ABSTRACTS

Abstracts for Invited Lectures:

IL1.

HEART FAILURE IN CHINA: PREVALENCE AND CURRENT TREATMENT

Philip YA Ding
Professor of Cardiology and Critical Care Medicine, National Yang-Ming University, Taipei Veterans General Hospital, Taipei, Taiwan

Heart failure (HF), a major cause of morbidity and mortality, is reported to consume 2% to 3% of the total health care costs in industrialized countries. The age-adjusted mortality for HF patients is four to eight times that of the general population, comparable to that of cancer diseases in the same age groups. The predominant causes of HF are hypertension and coronary heart disease (CHD). Other identified risk factors for HF include left ventricular (LV) hypertrophy, valvular heart disease, diabetes mellitus, cigarette smoking, obesity, and dyslipidemia. Population-based studies to date have shown different results concerning the relative importance of these risk factors. In the past decade, considerable knowledge has been gained regarding the pathophysiology of HF in the experimental setting, small clinical samples, and larger population-based studies. New mechanisms, such as insulin resistance, inflammation, and oxidative stress, have been investigated. Epidemiologic studies revealed that these mechanisms are largely established in the general population.

Based on the 2001 Chinese national survey of cardiovascular diseases and risk factors study, a total of 15,518 adults were collected from 10 provinces of China (5 in the North and 5 in the South) with an equal distribution from urban and rural populations. The prevalence of chronic heart failure (CHF) was 0.9%, 0.7% and 1.0% for the general population, the males and females, respectively. Females with CHF were more frequent than males ($p<0.05$). CHF prevalence was 0.4%, 1.0%, 1.3% and 1.3% in the 35-44, 45-54, 55-64, and 65-74 years of age, respectively. The prevalence rate of CHF increased substantially with aging. The figure of prevalence of CHF was 1.4% and 0.5% in northern and southern population, respectively; and the figure was 1.1% and 0.8% in urban and rural population, respectively. The risk of CHF was higher in northern than in southern China and was higher in urban than in rural area.

Over the last two decades, major advances have occurred in the treatment of heart failure patients. Randomized clinical trials showed that ACE-inhibitors, angiotensin receptor blockers, β-blockers, and aldosterone antagonists as well as mechanical circulatory support devices can reduce morbidity and mortality in patients with heart failure. Guidelines have been established to help physicians in reaching a clinical decision - making this a rapidly evolving field. In China, most physicians are increasingly encouraged to apply the most updated treatment guidelines in their practice. However, there is a considerable proportion of heart failure patients who do not receive evidence-based treatment. Several factors may explain the reported under-utilization of evidence-based treatment such as lack of knowledge and technical expertise of the physicians, economic restraints, and family wishes from patients.

In conclusion, among cardiovascular diseases, heart failure is becoming an important issue of public health in China.

IL4.

HEART FAILURE: A VASCULAR DISEASE?

V Richard
Department of Pharmacology, Rouen University Hospital, Rouen France

Although heart failure (HF) is by definition a disease mostly affecting the cardiomyocytes, there is also growing evidence that this disease has important consequences for the vasculature, and especially impacts the vascular endothelial cells, both at the coronary and peripheral levels.

At the coronary level, HF markedly alters coronary endothelial function and especially the release of endothelium-derived factors such as nitric oxide (NO). Given the role of this factor as a regulator of vasodilator tone, but also as an important inhibitor of platelet aggregation and leukocyte function, it is likely that such an impaired NO production not only will contribute to increased vasoconstriction, but also will favour thrombosis and atherosclerosis, thus increasing the risk of (re)infarction and aggravating HF. In parallel, the development of HF is associated with a progressive reduction of coronary arteriolar and capillary density (due at least in part to impaired coronary angiogenesis). Such reduced vascular density, and the resulting impaired cardiac perfusion is now recognized as a critical determinant of the aggravation of HF and of cardiac decompensation.

At the peripheral level, there is growing evidence that HF also profoundly impairs physiological NO production, notably at the level of small peripheral arteries. Such impairment is especially important since it will contribute to peripheral vasoconstriction and will potentiate the effects of the major vasoconstrictor systems known to be activated in HF (i.e. the renin-angiotensin, endothelin and sympathetic systems). This results in an increased peripheral vascular resistance which augments the afterload of the heart, ultimately aggravating HF. The impaired peripheral production of NO appears to be the consequence of interaction between mechanical (e.g. chronic decrease in blood flow), neurohumoral (e.g. angiotensin) and inflammatory (e.g. reactive oxygen species and TNFα) influences.

Importantly, endothelial dysfunction in HF can be reduced by various pharmacological approaches, including 'classic' treatments of HF (e.g. angiotensin converting enzyme inhibitors such as perindopril) and more recent treatments (e.g. heart rate lowering agents such as ivabradine). In addition, recent therapies have emerged and appear promising in the treatment of HF-induced endothelial dysfunction, including modulators of endothelial phosphorylation pathway (e.g. using tyrosine phosphatase inhibitors), which may provide new clinical opportunities for the treatment of HF.

ABSTRACTS

Abstracts for Invited Lectures:

IL6.

ENDOTHELIAL PROTECTIVE EFFECT OF NUCLEOSIDE UPTAKE INHIBITORS

GPH Leung
Department of Pharmacology, The University of Hong Kong, Hong Kong SAR, China

Inflammation of endothelium is closely associated with the development of atherosclerosis. It has been well established that interstitial level of adenosine is increased during inflammation. Adenosine possesses anti-inflammatory property so it may serve to protect tissues from injury and potentially slow down the progression of atherosclerosis. The increase in extracellular adenosine level at the sites of inflammation is mainly due to the up-regulation of ecto-5' nucleotidase by phosphoinositide 3-kinase (PI3K)-dependent pathways. The ecto-5' nucleotidase catalyses the conversion of extracellular adenosine nucleotides into adenosine.

Patients with diabetes mellitus suffer greater morbidity from atherosclerosis. Glucose *per se* does not affect ecto-5' nucleotidase but it increases the expression levels of equilibrative nucleoside transporters (ENTs) via mitogen-activating protein kinase (MAPK)-dependent pathways. It is speculated that the increase in ENTs may reduce the availability of adenosine in the vicinity of adenosine receptors, thereby attenuating the anti-inflammatory effect of adenosine in diabetes.

The anti-inflammatory effect of adenosine can be potentiated pharmacologically by ENT inhibitors, of which nitrobenzylmercaptopurine ribonucleoside (NBMPR) and dipyridamole are the representatives. No oral hypoglycemic agents can inhibit ENTs except troglitazone. Unfortunately, this thiazolidinedione has been withdrawn from the market. Screening of anti-hypertensive agents has revealed that ENTs are sensitive to dihydropyridine-type calcium channel antagonists, particularly nimodipine, which can inhibit ENTs in nM range. Those calcium channel antagonists are non-competitive inhibitors of ENTs, probably working through the reversible interactions with allosteric sites. In vitro study has demonstrated that nimodipine and nifedipine can reduce the lipopolysaccharide-induced interleukin-8 release in endothelial cells. This effect is independent of their inhibitory effects on calcium channels but is more likely to be due to the blockade of ENTs. Therefore, while treating vascular diseases such as hypertension and angina pectoris, dihydropyridines may have an additional beneficial effect in attenuating endothelial inflammation and hence, ameliorating atherosclerosis and its complications.

IL11.

BERBERINE AS A POTENTIAL DRUG FOR THE TREATMENT AND PREVENTION OF VASCULAR DYSFUNCTION IN OBESITY AND DIABETES

Y Wang,[1] Y Huang,[2] Karen SL Lam,[1] Chi-Wai Lau,[2] Paul M Vanhoutte,[3] A Xu[1,3]
[1]Department of Medicine, The University of Hong Kong; [2]Department of Physiology, The Chinese University of Hong Kong; [3]Department of Pharmacology, The University of Hong Kong, Hong Kong SAR, China

Introduction: Vascular disorder is a common soil for many deadly diseases and is one of the most common complications observed in Type 2 diabetes. Endothelial dysfunction, characterized by impaired vasodilation, is a key event that links obesity, diabetes, hypertension and vascular diseases. The AMP-activated protein kinase (AMPK) plays a key role in endothelial cell, including protection of cells from apoptosis, inhibition of inflammation and stimulation of angiogenesis. The objectives of this study are to evaluate the protective effect of berberine, an alkaloid purified from traditional Chinese medicine, against hyperglycemia-induced cellular injury, endothelial dysfunction, and to investigate the potential role of AMPK pathway in this process.

Method: Berberine was tested for its effect on the production of nitric oxide (NO), activation of eNOS as well as the association of eNOS with heat shock protein(HSP)90 and AMP-activated protein kinase (AMPK) in human umbilical vein endothelial cells (HUVEC). The effect of berberine on vascular reactivity was examined on aortic rings isolated from rats. In addition, berberine was also evaluated for its actions on inhibiting production of intracellular ROS, apoptosis and NF-κ B activation under hyperglycemia circumstance.

Results: In cultured endothelial cells and blood vessels, berberine dose-dependently enhanced eNOS phosphorylation and promoted the association of eNOS with heat shock protein (HSP)90, leading to an increased production of nitric oxide (NO). Furthermore, berberine attenuated high glucose-induced generation of reactive oxygen species (ROS), cellular apoptosis, NF-κappaB activation and expression of adhesion molecules, thus suppressing monocyte attachment to endothelial cells. In rat aortic rings, berberine elicited endothelium-dependent vasodilatations and alleviated ROS-mediated endothelial dysfunction. These beneficial effects of berberine on the endothelium were abolished by either pharmacological inhibition of AMP-activated protein kinase, or adenovirus-mediated overexpression of a dominant negative version of AMPK.

Conclusions: The present results demonstrate that berberine protects against endothelial injury and enhances NO-dependent vasodilatation through activation of the AMPK/eNOS signaling cascade. Berberine or its derivatives may be useful for the treatment and/or prevention of endothelial dysfunction associated with diabetes.

ABSTRACTS

Abstracts for Invited Lectures:

IL12.

A COMPOUND FROM CHINESE MEDICINAL HERB PROVIDES A POTENTIAL CURE FOR ATRIAL FIBRILLATION

GR Li
Departments of Medicine and Physiology, The University of Hong Kong, Hong Kong SAR, China

Atrial fibrillation (AF) is the most common form of cardiac dysrhythmia. It increases the risk of death, congestive heart failure, and embolic phenomena including stroke. AF is believed to be a lifetime risk in an aging population. Antiarrhythmic drug therapy remains the principal approach for suppressing AF and its recurrence. Class III anti-arrhythmic agents are effective in treating AF, but have major limitations, such as inducing severe ventricular arrhythmia (i.e. long QT syndrome). A key objective among the current strategies for suppressing AF is the development of new Class III antiarrhythmic agents that preferentially affect atrial rather than ventricular electrical parameters. Pharmaceutical researchers have been focusing on developing selective inhibitors of the human atrial I_{Kur} or hKv1.5 channels, which is present in atrium, but not in ventricles of the human hearts. However, there is no such drug commercially available yet. We have been investigating traditional Chinese medicine to find selective I_{Kur} blockers for the treatment of atrial fibrillation. By collaborating with Shanghai Institute of Materia Medica, Chinese Academy of Science, we have recently found that the natural flavone acacetin from the Chinese medicine *Xuelianhua* selectively inhibited human atrial ultra-rapid-delayed rectifier K^+ current (I_{Kur}) and transient outward K^+ current (I_{to}), and prolonged action potential duration in human atrial myocytes. The compound blocked acetylcholine-activated K^+ current; however, it had no effect on other currents in guinea pig cardiac myocytes. In anesthetized dogs, acacetin prolonged atrial effective refractory period (ERP) after intraduodenal administration without QTc prolongation, whereas the clinical drug sotalol prolonged atrial ERP, and ECG QTc interval. In addition, acacetin prevented AF induction in anesthetized dogs. Our study demonstrates that acacetin targets to human atrial repolarization currents and is an atrial selective agent. It effectively prevents AF induction in anesthetized dogs after intraduodenal administration, indicating that oral acacetin is a promising atrial-selective agent for the treatment of AF. Therefore, the natural compound acacetin from the traditional Chinese medicinal herb *Xuelianhua* provides a potential cure for atrial fibrillation.