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General Summary

We have 6 research groups across the broad field of cardiology. In these study groups, we have been studying the problems that face us in clinical practice. Our research is based on clinical studies that use a large database we have been developing. Specifically, we have recently used covariance structure analysis as a new solution for action assignments. Basic research is also performed to solve clinical questions.

Research Activities

Ischemic Heart Disease Research Group

Through examination and treatment, we are creating a database of all patients and are researching the relationship of risk factors for ischemic heart disease, treatment, prognosis, and other factors and hope to publish our findings. In addition, transcatheter aortic valve implantation was started in 2015, and we are investigating for our own data. We are giving presentations at all conferences we attend, including those overseas.

We are focusing on performing physiological examinations to evaluate myocardial ischemia. In particular, we evaluate functional ischemia by measuring the fractional flow reserve, the instantaneous wave-free ratio, and the resting full-cycle ratio. We are researching a prognostic evaluation and the relationship with many factors through physiological results. In percutaneous coronary intervention, the placement of drug eluting stents (DESs) is now mainstream. Considering the long-term results of and research on each DES, we are selecting appropriate DESs. Through the use of imaging devices, such as intravascular ultrasound and optical coherence tomography/optical frequency domain imaging, we are improving treatment results and clarifying the pathogenesis of coronary artery disease. Optical coherence tomography, angiosynchronization, and instantaneous wave-free ratio angiosynchronization have recently been available, and they would be useful methods for further treatment improvement. We are also participating in ongoing multi-institutional research studies and are contributing to the creation of new evidence by participating in national-scale clinical research at our hospital.

Arrhythmia Research Group

We are conducting clinical research based on electrophysiological examination for all supraventricular and ventricular arrhythmias. In clinical practice, atrial fibrillation (AF) accounts for the majority of arrhythmias; therefore, our main research focuses on AF. Although catheter ablation is now a curative therapy for AF, its safety and success rate are still insufficient; therefore, we provide new findings at home and abroad by conducting various clinical research studies.

With regard to paroxysmal AF, several balloon technologies, including the cryoballoon, hot balloon, and laser balloon, have been emerging, and a high success rate, equivalent to that of radiofrequency ablation, has been reported. However, the data regarding complications (such as pulmonary vein stenosis, phrenic nerve and esophagus injury, and asymptomatic cerebral infarction) and long-term outcomes after catheter ablation according to different ablation methods are still limited. In addition, we have investigated the clinical and procedural factors associated with AF recurrence and complications to clarify the optimal treatment for each patient. On the other hand, ablation therapy for persistent and chronic AF has not been established. We aim to clarify the mechanisms of AF with various mapping systems and to evaluate and compare the therapeutic effects by modifying AF substrates among various ablation strategies.

Heart Failure Research Group

We are constructing and updating a database of patients who have been hospitalized for treatment, such as cardiac catheterization and heart failure. Using this database, we are conducting analysis by Covariance Structure Analysis or Structural Equation Modeling to elucidate the relationship between factors based on actual clinical data that has not been able to be expressed until now. In the path diagram used for this, the relationship between each factor is easy to understand visually, and the dependency relationship and the correlation relationship can be numerically expressed. Furthermore, as a method of visually expressing the relationship, structural equation modeling by Bayesian estimation can be used. Subsequently, detailed data analysis of pathological changes due to chronic heart failure will be conducted, various conditions related to heart failure will be verified, analytic results useful for understanding and treatment of pathological changes will be published, and a wide range of clinical research will be promoted. In addition, we have supported these revisions of the “Acute and Chronic Heart Failure Treatment Guidelines” (2017 revised edition) and “Cardiomyopathy Treatment Guidelines” (2018 revised edition) published jointly by the Japanese Circulation Society and the Japan Heart Failure Association. We are also helping to translate these guidelines into English.

Imaging Research Group

Before transcatheter aortic valve implantation, a procedure that continues to be performed more often, cardiac computed tomographic and echocardiographic examinations are important for evaluating the aortic valve. The data of these examinations significantly contribute to the treatment of patients with aortic valvular stenosis. Moreover, new clinical research subjects are being sought for valuable case information. Other imaging methods, such as cardiac magnetic resonance imaging and myocardial isotopes, are being

investigated and analyzed for clinical research studies of such conditions as cardiomyopathy and arrhythmia. In particular, we are conducting research on cardiac function in lysosomal disease (particularly Fabry disease) and report the research results in collaboration with the Department of Pediatrics. In addition, in our university's new outpatient building, positron emission tomography-computed tomography has begun to be performed and is expected to be an important diagnostic tool for myocardial disease.

Molecular Biology Research Group

Glucose becomes an important preferential substrate for myocardial energy metabolism under acute conditions of ischemia-reperfusion injury (IRI). We reported that cardiac sodium glucose co-transporter 1 (SGLT1) plays a compensatory protective role during IRI via enhanced glucose utilization, particularly under insulin resistance condition, in which IRI-induced glucose transporter 4 (GLUT4) upregulation is compromised. The hearts from mice fed a high-fat diet (HFD) or a normal-fat diet (NFD) were perfused with the non-selective SGLT-inhibitor phlorizin during IRI using the Langendorff model. After IRI, a functional recovery was impaired with a HFD compared with a NFD. Although phlorizin perfusion impaired left ventricular developed pressure recovery in a NFD, recovery was further impaired in HFD with phlorizin perfusion. The immunoblotting with plasma membrane fractionations revealed that GLUT4 expression was significantly increased after IRI with a NFD, which was substantially attenuated with a HFD, associated with a significant reduction in myocardial glucose uptake. In contrast, SGLT1 expression was remained constant during IRI regardless of diet conditions. Of note, SGLT1 inhibition by phlorizin considerably attenuated myocardial glucose uptake after IRI, particularly in a HFD.

In addition to the various effects of natriuretic peptides (NPs) on cardiovascular systems, increasing attention is being paid to the possibility that NPs induce adipose tissue browning and an activate thermogenic program. We established a direct intracellular temperature measurement system using a fluorescent thermoprobe and reported that the thermogenic effects of A-type (atrial) natriuretic peptide (ANP) on brown adipocytes. We are now investigating whether ANP exerts significant effects on adipose tissues *in vivo*.

Cardiac Physiology Research Group

By examining human hearts obtained at autopsy, we have found, with an immunohistological method, the presence of thrombin, the final product of the coagulation cascade. Coagulability is increased in patients with dilated cardiomyopathy. In knock-in mice with a cardiac troponin T deletion mutation that causes human dilated cardiomyopathy (ΔK210 knock-in mouse [B6;129-Tnnt2^{tm2Mmto}]), we assessed the effects of a direct thrombin inhibitor, dabigatran. Dabigatran significantly improved fractional shortening in echocardiographic findings and survival outcomes. From these results, we conclude that tissue thrombin is involved in the pathogenesis of dilated cardiomyopathy and that thrombin inhibition can be beneficial for its treatment. To investigate the hemodynamics of thrombin, HiLyte^{TM}-thrombin (AnaSpec, Fremont, CA) was administered to mice so that whole *in-vivo* imaging could be performed. The HiLyte^{TM}-thrombin was internalized to hearts and livers. Because we did not detect messenger RNA of prothrombin in heart tissue by

means of real-time polymerase chain reaction, we believe that the tissue thrombin is derived not from the heart (namely internal prothrombin) but from blood.

Publications

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