Department of Internal Medicine
Division of Cardiology

Michihiro Yoshimura, *Professor*
Teiichi Yamane, *Professor*
Shingo Seki, *Associate Professor*
Makoto Kawai, *Associate Professor*
Takayuki Ogawa, *Associate Professor*
Chikara Mori, *Assistant Professor*
Tomohisa Nagoshi, *Assistant Professor*
Ikuo Taniguchi, *Professor*
Kenichi Hongo, *Professor*
Takahiro Shibata, *Associate Professor*
Kimiaki Komukai, *Associate Professor*
Tetsuya Ishikawa, *Assistant Professor*
Kosuke Minai, *Assistant Professor*
Seiichiro Matsuo, *Assistant Professor*

General Summary

We have 6 research groups for covering the broad field of cardiology. In respective study groups, we have been studying the problems that face us in clinical practice. Our research is based on clinical studies that use the large database we have been developing. In specific, we 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
We have converted patients' data, including risk factors and coronary lesion morphology, hemodynamic data, from cardiac catheterization examinations and treatments in patients with ischemic heart disease, into our large, precise database. Using this database, we have been performing a study comparing risk factors, clinical outcomes, and other data. We have recently reported the differences of risk factors between coronary organic stenosis and acute coronary syndrome by using covariance structure analysis. We have been using a similar method to study a contributing pattern of obesity to ischemic heart disease. In the analysis, we reported a possible risk of low-reactivity of natriuretic peptide. Furthermore, since fractional flow reserve is reportedly a good method for evaluating significant coronary stenosis, we have been collecting and analyzing information about the clinical data of fractional flow reserve (FFR).

Arrhythmia Research Group
In our arrhythmia team, we have been focusing on the curative treatment of atrial fibrillation. Our research activities include the comparison of efficiency and safety among different ablation methods (radiofrequency vs. cryoballoon ablation), factors associated with the occurrence of pulmonary vein stenosis following balloon ablation, and the association of ablation methods and asymptomatic cerebral ischemia.

Heart Failure Research Group
1. Study group on heart failure
Since last year, we have constructed and updated a database of approximately 3,000

patients who have been hospitalized for cardiac catheterization and treatment. Regarding this database, analysis is conducted using the Structural Equation Modeling (SEM) or Covariance Structure Analysis by adjusting the statistical analysis method, AMOS (Analysis of Moment Structures), which has been previously known but the use of which has been rarely reported in the cardiovascular field. In particular, we analyze the interrelationships of clinical factors that cannot be expressed by multivariate statistical analysis alone, focusing on statistical analysis research on clinical data including plasma BNP. Using a path diagram, it is easier to have a visual understanding of the relationships between each factor, and to perform multiple regression analysis and path analysis (repetition of multiple regression analysis) using factors and confirmatory factor analysis. Last year, with respect to the relationship between obesity and BNP, we reported the relationship between the change in BNP concentration before and after treatment along with the change in body weight. This spring, we published an article on the influence of remodeling changes in the left ventricular cavity on BNP concentration. By publishing articles on wide-ranging analysis results including detailed data analysis of the disease state of chronic heart failure along with the relationships between various valvular diseases and atrial fibrillation, we will continue to promote a wide range of clinical studies based on the experience gained from daily clinical practice. We are also continuing our efforts to clarify the mechanism of these findings via fundamental research.

Imaging Research Group

1. Study group on imaging

With the increasing number of cases involving transcatheter aortic valve replacement (TAVR) since last year, cardiac CT and echocardiograms are also vital as preoperative examinations for evaluating the aortic valve. From this valuable case information, we are seeking research agendas for clinical studies. Through other imaging modalities such as cardiac MRI and myocardial isotope tests, we are continuing to seek research agendas for clinical studies and conduct analyses on cardiomyopathy and arrhythmias.

Molecular Biology Research Group

Glucose becomes an important preferential substrate for cardiac metabolism and ATP generation during ischemia-reperfusion injury (IRI). Therefore, acceleration of glucose uptake and its metabolism is critical for myocardium to develop ischemic tolerance. Although insulin plays a pivotal role in this process, we have recently reported that insulin resistance increases during ischemic attack of acute coronary syndrome (ACS). The study also suggested that there are endogenous mechanisms of promoting glucose metabolism. One of the potential mechanisms is s sodium-glucose co-transporter 1 (SGLT1). A study of Langendorff murine heart perfusion demonstrated that the inhibition of SGLT1 during IRI reduces glucose uptake into the myocardium, leading to a decrease in the cardiac tissue ATP content. As a consequence, cardiac functional recovery after IRI was impaired by SGLT1-inhibition. The present findings provide the significant role of SGLT1 in optimizing cardiac energy metabolism during IRI.

Cardiac Physiology Research Group

We have demonstrated that thrombin, the final product of the coagulation cascade, in present in the heart. Coagulability is increased in patients with dilated cardiomyopathy (DCM). Using knock-in mice that have 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, in ΔK210 knock-in mice. Dabigatran significantly improved fractional shortening in echocardiographic findings and survival outcomes. In conclusion, tissue thrombin is involved in the pathogenesis of DCM, and thrombin inhibition can be beneficial for the treatment of DCM.

To investigate this mechanism, we practiced microarray analysis, which has demonstrated that Casq1・Postn・Myh7 may be involved in the mechanism. We further practiced Western blot analysis, but there were no significant differences between hearts of DCM mice and Wild type mice in these three gene protein products. We next investigated the apoptosis by the TUNEL assay. The apoptotic index, the percentage of TUNEL-positive nuclei, was significantly increased in the DCM group in comparison to that observed in the Wild group. Treatment with dabigatran significantly reduced the apoptotic index. The apoptosis may be involved in the mechanism.

Publications

Mizuno Y*[1]*, Hokimoto S*[2]*, Harada E*[1]*, Kinoshita K*[3]*, Nakagawa K*[2]*, Yoshimura M, Ogawa H*[2]*, Yasue H*[1] *([1]Kumamoto Kinoh Hosp, [2]Kumamoto Univ, [3]Mukogawa Women's Univ). Variant aldehyde dehydrogenase 2 (ALDH2*2) is a risk factor for coronary spasm and ST-segment elevation myocardial infarction. *J Am Heart Assoc.* 2016; **5:** pii: e003247.

Kosuga T, Komukai K, Miyanaga S, Kubota T, Nakata K, Suzuki K, Yamada T, Yoshida J, Kimura H, Yoshimura M. Diabetes is a predictor of coronary artery stenosis in patients hospitalized with heart failure. *Heart Vessels.* 2016; **31:** 671-6.

Kinoshita K, Kawai M, Minai K, Ogawa K, Inoue Y, Yoshimura M. Potent influence of obesity on suppression of plasma B-type natriuretic peptide levels in patients with acute heart failure: An approach using covariance structure analysis. *Int J Cardiol.* 2016; **215:** 283-90.

Nishizaki Y*[1]*, Shimada K*[1]*, Tani S*[2]*, Ogawa T, Ando J*[3]*, Takahashi M*[3]*, Yamamoto M, Shinozaki T*[3]*, Miyazaki T*[1]*, Miyauchi K*[1]*, Nagao K*[2]*, Hirayama A*[2]*, Yoshimura M, Komuro I*[3]*, Nagai R*[5]*, Daida H*[1] *([1]Juntendo Univ, [2]Nihon Univ, [3]Univ Tokyo, [4]Tokyo Takanawa Hosp, [5]Jichi Med Univ). Association between the docosahexaenoic acid to arachidonic acid ratio and acute coronary syndrome: a multicenter observational study. *BMC Cardiovasc Disord.* 2016; **16:** 143.

Natsuaki M*[1]*, Morimoto T*[2]*, Yamamoto E*[3]*, Shiomi H*[3]*, Furukawa Y*[4]*, Abe M*[5]*, Nakao K*[6]*, Ishikawa T, Kawai K*[7]*, Yunoki K*[8]*, Shimizu S*[9]*, Akao M*[5]*, Miki S*[10]*, Yamamoto M*[11]*, Okada H*[12]*, Hoshino K*[13]*, Kadota K*[14]*, Morino Y*[15]*, Igarashi K*[16]*, Tanabe K*[17]*, Kozuma K*[18]*, Kimura T*[3] *([1]Saiseikai Fukuoka General Hosp, [2]Hyogo Coll Med, [3]Kyoto Univ, [4]Kobe City Med Center General Hosp, [5]National Hosp Organization Kyoto Med Center, [6]Saiseikai Kumamoto Hosp, [7]Chikamori Hosp, [8]Osaka City General Hosp, [9]Mashiko Hosp, [10]Mitsubishi Kyoto Hosp, [11]Kimitsu Chuo Hosp, [12]Seirei Hamamatsu General Hosp, [13]Nagai Hosp, [14]Kurashiki Central Hosp, [15]Iwate Med Univ Hosp, [16]Hokkaido Social Insurance Hosp, [17]Mitsui Memorial Hosp, [18]Teikyo Univ Hosp). One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. *Cardiovasc Interv Ther.* 2016; **31:** 196-209.

Tokuda M, Yamane T, Sadaoka S, Tokutake K, Yokoyama K, Hioki M, Narui R, Tanigawa S, Inada K, Matsuo S, Yoshimura M. Percutaneous retrieval of a radiolucent anchoring sleeve embolized in pulmonary artery during pacemaker implantation. *Heart Vessels.* 2016; **31:** 1402-4.

Kimura H, Ishikawa T, Nakata K, Kubota T, Komukai K, Yoshimura M. A case of recoiling of everoimus-eluting stent at the ostium of the right coronary artery by out-stent plaque progression. *Jikeikai Med J.* 2016; **63:** 71-6.

Tokutake K, Tokuda M, Ogawa T, Matsuo S, Yoshimura M, Yamane T. Pulmonary vein stenosis after second-generation cryoballoon ablation for atrial fibrillation. *HeartRhythm Case Rep.* 2016;

3: 36–9.
Tokuda M, Matsuo S, Isogai R, Uno G, Tokutake K, Yokoyama K, Kato M, Narui R, Tanigawa S, Yamashita S, Inada K, Yoshimura M, Yamane T. Adenosine testing during cryoballoon ablation and radiofrequency ablation of atrial fibrillation: A propensity score-matched analysis. *Heart Rhythm.* 2016; **13:** 2128–34.
Watanabe M[1], Saito Y[1], Aonuma K[2], Hirayama A[3], Tamaki N[4], Tsutsui H[4], Murohara T[5], Ogawa H[6], Akasaka T[7], Yoshimura M, Sato A[2], Takayama T[3], Sakakibara M[4], Suzuki S[5], Ishigami K[8], Onoue K[1]; CINC-J study investigators ([1]Nara Medical Univ, [2]Tsukuba Univ, [3]Nihon Univ, [4]Hokkaido Univ, [5]Nagoya Univ, [6]Kumamoto Univ, [7]Wakayama Med Univ, [8]Saiseikai-Suita Hosp). Prediction of contrast-induced nephropathy by the serum creatinine level on the day following cardiac catheterization. *J Cardiol.* 2016; **68:** 412–8.
Seki S, Oki Y, Tsunoda S, Takemoto T, Koyama T, Yoshimura M. Impact of alcohol intake on the relationships of uric acid with blood pressure and cardiac hypertrophy in essential hypertension. *J Cardiol.* 2016; **68:** 447–54.
Hioki M, Matsuo S, Tokutake K, Yokoyama K, Narui R, Ito K, Tanigawa S, Tokuda M, Yamashita S, Anan I, Inada K, Sakuma T, Sugimoto K, Yoshimura M, Yamane T. Filling defects of the left atrial appendage on multidetector computed tomography: their disappearance following catheter ablation of atrial fibrillation and the detection of LAA thrombi by MDCT. *Heart Vessels.* 2016; **31:** 2014–24.
Takahashi M[1], Ando J[1], Shimada K[1], Nishizaki Y[2], Tani S[3], Ogawa T, Yamamoto M[4], Nagao K[3], Hirayama A[3], Yoshimura M, Daida H[2], Nagai R[5], Komuro I[1] ([1]Univ Tokyo, [2]Juntendo Univ, [3]Nihon Univ Hosp, [4]Sempo Takanawa Hosp, [5]Jichi Med Univ). The ratio of serum n-3 to n-6 polyunsaturated fatty acids is associated with diabetes mellitus in patients with prior myocardial infarction: a multicenter cross-sectional study. *BMC Cardiovasc Disord.* 2017; **17:** 41.
Mizuno Y[1], Hokimoto S[1], Harada E[1], Kinoshita K[2], Yoshimura M, Yasue H[1] ([1]Kumamoto Univ, [2]Mukogawa Women's Univ). Variant aldehyde dehydrogenase 2 (ALDH*2) in east asians interactively exacerbates tobacco smoking risk for coronary spasm — Possible role of reactive aldehydes. *Circ J.* 2017; **81:** 96–102.
Sato A[1], Aonuma K[1], Watanabe M[2], Hirayama A[3], Tamaki N[4], Tsutsui H[4], Murohara T[5], Ogawa H[6], Akasaka T[7], Yoshimura M, Takayama T[3], Sakakibara M[4], Suzuki S[5], Ishigami K[8], Onoue K[2], Saito Y[2] ([1]Univ Tsukuba, [2]Nara Med Univ, [3]Nihon Univ, [4]Hokkaido Univ, [5]Nagoya Univ, [6]Kumamoto Univ, [7]Wakayama Med Univ, [8]Saiseikai-Suita Hosp); CINC-J study investigators. Association of contrast-induced nephropathy with risk of adverse clinical outcomes in patients with cardiac catheterization: From the CINC-J study. *Int J Cardiol.* 2017; **227:** 424–9.
Miyamoto T[1], Ishikawa T, Nakano Y[1], Mutoh M ([1]Saitama Cardiovascular Respiratory Center). Very long-term clinical and angiographic outcomes after sirolimus- and paclitaxel-eluting stent placement for ST-elevation myocardial infarction: a propensity score-matched comparison. *Cardiovasc Interv Ther.* 2017; **32:** 24–35.
Ito K, Hongo K, Date T, Ikegami M, Hano H, Owada M, Morimoto S, Kashiwagi Y, Katoh D, Yoshino T, Yoshii A, Kimura H, Nagoshi T, Kajimura I, Kusakari Y, Akaike T, Minamisawa S, Ogawa K, Minai K, Ogawa T, Kawai M, Yajima J, Matsuo S, Yamane T, Taniguchi I, Morimoto S, Yoshimura M. Tissue thrombin is associated with the pathogenesis of dilated cardiomyopathy. *Int J Cardiol.* 2017; **228:** 821–7.
Ogawa K, Minai K, Kawai M, Tanaka T, Nagoshi T, Ogawa T, Yoshimura M. Parallel comparison of risk factors between progression of organic stenosis in the coronary arteries and onset of acute coronary syndrome by covariance structure analysis. *PLoS One.* 2017; **12:** e0173898.