Department of Internal Medicine
Division of Cardiology

Michihiro Yoshimura, *Professor*
Teiichi Yamane, *Professor*
Takahiro Shibata, *Associate Professor*
Kimiaki Komukai, *Associate Professor*
Chikara Mori, *Assistant Professor*
Tomohisa Nagoshi, *Assistant Professor*
Kazuo Ogawa, *Assistant Professor*
Satoshi Morimoto, *Assistant Professor*
Shingo Seki, *Professor*
Kenichi Hongo, *Professor*
Makoto Kawai, *Associate Professor*
Takayuki Ogawa, *Associate Professor*
Kosuke Minai, *Assistant Professor*
Seiichiro Matsuo, *Assistant Professor*
Yosuke Kayama, *Assistant Professor*

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.

In our team, catheter ablation therapy for arrhythmias has been the main subject, and we always aim to provide patients with the best treatment by adopting the novel therapies and investigating various clinical data.

Heart Failure Research Group

1. Study group on heart failure

Since last year, we have constructed and updated a database of approximately 4,800 patients who have been hospitalized for cardiac catheterization and treatment. This database has been analyzed with structural equation modeling or covariance structure analysis by adjusting analysis of moment structures, a statistical analysis method that has previously been known but has been rarely reported to be used in cardiovascular medicine. In particular, we have analyzed the relationships of clinical factors that cannot be expressed by multivariate statistical analysis alone, focusing on statistical analysis research on clinical data, including plasma B-type (brain) natriuretic peptide. With a path diagram the visual understanding of the relationships among factors is simplified and the multiple regression analysis and path analysis (repetition of multiple regression analysis) with factors and confirmatory factor analysis are made easier. In addition, Bayesian structure equation modeling successfully describes these results and is expected to be a next-generation statistical procedure for large clinical trials. Subsequently, we performed a detailed data analysis of chronic heart failure and published various analytic results, such as anemia and heart failure and the relationship of uric acid levels and cardiac function. We will promote clinical research widely based on the experience acquired from daily clinical practice. With regard to the mechanism of these findings, they are being clarified with basic research.

Imaging Research Group

1. Study group on imaging

With the increasing number of cases involving transcatheter aortic valve replacement,

also vital as preoperative examinations for evaluating the aortic valve are cardiac computed tomography and echocardiography. From this valuable case information, we are seeking research agendas for clinical studies. Through other imaging methods, such as cardiac magnetic resonance imaging and myocardial isotope tests, we are continuing to seek research agendas for clinical studies and to analyze cardiomyopathy and arrhythmias. We have also been investigating cardiac function in patients with lysosome diseases, especially Fabry's disease, in collaboration with the Department of Pediatrics.

Molecular Biology Research Group

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 activate thermogenic program. We established a direct intracellular temperature measurement system using a fluorescent thermoprobe and investigated the thermogenic effects of A-type (atrial) natriuretic peptide (ANP) on brown adipocytes. The thermoprobe was successfully introduced into rat brown adipocytes, and the temperature-dependent change in the fluorescence intensity ratio was significantly higher in ANP-treated adipocytes than in untreated controls. The ANP treatment increased levels of uncoupling protein 1 in a p38 mitogen-activated protein kinase-dependent manner. Intriguingly, these thermogenic actions of ANP were more prominent when brown adipocytes were incubated at 35°C than at 37°C. These findings reveal a previously underappreciated role for NPs in the compensatory thermogenic action when the core body temperature decreases owing to unfavorable hemodynamic conditions in a state of severe heart failure. We are now investigating whether ANP exerts significant effects on adipose tissues in vivo.

Although fatty acids are involved in the predominant metabolic pathway of the healthy adult heart, glucose becomes an important preferential substrate for metabolism under specific pathological conditions, such as ischemia-reperfusion injury. We have previously reported that sodium glucose co-transporter (SGLT) 1 is expressed at high levels in both human and murine hearts and have found in a murine Langendorff model that cardiac SGLT1 significantly contributes to cardioprotection against ischemia-reperfusion injury. We are now investing the regulation and functional significance of cardiac SGLTs under insulin-resistant conditions.

Cardiac Physiology Research Group

By examining human hearts obtained at autopsy, we have found, with a immunohistological method, the presence of thrombin, the final product of the coagulation cascade. Coagulability is increased in patients with dilated cardiomyopathy (DCM). In knock-in mice with a cardiac troponin T deletion mutation that causes human DCM (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 DCM and that thrombin inhibition can be beneficial for the treatment of DCM. 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

Tokutake K, Tokuda M, Matsuo S, Isogai R, Yokoyama K, Kato M, Narui R, Tanigawa S, Yamashita S, Miyanaga S, Yoshimura M, Yamane T. Dissociated pulmonary vein activity after cryoballoon ablation and radiofrequency ablation for atrial fibrillation: a propensity score-matched analysis. *Heart Vessels.* 2018; **33:** 529-36.

Ito K, Hongo K, Date T, Morimoto S, Yoshii A, Kimura H, Tanaka Y, Nagoshi T, Kusakari Y, Akaike T, Minamisawa S, Ogawa K, Minai K, Kawai M, Matsuo S, Yamane T, Yoshimura M. Mice with the Heart-Specific Overexpression of Prothrombin—Do Not Show Cardiac Insufficiency. *Transl Biomed.* 2018; **9:** 148.

Matsutani D, Sakamoto M, Kayama Y, Takeda N[1], Horiuchi R[2], Utsunomiya K ([1]Univ Tokyo, [2]Tsuruoka Kyoritsu Hosp). Effect of canagliflozin on left vetricular diastolic function in patients with type 2 diabetes. *Cardiovasc Diabetol.* 2018; **17:** 73.

Hongo K, Ito K, Date T, Anan I, Inoue Y, Morimoto S, Ogawa K, Kawai M, Kobayashi H, Kobayashi M, Ida H, Ohashi T, Taniguchi I, Yoshimura M, Eto Y[1] ([1]Advanced Clinical Research Ctr). The beneficial effects of long-term enzyme replacement therapy on cardiac involvement in Japanese Fabry patients. *Mol Genet Metab.* 2018; **124:** 143-51.

Itoh H[1] ([1]Keio Univ), Komuro I[2] ([2]Univ Tokyo), Takeuchi M (Kitasato Univ), Akasaka T (Wakayama Med Univ), Daida H (Juntendo Univ), Egashira Y (Sakura Hosp), Fujita H (Saitama Med Ctr, Jichi Med Univ), Higaki J (Ehime Univ), Hirata KI (Kobe Univ), Ishibashi S (Jichi Med Univ), Isshiki T (Ageo Central General Hosp), Ito S (Tohoku Univ), Kashiwagi A (Kusatsu General Hosp), Kato S (Univ Tokyo), Kitagawa K (Tokyo Women's Med Univ), Kitakaze M (Natl Cerebral Cardiovasc Ctr), Kitazono T (Kyushu Univ), Kurabayashi M (Gunma Univ), Miyauchi K (Juntendo Univ), Murakami T (Kyoto Univ), Murohara T (Nagoya Univ), Node K (Saga Univ), Ogawa S (Tohoku Univ), Saito Y (Nara Med Univ), Seino Y (Nippon Med School Chiba Hokuso Hosp), Shigeeda T (Ideta Eye Clinic), Shindo S (Tokyo Med Univ Hachioji Med Ctr), Sugawara M (Sugawara Medical Clinic), Sugiyama S (Jinnouchi Hosp), Terauchi Y (Yokohama City Univ), Tsutsui H (Kyushu Univ), Ueshima K (Kyoto Univ Hosp), Utsunomiya K, Yamagishi M (Kanazawa Univ), Yamazaki T (Univ Tokyo Hosp), Yo S (Yo Clinic), Yokote K (Chiba Univ), Yoshida K (Sakakibara Heart Institute of Okayama), Yoshimura M, Yoshimura N (Kitano Hosp), Nakao K (Kyoto Univ), Nagai R (Jichi Med Univ); EMPATHY Investigators. Intensive treat-to-target statin therapy in high-risk Japanese patients with hypercholesterolemia and diabetic retinopathy: report of a randomized study. *Diabetes Care.* 2018; **41:** 1275-84.

Suzuki K, Komukai K, Nakata K, Kan R, Oi Y, Muto E, Kashiwagi Y, Tominaga M, Miyanaga S, Ishikawa T, Okuno K, Uzura M, Yoshimura M. The usefulness and limitations of point-of-care cardiac troponin measurement in the emergency department. *Intern Med.* 2018; **57:** 1673-80.

Yokoyama K, Tokuda M, Matsuo S, Isogai R, Tokutake K, Kato M, Narui R, Tanigawa S, Yamashita S, Inada K, Yoshimura M, Yamane T. Pulmonary vein re-mapping after cryoballoon ablation for atrial fibrillation. *Europace.* 2018; **20:** 943-8.

Yoshida R, Seki S, Hasegawa J, Koyama T, Yamazaki K, Takagi A[1], Kojima T[1], Yoshimura M ([1]Nagoya Univ). Familial pulmonary thromboembolism with a prothrombin mutation and antithrombin resistance. *J Cardiol Cases.* 2018; **17:** 197-9.

Murakawa Y[1] ([1]Teikyo Univ), Yamane T, Goya M[1], Inoue K[2] ([2]Sakurabashi Watanabe Hosp), Naito S (Gunma Prefectural Cardiovasc Ctr), Kumagai K (Heart Rhythm Ctr Fukuoka Sanno Hosp), Miyauchi Y (Nippon Med School), Morita N (Tokai Univ Hachioji Hosp), Nogami A (Univ Tsukuba), Shoda M (Tokyo Women's Med Univ), Okumura K (Saiseikai Kumamoto Hosp), Hirao K[1] ([1]Heart Rhythm Ctr Tokyo Med and Tokyo Med and Dental Univ); Japanese Heart Rhythm Society Members. Influence of substrate modification in catheter ablation of atrial fibrillation on the incidence of acute complications: Analysis of 10795 procedures in J-CARAF Study 2011-2016. *J Arrhythm.* 2018; **34:** 435-40.

Suzuki K, Ishikawa T, Mutoh M, Sakamoto H, Kubota T, Ogawa T, Mori C, Hashimoto K, Komukai K, Yoshimura M; a Multicenter Registry in The Jikei Univ. Midterm angiographic outcomes with sirolimus- and everolimus-eluting stents for small vessels in diabetic patients: propensity-score-matched comparisons in three different vessel diameters. *Cardiovasc Interv Ther.* 2018; **33:** 205-16.

Narui R, Yamane T, Tokuda M, Ikewaki H, Okajima E, Sato H, Oseto H, Isogai R, Tokutake K, Yokoyama K, Kato M, Ito K, Tanigawa SI, Yamashita S, Inada K, Matsuo S, Miyanaga

S, Sugimoto K, Yoshimura M. Atrial fibrillation diagnosed by a medical checkup is associated with a poor outcome of catheter ablation. *Heart Vessels.* 2018; **33:** 770–6.

Nakao YM[1], Miyamoto Y[1], Higashi M[2], Noguchi T[1], Ohishi M[3], Kubota I[4], Tsutsui H[5], Kawasaki T[6], Furukawa Y[7], Yoshimura M, Morita H[8], Nishimura K[1], Kada A[9], Goto Y[1], Okamura T[10], Tei C[11], Tomoike H[12], Naito H[13], Yasuda S[1] ([1]Natl Cerebral Cardiovasc Ctr, [2]Osaka National Hospital, [3]Kagoshima Univ, [4]Yamagata Univ, [5]Kyushu Univ, [6]Shin-Koga Hosp, [7]Kobe City Med Ctr General Hosp, [8]Osaka Med College, [9]National Hosp Organization Nagoya Med Ctr, [10]Keio Univ, [11]Waon Therapy Research Institute, [12]Sakakibara Heart Institute, [13]Nissay Hosp). Sex differences in impact of coronary artery calcification to predict coronary artery disease. *Heart.* 2018; **104:** 1118–24.

Matsutani D, Sakamoto M, Minato S, Kayama Y, Takeda N[1], Horiuchi R[2], Utsunomiya K ([1]Univ Tokyo, [2]Tsuruoka Kyoritsu Hosp). Visit-to-visit HbA1c variability is inversely related to baroreflex sensitivity independently of HbA1c value in type 2 diabetes. *Cardiovasc Diabetol.* 2018; **17:** 100.

Adam M[1,2,3], Kooreman NG[1,4], Jagger A[1,3], Wagenhäuser MU[1,3], Mehrkens D[2], Wang Y[1], Kayama Y[1,3], Toyama K[1,3], Raaz U[1,3,5], Schellinger IN[1,3,5], Maegdefessel L[1,6], Spin JM[1,3], Hamming JF[4], Quax PHA[4], Baldus S[2], Wu JC[1], Tsao PS[1,3] ([1]Stanford Univ, [2]Univ Cologne, [3]VA Palo Alto Health Care System, [4]Leiden Univ Med Ctr, [5]Heart Ctr, Georg-August-Univ Göttingen, [6]Karolinska Institutet). Systemic Upregulation of IL-10(Interleukin-10) Using a Nonimmunogenic Vector Reduces Growth and Rate of Dissecting Abdominal Aortic Aneurysm. *Arterioscler Thromb Vasc Biol.* 2018; **38:** 1796–805.

Tokuda M, Yamashita S, Matsuo S, Kato M, Sato H, Oseto H, Okajima E, Ikewaki H, Isogai R, Tokutake K, Yokoyama K, Narui R, Tanigawa SI, Inada K, Yoshimura M, Yamane T. Radiofrequency needle for transseptal puncture is associated with lower incidence of thromboembolism during catheter ablation of atrial fibrillation: propensity score-matched analysis. *Heart Vessels.* 2018 Oct; **33**: 1238–44.

Wagenhäuser MU[1,2,3], Schellinger IN[4,5,6], Yoshino T[1,2], Toyama K[1,2], Kayama Y[1,2], Deng A[1,2], Guenther SP[7,8], Petzold A[4], Mulorz J[1,2,3], Mulorz P[1,2], Hasenfuß G[3], Ibing W[3], Elvers M[3], Schuster A[4,5,9], Ramasubramanian AK[10], Adam M[1,2], Schelzig H[3], Spin JM[1,2], Raaz U[4,5], Tsao PS[1,2] ([1]Stanford Univ, [2]VA Palo Alto Health Care System, [3]Univ Hosp Düsseldorf, [4]Heart Ctr at the Univ Med Ctr Göttingen, [5]German Ctr for Cardiovasc Research e.V, [6]Univ Leipzig, [7]Univ Hosp Munich, [8]Univ California, [9]Royal North Shore Hosp, [10]San Jose State Univ). Chronic Nicotine Exposure Induces Murine Aortic Remodeling and Stiffness Segmentation-Implications for Abdominal Aortic Aneurysm Susceptibility. *Front Physiol.* 2018; **9:** 1459.

Isogai R, Matsuo S, Narui R, Seki S, Yoshimura M, Yamane T. Perimitral atrial flutter with partial conduction block between left atrium and coronary sinus. *HeartRhythm Case Rep.* 2018; **5:** 179–82.

Sakamoto M, Matsutani D, Kayama Y. Possibility of New Therapeutic Strategy for Left Ventricular Dysfunction in Type 2 Diabetes. *J Clin Med Res.* 2018; **10:** 799–805.

Kashiwagi Y, Komukai K, Suzuki K, Oi Y, Tominaga M, Nakata K, Miyanaga S, Ishikawa T, Minai K, Nagoshi T, Yoshimura M. Predictors of oxygenation impairment in medical treatment for type B acute aortic dissection. *Heart Vessels.* 2018; **33:** 1463–70.

Tanigawa S, Matsuo S, Tokuda M, Tokutake K, Yokoyama K, Kato M, Narui R, Yamashita S, Inada K, Shibayama K, Miyanaga S, Sugimoto K, Yoshimura M, Yamane T. Impact of sleep-disordered breathing on early and late recurrence of atrial fibrillation following catheter ablation. *Jikeikai Med J.* 2018; **65:** 29–36.

Oki Y, Kawai M, Minai K, Ogawa K, Inoue Y, Morimoto S, Tanaka T, Nagoshi T, Ogawa T, Yoshimura M. High serum uric acid is highly associated with a reduced left ventricular ejection fraction rather than increased plasma B-type natriuretic peptide in patients with cardiovascular diseases. *Sci Rep.* 2019; **9:** 682.

Yamane T, Inoue K[1], Kusano K[2], Takegami M[2], Nakao YM[2], Miyamoto Y[2], Goya M[3], Uno K[4], Shoda M[5], Murakawa Y[6], Hirao K[3], Nogami A[7] ([1]Sakurabashi Watanabe Hosp, [2]Natl Cerebral Cardiovasc Ctr, [3]Heart Rhythm Ctr Tokyo Med and Dental Univ, [4]Heart Rhythm Ctr Chiba-Nishi General Hosp, [5]Tokyo Women's Med Univ, [6]Teikyo Univ, [7]Univ Tsukuba); J-AB registry investigators. Study design of nationwide Japanese Catheter Ablation Registry: Protocol for a prospective, multicenter, open registry. *J Arrhythm.* 2019; **35:** 167–70.

Okajima E, Yamashita S, Yoshimura M, Yamane T. Atrial tachycardia with fibrillatory activity in the superior vena cava. *J Cardiovasc Electrophysiol.* 2019; **30:** 446–7.

Tominaga M, Kawai M, Minai K, Ogawa K, Inoue Y, Morimoto S, Tanaka T, Nagoshi T, Ogawa T, Yoshimura M. Association between plasma B-type natriuretic peptide and anaemia in heart failure with or without ischaemic heart disease: a retrospective study. *BMJ Open.* 2019; **9:** e024194.

Reviews and Books

Nagoshi T, Yoshimura M. Nutritional status assessment as a potential prognostic indicator in patients before the development of symptomatic heart failure. *Circ J.* 2018; **82:** 1501–2.

Tanaka TD, Misawa S[1], Yoshimura M, Kuwabara S[1] ([1]Chiba Univ). Reversal of pulmonary arterial hypertension in POEMS syndrome with thalidomide: a case report. *Eur Heart J Case Rep.*

2018; **2:** yty051.
Yoshimura M. Coronary artery spasm. *Proc Jpn Acad Ser B.* 2019; **95:** Cover illustration.
Okuyama T, Tanaka TD, Nagoshi T, Yoshimura M. Coronary artery disease concomitant with immunoglobulin G4-related disease: a case report and literature review. *Eur Heart J Case Rep.* 2019; **3:** ytz013.