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General Summary

The Japanese Investigation of Kinetic Evaluation in Hypertensive Event And Remodeling Treatment (JIKEI HEART) Study began registration in January 2002. By the end of November 2004, 3,081 patients had been enrolled, exceeding the original target enrollment. We could obtain meaningful results from the valsartan-treated group, and these results were accepted for publication in *The Lancet*. The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM), the trial in which our cardiac arrhythmia group is taking a lead role, announced that its study portion was completed on April 3, 2006. We are now waiting for the results to be summarized. Enrollment in the Assessment of β-Blocker Treatment in Japanese Patients with Chronic Heart Failure (J-CHF) trial has been stalled because only patients with untreated heart failure are enrolled. New registrations will be accepted until the end of 2006.

Individual research groups are continuously obtaining results from clinical and basic research. In the cardiac catheterization group, an increasing number of patients have received drug-eluting stents. Clinical follow/up data from 6 to 12 months is being accumulated. Utilizing a network system among the main university hospitals and 4 affiliated hospitals, data control and results analyses are under way. In the cardiac arrhythmia group, as the number of cases of radical therapy for atrial fibrillation (isolating pulmonary vein using a catheter) increases, new studies to address unexpected issues or points requiring improvement are being developed. Since 2005, the lipid metabolic group has been performing metabolic experiments with stable isotopes and has been performing research in collaboration with institutions overseas. Individual groups are also promoting their own basic research using an original experimental system and preparing for presentations next year at the scientific meetings of the Japanese Circulation Society, the International Society for Heart Research, the American Heart Association, and other groups. This year, graduate students in both basic and clinical courses powerfully demonstrated very vigorous research activities by studying domestically or abroad and announcing their research results.

Research Activities

Clinical research

1. Large-scale clinical trials

1) JIKEI HEART Study

The JIKEI HEART Study is a large-scale clinical trial that examined the effect of oral administration of valsartan on the prognosis of patients with hypertension and ischemic heart disease or heart failure. The study, which was performed by means of the prospective, randomized, open, blinded endpoint method, is Japan's first clinical trial in this field and has enrolled more than 3,081 patients at various Jikei University Hospitals. The study was completed in November 2005. We could obtain meaningful results from the valsartan-treated group, and these results were accepted for publication in *The Lancet*.

2) J-RHYTHM

J-RHYTHM is a multicenter randomized comparative trial that is examining drug therapies for atrial fibrillation. The trial is comparing the efficacies of therapy to sustain sinus rhythm and of therapy to control heart rates. J-RHYTHM was initiated by the Japanese Society of Electrocardiology with the support of the Japanese Circulation Society. The Ethics Committee of The Jikei University approved our division's participation. The arrhythmia team took the initiative, began study registration in April 2004, and observed the clinical time courses for the enrolled subjects. The study end was announced on April 3, 2006, and procedures for registering case data for study analysis have begun.

3) J-CHF

Underway since 2005, this large-scale clinical trial aims to establish a standard β-blocker therapy for patients with chronic heart failure. Specifically, the trial aims to determine the optimal dosage by comparing the efficacy and safety of 3 dosages of the β-blocker carvedilol: 2.5, 5, and 20 mg. Registration began on July 5, 2003, and will continue until December 2007. Four patients from our division have been enrolled in the study.

2. Arrhythmia

In 2005, catheter ablation therapy was first used to treat atrial fibrillation. This field still has many unknowns, and we have been exploring several topics, including novel therapeutic approaches, expansion of therapeutic indications, and assessments of treatment efficacy. We have passed on this newly acquired knowledge to various academic societies. This year, we examined the following topics.

1) Evaluation of therapeutic efficacy of isolating the pulmonary vein in patients with sustained or chronic atrial fibrillation

2) Identification of the intra-atrial matrix and the efficacy of local cauterization in patients with chronic atrial fibrillation

3) Examination of the frequency, significance, and effects of additional cauterization for transient conduction in ATP-induced isolation of the pulmonary vein

4) Development of a method to prevent phrenic nerve injury during operations that isolate the superior vena cava

5) Examination by means of vector electrocardiography of the effects of operations that

isolate the pulmonary vein on the process of excitability to electrical stimulation of the atrium

6) Preoperative and postoperative changes in serum brain natriuretic peptide values and their significance when isolating the pulmonary vein

3. Lipid metabolism

1) Triple tracer study using stable isotope

We continue in vivo kinetic studies to assess the effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, and ezetimibe on lipid and glucose metabolism. Several international collaborations resulted in publication in prestigious journals, including the *New England Journal of Medicine* (University of Pennsylvania), the *Journal of Lipid Research* (Harvard School of Public Health), and *Kidney International* (University of Innsbruck). We are now focusing on several on-going projects.

4. Nuclear medicine

We are participating in a multicenter prospective cohort study to examine the prognosis for patients with heart failure using ^{123}I metaiodobenzylguanidine (MIBG) schintigraphy (Kanto MIBG Trial for Chronic Heart Failure; target number of cases to be enrolled: 300).

Basic research

1. Arrhythmia

Abnormalities in the expression of connexin, which controls intercellular transmission, are suggested to be an important underlining mechanism of atrial fibrillation. On the other hand, hypertension and heart failure are important factors in atrial fibrillation. This year, we used Dahl rats with hypertension-induced heart failure to observe changes in the expression of connexin due to decreased cardiac function and pressure loading. In the future, we will examine the localization of proteins, such as zona occludens 1, that are related to connexin.

2. Cellular cardiology

We have investigated the physiological and pathophysiological roles of intracellular Ca handling in cardiac excitation-contraction coupling. We are now using molecular biological methods combined with physiological methods.

This year, we published a paper regarding a new regulatory mechanism of α1-adrenoceptor stimulation on the L-type Ca channel in rat ventricular myocytes. We also estimated the function of the sarcoplasmic reticulum (SR) of genetically engineered mice in which the SR Ca pump function was selectively enhanced (SERCA-TG) or inhibited (SLN-TG). In addition, we have started to use a knock-in mouse model of dilated cardiomyopathy (DCM) to reveal its pathogenesis.

3. Myocardial metabolism

Impaired postischemic cardiac function and cytoplasmic ion movements in hearts from mice with type 2 diabetes: Myocardial function and cytoplasmic calcium movements were examined using fluorescence during ischemia-reperfusion in hearts from mice with type 2 diabetes. Exacerbation of postischemic cardiac dysfunction and cytoplasmic

calcium overload during ischemia-reperfusion were shown. Systems for regulating ion movements associated with this phenomenon will be examined.

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