

Circulation Journal Awards for the Year 2016

Toyoaki Murohara, MD, PhD

Dear Colleagues,

On behalf of the Editorial Team of *Circulation Journal*, I am pleased to announce the *Circulation Journal* Awards for the Year 2016.

The aim of these Awards is to recognize papers published in 2016, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 237 original papers published in the Journal in 2016, our 39 Japanese Associate Editors selected papers with a high scientific level in their respective fields, and in the second step, the 2 Associate Editorial Teams (20 on 1 team and 19 on the other) further evaluated the selected papers in terms of originality, contribution to cardiovascular science, manner of paper preparation, and future possibilities.

In the year of 2016, the following 7 papers have been selected for the *Circulation Journal* Awards.

First Place in the Clinical Investigation Section

Diagnostic Value of Right Ventricular Dysfunction in Tachycardia-Induced Cardiomyopathy Using Cardiac Magnetic Resonance Imaging

Atsushi Okada, Ikutaro Nakajima, Yoshiaki Morita, Yuko Y. Inoue, Tsukasa Kamakura, Mitsuru Wada, Kohei Ishibashi, Koji Miyamoto, Hideo Okamura, Satoshi Nagase, Takashi Noda, Takeshi Aiba, Shiro Kamakura, Toshihisa Anzai, Teruo Noguchi, Satoshi Yasuda, Kengo Kusano

(Department of Cardiovascular Medicine (A.O., I.N., Y.Y.I., T.K., M.W., K.I., K.M., H.O., S.N., T. Noda, T. Aiba, S.K., T. Anzai, T. Noguchi, S.Y., K.K.), Department of Radiology (Y.M.), National Cerebral and Cardiovascular Center, Suita; Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto (A.O., T. Anzai, S.Y., K.K.), Japan)



Background: Predicting tachycardia-induced cardiomyopathy (TIC) in patients presenting with left ventricular (LV) dysfunction and tachyarrhythmias remains challenging. We assessed the diagnostic value of early right ventricular (RV) dysfunction to predict TIC using cardiac magnetic resonance (CMR) imaging.

Methods and Results: A total of 102 consecutive patients with newly diagnosed LV dysfunction and atrial tachyarrhythmias were examined. Patients whose LV ejection fraction (EF) improved to $\geq 50\%$ during a 1-year follow-up were diagnosed with TIC, and with dilated cardiomyopathy (DCM) in those whose did not improve. CMR was performed at a median of 23 days after admission, and the TIC and DCM patients exhibited different distributions of EF and end-diastolic volume (EDV) between the LV and RV (both $P < 0.001$, ANCOVA). TIC patients had significantly lower RVEF/LVEF ratio (1.01 ± 0.23 vs. 1.36 ± 0.31 , $P < 0.001$) and higher RVEDV/LVEDV ratio (0.96 ± 0.21 vs. 0.73 ± 0.19 , $P < 0.001$) compared with DCM patients, suggesting that RV systolic dysfunction and RV dilatation were observed in TIC. In the multivariate analysis, age, RVEF/LVEF ratio, and RVEDV/LVEDV ratio were significant predictors of TIC, and RVEF/LVEF ratio of < 1.05 most highly predicted TIC with a sensitivity of 69.1% and specificity of 91.5% (area under the curve 0.860).

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Conclusions: Among patients with newly diagnosed LV dysfunction and atrial tachyarrhythmias, age and coexistence of RV dysfunction was a strong predictor of TIC.¹ (*Circ J* 2016; **80**: 2141–2148)

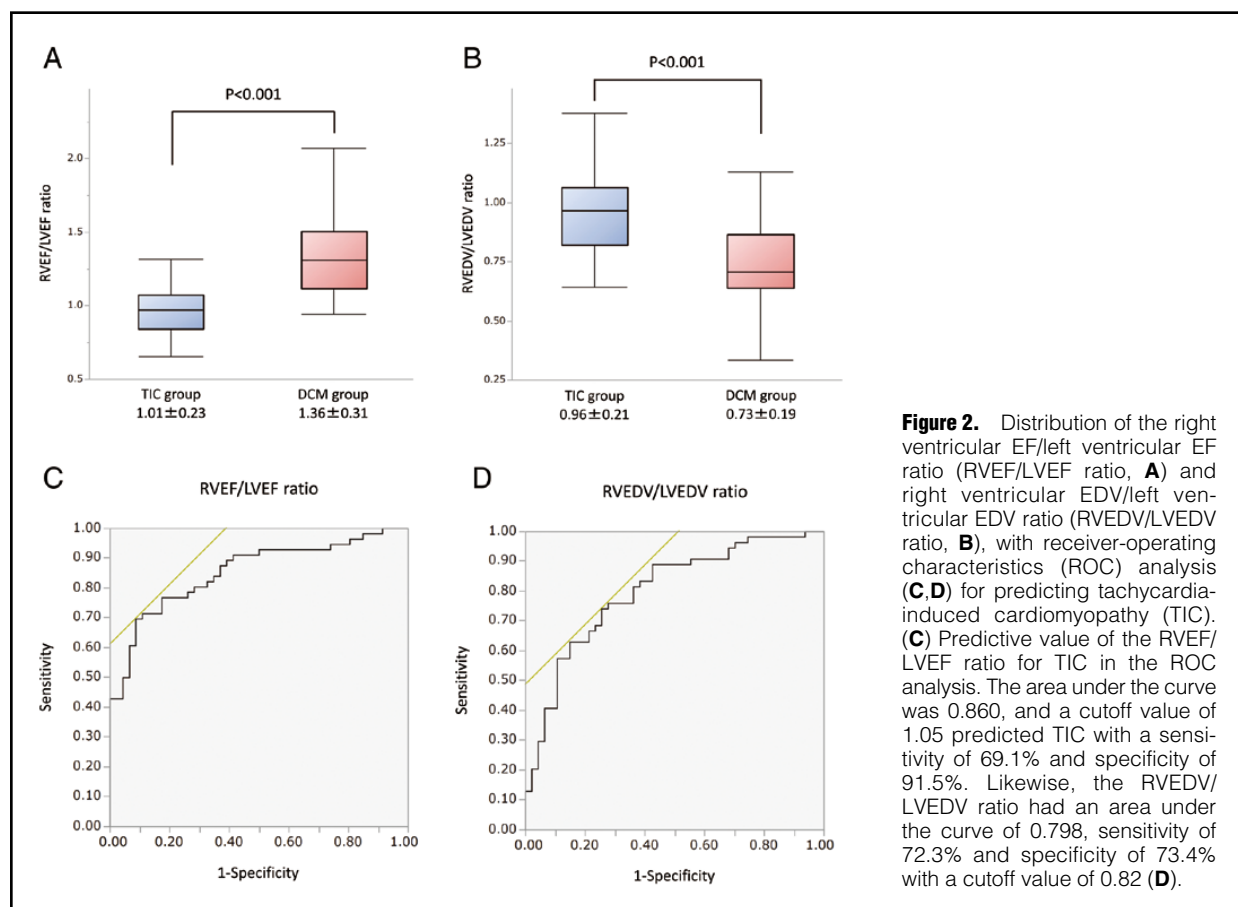


Figure 2. Distribution of the right ventricular EF/left ventricular EF ratio (RVEF/LVEF ratio, **A**) and right ventricular EDV/left ventricular EDV ratio (RVEDV/LVEDV ratio, **B**), with receiver-operating characteristics (ROC) analysis (**C,D**) for predicting tachycardia-induced cardiomyopathy (TIC). (**C**) Predictive value of the RVEF/LVEF ratio for TIC in the ROC analysis. The area under the curve was 0.860, and a cutoff value of 1.05 predicted TIC with a sensitivity of 69.1% and specificity of 91.5%. Likewise, the RVEDV/LVEDV ratio had an area under the curve of 0.798, sensitivity of 72.3% and specificity of 73.4% with a cutoff value of 0.82 (**D**).

Second Place in the Clinical Investigation Section

Valve Phenotype and Risk Factors of Aortic Dilatation After Aortic Valve Replacement in Japanese Patients With Bicuspid Aortic Valve

Takeshi Kinoshita, Shiho Naito, Tomoaki Suzuki, Tohru Asai

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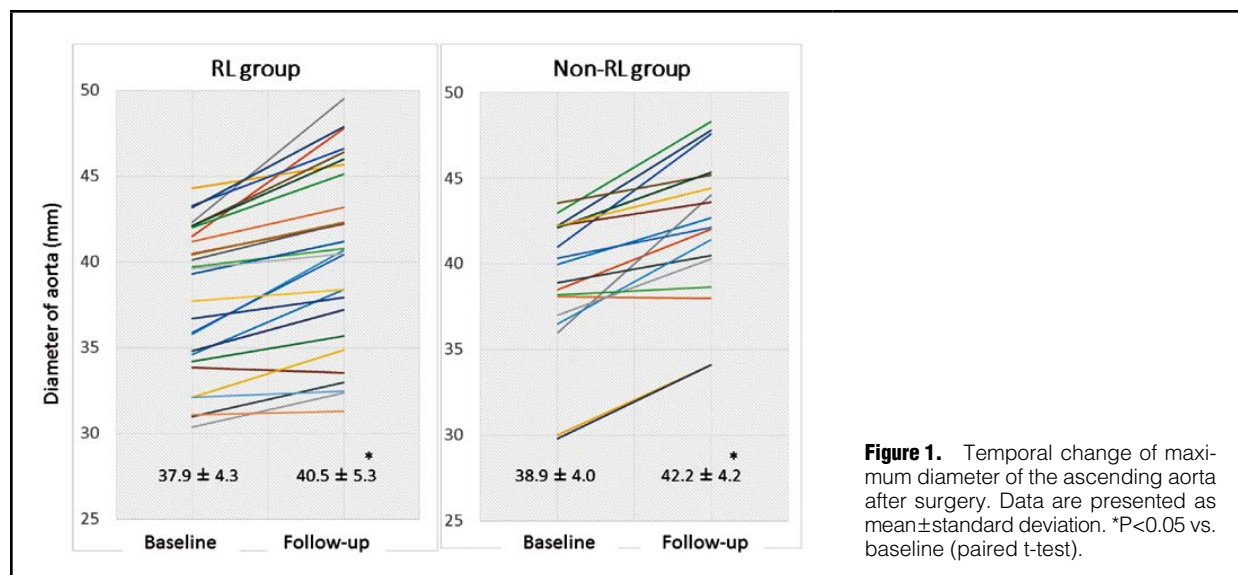


Background: The aim of this study was to assess the risk factors for dilatation of the aorta over time in Japanese patients with bicuspid aortic valve (BAV) undergoing aortic valve replacement (AVR), focusing on the possible impact of valve fusion phenotype.

Methods and Results: Of 167 BAV patients undergoing AVR (24% of overall AVR patients, n=702), 135 patients in whom surgical intervention for the aorta was not undertaken were focused on (74 had right-left fusion and 61 non-right-left fusion type). During a mean follow up of 5.2 years, aortic growth rate (mm/year) of the ascending aorta was similar between the valve phenotype. In multivariate logistic regression, the presence of aortic regurgitation > moderate was significantly associated with a rapid dilatation of the ascending aorta, defined as >0.7 mm/year (odds ratio 2.1, 95% confidence interval 1.2–3.7, P=0.03). Independent predictors of dilatation of the aorta up to more than 45 mm were: a diameter of the ascending aorta >40 mm at the time of

surgery (odds ratio 3.7, 95% confidence interval 1.2–11.4, $P=0.02$) and length of follow up (odds ratio 1.3-increase per year, 95% confidence interval 1.0–1.5, $P=0.04$).

Conclusions: The presence of aortic regurgitation and the ascending aorta of >40 mm at the time of surgery emerged as significant predictors of dilatation of the aorta after AVR but valve fusion phenotype was not.² (*Circ J* 2016; **80**: 1356–1361)



Second Place in the Clinical Investigation Section

Efficacy and Safety of Inhaled Iloprost in Japanese Patients With Pulmonary Arterial Hypertension – Insights From the IBUKI and AIR Studies –

Tsutomu Saji, Masafumi Myoishi, Koichiro Sugimura, Nobuhiro Tahara, Yutaka Takeda, Keiichi Fukuda, Horst Olschewski, Yoshimi Matsuda, Sylvia Nikkho, Toru Satoh

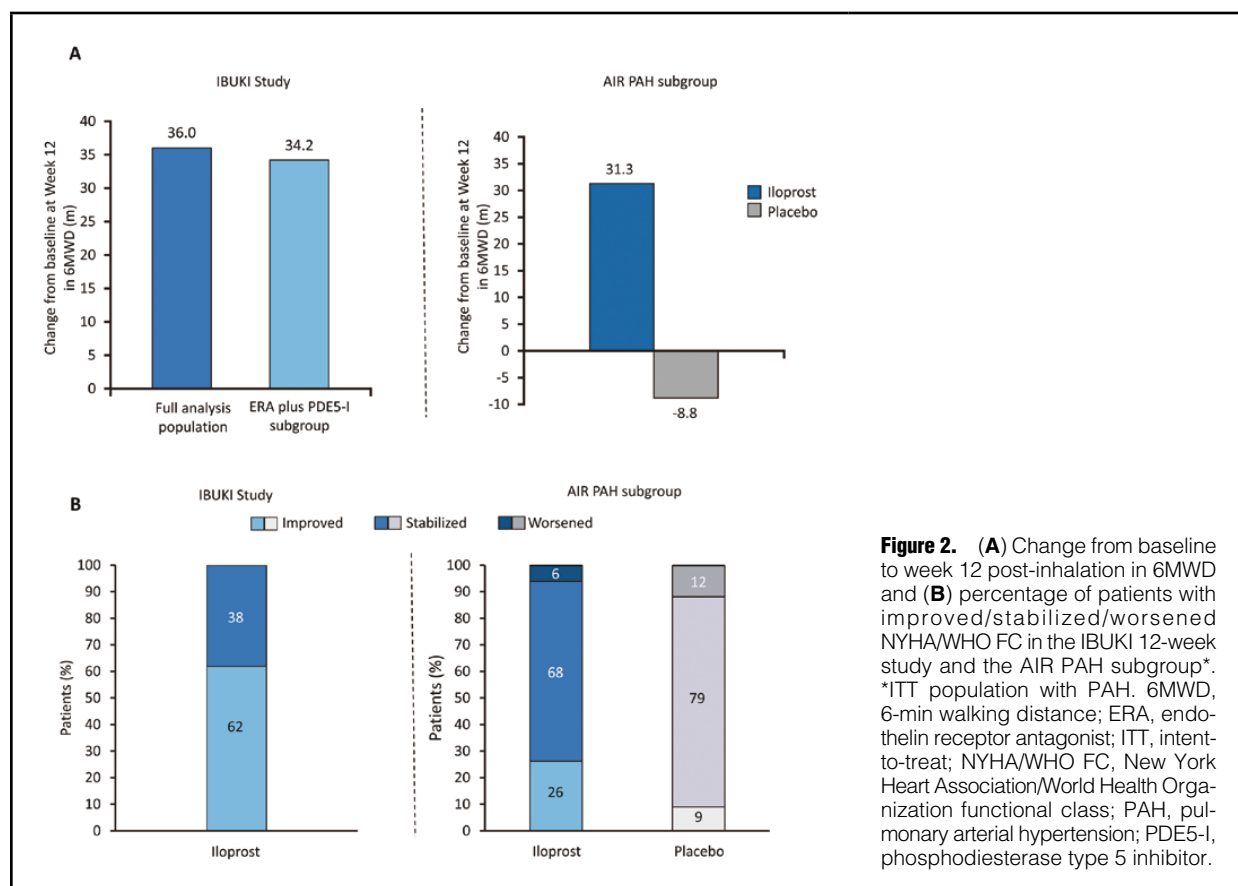
(Department of Pediatrics, Toho University Omori Medical Center, Tokyo (T. Saji); Bayer Yakuhin Ltd, Osaka (M.M., Y.M.); Tohoku University Graduate School of Medicine, Sendai (K.S.); Kurume University, Kurume (N.T.); Nagoya City University, Nagoya (Y.T.); Keio University School of Medicine, Tokyo (K.F.), Japan; Medical University of Graz, Graz (H.O.), Austria; Bayer Pharma AG, Berlin (S.N.), Germany; Kyorin University Hospital, Tokyo (T. Satoh), Japan)



Background: Inhaled iloprost is approved for pulmonary arterial hypertension (PAH) in many countries. IBUKI was a phase III, non-randomized, open-label study of the efficacy and safety of inhaled iloprost in Japanese patients with PAH.

Methods and Results: Adults with PAH who were treatment-naïve or administered endothelin receptor antagonists (ERAs) and/or phosphodiesterase type 5 inhibitors (PDE5-Is) and in NYHA/WHO functional class (FC) III/IV had inhaled iloprost (2.5 μ g, increased to 5.0 μ g if tolerated) 6–9 times daily for 12 weeks. Eligible patients entered a 40-week extension phase. Endpoints included change from baseline to week 12 in pulmonary vascular resistance (PVR; primary endpoint), other efficacy parameters, and safety. Data were compared with new subgroup analyses of treatment-naïve Western PAH patients from the global phase III AIR study. 27 patients received iloprost: 89% were treated with an ERA and/or PDE5-I; 70% with both. At week 12, PVR improved from baseline by -124 dyn \cdot sec \cdot cm $^{-5}$ (95% CI, -177 to -72) and 6-min walking distance increased by 36.0 m (95% CI, 14.9 to 57.1). NYHA/WHO FC improved in 62%; none worsened. Common drug-related adverse events were headache (37%) and cough (15%); 1 patient experienced hypotension; none reported syncope or hemoptysis. There were no deaths and no unexpected long-term safety findings. AIR PAH subgroup analyses showed similar results.

Conclusions: Inhaled iloprost appeared effective and safe in Japanese PAH patients, including ERA- and PDE5-I-treated patients, consistent with findings of the AIR PAH subpopulation and previous iloprost studies.³ (*Circ J* 2016; **80**: 835–842)



Second Place in the Clinical Investigation Section

Hippocampal Blood Flow Abnormality Associated With Depressive Symptoms and Cognitive Impairment in Patients With Chronic Heart Failure

Hideaki Suzuki, Yasuharu Matsumoto, Hideki Ota, Koichiro Sugimura, Jun Takahashi, Kenta Ito, Satoshi Miyata, Katsutoshi Furukawa, Hiroyuki Arai, Yoshihiro Fukumoto, Yasuyuki Taki, Hiroaki Shimokawa

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Background: Depressive symptoms and memory impairment are prevalent in patients with chronic heart failure (CHF). Although the mechanisms remain to be elucidated, the hippocampus (an important brain area for emotion and memory) may be a possible neural substrate for these symptoms.

Methods and Results: We prospectively enrolled 40 Stage C patients, who had past or current CHF symptoms, and as controls 40 Stage B patients, who had structural heart disease but had never had CHF symptoms, in Brain Assessment and Investigation in Heart Failure Trial (B-HeFT) (UMIN000008584). As the primary index, we measured cerebral blood flow (CBF) in the 4 anterior-posterior segments of the hippocampus, using brain MRI

analysis. Depressive symptoms, immediate memory (IM) and delayed memory (DM) were assessed using Geriatric Depression Scale (GDS), and Wechsler Memory Scale-revised (WMS-R), respectively. Hippocampus CBF in the most posterior segment was significantly lower in Stage C than in Stage B group ($P=0.029$ adjusted for Holm's method). Multiple regression analysis identified significant association between hippocampus CBF and GDS or DM score in Stage C group (all $P<0.05$). GDS score was significantly higher, and IM and DM scores were lower in Stage C patients with hippocampus CBF below the median than those with hippocampus CBF above the median (all $P<0.05$).

Conclusions: Hippocampus abnormalities are associated with depressive symptoms and cognitive impairment in CHF patients.⁴ (*Circ J* 2016; **80**: 1773–1780)

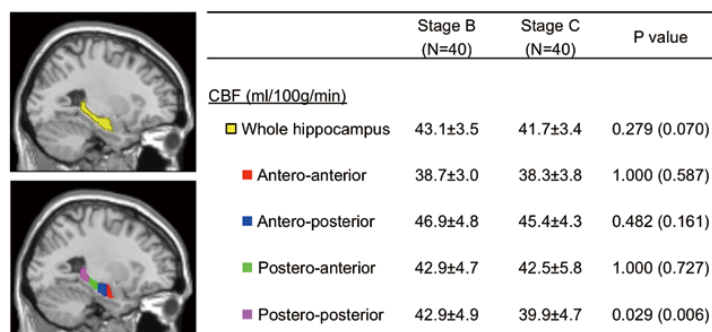


Figure 2. Cerebral blood flow (CBF) in the hippocampus in Stage B and C groups of chronic heart failure patients. The whole, antero-anterior, antero-posterior, postero-anterior and postero-posterior ROI of the hippocampus (yellow, red, blue, green and pink regions, respectively) are displayed on the selected slice of the MRI template available in the SPM8 system. The numbers in the parentheses are nominal P values without correction for multiple comparisons. MRI, magnetic resonance image; ROI, region of interest.

First Place in the Experimental Investigation Section

Next Generation Sequencing and Linkage Analysis for the Molecular Diagnosis of a Novel Overlapping Syndrome Characterized by Hypertrophic Cardiomyopathy and Typical Electrical Instability of Brugada Syndrome

Ruggiero Mango, Andrea Luchetti, Raffaele Sangiuolo, Valentina Ferradini, Nicola Briglia, Emiliano Giardina, Fabrizio Ferrè, Manuela Helmer Citterich, Francesco Romeo, Giuseppe Novelli, Federica Sangiuolo

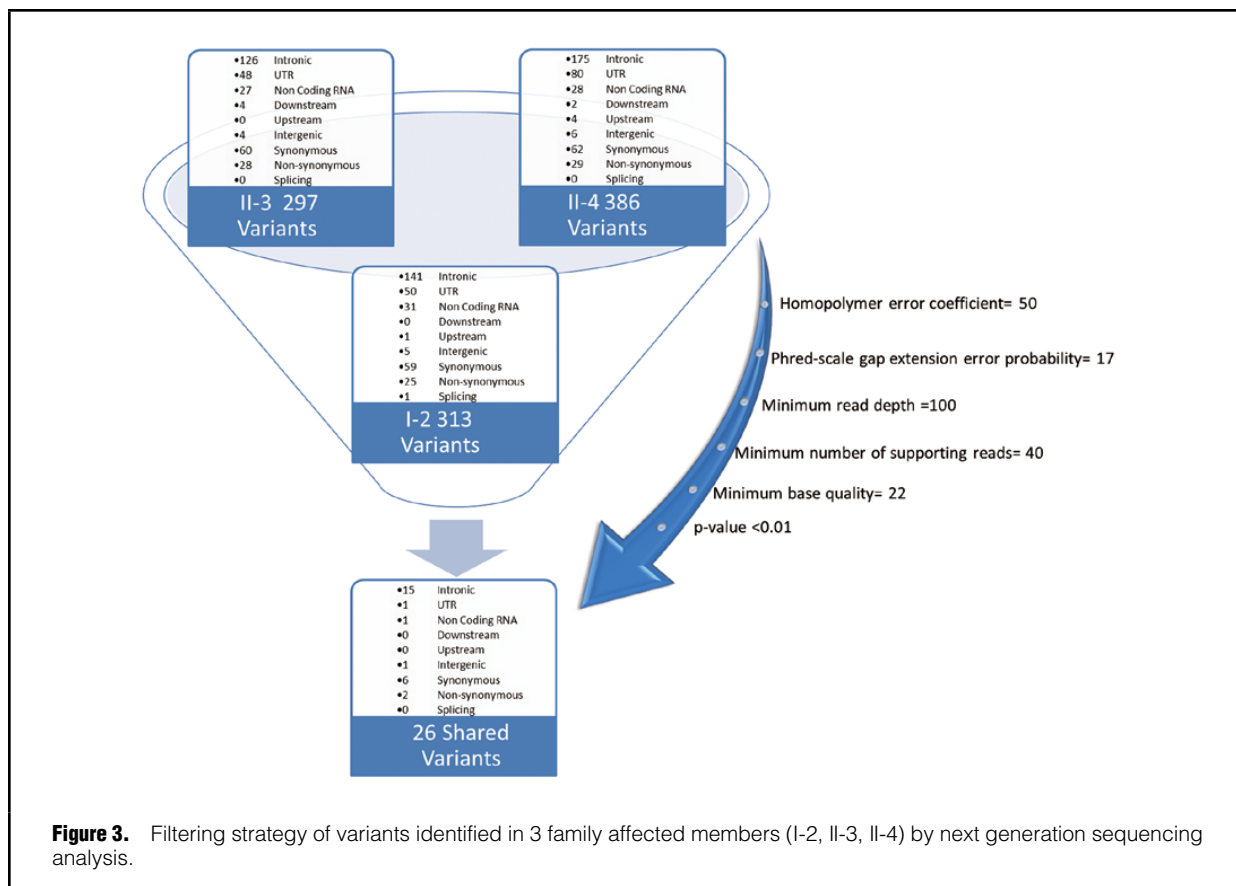
(Department of Emergency and Critical Care, Section of Cardiology, Policlinic of Tor Vergata, Rome (R.M., F.R.); Department of Biomedicine and Prevention (A.L., V.F., E.G., G.N., F.S.), Department of Biology (F.F., M.H.C.), Tor Vergata University, Rome; Ospedale Buon Consiglio Fatebenefratelli, Napoli (R.S., N.B.); and Department of Pharmacology and Biotechnology, University of Bologna Alma Mater, Bologna (F.F.), Italy)



Background: Familial hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disorder; mutations in at least 20 genes have been associated. Brugada syndrome (BrS) is an autosomal dominant inherited disorder caused by mutations mainly in the *SCN5A* gene. A new clinical entity that consists of HCM, typical electrical instability of BrS and sudden death (SD), is described.

Methods and Results: The family was constituted by 7 members, 4 of who presented clinical features of HCM and electrical instability of BrS. The clinical presentation of proband was ventricular fibrillation. All members were clinically evaluated by physical examination, 12-lead electrocardiography, 2-dimensional echocardiography, stress test, electrocardiogram Holter, flecainide test, and electrophysiological study. An integrated linkage analysis and next generation sequencing (NGS) approach was used to identify the causative mutation. Linkage with the α -tropomyosin (*TPM1*) gene on chromosome 15q22 was identified. The NGS study identified a missense mutation within the *TPM1* gene (c.574G>A; p.E192K), exactly located in a binding domain with polycystin-2 protein. No other pathogenic mutations were identified.

Conclusions: This is the first report of an association between HCM and BrS, and the first to use a combined approach of linkage and NGS to identify a causative mutation in SD. The present study expands the clinical spectrum of disorders associated with the *TPM1* gene and may be useful to report novel mechanisms of electrical instability in HCM and BrS.⁵ (*Circ J* 2016; **80**: 938–949)



Second Place in the Experimental Investigation Section

Glucose Fluctuations Aggravate Cardiac Susceptibility to Ischemia/Reperfusion Injury by Modulating MicroRNAs Expression

Shotaro Saito, Luong Cong Thuc, Yasushi Teshima, Chisato Nakada, Satoru Nishio, Hidekazu Kondo, Akira Fukui, Ichitaro Abe, Yuki Ebata, Tetsunori Saikawa, Masatsugu Moriyama, Naohiko Takahashi

(Department of Cardiology and Clinical Examination (S.S., L.C.T., Y.T., S.N., H.K., A.F., I.A., Y.E., T.S., N.T.), Department of Molecular Pathology (C.N., M.M.), Faculty of Medicine, Oita University, Yufu, Japan)

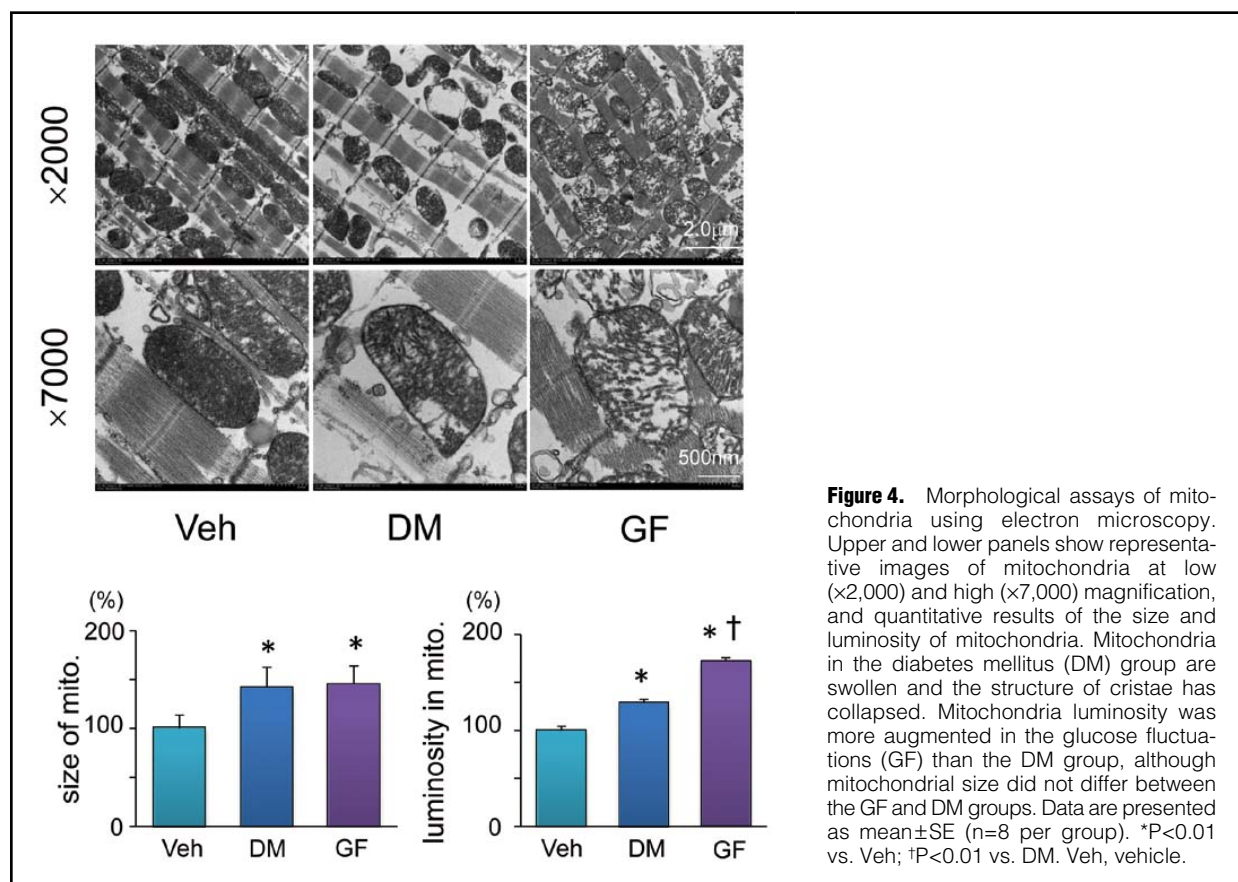


Background: The influence of glucose fluctuations (GF) on cardiovascular complications of diabetes mellitus (DM) has been attracting much attention. In the present study, whether GF increase susceptibility to ischemia/reperfusion in the heart was investigated.

Methods and Results: Male rats were randomly assigned to either a control, DM, and DM with GF group. DM was induced by an injection of streptozotocin, and glucose fluctuation was induced by starvation and insulin injection. One sequential program comprised 2 hypoglycemic episodes during 4 days. The isolated hearts were subjected to 20-min ischemia/30-min reperfusion. The infarct size was larger in hearts with GF than those with sustained hyperglycemia. Activities of catalase and superoxide dismutase were decreased, and expressions of

NADPH oxidase and thioredoxin-interacting protein were upregulated by GF accompanied by an increase of reactive oxygen species (ROS). Swollen mitochondria with destroyed cristae were observed in diabetic hearts; they were further devastated by GF. Microarray analysis revealed that the expressions of microRNA (miRNA)-200c and miRNA-141 were abundant in those hearts with GF. Overexpression of miRNA-200c and miRNA-141 decreased mitochondrial superoxide dismutase and catalase activities, and increased ROS levels. Meanwhile, knockdown of miRNA-200c and miRNA-141 significantly decreased ROS levels in cardiomyocytes exposed to GF.

Conclusions: GF increased ROS generation and enhanced ischemia/reperfusion injury in the diabetic heart. Upregulated miRNA-200c and miRNA-141 may account for the increased ROS.⁶ (*Circ J* 2016; **80**: 186–195)



Circulation Journal Asian Award

Calcium-Channel Blockers and Dementia Risk in Older Adults – National Health Insurance Service – Senior Cohort (2002–2013) –

Deri Hwang, Sunyoung Kim, Hangseok Choi, In-Hwan Oh, Byung Sung Kim, Hyun Rim Choi, So Yeon Kim, Chang Won Won

(Department of Family Medicine, College of Medicine (D.H., B.S.K., H.R.C., S.Y.K., C.W.W.), Department of Medicine, Graduate School (S.K.), Preventive Medicine, College of Medicine (I.-H.O.), Kyung Hee University, Seoul; Statistics and Information Analysis Center, Social Security Information Service, Seoul (H.C.), Korea)



Background: Some disagreements surround the effects of calcium-channel blockers (CCBs) on the risk of dementia. The purpose of this study was to investigate the protective effects of CCBs on dementia among elderly hypertensive Koreans.

Methods and Results: We conducted a large population-based cohort study using the senior cohort database of the Korean National Health Insurance Service (2002–2013). Subjects were elderly hypertensive Koreans older than 60 years of age. A total of 18,423 patients (CCB user group: 13,692 patients; non-CCB antihypertensive user group: 4,731 patients) were statistically analyzed using the Cox proportional hazard regression model to estimate the adjusted hazard ratio (aHR) and confidence intervals (CIs) of dementia associated with CCB use. There were 2,881 cases (21.0%) of dementia in the CCB user group and 1,124 cases (23.8%) in the non-user group. CCB use significantly reduced the risk of total dementia (aHR 0.81, 95% CI 0.75–0.87, $P<0.0001$), Alzheimer's dementia (aHR 0.80, 95% CI 0.72–0.88, $P<0.0001$), and vascular dementia (aHR 0.81, 95% CI 0.70–0.94, $P=0.0067$).

Conclusions: CCB use had a protective effect on the risk of dementia among elderly hypertensive Koreans.⁷ (*Circ J* 2016; **80**: 2336–2342)

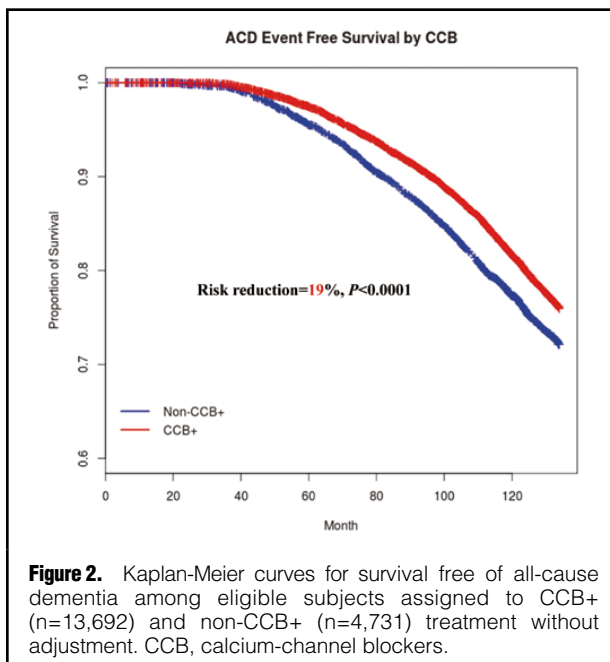


Figure 2. Kaplan-Meier curves for survival free of all-cause dementia among eligible subjects assigned to CCB+ (n=13,692) and non-CCB+ (n=4,731) treatment without adjustment. CCB, calcium-channel blockers.

Awards will be presented to the 7 research groups during the 81st Annual Scientific Meeting of the Japanese Circulation Society, and will also be announced on the Society website. We look forward to receiving manuscripts with high scientific impact for publication in *Circulation Journal* in 2017.

Toyoaki Murohara, MD, PhD
Editor-in-Chief
Circulation Journal

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