



Circulation Journal Awards for the Year 2015

Hiroaki Shimokawa, 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 2015.

The aim of these Awards is to recognize papers published in 2015, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 241 original papers published in the Journal in 2015, our 35 Japanese Associate Editors selected papers with a high scientific level in their respective fields, and in the second step, the 2 Associate Editorial Teams (17 on 1 team and 18 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 2015, the following 7 papers have been selected for the *Circulation Journal* Awards.

< First Place in the Clinical Investigation Section >

Safety and Efficacy of Autologous Skeletal Myoblast Sheets (TCD-51073) for the Treatment of Severe Chronic Heart Failure Due to Ischemic Heart Disease

Yoshiki Sawa, Yasushi Yoshikawa, Koichi Toda, Satsuki Fukushima, Kenji Yamazaki, Minoru Ono, Yasushi Sakata, Nobuhisa Hagiwara, Koichiro Kinugawa, Shigeru Miyagawa

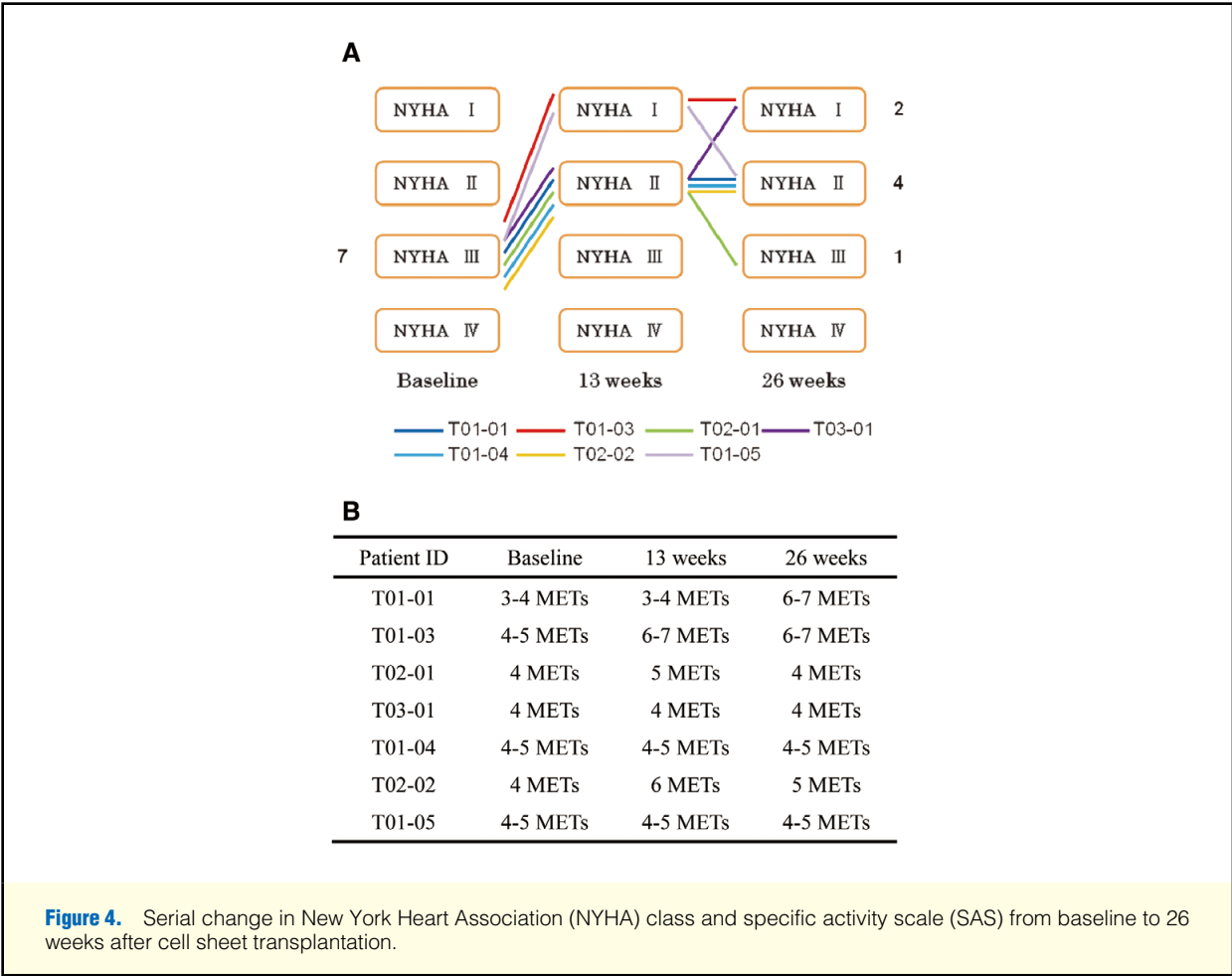
(Department of Cardiovascular Surgery (Y. Sawa, Y.Y., K.T., S.F., S.M.), Department of Cardiovascular Medicine (Y. Sakata), Osaka University Graduate School of Medicine, Suita; Department of Cardiovascular Surgery (K.Y.), Department of Cardiology (N.H.), Tokyo Women's Medical University, Tokyo; and Department of Thoracic Surgery (M.O.), Department of Therapeutic Strategy for Heart Failure (K.K.), Graduate School of Medicine, University of Tokyo, Tokyo, Japan)



Background: Poor survival outcomes for patients with severe heart failure (HF) and the donor shortage for heart transplantation warrant the development of myocardial regenerative therapy. We performed a multicenter, phase II study to evaluate the safety and efficacy of autologous skeletal myoblast sheets (TCD-51073).

Methods and Results: In 3 study sites, we enrolled 7 patients with severe chronic HF due to ischemic heart disease despite maximal therapy, all of whom underwent transplantation of TCD-51073. No serious arrhythmia was reported, and no changes were noted in the frequency of ventricular extrasystole frequency. The primary efficacy endpoint of the change in left ventricular ejection fraction (LVEF) on gated blood-pool scintigraphy at 26 weeks after transplantation showed that 5 subjects were responders (classified as “improved” or “unchanged”). In addition, LVEF on echocardiography improved over time, with a change in LVEF of $7.1 \pm 2.8\%$ at 26 weeks posttransplantation. Among the 7 subjects, 6 showed improvement in New York Heart Association functional class by at least 1 class. The 6-min walk distance was 410.1 ± 136.1 m before transplantation and 455.4 ± 103.7 m at 26 weeks after transplantation.

Conclusions: This study demonstrated the feasibility and safety of the transplantation of TCD-51073 in the patients with severe chronic HF due to ischemic heart disease, suggesting that TCD-51073 might maintain or improve cardiac function, symptoms, and physical function.¹ (*Circ J* 2015; **79**: 991–999)



< Second Place in the Clinical Investigation Section >

Serum Trans-Fatty Acid Concentration Is Elevated in Young Patients With Coronary Artery Disease in Japan

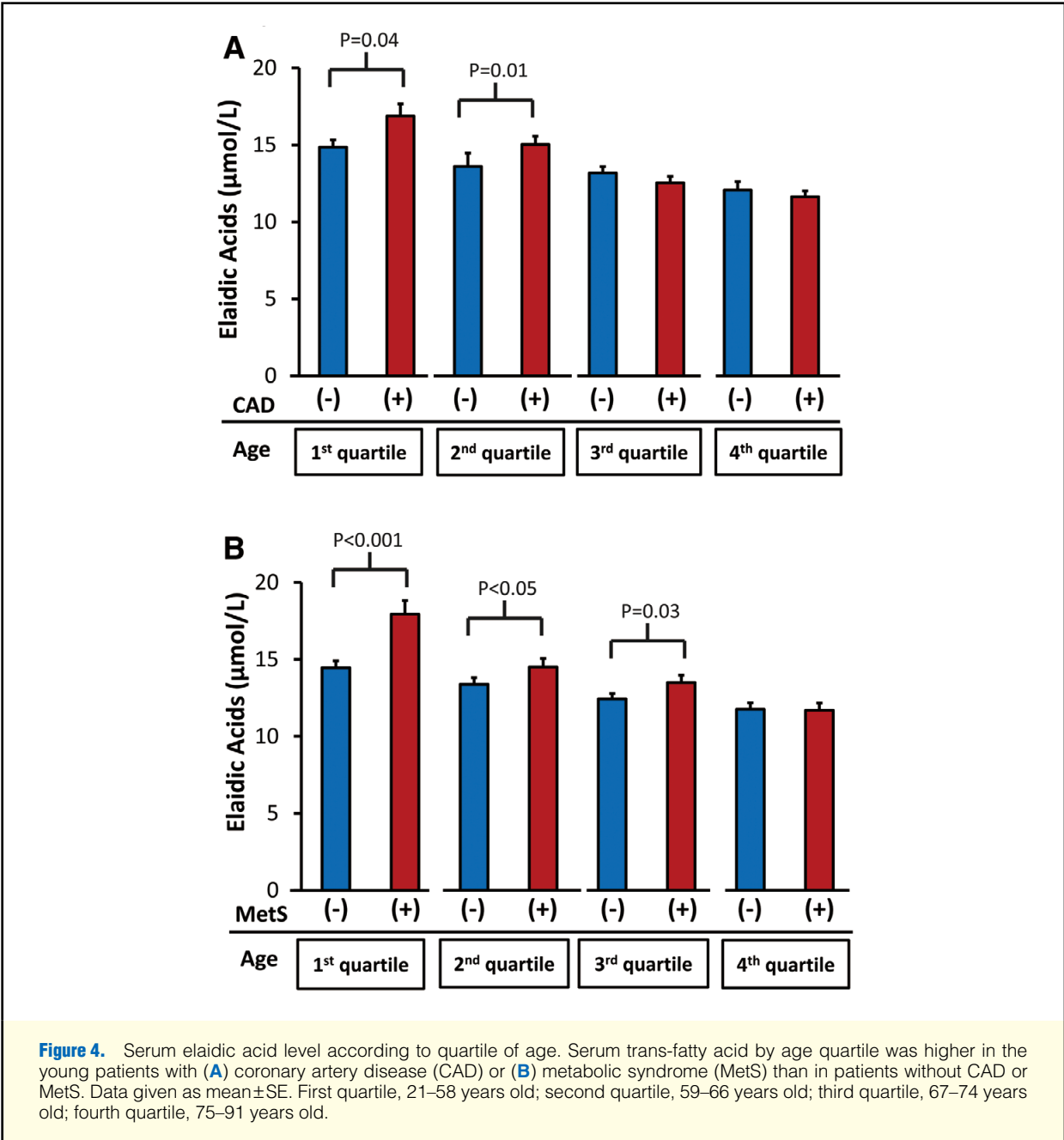
Kenta Mori, Tatsuro Ishida, Tomoyuki Yasuda, Minoru Hasokawa, Tomoko Monguchi, Maki Sasaki, Kensuke Kondo, Hideto Nakajima, Masakazu Shinohara, Toshiro Shinke, Yasuhiro Irino, Ryuji Toh, Kunihiro Nishimura, Ken-ichi Hirata

(Division of Cardiovascular Medicine (K.M., T.I., T.Y., M.H., T.M., M. Sasaki, K.K., H.N., M. Shinohara, T.S., K.H.), Division of Evidence-based Laboratory Medicine (Y.I., R.T.), Kobe University Graduate School of Medicine, Kobe; Department of Preventive Medicine and Epidemiologic Informatics, Office of Evidence-Based Medicine and Risk Analysis, National Cerebral and Cardiovascular Center, Suita (K.N.), Japan)



Background: Adverse effects of dietary intake of trans-fatty acids (TFA) on the incidence of coronary artery disease (CAD) are well recognized in Western countries. The risk of TFA, however, has not been well clarified in Japan. We investigated the association of serum TFA concentration with serum lipid profile, coronary risk factors, and prevalence of CAD.

Methods and Results: A total of 902 patients, who were hospitalized at Kobe University Hospital from July 2008 to March 2012 and gave written informed consent, were enrolled in this study. Among them, 463 patients had CAD, and 318 patients had metabolic syndrome (MetS). Serum TFA, elaidic acid (trans-9-C18:1) and linolelaidic acid (trans-9, 12-C18:2), were measured on gas chromatography/mass spectrometry. Serum TFA level had a positive correlation with body mass index, waist circumference, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B48, and



an inverse correlation with age and high-density lipoprotein cholesterol. Fasting serum TFA, by age quartile in the young generation with CAD and/or MetS, was higher than that in patients without CAD and/or MetS. On multivariate logistic regression, TFA was identified as a CAD risk after adjustment for classical risk factors.

Conclusions: Serum TFA concentration was elevated in young patients with CAD and/or MetS. Diet-derived TFA may cause a serious health problem, particularly in the young generation in Japan.² (*Circ J* 2015; **79**: 2017–2025)

< Second Place in the Clinical Investigation Section >

Clinical and Pathological Impact of Tissue Fibrosis on Lethal Arrhythmic Events in Hypertrophic Cardiomyopathy Patients With Impaired Systolic Function

Yuko Wada, Takeshi Aiba, Taka-aki Matsuyama, Ikutaro Nakajima, Kohei Ishibashi, Koji Miyamoto, Yuko Yamada, Hideo Okamura, Takashi Noda, Kazuhiro Satomi, Yoshiaki Morita, Hideaki Kanzaki, Kengo Kusano, Toshihisa Anzai, Shiro Kamakura, Hatsue Ishibashi-Ueda, Wataru Shimizu, Minoru Horie, Satoshi Yasuda, Hisao Ogawa (Department of Cardiovascular Medicine (Y.W., T. Aiba, I.N., K.I., K.M., Y.Y., H. Okamura, T.N., K.S., H.K., K.K., T. Anzai, S.K., W.S., S.Y., H. Ogawa), Department of Clinical Pathology (T.M., H.I.-U.), Department of Radiology (Y.M.), National Cerebral and Cardiovascular Center, Suita; Department of Cardiovascular Medicine, Nippon Medical School, Tokyo (W.S.); and Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu (Y.W., M.H.), Japan)



Background: The natural history of hypertrophic cardiomyopathy (HCM) varies from an asymptomatic benign course to a poor prognosis. Myocardial fibrosis may play a critical role in ventricular tachyarrhythmias (VT/VF); however, the clinical significance of tissue fibrosis by right ventricular (RV) biopsy in the long-term prognosis of HCM patients remains unclear.

Methods and Results: We enrolled 185 HCM patients (mean age, 57±14 years). The amount of fibrosis (%area) was quantified using a digital microscope. Hemodynamic, echocardiographic, and electrophysiologic parameters were also evaluated. Patients with severe fibrosis had longer QRS duration and positive late potential (LP) on signal-averaged ECG, resulting in a higher incidence of VT/VF. At the 5±4 year follow-up, VT/VF occurred in 31 (17%) patients. Multivariate Cox regression analysis revealed that tissue fibrosis (hazard ratio (HR): 1.65; P=0.003 per 10% increase), lower left ventricular ejection fraction (HR: 0.64; P=0.001 per 10% increase), and positive SAECG (HR: 3.14; P=0.04) led to a greater risk of VT/VF. The combination of tissue fibrosis severity and lower left ventricular ejection fraction could be used to stratify the risk of lethal arrhythmic events in HCM patients.

Conclusions: Myocardial fibrosis in RV biopsy samples may contribute to abnormal conduction delay and spontaneous VT/VF, leading to a poor prognosis in HCM patients.³ (Circ J 2015; 79: 1733–1741)

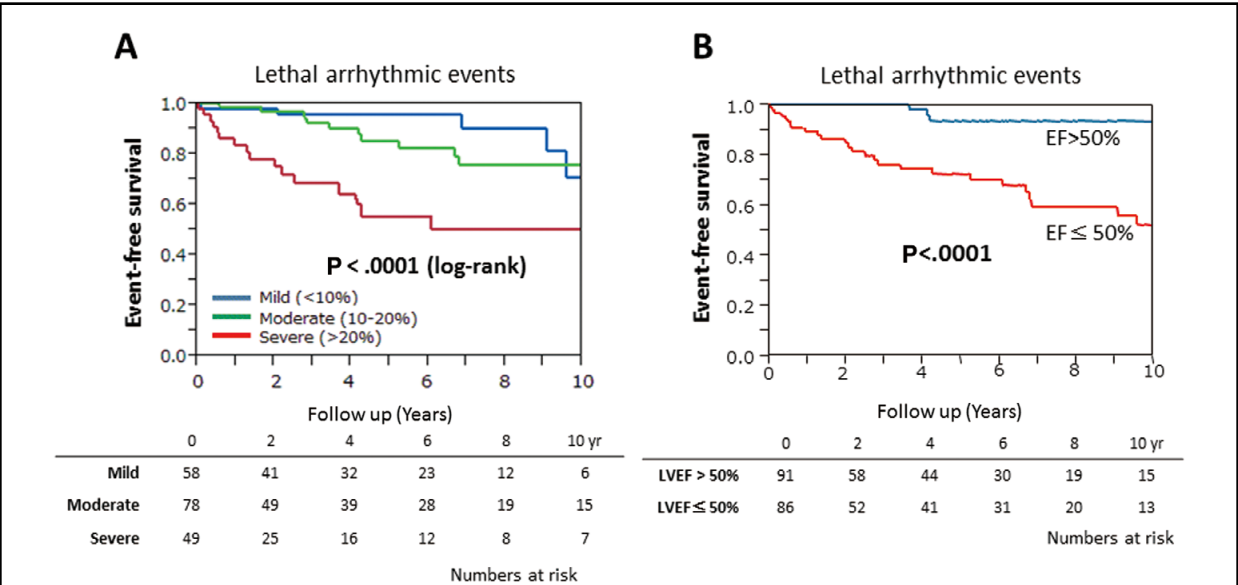


Figure 3. Lethal arrhythmic events and degree of tissue fibrosis or left ventricular ejection fraction (LVEF). Kaplan-Meier unadjusted estimates of freedom from lethal arrhythmic events or sudden cardiac death according to the degree of fibrotic change (A) or LVEF (B) in 185 patients with hypertrophic cardiomyopathy.

< Second Place in the Clinical Investigation Section >

Risk Factors for Progression of Degenerative Aortic Valve Disease in the Japanese – The Japanese Aortic Stenosis Study (JASS) Prospective Analysis –

Kazuhiro Yamamoto, Hideya Yamamoto, Masaaki Takeuchi, Akira Kisanuki, Takashi Akasaka, Nobuyuki Ohte, Yutaka Hirano, Kiyoshi Yoshida, Satoshi Nakatani, Yasuharu Takeda, Takashi Sozu, Tohru Masuyama

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Background: Because of ethnic difference in the risk of degenerative aortic valve disease (DAVD), risk factors should be clarified in each race to establish prophylactic strategies for severe aortic valve stenosis (AS).

Methods and Results: This study prospectively followed 359 Japanese subjects with DAVD and age ≥ 50 years for 3 years. As both patients with peak aortic transvalvular flow velocity ≥ 2 m/s and < 2 m/s were enrolled, subgroup analysis was also conducted. Most patients were under treatment for their comorbidities. The use of warfarin, but none of the traditional risk factors for atherosclerosis, was related to greater reduction in aortic valve area indexed to body surface area (iAVA). In patients with peak aortic transvalvular flow velocity < 2 m/s, the use of an angiotensin-receptor blocker (ARB) was associated with less decrease in iAVA. In patients with peak velocity ≥ 2 m/s, changes in iAVA were not related to any baseline characteristics, but peak velocity was less increased under treatment with an angiotensin-converting enzyme inhibitor (ACEI).

Conclusions: In Japanese, the use of warfarin may exacerbate DAVD, and augmented management of atherosclerotic risk factors beyond the recommendations in the current guidelines is unlikely to exert additional benefit. The prescription of ARB for DAVD patients before the development of AS or ACEI after the development of AS may be useful.⁴ (Circ J 2015; 79: 2050–2057)

Table 4. P Value for Association of Medication With Δ iAVA in Japanese Subjects With Degenerative Aortic Valve Disease

	All	Without AS	With AS
ACEI	0.382	0.869	0.401
ARB	0.396	0.039	0.564
β -blocker	0.042	0.013	0.274
Calcium-channel blocker	0.799	0.953	0.676
Mineralocorticoid receptor blocker	0.370	0.848	0.166
Nonpotassium-sparing diuretics	0.679	0.790	0.504
Antiplatelet agents	0.524	0.914	0.510
Warfarin	0.026	0.054	0.116
Statins	0.409	0.339	0.763
Oral hypoglycemic medications	0.553	0.692	0.669
Insulin	0.730	0.713	0.309

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; AS, aortic valve stenosis; iAVA, aortic valve area indexed to body surface area.

< First Place in the Experimental Investigation Section >

Regeneration of the Cardiac Conduction System by Adipose Tissue-Derived Stem Cells

Toshinao Takahashi, Toshio Nagai, Masato Kanda, Mei-Lan Liu, Naomichi Kondo, Atsuhiko T Naito, Takehiko Ogura, Haruaki Nakaya, Jong-Kook Lee, Issei Komuro, Yoshio Kobayashi

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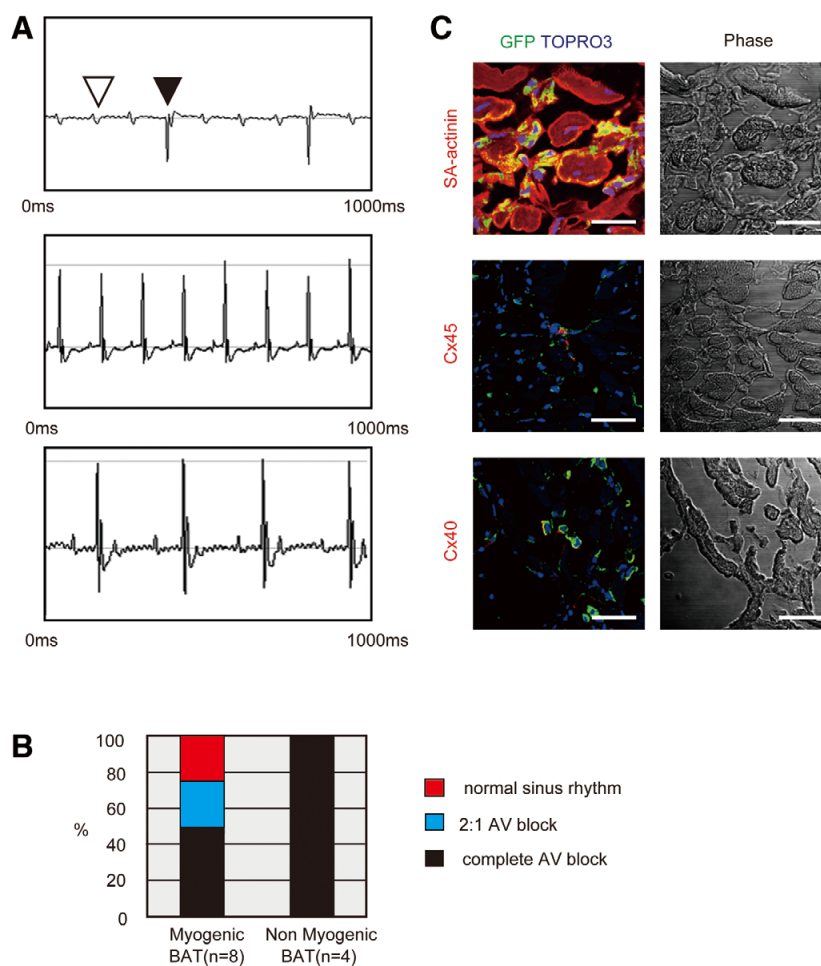


Figure 7. Transplanted brown adipose tissue (BAT)-derived cells show the phenotype of the cardiac conduction system and restore atrioventricular (AV) conduction. **(A)** Typical electrocardiogram (ECG) recordings after the creation of the complete AV block (Top). Note that atrial activation corresponding to P waves (white arrowhead) continues with slower ventricular escape beats (black arrowhead). Representative ECG recordings from one of the mice after injection of BAT-derived myogenic cells (Middle and Bottom). Note that normal alternative electrical activation of atrium and ventricles (Middle) and incomplete AV block (Bottom) are observed. **(B)** The percentage of mice that showed full or partial recovery of AV conduction after injection of differentiated BAT-derived cells or non-myogenic BAT-derived cells. **(C)** Immunohistochemical images of the muscular septum adjacent to the injection site obtained from the mouse that recovered AV conduction completely. Green fluorescent protein-positive (GFP)-expressing BAT-derived cells co-express sarcomeric α (SA)-actinin (yellow in Top). GFP-expressing BAT-derived cells form a cluster and co-express connexin (Cx) 45 (yellow and red in the Middle) and Cx40 (yellow and red at the Bottom). Nuclei are stained in blue and the phase contrast image of the corresponding field is presented in the right panels. Scale bars, 50 μ m.

Background: Adipose tissue is one of the sources of mesenchymal stem cells, which have the potential to differentiate into various types of cells, including myocytes. Whether brown adipose tissue (BAT)-derived cells might differentiate into the cardiac pacemaking-conducting cells, and have the potential to regenerate the cardiac conduction system (CCS), is investigated in this study.

Methods and Results: BAT was isolated from the interscapular area of mice and enzymatically digested before culture. Round or fusiform cells showed spontaneous beating at 4–7 days after culturing of BAT-derived cells. Reverse transcriptase-polymerase chain reaction analysis and immunocytochemical analysis revealed that BAT-derived cells expressed several cardiomyocytes, the CCS and pacemaker (PM) cell marker genes and proteins. Patch-clamp techniques revealed that spontaneous electrical activity and the shape of the action potential showed properties of cardiac PM cells. Next, a complete atrioventricular (AV) block was created in mice and green fluorescent protein-positive (GFP (+)) BAT-derived cells were injected intramyocardially around the AV node. At 1 week after transplantation, 50% of BAT-derived cells injected mice showed a sinus rhythm or a 2:1 AV block. Immunohistochemical analysis revealed that injected GFP (+) cells were engrafted and some GFP (+) cells co-expressed several cardiac PM cell marker proteins.

Conclusions: BAT-derived cells differentiate into the CCS and PM-like cells in vitro and in vivo, and may become a useful cell source for arrhythmia therapy.⁵ (*Circ J* 2015; **79**: 2703–2712)

< Second Place in the Experimental Investigation Section >

Molecular Mechanisms Underlying Urate-Induced Enhancement of Kv1.5 Channel Expression in HL-1 Atrial Myocytes

Nani Maharani, Ya Kuang Ting, Jidong Cheng, Akira Hasegawa, Yasutaka Kurata, Peili Li, Yuji Nakayama, Haruaki Ninomiya, Nobuhito Ikeda, Kumi Morikawa, Kazuhiro Yamamoto, Naomasa Makita, Takeshi Yamashita, Yasuaki Shirayoshi, Ichiro Hisatome

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Background: Hyperuricemia induces endothelial dysfunction, oxidative stress and inflammation, increasing cardiovascular morbidities. It also raises the incidence of atrial fibrillation; however, underlying mechanisms are unknown.

Methods and Results: The effects of urate on expression of Kv1.5 in cultured mouse atrial myocytes (HL-1 cells) using reverse transcriptase-PCR, immunoblots, flow cytometry and patch-clamp experiments were studied. Treatment with urate at 7 mg/dl for 24 h increased the Kv1.5 protein level, enhanced ultra-rapid delayed-rectifier K⁺ channel currents and shortened action potential duration in HL-1 cells. HL-1 cells expressed the influx uric acid transporter (UAT), URATv1, and the efflux UATs, ABCG2 and MRP4. An inhibitor against URATv1, benzbromarone, abolished the urate effects, whereas an inhibitor against ABCG2, KO143, augmented them. Flow cytometry showed that urate induced an increase in reactive oxygen species, which was abolished by the antioxidant, N-acetylcysteine (NAC), and the NADPH-oxidase inhibitor, apocynin. Both NAC and apocynin abolished the enhancing effects of urate on Kv1.5 expression. A urate-induced increase in the Kv1.5 proteins was accompanied by phosphorylation of extracellular signal-regulated kinase (ERK), and was abolished by an ERK inhibitor, PD98059. NAC abolished phosphorylation of ERK by urate.

Conclusions: Intracellular urate taken up by UATs enhanced Kv1.5 protein expression and function in HL-1 atrial myocytes, which could be attributable to ERK phosphorylation and oxidative stress derived from nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase.⁶ (*Circ J* 2015; **79**: 2659–2668)

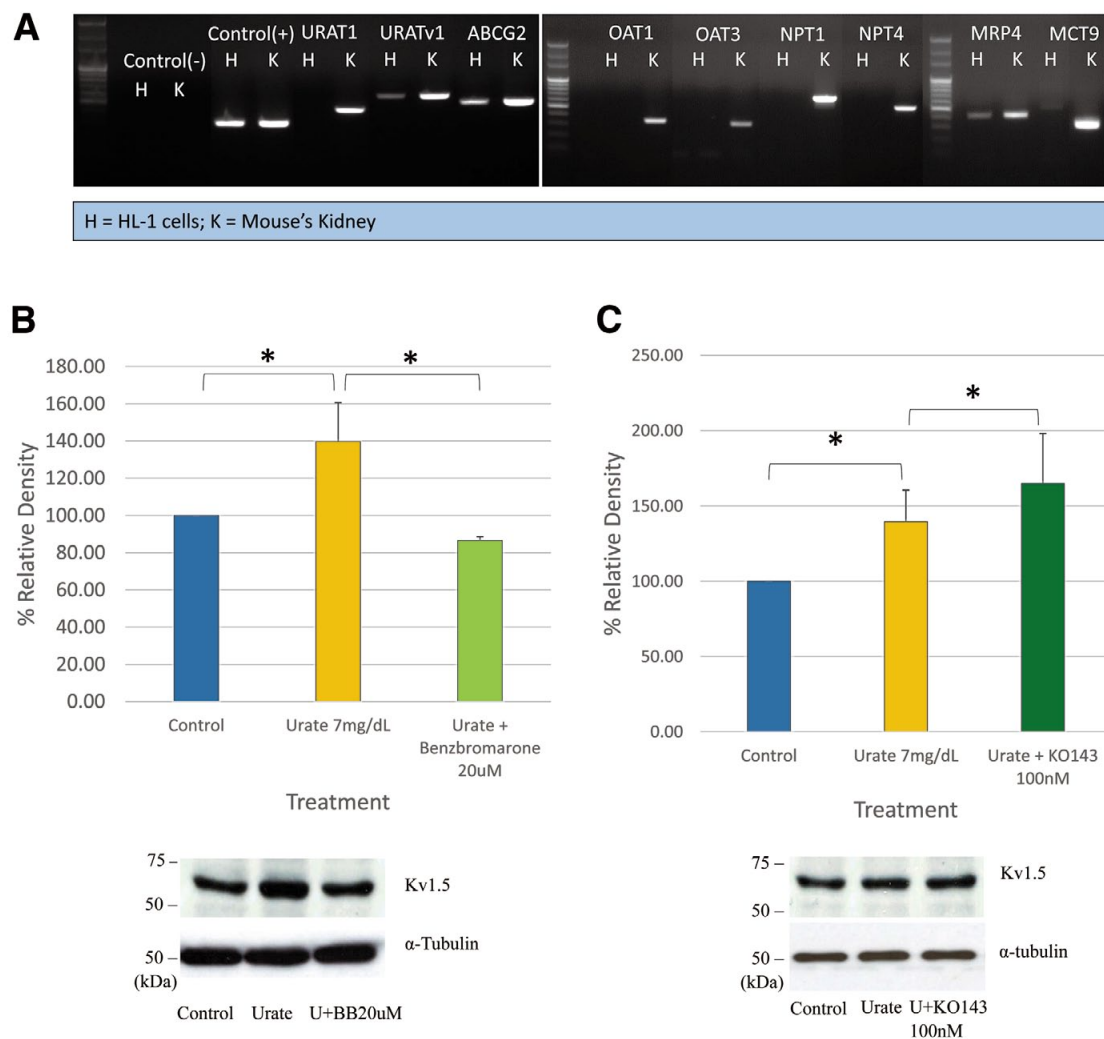


Figure 4. Expression of uric acid transporters (UATs) and their roles in urate-induced Kv1.5 upregulation in HL-1 cells. **(A)** mRNA expressions of UATs in HL-1 cells determined by polymerase chain reaction (PCR) analyses. Data for HL-1 cells' cDNA (H) and mouse kidney's cDNA as a control (K) are shown in pairs. HL-1 cells expressed URATv1, ABCG2 and MRP4. Control (-) indicates a control for gDNA contamination during reverse-transcriptase reaction, of which the reverse-transcriptase enzyme was not added to the reaction. Control (+) means a control for the reverse-transcription process, indicating that cDNAs could be well synthesized. During amplification, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) primers were added to both Controls. **(B)** Effect of benzbromarone on the expression of Kv1.5 proteins. HL-1 cell cultures were assigned to 3 groups, and treated with 10 mmol/L of NaOH as a control, 7 mg/dl urate alone, or 7 mg/dl urate with 20 μ mol/L benzbromarone. Protein lysates were taken after 24 h. Representative Western blots (**Lower**) and the averaged density of Kv1.5 proteins normalized to that of α -tubulin (**Upper**) are shown. The averaged density data shown as percentages to the control values revealed a significant increase of Kv1.5 expression in the group administered urate alone, and a reduction of the urate effect in the presence of 20 μ mol/L benzbromarone ($n=3$; $*P<0.05$). **(C)** Effect of KO143 on the expression of Kv1.5 proteins. HL-1 cell cultures were assigned to 3 groups, treated with 10 mmol/L NaOH as a control, 7 mg/dl urate alone, or 7 mg/dl urate with 100 nmol/L KO143. Protein lysates were taken after 24 h. Representative Western blots (**Lower**) and the averaged density of Kv1.5 normalized to that of α -tubulin (**Upper**) are shown. The averaged density data demonstrate an increased Kv1.5 expression in the group treated with urate alone, and a further increase of Kv1.5 expression in the presence of KO143 ($n=4$; $*P<0.05$).

< Circulation Journal Asian Award >

Chronic Hypoxia Increases Intracellular Ca^{2+} Concentration via Enhanced Ca^{2+} Entry Through Receptor-Operated Ca^{2+} Channels in Pulmonary Venous Smooth Muscle Cells

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Background: Hypoxic pulmonary hypertension (HPH) is characterized by pulmonary vascular remodeling. Intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) is an essential signal for myocyte proliferation. Whether chronic hypoxia (CH) affects the basal $[\text{Ca}^{2+}]_i$ and Ca^{2+} entry through store- and/or receptor-operated calcium channels (SOCC, ROCC), and whether canonical transient receptor potential (TRPC) proteins are involved in CH-induced Ca^{2+} influx and proliferation in pulmonary venous smooth muscle cells (PVSMCs) is examined.

Methods and Results: Rats were exposed to CH. PVSMCs were isolated from distal pulmonary veins. In freshly isolated PVSMCs, CH increased the basal $[\text{Ca}^{2+}]_i$; removal of Ca^{2+} or application of SKF-96365 reversed the elevated $[\text{Ca}^{2+}]_i$, whereas nifedipine had no effect. Receptor-operated Ca^{2+} entry (ROCE) was expressed in PVSMCs. In fresh-

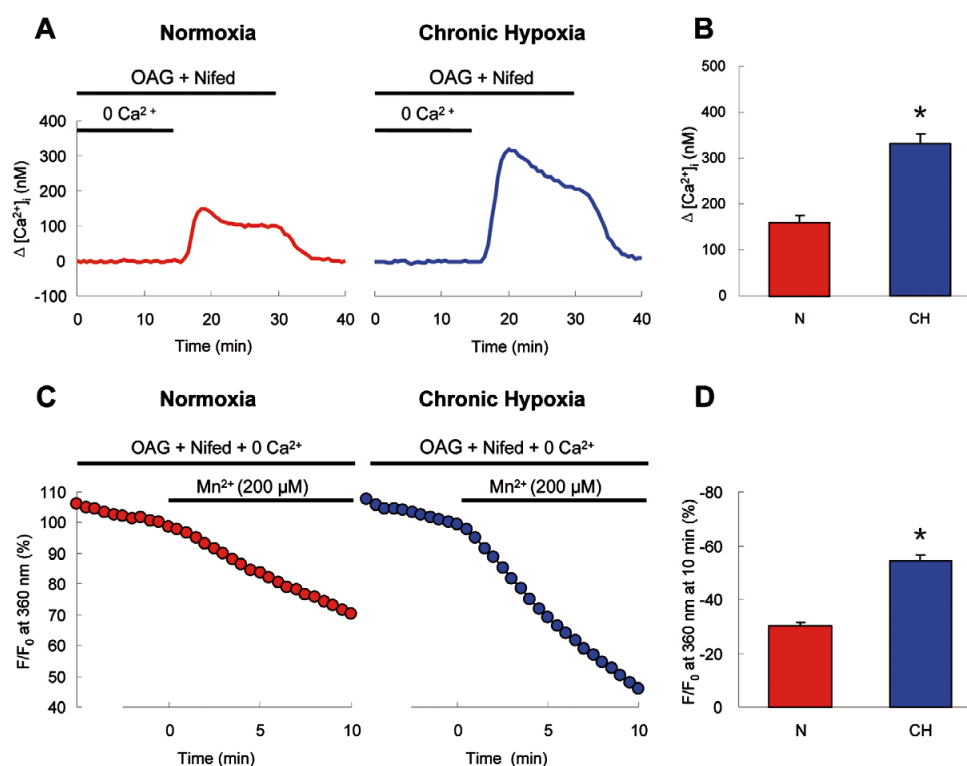


Figure 5. Effect of chronic hypoxia on receptor-operated Ca^{2+} entry (ROCE) in pulmonary venous smooth muscle cells (PVSMCs). (A) Time-course of intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) change ($\Delta[\text{Ca}^{2+}]_i$) before and after restoration of extracellular Ca^{2+} to 2.5 mmol/L in PVSMCs from normoxic (N) and chronically hypoxic (CH) rats perfused with Ca^{2+} -free KRB solution containing 100 $\mu\text{mol/L}$ 1-oleoyl-2-acetyl-sn-glycerol (OAG) and 5 $\mu\text{mol/L}$ nifedipine. (B) Average peak change in $\Delta[\text{Ca}^{2+}]_i$ after restoration of extracellular Ca^{2+} in cells from N and CH rats. (C) Time-course of fura-2 fluorescence at 360 nm normalized to values at time 0 before and after administration of MnCl_2 (200 $\mu\text{mol/L}$) to distal PVSMCs from N and CH rats perfused with Ca^{2+} -free KRB solution containing 100 $\mu\text{mol/L}$ OAG and 5 $\mu\text{mol/L}$ nifedipine. (D) Average change in fura-2 fluorescence at 360 nm in cells from N and CH rats. *Significant difference from normoxia value ($P < 0.001$).

ly isolated PVSMCs from CH rats, ROCE was enhanced, whereas store-operated Ca^{2+} entry had no alteration. Furthermore, real-time polymerase chain reaction and western blotting showed that mRNA and protein expression level of TRPC6, but neither TRPC1 nor TRPC3, in pulmonary venous smooth muscle (PV) from CH rats and PVSMCs exposed to CH was greater than in normal PV and PVSMCs. The knockdown of TRPC6 in hypoxic PVSMCs with siRNA inhibited the enhanced ROCE and attenuated CH-induced PVSMCs proliferation.

Conclusions: The enhanced Ca^{2+} entry through ROCC, due to upregulated TRPC6, is a novel pathogenic mechanism contributing to the increased basal $[\text{Ca}^{2+}]_i$ in PVSMCs and excessive PVSMC proliferation during the development of HPH.⁷ (*Circ J* 2015; **79**: 2058–2068)

Awards will be presented to the 7 research groups during the 80th 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 2016.

Hiroaki Shimokawa, MD, PhD

Editor-in-Chief

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