± 0.3 mN, n = 8 versus 4.0 ± 0.2 mN, n = 10, p = 0.04). In the rings precontracted by U_{46619}, bradykinin induced a concentration-dependent relaxation in the presence of indomethacin and N^G-nitro-L--arginine. The maximal relaxation was significantly less in the atherosclerotic (34.0 ± 4.8%, n = 10) than in the control (53.3 ± 4.4%, n = 8, p = 0.01) group. Conclusion: These results suggest that in the downstream coronary micro-arteries of patients with coronary atherosclerosis, EDHF-mediated endothelial function is also affected.

19.

CORONARY ARTERY BYPASS GRAFTING: TOWARDS THE NEW MILLENNIUM

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Coronary artery disease as a single disease is the number 1 killer in Hong Kong, China, and world-wide. Coronary artery bypass grafting (CABG) is still the major surgical treatment. **1. Use of arterial grafts.** The grafts include saphenous vein (SV) and a number of arteries such as the internal mammary artery (IMA), radial artery, gastroepiploic artery, and inferior epigastric artery, exc. Venous grafts have high incidence of occlusion (38-45% at 10 years), compared to 85-95% of IMA, that may require reoperation and reduces the efficacy of CABG. On the other hand, arterial grafts have vasospasm problems, which may cause mortality or morbidity. **Biological characteristics of arterial grafts.** Histologic and comparative functional studies have demonstrated that there are differences in arterial grafts with regard to structure of smooth muscle, contractility and endothelial function. We have classified all arterial grafts into three types: Type II (splanchnic arteries) and Type III (limb arteries) are more spastic than the Type I (somatic arteries). **Considerations in Graft Choosing.** 1) General condition of the patient. 2) Biological characteristics. 3) Anatomy of the coronary artery. 4) Vessel match between the graft and the coronary artery. 5) Technical considerations. **2. Complex arterial conduits.** Use of complex arterial conduit is a trend whenever necessary. 1) LIMA plus RA or IEA; 2) RIMA plus IEA/RA; 3) IMA plus ulnar artery. 4) Use of GEA. **3. Myocardial protection.** 1) The myocardial protection from the view of both myocytes and endothelial cells; 2) Hyperpolarizing versus depolarizing cardioplegia. **4. Minimally or less invasive procedures.** 1) OPCAB: MIDCAB; OPCAB with median sternotomy; 2) Port-access technology (closed-chest CPB). **Conclusions.** 1. The indications and methods of coronary surgery are still in evolution; 2. More understanding of the biological characteristics of coronary bypass grafts is necessary; 3. New methods of myocardial protection may be possible in the new millennium; 4. Balance of arterial and venous grafts is a challenge; 5. Advantages and disadvantages of minimally and less invasive CABG are to be determined.

20.

AGE AND GENDER DEPENDENT IMPACT OF CHILDHOOD OBESITY ON BLOOD PRESSURE

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Obesity is associated with elevated blood pressure (BP) both in adults and children. Childhood obesity has become a severe health problem especially during the last few decades. So far there has not been any proper and large-scale study specifically focusing on the association between obesity and BP in early life. The aim of the present study was to systematically examine the association between obesity and BP in preschool Chinese children in mainland China. Specifically weight, height and BP values were collected from a nationwide case-control study of 748 boys and 574 girls aged from 0.1 to 6.9 years in 8 cities in mainland China undertaken in 1996. One obese child and one non-obese child were matched for gender and age. The mean BP differences between the obese and control groups were 6.0 mm/Hg for systolic and 4.6 mm/Hg for diastolic ($P < 0.05$) between 3.0 and 6.9 years of age for both genders. The elevated BP was positively correlated with the BMI value of the child ($P < 0.05$). For younger children (0.1 - 2.9 years) only girls showed a significant difference ($P < 0.05$) in the mean BP between the cases and the controls. Based on this large population based case-control study, during the first seven years of life, we conclude that obesity is clearly associated with an elevated systolic and diastolic BP. The association was however not so distinct during the first three years of life indicating that childhood obesity, rather than infant obesity, may have a more profound influence on or association with BP.

ABSTRACTS

21.

OXYGEN UPTAKE AND HEART RATE RESPONSES DURING TAI CHI IN PATIENTS WITH CARDIOVASCULAR DISEASE AND NORMAL SUBJECTS

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Background: Tai Chi is a form of exercise performed by the Chinese which is potentially suitable to be adopted for exercise rehabilitation in patients with cardiovascular diseases. The purpose of this study was to investigate the energy expenditure and heart rate responses while performing Tai Chi in patients with cardiovascular disease and compared to normal subjects. **Method:** Ten patients with cardiovascular diseases (hypertension, ishemic heart disease, hypertension or valvular disease) and 10 normal controls (age 65 ± 5.6 Vs 57 ± 8.6 years, p =NS) were studied. All subjects had performed Tai Chi for more than 1 month. Breath-by-breath oxygen uptake and heart rates were assessed with an ambulatory metabolic analyzer (TEEM 100 Metabolic Analysis System, AeroSport Inc., USA). **Results:** Compared to the controls, patients with cardiovascular disease achieved a lower oxygen uptake (9.5 ± 1.34 Vs 12.6 ± 1.68ml/min/kg, $p<0.05$), a lower Carbon Dioxide production rate (7.4 ± 1.0 Vs 9.7 ± 1.4ml/min/kg, $p<0.05$) and a lower metabolic equivalent (2.7 ± 0.39 Vs 3.6 ± 0.48 METs, $p <0.05$), but similar percentage of age-predicted maximal heart rate (63 ± 9.0 Vs 69 ± 9.6%, p = NS) and Borg's scale with similar rate of 11 to 12. **Conclusion:** A mild to moderate energy expenditure was required on performing Tai Chi, which was lower in patients with cardiovascular disease than normal controls. Patients performing Tai Chi attained sufficient heart rate and energy expenditure in order to be useful for cardiovascular training. Therefore, Tai Chi is a potentially suitable mode of exercise for cardiac rehabilitation.

22.

ARTERIAL RELAXATION INDUCED BY PURIFIED GREEN TEA (-)EPICATECHIN: ROLE OF ENDOTHELIUM

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Green tea has recently received much attention as a protective agent against cardiovascular disease and cancer, two important targets of preventive medicine. We have recently purified four catechin derivatives from Jasmine green tea, of which (-) epicatechin and (-) epigallocatechin were circulating in aorta blood after oral administration. The present study investigated the involvement of endothelial nitric oxide in relaxation induced by purified green tea (-) epicatechin in rat isolated mesenteric arteries. (-) Epicatechin caused both endothelium-dependent and -independent relaxation. N^G-Nitro-L-arginine methyl ester (L-NAME, 100 μM) and methylene blue (10 μM) significantly attenuated (-) epicatechin-induced relaxation in endothelium-intact tissues. L-arginine at 1 mM partially antagonized the effect of L-NAME. (-) Epicatechin-induced relaxation was inhibited by Rp-guanosine 3',5'-cyclic monophosphothioate triethylamine. In contrast, indomethacin and glibenclamide had no effect. (-) Epicatechin (100 μM) significantly increased the tissue content of cyclic GMP and N^G-nitro-L-arginine (100 μM) or removal of the endothelium abolished this increase. (-) Epicatechin (100 μM) induced an increase in intracellular Ca^{2+} levels in cultured human umbilical vein endothelial cells. Iberiotoxin at 100 nM attenuated (-) epicatechin-induced relaxation in endothelium-intact arteries and this effect was absent in the presence of 100 μM L-NAME. In summary, (-) epicatechin-induced endothelium--dependent relaxation is primarily mediated by nitric oxide and partially through nitric oxide-dependent activation of iberiotoxin-sensitive K^+ channels. In addition, there may be a causal link between increased Ca^{2+} levels and nitric oxide release in response to (-) epicatechin (supported by Hong Kong Research Grants Council).

23.

INHIBITORY EFFECTS OF BAICALEIN AND BAICALIN ON ENDOTHELIUM-DEPENDENT VASORELAXATION

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The dry roots of *Scutellaria baicalensis* Georgi (Huangqin) has been widely used in traditional Chinese herbal medicine. Baicalin and baicalein, flavonoids contained in the roots of *Scutellaria baicalensis* Georgi were reported to have hypotensive effects. However, the mechanisms by which baicalin and baicalein exert their vascular effects are basically unknown. It is possible that baicalin and baicalein may have multiple sites of action on both endothelium and vascular smooth muscle cells. Baicalin and baicalein were isolated from *Scutellaria baicalensis* Georgi (Huangqin) and purified. Their effects on endothelium-dependent relaxation were investigated in rat isolated mesenteric artery and aortic rings. Baicalin (50 μM), baicalein (μM) or 3 μM N^G-nitro-L-arginine (L-NNA) fully reversed the relaxation induced 300 nM acetylcholine (Ach) and 10 μM cyclopiazonic acid (CPA), while these agents had no effect on nitroprusside (SNP)--induced relaxation. Methylene blue at 3 μM reversed SNP-induced relaxation. In addition, baicalin and baicalein had no effect on relaxation induced by K^+ channel activators, NSl619 and pinacidil. Pretreatment with 3 μM L-arginine potentiated Ach--induced relaxation but it significantly antagonized the effects of baicalin or baicalein. These results indicate that both baicalin and baicalein attenuated the endothelium--dependent relaxation mainly through inhibition of endothelial nitric oxide production/ release. Whilst, neither baicalin nor baicalein influence endothelium--independent relaxation mediated by cyclic GMP-dependent mechanisms. (Supported by Hong Kong Research Grants Council).

24.

OPPOSITE EFFECTS OF GLIBENCLAMIDE AND TOLBUTAMIDE ON CONTRACTILITY OF RAT ARTERIES

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Glibenclamide and tolbutamide, the oral hypoglycemic drugs, are inhibitors of ATP-sensitive K^+ channel blockers and of the effects of K^+ channel activators. Blockade of K^+ channels would cause membrane depolarization and thus contraction in vascular smooth muscle. However, it was also reported that glibenclamide at high concentrations relaxed the vascular smooth muscle contracted by prostanoids. It was suggested that glibenclamide may be a competitive antagonist of prostanoid receptors. The present work aimed to investigate the possible mechanisms by which glibenclamide and tolbutamide affect muscle contractility in rat arterial rings. Glibenclamide reduced the constrictor-induced tension in a concentration-dependent manner in endothelium-intact arteries. The concentration--relaxation curve for glibenclamide was significantly shifted to the right upon removal of the functional endothelium or pretreatment with N^G-nitro-L-arginine (L-NNA) or with methylene blue. Glibenclamide increased the tissue content of cyclic GMP in endothelium-intact arteries and this effect was inhibited by L-NNA. In addition, glibenclamide induced an increase of intracellular Ca^{2+} concentration in cultured endothelial cells. In contrast, tolbutamide caused Ca^{2+}-dependent contractile response in blood vessels. Various inhibitors such as nifedipine, prazosin, staurosporine did not affect tolbutamide-induced contraction. Pretreatment with nickel reduced the contractile response to tolbutamide. The results provide novel information on glibenclamide induces both endothelium/nitric-oxide-dependent and -independent relaxation. However, the exact mechanism by which glibenclamide induces endothelium-independent relaxation is yet to be elucidated. Whilst, tolbutamide increases muscle tension probably through increased influx of calcium through an unknown pathway (supported by HKRGC).

25.

IS THE MECHANISM OF K^+-LNDUCED CONTRACTION IN NORMAL PHYSIOLOGICAL SALT SOLUTION (PSS) AND IN CA^{2+}-FREE, MG^{2+}-FREE MEDIUM CONTAINING EDTA SIMILAR?

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K^+ evokes similar contractile responses of different smooth muscles such as human saphenous vein, quail caecum, rat mesenteric artery and aorta in both Ca^{2+}-rich solution ($[Ca^{2+}]_{ex}$ = 2.5 mM) and Ca^{2+}-free medium containing the calcium chelator, EDTA ($[Ca^{2+}]_{ex}$ < 7 nM) . K^+ fails to elicit any muscular responses in Ca^{2+}-free medium containing EGTA. In contrast to the K^+ response in normal PSS which is accompanied by increased intracellular calcium concentration ($[Ca^{2+}]_i$), a considerable K^+-EDTA contraction of rat aortic rings is accompanied by a reduced basal level of $[Ca^{2+}]_i$ as estimated by fura-2. K^+-EDTA-induced shortening of freshly-isolated smooth muscle cells from rat aorta also is not associated with an enhancement in $[Ca^{2+}]_i$. However, despite a lack of $[Ca^{2+}]_i$ rise, K^+-EDTA contractile responses, just as in K^+-induced contractions in PSS, are inhibited by antagonists of Ca^{2+} channels (nifedipine, felodipine, verapamil and Ni^{2+}) and are accompanied by increased $^{45}Ca^{2+}$ efflux from aortic strips. In addition, it is revealed that the nifedipine-inhibited increment of $^{45}Ca^{2+}$ uptake in cells produced by K^+ is composed mainly of a net Ca^{2+} binding. These results suggest that K^+-induced contractile responses in Ca^{2+}-rich solution and Ca^{2+}-free medium containing EDTA are similar in nature. However, in contrast a widely -accepted point that $[Ca^{2+}]_i$ is a trigger of smooth muscle contractions, increased Ca^{2+} binding to the plasma membrane is proposed to underlie both K^+-dependent responses. The alteration of hydrophobic interactions between the membrane proteins and cytoskeleton promoted by such Ca^{2+} binding seems to be the main mechanism of muscular responses.

26.

INTERACTION OF DIETARY GUAR GUM WITH β-BLOCKERS

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Dietary guar gum is known to attenuate hyperglycaemia and reduce HbA_1C in diabetic patients, and more recently, as a vehicle for colonic drug delivery. As the diabetic condition is often associated with nephropathy and hypertension, the use of multiple drug therapy is very common. Under such circumstances, the interaction between concomitantly administered drugs might play an important role in the effective use of these therapeutic agents. Among our diabetic patients receiving atenolol, control of high blood pressure appeared to be impaired after starting guar gum. In this study, we therefore set out to explore the effect of guar gum on the plasma concentrations of different β-blockers among diabetic hypertensive patients who were also in receipt of dietary treatment and hypoglycemic drugs. With their informed consent, 7 patients taking atenolol and 6 taking metoprolol were entered into these studies. According to a randomized, double-blind crossover protocol, they took guar gum (5g) or placebo (baby cereal) 15 minutes prior to their daily morning dose of β-blocker for 7 days. On the 7th day, each patient was admitted to hospital for repeated blood sampling following their β-blocker therapy. Plasma was freshly separated, frozen and later analyzed to determine the β-blocking drug concentration by HPLC. In patients receiving atenolol, on average the Area under time/concentration curve (AUC_{0-4H}) was reduced by 38% (p = 0.02). This finding might explain the previous observation of decreased therapeutic effectiveness of this agent in controlling hypertension in diabetics taking guar gum as diet supplement. The absorption of metoprolol, the more lipid soluble β-blocker, was not affected by guar gum administration. The absorption of other water soluble drugs is also known to be impaired by dietary guar gum. Among β-blockers, lipid soluble agents may therefore be preferable for treating hypertension in patients using guar gum.

27.

FUNCTIONAL EVIDENCE FOR THE EXISTENCE OF A NOVEL CONSTITUTIVE NITRIC OXIDE SYNTHASE IN VASCULAR SMOOTH MUSCLE

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Introduction and Methods: Nitric oxide, enzymatically produced from nitric oxide synthase (NOS) first discovered in the vascular endothelium, plays many important roles in health and diseases. NOS is present in several isoforms in a large number of cells besides endothelial cells, such as the constitutive eNOS (e for endothelial) and nNOS (n for neuronal) under physiological conditions, and iNOS (I for inducible) which are induced by cytokines under pathophysiological conditions. In vascular tissue, only eNOS and iNOS have been identified and studied so far. Recently, we have identified a nNOS-like constitutive form of NOS in vascular smooth muscle (VSM) using functional contractility approach and observed the following: **Results:**[1] We have found that L-NAME, L-NMMA and L-NOARG, the competitive inhibitors of NOS, inhibited Mg^{2+}-induced relaxation of de-endothelialized vessels pre-contracted by phenylephrine (PE). This Mg^{2+}-relaxation of VSM was not affected by inhibitors of iNOS.[2] Electrical-field-stimulation (EFS; 30-70 Hz) caused relaxation of rat aorta and other blood vessels in the presence of TTX (therefore not a neurogenic effect) and this EFS-relaxation was effectively inhibited by L-NOARG, oxyhemoglobin and methylene blue.[3] Immunohistochemical studies indicated prominent staining with antibodies raised against nNOS in guinea pig along the plasmalemma in a punctate pattern similar to the distribution of antibodies against caveolin-1, a major constituent of the plasmalemmal caveolae. **Conclusion:** The above findings support our earlier suggestion[4] that rat aortic VSM contains a non-endothelial NOS, which bears nNOS-like feature.

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28.

ATYPICAL β-ADRENOCEPTOR-MEDIATED INHIBITION OF L-TYPE CALCIUM CHANNEL CURRENT OF GUINEA-PIG SINGLE VENTRICULAR MYOCYTES

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In addition to β_1- and β_2-adrenoceptors (AR), recent evidence demonstrated the presence of other subtype(s) of β-AR (the so called β_3- and β_4-) in cardiac ventricular preparations. Unlike the well- known stimulatory β_1- and β_2-ARs in the heart, activation of β_3-AR elicited a depressant response on ventricular contraction. In view of the importance of the voltage-dependent L-type Ca^{2+} channels (I_{CaL}) involved in cardiac contractility, in this study, we investigated the effects of isoprenaline (ISO) (a non-selective β-AR agonist) on basal I_{CaL} amplitude of guinea-pig single ventricular myocytes. Single ventricular myocytes were dissociated using standard collagenase/protease methods. I_{CaL} amplitude was measured (2 mM $[Ca^{2+}]_o$ with Cs^+ present) using amphotericin B (240 μg ml^{-1}) perforated-patch whole-cell patch-clamp technique (22-24°C). I_{CaL} was elicited by a standard train-pulse protocol (HP = -40mV, pulsed to 10 mV for 40 ms at 0.2 Hz). Application of ISO (30 nM) increased the basal I_{CaL} amplitude (~ 180 % of control) (n = 8) and the stimulatory effect could be reversed upon washout. However, in the presence of nadolol (1 μM, a β_1-/β_2-AR antagonist), the stimulatory effect of ISO on I_{CaL} was abolished and an inhibition of the basal I_{CaL} was recorded (68 ± 11 % of control) (n = 9). A similar degree of inhibition of the basal I_{CaL} amplitude was observed in the presence of a selective β_3-AR agonist BRL 37344 (3 μM) (57 ± 8 % of control) (n = 7). The inhibitory effect of ISO (in the presence of nadolol) and BRL 37344 on basal I_{CaL} persisted after washout with drug-free solution. Pre-treating the ventricular myocytes with L-NAME (0.1 μM), but not D-NAME (0.1 μM), and LY 83583 (1 μM, a soluble guanylyl cyclase inhibitor) abolished the inhibitory effect of ISO and BRL 37344 on basal I_{CaL} (n = 5-8). In conclusion, these results suggest that, for the first time, the inhibitory β_3-ARs are present in the ventricular myocytes and the β_3-AR-mediated inhibition of the basal I_{CaL} amplitude involved the NO/cGMP pathways.

Acknowledgements: Data analysis performed by Ms. K.Y. Tam & M.Y. Tse & Mr.Y.H. Man & T.L. Ko (candidates of Work Attachment for Sixth Formers 99, CUHK) is acknowledged.

29.

MODULATION BY EXTRACELLULAR ATP OF DELAYED RECTIFIER K^+ CHANNELS OF GUINEA-PIG SINGLE SINOATRIAL NODAL CELL

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Delayed rectifier potassium current (I_K), which is activated during the phase 3 of the action potential, is important in the repolarization of the mammalian heart. It has been demonstrated that I_K consists of two components, the rapidly-activating component I_{Kr} and a slowly-activating component I_{Ks}. The sinoatrial node (SAN) is the heart beat origin and is highly innervated by the autonomic nervous system. Extracellular adenosine 5'-triphosphate ($[ATP]_o$) is an important neurotransmitter and can be released upon nerve stimulation. In this study, the effects of $[ATP]_o$ on the I_{Ks} component of the delayed rectifier K^+ channels were examined in enzyme dissociated guinea-pig single SAN cells using the whole-cell patch-clamp technique (22-24ºC). IKs currents were elicited from a holding potential of -40 mV by a series of depolarizing pulses (2 s duration, -40 mV to 100 mV with a 20 mV increment) at 0.2 Hz in the presence of 1 μM nifedipine. Application of $[ATP]_o$ caused an enhancement of the outward I_{Ks} amplitude. The % increase by 100 μM $[ATP]_o$ (measured at the end of 2 s depolarizing pulse at 100 mV) was 155 ± 12 % of control (n = 7). A similar % increase of I_{Ks} was observed when the SAN cell was challenged with 100 μM ATP-γ-S (155 ± 16 % of control; n = 5) and 100 μM adenosine (150 ± 10 % of control; n = 5). Moreover, the enhancement effects of $[ATP]_o$, ATP-γ-S and adenosine on I_{Ks} of the SAN cell could not be reversed after washout. The presence of GTP-γ-S (250 μM) in the pipette solution caused ~ 40 % inhibition of the control I_{Ks} (measured at 5 min after GTP-γ-S dialyzed into the SAN cell). The subsequent challenge with 100 μM $[ATP]_o$ resulted in a ~ 155 % increase of the "reduced" I_{Ks} amplitude (n = 4). These results suggested that $[ATP]_o$ has significant modulatory effect on I_{Ks} and the $[ATP]_o$-mediated enhancement of I_{Ks} probably did not involve G protein. However, the type(s) of purinoceptors involved in $[ATP]_o$-mediated effects in SAN cells remains to be determined. **Acknowledgements:** This project was financially supported by Direct Grant for Research (CUHK) (A/C: 2040646).

30.

UPREGULATION OF MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) IN NEOINTIMAL FORMATION AFTER CAROTID BALLOON INJURY IN RATS

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Although percutaneous transluminal coronary angioplasty (PTCA) is a highly effective procedure to reduce the severity of stenotic coronary atherosclerotic disease, its long-term success is significantly limited by the high rate of restenosis. There are several cellular and molecular mechanisms have been implicated in the development of restenosis post-PTCA, including the production of growth factors, vascular smooth muscle cell (VSMC) proliferation, migration, macrophage and T cell accumulation. However, the key factors regulating this neointimal thickening during restenosis remain largely unknown. Macrophage migration inhibitory factor (MIF), a potent macrophage activator, has been reported to regulate cell growth, involving in endothelial cell proliferation and angiogenesis. Thus, the present study investigated whether MIF is upregulated by vascular cells and whether MIF upregulation contributes to neointimal formation after carotid balloon injury in rats. Histologically, there was marked increase in neointimal thickening (1.0 ± 0.1 vs normal, $p<0.01$) at 2 weeks after balloon injury. This is steady increased over 8 week periods (neointimal/medial ratio: 1.9 ± 0.4), resulting in the development of restenosis. Immunohistochemically, there was weak expression of MIF by both endothelial cells and VSMC. However, a marked upregulation of MIF by endothelial cells and proliferating VSMC was evident, leading to neointimal thickening. In high contrast, MIF was not upregulated by those VSMC that showed no proliferating activity within the medial area of artery. These findings strongly indicate that MIF may be a key local mediator regulating VSMC activation, proliferation. In conclusion, upregulation of vascular MIF may contribute to neointimal thickening and restenosis after balloon angioplasty.

31.

GENISTEIN, A PHYTOESTROGEN, RELAXES PORCINE CORONARY ARTERY *IN VITRO*, IS INDEPENDENT OF THE ENDOTHELUM

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Phytoestrogens, a group of naturally occurring compounds found in many plant foods, specifically refers to those substances that are structurally or functionally similar to estradiol. Genistein, one of the phytoestrogens that are predominantly found in soybeans, is well documented as to its weak estrogenicity. It produces beneficial effects to the human cardiovascular system through its antioxidant and hypocholesterolemic abilities [(1)]. A study had demonstrated that genistein can produce direct relaxation when the endothelium was disrupted [(2)]. Based on the above findings, we found that at high concentrations, genistein can directly exert vasodilatory effects on porcine coronary arteries that were precontracted with the constricting agent, u46619, a thromboxane A_2 analog. At achievable plasma levels (10^{-6} M - 3 X 10^{-6} M) in the tissue bath, it enhanced the vasodilatory effects to sodium nitroprusside (SNP) and cromakalim, but not to bradykinin. Shifting of the SNP dose-response curve was also preserved with a nitric oxide synthase inhibitor, L-NAME- (300μM) and 0.5% Triton- treated rings. This implied that the potentiating effect of genistein acts on the smooth muscle directly and the endothelium was not involved in it. To conclude, at achievable plasma levels through diet or supplementation, genistein produces increased relaxation to porcine coronary arteries that are independent of the effect of endothelium.

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32.

CHANGES OF PLASMA F_{1+2} AND D-DIMER LEVELS IN PATIENTS WITH LOWINTENSITY ANTICOAGULATION AFTER MECHANICAL VALVE REPLACEMENT

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Objective: This study was designed to evaluate the effect of low-intensity anticoagulation in patients with mechanical heart valve prostheses by measuring plasma levels of prothrombin fragment 1+2 (F_{1+2}) and D-Dimer, which are the activation peptides respectively released after proteolysis of prothrombin by factor X_a and resulting from the proteolytic action of plasmin upon fibrin, and both have been reported to have good sensitivity for the diagnosis of thrombosis diseases. **Method:** A total of 58 randomized patients who underwent cardiac valve replacement, and receiving warfarin orally to prevent thromboembolism, were divided into two groups by anticoagulation intensity. Namely, group A, 30 patients with international normalized ratio (INR) ranging from 2.0 to 2.99 and group B, 28 patients with INR ranging from 3.0 to 4.5. The plasma levels of F_{1+2} and D-Dimer in these 58 patients were determined by the Elisa method. **Result:** F_{1+2} values were 0.67 ± 0.31nmol/L and 0.63 ± 0.28nmol/L, while D-Dimer values were 0.23 ± 0.11 mg/L and 0.24 ± 0.10 mg/L in group A and B, respectively. F_{1+2} values were much lower in the two groups when compared with normal controls ($P< 0.01$). However, the F_{1+2} value in group A was not significantly different from that in group B ($P>0.05$). The D-Dimer values in the two groups were not statistically different from the control ($P>0.05$). **Conclusion:** These findings show that significant inhibition of blood coagulation cascade can be achieved in patients with low-intensity anticoagulation after mechanical heart valves replacement, and a higher INR range could not be associated with a further decrease in F_{1+2} and D-Dimer levels. Therefore, the low-intensity anticoagulation seems efficacious and safe and is more advisable in patients with mechanical heart valve replacement.

33.

EFFECTS OF CARDIAC FUNCTIONAL STATUS AND ATRIAL FIBRILLATION ON ACTIVITY OF COAGULATION IN PATIENTS WITH ORAL ANTICOAGULANT AFTER MECHANICAL VALVE REPLACEMENT

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Objective: The patients with mechanical heart valve prostheses require lifelong coagulation therapy to prevent thrombotic and thromboembolic complications. The design and materials of prostheses have been considered to be main factors contributing to thrombosis, while the influence of cardiac factors (atrial fibrillation, left atrial dilatation, reduced cardiac output) on intracardiac thrombosis was ignored traditionally. The study was designed to investigate the effects of cardiac function and atrial fibrillation on activity of coagulation in patients with oral anticoagulant after mechanical valve replacement by measuring prothrombin fragment 1+2 (F_{1+2}) and D-Dimer, which have been reported to be special and sensitive markers of coagulation activation. **Methods:** A total of 45 patients were divided into sinus rhythm group (n = 22) and atrial fibrillation group (n = 23) by ECG. A total of 36 patients were divided into NYHA class II group (n = 20) and NYHA class III - IV group (n = 16) by cardiac function. The plasma concentrations of prothromobin fragment 1+2 (F_{1+2}) and D-Dimer were analyzed by ELISA. **Results:** The values of F_{1+2} and D-dimer were 1.17 ± 0.49 nmol/L, 0.32 ± 0.16 mg/L in atrial fibrillation group, 0.64 ± 0.33 nmol/L, 0.24 ± 0.10 mg/L in sinus rhythm group, 1.13 ± 0.48 nmol/L, 0.32 ± 0.15 mg/L in NYHA class III- IV group, 0.66 ± 0.32 nmol/L, 0.24 ± 0.11mg/L in NYHA class II group. The levels of F_{1+2} and D-Dimer in patients with atrial fibrillation or with NYHA class III were significantly higher than those with sinus rhythm or NYHA class II, respectively ($p<0.01$). **Conclusions:** Atrial fibrillation and cardiac function are important factors affecting coagulation activation in patients after mechanical valve replacement.

34.

AGE AFFECTS BLOOD PRESSURE AND HEART RATE FOLLOWING IV DIAZEPAM

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Previous studies of diazepam showed that both its beneficial effects (sedation, anxiolysis) and side effects (drowsiness, disorientation) are more marked in the elderly. Transient hypotension is also a rare side effect of diazepam. We therefore evaluated the influence of age on transient hypotension induced by diazepam. This study was part of an ongoing pharmacokinetic investigation approved by the Faculty Ethics Committee. After obtaining written, informed consent, patients pending abdominal surgery were recruited (n=20, age range 30-73 years) and diazepam was infused over 30 minutes (min) according to a standard protocol. Patients weighing 3 50 kg and < 50 kg received 10 and 7. 5 mg diazepam respectively, diluted in 100 ml of saline (using an IMED infusion pump). Supine blood pressure (BP) and heart rate (HR) were measured automatically prior to the infusion and at intervals thereafter for 90 min. Data was analyzed by Student's paired t test and regression analysis. Corresponding mean systolic and diastolic BP (±SE) pre infusion and at 15, 30, 45, 60, 75 and 90 min after starting the infusion were 130(5)/73(2), 129(5)/71(2), 122 (4)**/69(2)*, 122(4)**/71(3), 121(4)**/68(3)*, 124(5)/71(3) and 126(5)/72 (4) mmHg respectively. Corresponding HR values were 70 (8), 69(7), 69(8), 68(9), 66(8)*, 68(8) and 68(9) beats/min. There were statistically significant correlation between age and the reduction in systolic BP at 60 min ($r = 0.46$, $p = 0.04$), diastolic BP at 30 min ($r = 0.44$, $p = 0.049$) and the fall in HR at 45 min ($r = 0.47$, $p = 0.04$). In conclusion, after IV diazepam, transient hypotensive and bradycardiac effects were more likely with increasing age.
[* $p < 0.05$ compared to baseline value, ** $p < 0.01$ compared to baseline value]

35.

CLINICAL STUDY OF TREATING VIRAL MYOCARDITIS WITH COMBINATION OF YU DAN RONG XIN WAN AND ASTRAGALE

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Objective: Clinical effective observation on treatment of viral myocarditis with combination of YU DAN RONG XIN Wan and ASTRAGALE. **Methods:** A total of 120 viral myocarditis patients were randomly divided into three groups. Group 1 (40) was treated with YU DAN RONG XIN Wan and ASTRAGALE. Group 2 (40) was treated with ASTRAGALE and Energy Mixture. Control Group 0 (40) was treated with SHENGMAI and Glucose-Insulin Kalium. **Result:** The total effective rates of three groups were 95%, 90% and 80% respectively. There was no significant difference in the treatment between the group 1 and group 2 ($X^2 = 0.901$, $P>0.05$). There was a statistically significant difference between the group 1 and control group ($X^2 = 3.841$, $P<0.05$) There was no significant difference between the group 2 and control group ($X^2 = 3.644$, $P>0.05$).There was no damage to renal or hepatic function, without side effects. **Conclusion:** The effect on viral myocarditis treatment by YU DAN RONG XIN Wan and ASTRAGALE was satisfactory. That method could enhance the curative effect of viral myocarditis.

36.

THE DIFFERENCES OF ENDOTHELIUM-DERIVED HYHPERPOLARIZING FACTOR (EDHF)-MEDLATED HYPERPOLARIZATION IN HUMAN INTERNAL MAMMARY ARTERY (IMA) AND SAPHENOUS VEIN (SV)

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Background: The superiority of IMA as a coronary artery bypass graft to SV has been well established. However, the main causes contributing to the different patency rate between these two vessels still remain unknown. The present study was designed to examine the differences of EDHF-mediated hyperpolarization in IMA and SV. **Methods:** Human IMA and SV segments taken from patients undergoing coronary artery bypass grafting were placed in an organ bath. A glass microelectrode was impaled into a smooth muscle cell and the membrane potential was recorded. The membrane potential changes of 1MA and SV in response to acetylcholine (ACh, -8 to -5 logM) and bradykinin (BK, -10 to -7 logM) were measured before and after incubation with indomethecin (7μM), N^G-nitro-L-arginine (300μM), and hemoglobin (20μM) for 60 minutes. **Results:** The resting membrane potentials of IMA and SV were -58 ± 0.84 (n = 61) and -62 ± 0.93mV (n = 61), respectively. The maximum hyperpolarization induced by ACh and BK in IMA (n = 8) was similar to that in SV (n = 10) (for ACh: 12.6 ± 2.1 vs. 11.3 ± 1.3mV, $p = 0.82$; for BK: 14.3 ± 2.0 vs. 12 ± 1.4mV, $p = 0.37$). In contrast, EDHF-mediated hyperpolarization in IMA was significantly greater than that in SV (for ACh: -10.7 ± 1.7, n=8, vs. -5.1 ± 0.6mV, n = 10, $p<0.001$; for BK: -9.4 ± 1.5, n = 7, vs. -3.8 ± 0.8mV, n = 8, $p<0.01$). **Conclusions:** EDHF-mediated hyperpolarization in IMA is significantly greater than that in SV. EDHF may play a more important role in IMA and this might contribute to the different patency rate of these two grafts.

37.

SURGICAL PREPARATION OF SAPHENOUS VEIN ABOLISHES NITRIC OXIDE RELEASE IN THE VEIN

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Background: Surgical preparation (dilation) is routinely applied in saphenous vein (SV) harvesting during coronary artery bypass grafting (CABG). Mechanical distention may impair the endothelium which plays an important role in long-term patency. The present study investigated the effect of surgical preparation of SV on the endothelium-derived nitric oxide (NO) release by direct measurement of NO. **Methods:** Human SV segments taken from CABG patients were cut open longitudinally and placed in an organ chamber. A NO-sensitive electrode and NO meter (ISO-NOP, WPI) were used to measure the concentration of NO released from the endothelium, induced by acetylcholine (ACh) and bradykinin (BK) in surgically prepared veins (PV), compared with the control (non-distended veins). **Results:** The peak concentrations of NO (nM) induced by either ACh or BK in the PV group were significantly lower than that in the control group (ACh [n = 8]: 11.8 ± 3.7 vs. 22.3 ± 3.5 at -7 log M, $p<0.05$; 9.6 ± 3.1 vs. 41.9 ± 11.2 at -6 log M, $p<0.01$; and 4.8 ± 3.2 vs. 25.1 ± 4.9 at -5 log M, $p<0.0$l. BK [n = 8]: 7.5±2.7 vs. 24.6 ± 4.9 at -9 log M, $p<0.05$; 8.3 ± 3.7 vs. 37.9 ± 6.1 at -8 log M, $p<0.001$, and 7.0 ± 3.6 vs. 43.7 ± 8.2 at -7 log M, $p<0.01$). Further, the duration of NO release elicited by BK was significantly shorter in the PV group (1.3 ± 1. 1 vs. 8.1 ± 1.9 min, $p< 0.001$). **Conclusions:** Surgical preparation almost abolishes NO release from the endothelium of the SV and this may significantly contribute to the low long-term patency rate.

38.

LEFT VENTRICULAR VOLUME REDUCTION SURGERY USING RAT ISCHEMIC CARDIOMYOPATHY MODEL

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Background: The effect of volume reduction surgery (VRS) for ischemic cardiomyopathy is not fully understood. Development of proper animal model will help solving this issue. **Methods:** Twenty-six rats developed ischemic cardiomyopathy including akinetic LV aneurysm after the LAD ligation via left thoracotomy. Four weeks after the surgery, 13 rats had VRS using plication method (VRS group) and 13 had just re-thoracotomy (Sham Group). LV dimension was measured by echocardiography before ligation and before and after the 2nd surgery. In 9 rats of VRS group and 10 rats of sham group in other group, LV pressure was measured by catheter-tipped manometer before and after the 2nd surgery. **Results:** All rats survived the 2nd surgery and 5 days until euthanasia. After the 2nd surgery, LV end-diastolic (EDD) and end-systolic diameters (ESD), LV fractional shortening (FS) had improved (Table), but LV end-systolic/ end-diastolic pressure or heart rate did not change in either group. Conclusions: We developed a surgical model for ischemic cardiomyopathy. Since the model provides detailed physiological data and perhaps chronic information such as molecular one, it may help investiaating various aspects of surgical and/or medical treatment for ischemic cardiomyopathy.

	Group	Before ligation	Before 2nd surgery	After 2nd surgery
EDD(mm)	VRS	6.3 + 0.6	9.6 + 0.8	7.1 + 1.2*
	Sham	6.5 + 0.5	9.8 + 0.9	9.6 + 0.7
ESD(mm)	VRS	2.7 + 0.6	7.6 + 0.7	4.24 + 1.4*
	Sham	2.8 + 0.9	8.0+ 0.9	7.9 + 0.8
FS (%)	VRS	57.9 + 7.7	20.3 + 3.3	41.3 + 12.9*
	Sham	57.7 + 7.1	18.7 + 3.4	18.0 + 5.0

*$p<0.001$ (vs. Sham group)

39.

CURRENT STRATEGIES TOWARD BETTER LONG-TERM OUTCOME IN CORONARY ARTERY BYPASS GRAFTING: 7 YEARS EXPERIENCE IN NIPPON MEDICAL SCHOOL

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Use of the internal thoracic artery (ITA) for myocardial revascularization provides excellent results The right gastroepiploic artery (GEA) has been developed as a third in situ arterial graft. Over the last seven years, we have performed 630 isolated CABG. In an attempt to use as many in situ arterial grafts as possible, sequential anastomotic techniques have been aggressively applied. The sequential anastomoses were also constructed with a composite-RITA by attaching its proximal end to the side wall of the LITA. Veins were used as the graft of choice for the proximal segment of the Cx or RCA. Increased numbers of grafted vessels with in situ arterial grafts, of which the characteristics and long-term outcome are well-defined, can be expected to provide a better postoperative cardiac status. The composite T-graft enables us to revascularize whole left coronary system with the bilateral ITAs. Dobutamine stress echocardiographic study demonstrates a composite T-graft has sufficient flow capacity to perfuse not only the LAD to Dx but also the entire circumflex system as well. Role of off-pump CABG (op-CAB) in patients with malignant neoplastic disease: The evolution and establishment of the op-CAB has made it possible to revascularize patients who otherwise could not undergo effective myocardial revascularization due to the presumed high morbidity associated with cardiopulmonary bypass. Over the last 2 years, 60 patients underwent op-CAB in our institute. Of these, there were 10 patients who had malignant disease requiring non-cardiac surgery. The coexistent disorders included; gastric cancer (5), urinary bladder cancer (2), and cholangioma, lung cancer, colon cancer in one respectively. An op-CAB was performed through a sternotomy, left thoracotomy or subxiphoid incision. Five patients received single grafting and 4 double. Simultaneous non-cardiac operations were carried out in 6 patients. The other 4 patients also underwent subsequent operations uneventfully. Op-CAB is quite efficient and is of great advantage in patients with malignancy who require myocardial revascularization as well as an additional non-cardiac operation for the cancer.

40.

ATTENUATED INTRACELLULAR CA^{2+} RESPONSE TO B-ADRENOCEPTOR STIMULATION IS DUE TO CONVERSION OF A 45KDA GSα ISOFORM TO A 52KDA GSα ISOFORM IN THE HEART OF CHRONICALLY HYPOXIC RAT

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The cardiac responses to β-adrenoceptor stimulation are attenuated in hypertrophied and failing heart. In addition to down-regulation of the β-adrenoceptor receptor it is believed that the intracellular signaling mechanisms may also be altered. In the present study we determined firstly the electrically induced intracellular Ca^{2+} ($[Ca^{2+}]i$) transient in response to activation of β-adrenoceptor with isoproterenol (Iso), Gs protein with cholera toxin (CTX) and adenylate cyclase (AC) with forskolin in isolated myocytes of the right hypertrophied rat induced by treatment with 10% oxygen for 4 weeks. The electrically induced intracellular $[Ca^{2+}]i$ transient was determined with a spectrofluorometric method using fura-2A as Ca^{2+} indicator. 1μM Iso, 20 μg/ml CTX for 6 h and 1μM forskolin increased the electrically induced $[Ca^{2+}]i$ transient in both types of rats. The response to Iso and CTX was significantly attenuated, while that to forskolin not changed, in the right ventricle of chronically hypoxic rats. Secondly we determined with an immunoblotting method the contents of the 45kDa and a 52 kDa isoforms of Gsα in the right ventricle of normoxic and hypoxic rats. We found that the 45kDa isoform was significantly reduced, while the 52 kDa protein increased, in the ventricle of hypoxic rats. Since the 45kDa isoform is the active isoform, the attenuated Ca^{2+} response to activation of Gs-protein may be due to the conversion of the active isoform to the less active isoform in the heart of hypoxic rats. (The study was supported by a grant from the Institute of Cardiovascular Science and Medicine).

ABSTRACTS

41.

A NOVEL IMPELLER PUMP FOR LONG-TERM CIRCULATION SUPPORT

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Our former works demonstrated that the author's impeller Pump could support the circulation of experimental animals for several months without harm to blood elements and organ function of the animals. The termination of the experiments was mostly related to wear of the mechanical bearing and the thrombosis along the bearing. To solve bearing problem, a magnetic bearing was investigated in our lab, resulting in some new problems, such as complicated design and control, energy consume and lower reliability, etc. Progress in developing an impeller pump for long-term application has been achieved recently. Instead of using slide bearing, a ball bearing system has been devised, its service life is more than ten years due to wear-proof ball made of ultra-high-molecular weight polythene. In order to avoid thrombus formation, a special purge system was introduced to the bearing, thus the saline with heparin can be infused through the bearing into the pump. Therefore, the bearing keeps working in the saline, and no thrombus will be formed along the bearing. This simple but reliable approach enables the impeller pump to support the clrculation permanently.

Figure 1. *The implantable and pulsatile impeller pump for long-term circulation support.*

The device weighing 150g is fully implantable, consumes round 7W electric energy by delivering 4 l/min blood flow against 100 mmHg mean pressure and can produce both pulsatile and nonpulsatile flow according to the requirements.

42.

A SIMPLIFIED QUESTIONNAIRE ON QUALITY OF LIFE ASSESSMENT OF PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

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Background: To quantitate the outcome of patients after major open heart surgery, a scoring system of patients' quality of life including emotional, functional and psychosocial aspects is required. The present study was undertaken to establish the internal reliability and validity of a simplified questionnaire of quality of life assessment including different aspects of pre-operative and post-operative factors in a group of patients undergoing coronary artery bypass grafting (CABG). **Methods:** Two different questionnaires in pre-operative and post-operative assessments were translated in Chinese and distributed to total thirty-two patients on Day l0 after CABG. The pre-operative questionnaire assessing emotional status and social support system were assessed with total eleven items. The post-operative questionnaire on the emotional, physical activity and psycho-social aspects included eighteen items. Guttman split-half was used to test the internal reliability for pre-operative and post-operative factors. Pearson's correlation coefficient was used to test the correlation between the different aspects of pre-operative and post-operative functions. **Results:** Thirty-two sets of questionnaires were sent out and thirty patients responded. Two patients failed to return the questionnaires. Three patients required little assistance in filling the questionnaires. The Guttman Split-half was 0.8114 for the internal reliability on pre-operative emotional status, 0.8437 for pre-operative social support function, 0.9374 for post-operative status. There is significant correlation between pre-operative emotional stability and post-operative emotional status, physical well-being and confidence and self-esteem aspects. In addition, the pre-operative social support status was strongly correlated with post-operative confidence and self-esteem. Furthermore, there are significant correlations among the three aspects of post-operative functions and total score. **Conclusion:** This simplified questionnaire on different aspects of quality of life could be used with good internal reliability and validity to patients after major cardiac surgery. Besides operative mortality and morbidities, this quality of life assessment could be applied to assess and compare the outcomes after major cardiac surgery.

43.

COMPARISON OF OPERATIVE MORTALITY AND MORBIDITIES OF DOUBLE VALVE VERSUS MITRAL VALVE REPLACEMENT

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Background: Replacement of both the aortic and mitral valves requires additional assessment in the peri-operative management. The present study was undertaken to compare the incidence in operative mortality and morbidities and to identify the risk factors for development of these complications in patients undergoing double valve replacement (DVR) versus mitral valve re. placement (MVR). **Methods:** All the records of 125 patients operated on for DVR with or without rheumatic heart disease from 1992 to 1996 were reviewed. The mean age age was 48.86 ± 11.41 (SD) years (range 17-71). There were 52 male and 73 female patients. A total of 103 variables, including pre-operative, operative and post-operative variables were included in the univariate analyses. Significant variables for post-operative low cardiac output syndrome, post-operative renal and respiratory dysfunction were included in multivariate analyses. **Results:** The hospital mortality was 2.4% (3 out of 125) for DVR versus 3.8% for MVR in the same study period (p = NS). The incidence of post-operative low cardiac output syndrome occurred in 24.8% (31 out of 125) for DVR versus 20.4% for MVR p = NS). The risk factors for development of low cardiac output syndrome were pre-operative renal function impairment ($p<0.05$) and NYHA Class IV ($p<0.05$). 5.6% (7 out 125) of patients developed respiratory dysfunction versus 8.1% in patients undergoing MVR (p = NS). The risk factor for development of respiratory dysfunction in DVR was NYHA class IV ($p<0.05$). 8% (10 out of 125) of patients had renal dysfunction in DVR versus 7.8% in MVR (p = NS). The risk factors for post-operative renal dysfunction included age above 60 years ($p<0.05$), pre-operative renal function impairment ($p<0.05$), mitral stenosis ($p<0.005$), and severe tricuspid regurgitation ($p<0.005$). **Conclusion:** This study suggests that patient pre-operative variables including elderly age, NYHA class IV, renal function impairment, severe mitral and tricuspid valves disease are risk factors for development of post-operative morbidities. Furthermore, there is no significant increase in operative complications in patients undergoing DVR when compared to MVR.

44.

SEVERAL CHALLENGING ASPECTS IN VALVULAR REPLACEMENT

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The clinical application of valve replacement (V.R) has passed more than 35 years already. Following the progress of the design of artificial valve, surgical technique, anaesthesia and postoperative intensive care. V R has reached in a mature state in cardiac surgery . By thousands of cases suffer with heart valvular disease were salvaged by V.R, but there still have several challenging aspects in this field.

1. the option of surgical form in mitral valvular replacement: M.V R vs M. V R.P.
2. How to preserve the subvalvular apparatus of mitral valve.
3. The indication of aortic valve replacement.
4. The management of myocardial stunning during V R.

From the author review, M.V.R.P has more benefits for the patients after operation. In author data from 60 cases of mitral valve disease, underwent M V.R / M. V. R.P, each group with 30 cases in randomize after operation in M. V.R.P group, the spontaneous resuscitation rate of heart beat was high, the postoperative hemodynamic was more stable, The morbidity and mortality were reduced, the diameter of L.V. was reduced, A modification of Feikes procedures for the preservation of subvalvular apparatus of mitral valve was introduced by author. According to the indication of A.V.R in author opinion, the earlier, the better. A decreasing of pressure gradient in a severe aortic stenosis indicate that severe myocardial damage has happened, during the operation, the resuscitation may be very difficult with the stone heart. A rational management of myocardial stunning during operation was suggested by author. The principle of treatment includes: antiacidosis, vasoactive medicine, prolonged assisted circulation, manitol for promote fluid excretion, appropriate Mg^{2+} supplement.

45.

THE RELEASE OF ADRENOMEDULLIN FROM THE HEART IS INCREASED IN RATS WITH RENOVASCULAR HYPERTENSION

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Male S.D. rats weighing 280-320 g (10 weeks old) were used. To produce two kidney-one clip (2K1C) renovascular hypertension, a solid silver clip (0.2 mm in diameter) was placed on the left renal artery and the contralateral kidney was undisturbed. Sham-operated control rats underwent the same procedure except that no clip was placed on the left renal artery. Two weeks after the operation, the systolic blood pressure of the rats were measured by the tail-cuff method. Only rats with blood pressure higher than 150 mm Hg were used as hypertensive rats. The renin levels were increased in the renovascular hypertensive rats at 5 weeks but not at 2 weeks after clipping. Adrenomedullin (AM) in the left atrium was found to be reduced while its mRNA concentration was increased, suggesting an increase in the release of the peptide. Left ventricular AM and its mRNA were also increased in 5-week 2K1C renovascular hypertensive rats. In the right ventricle, only AM level was slightly elevated. The increase in atrial and ventricular AM release suggest that AM may participate in the regulation of ANP secretion and cardiac contractility in this kind of hypertension. As for the thoracic aorta and the mesenteric artery, we found no difference in the levels of AM and AM mRNA. A study of receptor binding in the vasculature for AM is under way.

46.

CLINICAL FEATURES AND CORONARY HEART DISEASE RISK IN HONG KONG CHINESE WITH FAMILIAL HYPER-CHOLESTEROLAEMIA

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Purpose: This study examined the clinical features, lipid levels and risk for coronary heart disease (CHD) in Chinese patients with familial hypercholesterolaemia (FH) in Hong Kong. **Methods:** Adult patients were identified as possible FH probands if serum total cholesterol was greater than 7.5 mmol/l. A clinical diagnosis of FH was made if: the pattern of hypercholesterolaemia in the family appeared to be of dominant inheritance or tendon xanthomata were present in the proband or a first degree relative. The history of CHD in the proband or family members was recorded. **Results:** Clinical FH was found in 89 male and 123 female patients, aged 36.9 ± 16.7 yrs (range 2 - 80 yrs), from 73 families. Baseline lipids were TC 9.1 ± 1.5 (range 5.6 - 13.3), LDL-C 7.2 ± 1.5 (range 4.2 - 11.7), HDL-C 1.34 ± 0.38, triglycerides 1.25 ± 0.71 mmol/L. LDL-C and TC significantly increased with age and were significantly higher in patients with xanthomata [n = 79 (37%), mean TC 10.0 ± 1.3, LDL-C 8.1 ± 1.2 mmol/L] than in those without xanthomata [n = 114 (54%), mean TC 8.6 ± 1.4, LDL-C 6.7 ± 1.4 mmol/L] but there was considerable overlap. In stepwise multiple regression analyses, the prevalence of xanthomata was significantly related to TC, LDL-C and age. 16 of 49 (33%) patients with age ≥ 50 yrs had evidence of CHD and where information was available 34 of 68 families (50%) had a history of any CHD and 13 families (19%) of premature (male<50 or female<60 yrs) CHD. These incidences were lower than in data published from Western countries, which indicate the risk for premature CHD is 45% in FH heterozygotes. **Conclusions:** FH occurs in Chinese patients in Hong Kong with similar lipid levels to those described in western countries and Japan but there appears to be a lower incidence of premature CHD suggesting there may be other factors which protect these patients from atheroma.

47.

THE ROLE OF LOCAL ANGIOTENSIN II AND ITS RECEPTOR ON THE PATHOGENESIS OF DIABETIC CARDIOMYOPATHY

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Object: to investigate the role of local angiotensin II and its receptor on the pathogenesis of diabetic cardiomyopathy. **Material and methods:** Wistar rats were randomly divided into two groups:3rd-month group: group(A)control I (n = 8) and group (B) streptozotocin-induced diabetes I (n = 8, rats were administrated by streptozotocin 60mg/kg intraperitoneally) and 6th -month group : group (C) control II(n = 10), (D) Losartan treated diabetic group (oral dose = $3mg.kg^{-1}.d^{-1}$, duration of treatment from 3rd to 6th month after diabetes induced, n = 10) and (E) diabetes II (n = 10). The cardiac function and some related parameters were determined in each group. **Results:** The left ventricular diastolic dysfunction appeared in group (B) ($-dp/dt_{max}$:687 ± 85.9 vs 864 ± 94.3 mmHg/s, P<0.05), both $+dp/dt_{max}$ and $-dp/dt_{max}$ decreased in group(E) compared with group(C) (748 ± 86.5 vs 1030 ± 120.8mmHg/s; 632 ± 63.9 vs 844 ± 64.6 mmHg /s, P<0.05, respectively) with no change of blood pressure. In group(D), blood pressure was lower than group(E) p<0.05, $+dp/dt_{max}$ and $-dp/dt_{max}$ increased but did not reach to the normal degree. Circulating and tissue angiotensin II (AII) increased significantly in group(B) (976.5 ± 131. 16 vs 416.9 ± 75.56pg/ml, P<0.01; 675.8 ± 57.84 vs 639.9 ± 54.87pg/g, P> 0.05 respectively) and group(E) (885.4 ± 103.11 vs 399.9 ± 62.93 pg/ml, P<0.05; 753.4 ± 52.03 vs 544.1 ± 58.24pg/g, P<0.05, respectively) compared with controls,and without significant change in group (D) Angiotensin II receptor dissociation constant of ventricular membranes (Kd) was significantly lower in group (E) than in group(C) without significant change of the maximal binding sites at 6th month which shows that angiotensin II receptor in myocardial has a high affinity in diabetes. **Conclusion:** These findings demonstrated that both local and circulating AII may play a role in the pathogenesis of diabetic cardiomyopathy.

48.

CLINICAL PREDICTORS OF PROGNOSIS IN PATIENTS WITH ISCHEMIC HEART DISEASE WHO UNDERWENT CARDIAC REHABILITATION - THE IMPORTANCE OF DIABETES MELLITUS AND EXERCISE

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Background: This prospective, follow-up study examined whether baseline clinical and investigational parameters could predict cardiovascular morbidity and mortality in patients enrolled into cardiac rehabilitation program (CRP). Methods and Results: 418 patients with coronary artery disease (CAD) who joined the CRP were followed for a mean duration of 3.2 ± 1.1 yrs. Among them, 70% were male, 54% had recent myocardial infarction [MI] & 45% had coronary angioplasty performed, in which mostly (89%) before entered CRP. The cumulative mortality was 13%. In the Cox proportional hazard model, factors that independently predicted mortality included low exercise capacity ($X^2 = 6.5$, p = 0.01) & the presence of diabetes ($X^2 = 6.1$, p = 0.01), and the latter was important in both patients with (log rank $X^2 = 18.9$, p<0.0001) and without (log rank $X^2 = 5.1$, p = 0.02) MI. Also, patients who required insulin therapy also had a higher mortality than dietary control (log rank $X^2 = 4.7$, p<0.03). 106 patients were re-hospitalized for non-fatal cardiovascular events. The predictive factors were diabetes ($X^2 = 4.8$, p = 0.03) & low METs at treadmill test (p = 0.02). Diabetic patients also had more frequent hospitalization (2.3 ± 2.1 Vs 1.6 ± 1.4, p = 0.04), longer hospital stay (25.5 ± 34.6 Vs 11.4 ± 19.6 days, p = 0.02), and a higher prevalence of multivessel disease ($X^2 = 22.2$, p<0.001) than those without. The LDL-cholesterol reduction was satisfactory (3.2 ± 1.0 Vs 2.7 ± 0.7 mmol/L, p<0.001). **Conclusion:** Therefore despite a combined regimen of medical therapy, aggressive lipid lowering, revascularization and exercise training, diabetes and low exercise capacity still unfavorably affect the prognosis in patients with CAD. Thus the CRP should concentrate on aggressive diabetic control and promotion of exercise capacity.

49.

CLINICAL EXPERIENCE WITH COMPREHENSIVE MITRAL VALVE REPAIR

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Objective: To evaluate the early and mid-term outcome of comprehensive mitral valve reconstruction. **Methods:** One hundred and twenty one patients with mitral valve reconstruction between September 1993 and January 1999 including 69 cases of mitral prolapse, 35 of rheumatic mitral valve disease, 8 of native valve endocarditis, 6 of congenital and 2 of other etiology, were analyzed retrospectively. All patients underwent mitral valve repair with mortified Carpentier's technique under standard cardiopulmonary bypass. Mitral valve regurgitation were evaluated by the color Doppler echocardiography before and after operation. **Results:** Eight patients were switched to prosthetic mitral valve replacement during the operation. There were 3 early postoperative deaths with a mortality of 2.65%. Follow-up, ranged from 6 months to 4.7 years, revealed 83 patients were in NYHA class 1, 19 in Class II, 6 in class III and 2 in class IV. Mitral systolic murmur was documented in 13 cases with reoperative valve replacement performed in three patient. Three-year postoperative echocardiographic evaluation showed that mitral regurgitation less than 1.0 ml was noted in 83.6% patients. The incidence of freedom from thromboembolic event at three postoperative years was 97%. **Conclusion:** Mitral valve reconstruction can be performed in most of the patients with mitral insufficiency from mitral prolapse with chordal rupture or elongation. Young patients with moderate valvular lesion of rheumatic process seems to have a satisfied clinical outcome whereas mid-term results have been less satisfactory in older patients with extensive rheumatic pathology, especially severe calcification.

50.

MYOCARDIAL EXPRESSIONS OF ENDOGENOUS OPIOID PEPTIDES IN RHEUMATIC HEART DISEASE AND THEIR EFFECTS ON CARDIAC PERFORMANCE

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Objectives: To elucidate the role of endogenous opioid peptides (EOP) in modulating cardiac dysfunction. **Methods:** The expressions of EOP including β-endorphin (β-EP), enkaphalin (Leu-ENK) and dynorphin A_{1-13} ($DynA_{1-13}$) and the gene of their precursors --pro-opiomelanocortin (POMC), preproenkephalin (PPENK) and preprodynorphin (PPDYN) were investigated on fresh frozen myocardium specimen by immunohistochemistry and in situ hybridization in 23 patients with rheumatic heart disease (RHD). There were 9 males and 14 females with an average age of 43.2 years. The patients were divided into two groups: group A (n = 14) with NYHA II-III plus LVEF≥50%, FS≥25% and group B (n = 9) with NYHA IV plus LVEF<50%, FS<25%. **Results:** β-EP, Leu-ENK and Dyn A_{1-13} expressions were found in 50~80% of all patients, whereas the degree of positivity ranged from about 40~70% of the myocytes of group A and 70~90% of group B. The mRNA levels of POMC, PPENK and PPDYN were 8.37 ± 1.55, 7.24 ± 2.97 and 5.04 ± 0.97 of group A and 12.94 ± 2.79, 13.47 ± 2.91 and 7.16 ± 0.72 of group B, respectively, and the precursors mRNA levels consistent with the levels of β-EP, Leu-ENK and Dyn A_{1-13} contents in the myocardium. There were close correlationships between the myocardial EOP levels and LVEF as well as FS. **Conclusion:** Our data indicate that EOP are expressed in human myocardium and regulated by the transcriptional levels of their precursors mRNA, which strongly suggests that EOP can be synthesized in situ in human heart. The increases of myocardial EOP levels in RHD patients are reversely correlated to the decrease of cardiac contractility and the impaired heart pump function.

51.

COMPARISON OF EXPERIMENTAL EFFICACY BETWEEN TWO METHODS OF TRANSMYOCARDIAL LASER REVASCULARIZATION

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Purpose: The purpose of this experiment is to study the long term open effect of laser channels by two methods of transmyocardial laser revascularization. **Method:** The acute myocardial infarction was produced by ligation of LAD in 36 dogs. The ischemic zone was divided into A and B zones at random. A zone was irradiated by laser acupuncture with Mirhoseini's method and B zone by laser acupuncture with "Filter wave slide" method. The hearts of experimental dogs were acquired at 4 hour, 0.5, 1, 3 and 6 months after the operation .The patency of laser holes was identified by pathology and myocardial cast. **Result:** At 4 hour after the operation, laser channels in "Filter wave slide" method were free of the layer of carbonization and oedema layer was only 50 mm. The channels together with ting vessels can be readily visualized and are seen filled with blood corpuscles. At the same time, the 7 mm carbonization and 270 mm coagulation necrosis can been seen in Mirhoseini's laser holes. The outlets of minimal vessels beside laser holes were closed by carbonization. At 6 month after the operation, the open rate of Mirhoseini's holes is 38% and the rate of "Filter wave slide" holes is 70%. The laser holes are still clear 36 months later. **Conclusion:** The method of "Filter wave slide" is superior to Mirhoseini's method. The two methods are all improvement for myocardial ischemia.

52.

THIRTY-EIGHT CASES OF MINIMALLY INVASIVE CARDIAC OPERATIONS

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Purpose: To evaluate the clinical cases of 38 cases of minimally invasive cardiac operations. **Material and method:** From October 1998 to July 1999, 38 patients with congenital heart defects or heart valve diseases underwent minimally invasive cardiac operations. Right anterior thoracotomy and cardiopulmonary bypass and heart arrest: ASD 2 cases and VSD 2 cases. Right anterior thoracotomy and cardiopulmonary bypass and heart unarrest: ASD 12 cases. VSD 2 cases. Reoperative MVR 1 case and Ebstein's anomaly 1 case. Median sternotomy and cardiopulmonary bypass and heart unarrest : VSD 3 cases. F4 2 cases. PDA 3 cases. MVR 6 cases and DVR 4 cases. **Result:** There was no operation death. Postoperative complications included bleeding and acute kidney failure. **Conclusion:** The preliminary results of this study suggest that MICS is an effective and safe method for the patients with selective heart diseases. It can provide significant injure relief. incision prettify and incidence of heart failure drop.

ABSTRACTS

53.

ASSESSMENT OF LEFT ATRIAL AND VENTRICULAR FUNCTION BY ACOUSTIC QUANTIFICATION

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Background: Acoustic quantification (AQ) is a recent echocardiographic advance for quantitative assessment of cardiac function by automatic tracking of the endocardial border during the cardiac cycle. This study assessed the use of AQ to assess left ventricular and left atrial function. **Methods:** 43 patients (mean age: 64 ± 13 years, 84% male, 81% had myocardial infarction) undergoing echocardiography were assessed by AQ under harmonic imaging at apical 4-chamber view for the left ventricular (LV) and left atrial (LA) function. The results were correlated with conventional M-mode assessment of systolic function. **Results:** The mean LV ejection fraction (EF) measured by AQ was significantly lower than that by M-mode (43 ± 14 Vs 54 ± 19%, $p < 0.001$). There was a significant correlation between these 2 measurements ($r = 0.72$, $p < 0.001$). In addition, the peak left ventricular emptying rate calculated by AQ correlated with LV-EF estimated by both AQ ($r = 0.89$, $p < 0.001$) and M-mode ($r = 0.58$, $p = 0.002$). For LA function, both the peak atrial filling rate and peak atrial emptying rate correlated positively with LV-EF by either AQ (peak filling: $r = 0.73$, $p < 0.001$; peak emptying: $r = 0.74$, $p < 0.001$;) or M-mode (peak filling: $r = 0.69$, $p = 0.003$; peak emptying: $r = 0.67$, $p = 0.005$). The fractional area change in LA also predicts EF, though it was weaker (AQ: $r = 0.43$, $p = 0.047$; M-mode: $r = 0.48$, $p = 0.04$). It was found that the greater the LA area, the lower the peak LA emptying and filling rate (both $r = -0.70$, $p < 0.001$). On the other hand, the LA peak emptying rate ($r = 0.51$, $p = 0.09$), filling rate ($r = 0.52$, $p = 0.09$) and fractional area change ($r = 0.52$, $p = 0.08$) only weekly correlate with transmitral atrial filling velocity. **Conclusion:** AQ is a useful tool to assess both LV and LA function. In addition, in patients with cardiac diseases, the LA indexes derived from AQ provide additional insight for LV systolic function. This is likely related to the dependence of LV on atrial filling in the presence of delayed diastolic relaxation.

54.

RECORDING OF A MECHANOSENSITIVE CA2+-PERMEABLE CHANNEL IN VASCULAR ENDOTHELIAL CELLS

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The hemodynamic force generated by blood flow is considered to be the physiologically most important stimulus for the release of nitric oxide (NO) and prostacyclin (PGI_2) from vascular endothelial cells. NO and PGI_2 then act on the underlying smooth muscle cells, causing vasodilation and thus lowering blood pressure. One critical early event occurring in this flow-induced regulation of vascular tone is that blood flow induces Ca^{2+} entry in vascular endothelial cells, which in turn leads to the formation of NO. In the present study, we report a mechanosensitive Ca^{2+}-permeable channel in vascular endothelial cells. The activity of the channel was inhibited by 8-Br-cGMP, a membrane-permeant activator of protein kinase G (PKG), in cell-attached patch clamp study. The inhibition could be reversed by PKG inhibitor, KT5823 or H-8. A direct application of active PKG in inside-out patches blocked the channel activity. The channel activity was also inhibited by Gd^{3+}, Ni^{2+}, or SK&F-96365. This channel could be a mechano-transducer transforming the mechano-signals generated by blood flow into a chemical messenger of intracellular Ca^{2+}.

55.

COMPARISON OF VALSARTAN AND FOSINOPRIL IN THE SUPPRESSION OF MYOCARDIAL FIBROSIS AND MATRIX CELLULAR INFILTRATION IN RATS AFTER ACUTE MYOCARDIAL INFARCTION

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Background: Myocardial interstitial fibrosis and cellular infiltration may play an important role in myocardial remodeling early after acute myocardial infarction (MI). Since angiotensin II type I receptor antagonist (AIIA) has more complete suppression of angiotensin II production, we hypothesized that AIIA is superior to angiotensin converting enzyme inhibitor (ACEI) for the suppression of these histopathological changes. **Methods:** 67 post MI rats were randomized to receive fosinopril (Fo), an ACEI; valsartan (Val), an AIIA; or a combination of these 2 agents (Cx) for 2 or 4 weeks. The interstitial collagen type I & III, activated myofibroblasts & macrophages were stained by immunohistochemistry and quantified by morphometry. **Results:** The mean blood pressure was significantly lower in all the treatment groups at 2-wk post-MI, but was only lower in Cx group at 4-wk. In MI rats, the type I collagen in the non-infarcted septum was increased at 2- and 4-wk after MI, but not in the right ventricle. At 2-wk, both Fo (1.3 ± 0.7 Vs 0.4 ± 0.2%, $p<0.001$) & Val (1.3 ± 0.7 Vs 0.7 ± 0.6%, $p=0.001$) decreased type I collagen, but was only suppressed by Cx at 4-wk (1.0 ± 0.5 Vs 0.6 ± 0.4%, $p=0.02$). The type III collagen content in both septum & RV was unchanged after MI, though it was decreased at both sites by Val (both $p<0.01$). In the infarct zone, Val and Cx decreased the infiltration of both activated myofibroblasts (MI: 38.5 ± 13.7, Val: 24.8 ± 6.8, Cx: 17.4 ± 5.9 cells/ROI; both $p=0.001$), and macrophages (MI: 60.8 ± 20.8, Val: 49.6 ± 10.3, Cx: 45.4 ± 9.5 cells/ROI; both $p=0.001$), but not by Fo (Myofibroblast: 35.6 ± 10.5; Macrophage: 57.8 ± 14.6). **Conclusion:** Accumulation of type I collagen in the non-infarcted septum occurred even early after MI, which was prevented by Fo and Val. However, matrix cellular infiltration in the infarct zone was only inhibited by AIIA containing regimen, but not ACEI. Therefore, AIIA might have therapeutic advantage over ACEI after acute MI.

56.

TOWARD MORE SCIENTIFIC EVALUATION OF PARTIAL LEFT VENTRICULECTOMY (BATISTA OPERATION) USING DILATED CARDIOMYOPATHY MODEL

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Background: Scientific investigation of partial left ventriculectomy (PLV) for dilated cardiomyopathy (DCM) is not necessarily easy, in part because there is no good small animal model for this operation. **Purpose:** To evaluate LV dimension and function before and after the PLV using a Dahl rat model of DCM which we developed. **Methods:** Twelve Dahl salt-sensitive (DS) rats started having high-salt diet from the age of 9 weeks, and at 25-28 weeks developed marked LV dilatation (with the LV diameter of 1.5-2 times as large as the control) and congestive heart failure secondary to hypertension. Under general anesthesia and via left thoracotomy, twelve rats had PLV with beating condition using plication method by pledgetted monofilament sutures. LV dimension and pressure was measured by echocardiography with 12.5MHz probe ($n = 8$) and micromanometer-tipped catheter via right carotid artery just before and after the surgery ($n = 4$). **Results:** Six rats died of arrhythmia or bleeding related to hypertension, but rest of the rats survived. All survivors had less signs of heart failure (e.g. tachypnea). After the PLV, LV end-diastolic diameter (mm) decreased from 8.3 ± 0.4 to 6.7 ± 0.8 ($p<0.001$ by paired t-test), LV fractional shortening (%) increased from 31.7 ± 4.6 to 50.9 ± 7.0 ($p<0.001$). Emax increased from 0.36 ± 0.12 to 0.74 ± 0.29, and LV wall stress (dyne/cm^2) decreased from 253 ± 41 to 118 ± 32. However, LV end-diastolic pressure (mmHg) increased from 4.3 ± 1.9 to 14.7 ± 2.1 and Tau (ms) tended to increase from 36.7 ± 2.7 to 46.0 ± 6.2. **Conclusion:** The partial left ventriculectomy improved LV systolic function and dimensions soon after the PLV surgery in the DCM DSrat model. However, the LV diastolic function did not improve. Further investigation using the rat model, especially for surgical indication, late effects and molecular aspects of the PLV is warranted.

57.

OUTCOME OF NEONATES WITH CONGENITAL HEART BLOCK

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Background: Congenital heart block (CHB) is a rare cardiac arrhythmia in neonates. In this study we investigate the clinical course of 24 cases of neonatal CHB and the risk factors which might predict development of symptoms. **Method:** We reviewed the hospital records of 24 neonates with CHB admitted between 1981-1999. The patients were divided into those without (n = 18) and with (n=6) intracardiac lesions and their outcome was compared. In patients with isolated CHB, they were subdivided into symptomatic and asymptomatic groups and their clinical variables of ventricular rate (VR) at rest, QRS duration, corrected QT intervals(QTc), and cardiothoracic(CT) ratio were compared. Student's t test and Chi square test were used for statistical analysis. **Results:** The patients were aged 1 day to 18 years (median = 4 years) at the time of death or latest follow up. CHB was diagnosed antenatally in 13 (54%) patients. Three of the 4 patients presented with neonatal second degree CHB progressed to complete CHB. Permanent pacing were performed in 8 patients with heart failure and in 1 without symptom. Four neonates died because of heart failure, including 3 with intracardiac lesions. Beyond the neonatal period, 3 infants died of sepsis/pneumonia and 1 died suddenly (without pacemaker). The 1,5, 10 years survival rate for the whole group were 74%, 70% and 60%, respectively. The mortality for patients with intracardiac lesions were significantly higher than those without (4/6 vs 4/18) $p<0.05$. Of the patients with isolated CHB, 11 developed heart failure and 1 Stokes-Adams attack. Symptomatic patients had a larger CT ratio (0.63+/-0.06) $p = 0.03$ and lower VR at rest (52+/-12 beats per minute) $p = 0.04$. The QTc and QRS duration did not predict development of symptoms. **Conclusions:** Amongst neonates with isolated CHB a larger CT ratio (0.63) and slow ventricular rate (52 beats per minutes) predicted the development of symptoms. The presence of associated structural heart lesions carries a poorer prognosis.

58.

SURGICAL INTERVENTION OF COMPLEX ENDOCARDITIS

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Objective: To investigate the clinical outcome of surgical treatment for complex endocarditis. **Clinical materials and methods:** From December 1988 through April 1999, 40 patients including 27 male and 13 female (mean age, 39.8 years) with complex endocarditis underwent surgical intervention. Infecting organisms were detected in 19 patients (47.5%) including staphylococcus aureus in 9, streptococcus viridan in 4 and gram-negative cocci in 6. Intraoperative findings demonstrated valvular vegetations (n = 38), valve leaflet massive destruction (n = 24), annular abscesses (n = 9) and myocardial abscesses (n = 6). Left ventricular-aortic discontinuity was noted in 3 patients. One patient with a ventricular septal defect had significant valve regurgitation because of an acute bacterial endocarditis which invaded to all the four valves (mitral, aortic, tricuspid and pulmonary) and resulted in severe valve leaflet destruction. After careful debridment of the infected tissue, complex reconstruction of the annulus was required in 12 patients and associated procedures including aortic valve replacement in 20, mitral valve replacement in 7, mitral valve repair in 3, concomitant mitral and aortic valve replacements in 6 and triple (mitral, aortic and tricuspid) valve replacement with pulmonary valve reconstruction by using autologous pericardium in 1. Bentall's procedure was performed in 3 patients. **Results:** There were three operative deaths (one of uncontrolled heart failure and two of sepsis), giving an early postoperative mortality of 7.5%. Follow-up, ranged from 4 months to 9 years, revealed no patient has had recurrence of endocarditis. Eighteen patients were in NYHA class 1, 15 in Class II and 2 in class III. Actuarial survival at 5 years was 66.2+8.9%. **Conclusion:** Careful debridment of the infected tissue with valve replacement and Bentall procedure can facilitated complex endocarditis with a satisfactory clinical outcome when hemograft or allograft is not available.

59.

VIABILITY STUDIES OF NEONATE CRYOPRESERVED ALLOGRAFT VALVED CONDUIT

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Samples of aortic and pulmonary walls with their valves from 11 neonates were assessed for histological ultrastructure, cytometabolic capability and valved conduit mechanical behavior by histology technique, radioautography and biomechanical test to evaluate the function and structure of neonate allograft valved conduit before and after cryopreserved. Histoviability with different warm ischemic times (WITs) were compared, also between aortic and pulmonary walls. Results showed: Metabolic capability of neonate histocyte was exuberant, the elastic fibers in fibric components was minority, which were suitable for correcting malformations of the infant complex congenital heart diseases; Endothelium cells (ECs) was susceptible to alterations in WITs, the changes of histologic ultrastructure had a positive correlation with the prolongations of WITs, which may need to be restricted to 12 hours to retent the original architecture except for reversible cellular injury. Thus, cryopreservation was responsible for the viability of ECs, but not for others cellular ingredients and extracellular matrix (ECM). The changes of metabolic capability of ^{3}H-proline marked histocyte conformed to the alteration of structure, meant within the same WITs the synthetic activity of fibroblasts had more resistance to proceeding factors such as cryopreservation. An intact ground substance of allograft valved conduit allowed to the fibers to rearrange their orientation in response to the applied tensile forces and thus reduced the interrall stresses, which indicated that the shorter WITs, intrarral stresses would cause less destroys. The elastic modulus and the stress strength were demonstrated statistically significant ($P<0.01$) decrease between WITs within 2 hours and over 12 hours before and after cryopreservation, but no significant ($P>0.05$) difference between fresh and cryopreserved tissues. The resilence of pulmonary walls was similar to that of aortic, and the stress strength was superior but no statistical significant.

60.

MINIMALLY INVASIVE MITRAL AND AORTIC VALVE REPLACEMENT ---THE MINISTERONOTOMY APPROACH

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Objective: The minimally invasive mitral and aortic valve replacement were designed. A series of patients were studied for ministeronotomy approach. **Material and methods:** Eight patients underwent minimally invasive valve replacement through partial steronotomy. 5 mitral valve replacements and 3 aortic +mitral valve replacements. The incision was 7 to 9cm. The operative technique, aortic crossclamp time, postoperative mediastinal drainage, ICU stayed time and extubation time, postoperative morbidity, sternum-healing and patient satisfaction was analyzed. **Results:** There was no operative mortality and complication in this group. The approach accelerated postoperative patients recovery, limited surgical trauma, reduced blood loss, decreased pain and made a excellent wound-healing. **Conclusions:** The new minimal-access median sternorotomy that maintained the integrity of sternum was safety, it lessen surgical trauma and created cosmetically result attractive to patients.

61.

ATTENUATED [Ca^{2+}]i AND [pH]i RESPONSES TO K-OPIOID RECEPTOR STIMULATION IN THE HEART OF RATS SUBJECTED TO CHRONIC HYPOXIA

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In the present study we determined the [Ca^{2+}]i and [pH]i responses to κ-opioid receptor stimulation in the hypertrophied right heart induced by chronic hypoxia. U50,488H, a selective κ-opioid receptor agonist, at 10 - 30 μM, dose-dependently decreased the electrically-induced [Ca^{2+}]i transient. 20 μM U50,488H also increased the [pH]i. The effects of the k-opioid receptor agonist at 20 μM were completely abolished by 5 μM nor-binaltorphimine (nor-BNI), a selective κ-opioid receptor antagonist and 1 μM calphostin C, a specific inhibitor of protein kinase C (PKC). We further investigated the [Ca^{2+}]i and [pH]i responses to activation of PKC, known to mediate the actions of κ-opioid receptor stimulation. PMA, an activator of PKC, at 0.01 - 1 μM also dose-dependently decreased the electrically-induced [Ca^{2+}]i transient and at 0.1 μM it increased the [pH]i. The effects of 0.1 μM PMA were abolished by 1 μM calphostin C. The effect of 0.1 μM PMA on [pH]i was also blocked by EIPA, a potent Na^{+}-H^{+} exchange (NHE) blocker. In the right hypertrophied heart of rat subjected to hypoxia for 4 weeks, the effects of U50,488H and PMA on [Ca^{2+}]i transient and [pH]i were significantly attenuated and completely abolished, respectively. The responses to The results demonstrated for the first time that the [Ca^{2+}]i transient and [pH]i responses to κ-opioid receptor stimulation were impaired in the heart of rats subjected to chronic hypoxia, which may be due to impaired PKC functions.

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