Circulation Journal Awards for the Year 2019

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 2019.

The aim of these Awards is to recognize papers published in 2019, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 248 original papers published in the Journal in 2019, our 42 Japanese Associate Editors selected papers with a high scientific level in their respective fields, and in the second step, the 4 Associate Editorial Teams (10–11 on 1 team) further evaluated the selected papers in terms of originality, contribution to cardiovascular science, manner of paper preparation, and future possibilities.

In the year of 2019, the following 7 papers have been selected for the *Circulation Journal* Awards.

First Place in the Clinical Investigation Section

(Circ J 2019; 83: 831–836)¹

Polysplenia Syndrome as a Risk Factor for Early Progression of Pulmonary Hypertension

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Background: Recent progress in surgical and intensive care has improved the prognosis of congenital heart disease (CHD) associated with heterotaxy syndrome. Less is known, however, about pulmonary vascular complications in these patients.

Methods and Results: We reviewed medical records of 236 patients who were diagnosed with polysplenia syndrome at 2 institutions for pediatric cardiology in Japan from 1978 to 2015. We selected and compared the clinical records of 16 patients with polysplenia who had incomplete atrioventricular septal defect (AVSD) as the polysplenia group, and 22 age-matched patients with incomplete AVSD without any syndromes including polysplenia as the control group. Although the severity of systemic to pulmonary shunt was not significantly different between the groups, mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance index (PVRI) were significantly higher in the polysplenia group than the control (mPAP, 37.3 vs. 19.1 mmHg, $P=0.001$; PVRI, 5.7 vs. 1.4 $\text{WU} \cdot \text{m}^2$, $P=0.014$) before surgical intervention. On regression analysis, polysplenia influenced the development of pulmonary hypertension (PH) regardless of age at evaluation or degree of systemic to pulmonary shunt in the patients with incomplete AVSD.

Conclusions: Polysplenia syndrome is an independent risk factor for CHD-associated PH. Earlier intervention may be required to adjust the pulmonary blood flow in polysplenia syndrome with CHD to avoid the progression of PH.

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Figure 1. (A) Mean pulmonary artery pressure (mPAP) and (B) pulmonary vascular resistance index (PVRI) according to presence of polysplenia in patients with incomplete atrioventricular septal defect. Data given as mean and standard error.

Figure 2. Mean pulmonary artery pressure (mPAP) vs. ratio of pulmonary to systemic blood flow (Qp/Qs) in the (A) polysplenia group (polysplenia+incomplete atrioventricular septal defect [AVSD]; n=16); and (B) control group (incomplete AVSD; n=22).

Second Place in the Clinical Investigation Section

(Circ J 2019; 83: 2049–2060)²

Efficacy and Safety of Ivabradine in Japanese Patients With Chronic Heart Failure — J-SHIFT Study —

Hiroyuki Tsutsui, Shin-ichi Momomura, Akira Yamashina, Hiroaki Shimokawa, Yasuki Kihara, Yoshihiko Saito, Nobuhisa Hagiwara, Hiroshi Ito, Masafumi Yano, Kazuhiro Yamamoto, Junya Ako, Takayuki Inomata, Yasushi Sakata, Takashi Tanaka, Yasushi Kawasaki on behalf of the J-SHIFT Study Investigators

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Background: Increased heart rate (HR) is an independent risk factor for cardiovascular outcomes in chronic heart failure (HF). Ivabradine, an If inhibitor, improved outcomes in patients with HF and reduced ejection fraction (HFrEF) in the SHIFT study. We evaluated its efficacy and safety in Japanese HFrEF patients in a randomized, double-blind, placebo-controlled phase III study: the J-SHIFT study. The main objective was to confirm a hazard ratio of <1 in the primary composite endpoint of cardiovascular death or hospital admission for worsening HF.

Methods and Results: Patients with NYHA functional class II–IV, left ventricular EF $\leq 35\%$, and resting HR ≥ 75 beats/min in sinus rhythm under optimal medical therapy received ivabradine (n=127) or placebo (n=127). Mean reduction in resting HR was significantly greater in the ivabradine group (15.2 vs. 6.1 beats/min, $P < 0.0001$). However, symptomatic bradycardia did not occur. A total of 26 (20.5%) patients in the ivabradine group and 37 (29.1%) patients in the placebo group had the primary endpoint event (hazard ratio 0.67, 95% CI 0.40–1.11, $P = 0.1179$) during median follow-up of 589 days. Mild phosphenes were reported in 8 (6.3%) patients in the ivabradine group and 4 (3.1%) patients in the placebo group ($P = 0.3760$).

Conclusions: The J-SHIFT study supported the efficacy and safety of ivabradine for Japanese HFrEF patients, in accord with the SHIFT study.

Second Place in the Clinical Investigation Section

(Circ J 2019; 83: 130–138)³

Cardiac Function and Type of Mitral Valve Surgery Affect Postoperative Blood Flow Pattern in the Left Ventricle

Shohei Yoshida, Shigeru Miyagawa, Satsuki Fukushima, Yasushi Yoshikawa, Hiroki Hata, Shunsuke Saito, Daisuke Yoshioka, Satoshi Kainuma, Keitaro Domae, Ryohei Matsuura, Satoshi Nakatani, Koichi Toda, Yoshiki Sawa

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Figure 6. Schema of left ventricular vortical blood flow in all groups. (Upper) Mid-diastolic phase. (Middle) Isovolumic contraction time. (Lower) Systolic phase. EF, ejection fraction; MV, mitral valve.

Background: To determine the impact of cardiac function and type of mitral valve (MV) surgery on blood flow and energy loss in the left ventricle (LV).

Methods and Results: This study enrolled patients with ejection fraction (EF) $< 35\%$ or $> 50\%$; both groups had native (n=27 and n=16), repaired (n=19 and n=33), or prosthetic MVs (n=18 and n=19). They were examined by echocardiography-based vector flow mapping to assess the LV blood flow pattern and energy loss per heartbeat. Among patients with preserved EF, those with native MVs displayed a clockwise vortex and relatively low energy loss. In contrast, MV replacement induced a counterclockwise vortex producing higher energy loss than MV repair, which induced a normal clockwise vortex. This indicated the need for MV repair to minimize LV energy loss after surgery. Among the patients with reduced EF, those with native MVs showed a blood flow pattern similar to those with preserved EF and native MVs; furthermore, those with repaired MVs and half of the patients with prosthetic MVs displayed a clockwise vortex, resulting in no difference in energy loss between the 2 types of MV surgery.

Conclusions: Cardiac function and the type of MV surgery are factors affecting the postoperative LV blood flow pattern. MV replacement resulted in abnormal blood flow with normal cardiac function, whereas advanced cardiomyopathy modified the blood flow pattern post-MV replacement.

Second Place in the Clinical Investigation Section

(Circ J 2019; 83: 1254–1260)⁴

Cardiovascular Risk Assessment Chart by Dietary Factors in Japan — NIPPON DATA80 —

Keiko Kondo, Katsuyuki Miura, Sachiko Tanaka-Mizuno, Aya Kadota, Hisatomi Arima, Nagako Okuda, Akira Fujiyoshi, Naoko Miyagawa, Katsushi Yoshita, Tomonori Okamura, Akira Okayama, Hirotsugu Ueshima for the NIPPON DATA80 Research Group

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Figure. Risk assessment chart for death from cardiovascular diseases according to intake of different dietary factors, calculated using data from 4,002 men and 5,113 women aged 30–79 years from the NIPPON DATA80 study. The hazard ratio (HR) of cardiovascular disease mortality according to the dietary intake of a combination of factors (vegetables, fruit, fish, and salt) was calculated by multiplying together the HRs for each of the dietary factors.

Background: Many studies show that dietary factors such as vegetables, fruit, and salt are associated with cardiovascular disease (CVD) risk. However, a risk assessment chart for CVD mortality according to combinations of dietary factors has not been established.

Methods and Results: Participants were 9,115 men and women aged 30–79 years enrolled in the National Nutritional Survey of Japan in 1980 with a 29-year follow-up. Dietary intake was assessed using a 3-day weighed dietary record at baseline. Cox regression models were used to estimate the hazard ratio (HR) of CVD mortality stratified by vegetables, fruit, fish, and salt consumption. HRs of CVD mortality according to combinations of dietary factors were color coded on an assessment chart. Higher intakes of vegetables, fruit, and fish, and lower salt intake were associated with lower CVD mortality risk. HRs calculated from combinations of dietary factors were displayed using 5 colors corresponding to the magnitude of the HR. People with the lowest intake of vegetables, fruit, and fish, and higher salt intake had a HR of 2.87 compared with those with the highest intake of vegetables, fruit, and fish, and lower salt intake.

Conclusions: Vegetables, fruit, fish, and salt intake were independently associated with CVD mortality risk. The assessment chart generated could be used in Japan as an educational tool for CVD prevention.

First Place in the Experimental Investigation Section

(Circ J 2019; 83: 1072–1079)⁵

Working Hours and Risk of Acute Myocardial Infarction and Stroke Among Middle-Aged Japanese Men — The Japan Public Health Center-Based Prospective Study Cohort II —

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	Working hours (h/day)				P for trend†
	<7	7 to <9	9 to <11	≥11	
Salaried employees					
Person-years	4,018	52,059	37,700	12,070	
No. at risk at baseline	129	3,944	3,196	858	
No. at risk at 10-year survey	306	1,743	881	464	
No. of cases	8	33	27	10	
Multivariable-adjusted HR (95% CI)†	2.49 (1.12–5.56)	1.00	1.46 (0.87–2.46)	2.11 (1.03–4.35)	0.08
Non-salaried employees					
Person-years	27,895	47,037	35,122	15,062	
No. at risk at baseline	552	2,586	2,706	1,173	
No. at risk at 10-year survey	2,483	2,449	1,020	430	
No. of cases	29	34	25	14	
Multivariable-adjusted HR (95% CI)†	1.25 (0.73–2.13)	1.00	1.11 (0.65–1.90)	1.48 (0.78–2.81)	0.31
Age, 40–49 years					
Person-years	13,720	63,116	48,632	19,573	
No. at risk at baseline	260	3,580	3,386	1,226	
No. at risk at 10-year survey	1,212	3,235	1,807	878	
No. of cases	10	30	28	10	
Multivariable-adjusted HR (95% CI)†	1.03 (0.45–2.34)	1.00	1.24 (0.71–2.15)	0.94 (0.42–2.10)	0.87
Age, 50–59 years					
Person-years	29,740	43,387	29,625	9,435	
No. at risk at baseline	434	3,016	2,559	816	
No. at risk at 10-year survey	2,883	1,759	677	221	
No. of cases	40	46	30	18	
Multivariable-adjusted HR (95% CI)†	1.52 (0.85–2.71)	1.00	1.25 (0.75–2.07)	2.60 (1.42–4.77)	0.004

HR, hazard ratio; CI, confidence interval. *Calculated among ≥7 h/day workers. [†]Adjusted for age, body mass index, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, smoking, alcohol consumption, hours of walking or standing, and sleep duration (hours). [‡]Adjusted further for occupation.

Background: Evidence from prospective cohort studies regarding the relationship between working hours and risk of cardiovascular disease is limited.

Methods and Results: The Japan Public Health Center-Based Prospective Study Cohort II involved 15,277 men aged 40–59 years at the baseline survey in 1993. Respondents were followed up until 2012. During the median 20 years of follow up (257,229 person-years), we observed 212 cases of acute myocardial infarction and 745 stroke events. Cox proportional hazards models adjusted for sociodemographic factors, cardiovascular risk factors, and

occupation showed that multivariable-adjusted hazard ratios (HRs) associated with overtime work of ≥ 11 h/day were: 1.63 (95% confidence interval [CI] 1.01–2.63) for acute myocardial infarction and 0.83 (95% CI 0.60–1.13) for total stroke, as compared with the reference group (working 7 to <9 h/day). In the multivariable model, increased risk of acute myocardial infarction associated with overtime work of ≥ 11 h/day was more evident among salaried employees (HR 2.11, 95% CI 1.03–4.35) and men aged 50–59 years (HR 2.60, 95% CI 1.42–4.77). **Conclusions:** Among middle-aged Japanese men, working overtime is associated with a higher risk of acute myocardial infarction.

Second Place in the Experimental Investigation Section

(Circ J 2019; 83: 368–378)⁶

Loss of Endogenous HMGB2 Promotes Cardiac Dysfunction and Pressure Overload-Induced Heart Failure in Mice

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Background: The rapid increase in the number of heart failure (HF) patients in parallel with the increase in the number of older people is receiving attention worldwide. HF not only increases mortality but decreases quality of life, creating medical and social problems. Thus, it is necessary to define molecular mechanisms underlying HF development and progression. HMGB2 is a member of the high-mobility group superfamily characterized as nuclear proteins that bind DNA to stabilize nucleosomes and promote transcription. A recent in vitro study revealed that HMGB2 loss in cardiomyocytes causes hypertrophy and increases HF-associated gene expression. However, its in vivo function in the heart has not been assessed.

Methods and Results: Western blotting analysis revealed increased HMGB2 expression in heart tissues undergoing pressure overload by transverse aorta constriction (TAC) in mice. *Hmgb2* homozygous knockout (*Hmgb2*^{-/-}) mice showed cardiac dysfunction due to AKT inactivation and decreased sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA)2a activity. Compared to wild-type mice, *Hmgb2*^{-/-} mice had worsened cardiac dysfunction after TAC surgery, predisposing mice to HF development and progression.

Conclusions: This study demonstrates that upregulation of cardiac HMGB2 is an adaptive response to cardiac stress, and that loss of this response could accelerate cardiac dysfunction, suggesting that HMGB2 plays a cardioprotective role.

Figure 4. *Hmgb2*^{-/-} mice show enhanced development of transverse aorta constriction (TAC)-induced heart failure. **(A)** Shown are representative M-mode echocardiography recordings (top row), hematoxylin-eosin (HE)-stained sections of heart mid-portion (second row, Scale bar, 1 mm), gross appearance of a whole heart (third row, Scale bar, 5 mm) and lung (fourth row, Scale bar, 5 mm) and sections of Masson's Trichrome (MT)-stained heart tissue (bottom row, Scale bar, 100 μm) from 12-week-old *Hmgb2*^{-/-} (-/-) and wild-type (WT) littermate controls 4 weeks after TAC surgery (n=5–6 per group). **(B)** BW (g), heart weight per body weight (HW/BW) ratio (mg/g) and lung weight per body weight (LW/BW) ratio (mg/g). **(C)** Left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs) and percent fractional shortening (%FS). **(D)** Shown are representative left ventricle sections stained with wheat germ agglutinin (WGA; as an indicator of cardiomyocyte size) (**Upper**, Scale bar, 100 μm) and 4',6-diamidino-2-phenylindole (DAPI) (**Lower**, Scale bar, 100 μm). **(E)** Distribution of myocardial cell size (μm², **Left**) and changes in relative cardiomyocyte size (**Right**). **(F)** Percentage of fibrosis area (%). **(G)** Relative expression of genes associated with heart failure and fibrosis in hearts of 12-week-old *Hmgb2*^{-/-} mice relative to littermate mice. WT values were set to 1 (n=5–6 per group). Data are presented as means ± SEM. Statistical significance was determined by using an unpaired Student's t-test. *P<0.05, **P<0.01, †P<0.001 between groups. n.s., not significant.

Circulation Journal Asian Award

(Circ J 2019; 83: 410–417)⁷**Prognostic Impact of β -Blocker Dose After Acute Myocardial Infarction**

Doyeon Hwang, Joo Myung Lee, Hyun Kuk Kim, Ki Hong Choi, Tae-Min Rhee, Jonghanne Park, Taek Kyu Park, Jeong Hoon Yang, Young Bin Song, Jin-Ho Choi, Joo-Yong Hahn, Seung-Hyuk Choi, Bon-Kwon Koo, Young Jo Kim, Shung-Chull Chae, Myeong Chan Cho, Chong Jin Kim, Hyeon-Cheol Gwon, Myung Ho Jeong, Hyo-Soo Kim, The KAMIR Investigators

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Figure 4. Cumulative incidence of cardiac death according to level of β -blocker dose at 1 year of β -blocker treatment.

Background: The differential prognostic impact of β -blocker dose after acute myocardial infarction (AMI) has been under debate. The current study sought to compare clinical outcome after AMI according to β -blocker dose using the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH).

Methods and Results: Of the total population of 13,104 consecutive AMI patients enrolled in the KAMIR-NIH, the current study analyzed 11,909 patients. These patients were classified into 3 groups (no β -blocker; low-dose [$<25\%$ of target dose]; and high-dose [$\geq 25\%$ of target dose]). The primary outcome was cardiac death at 1 year. Compared with the no β -blocker group, both the low-dose and high-dose groups had significantly lower risk of cardiac death (HR, 0.435; 95% CI: 0.363–0.521, $P<0.001$; HR, 0.519; 95% CI: 0.350–0.772, $P=0.001$, respectively). The risk of cardiac death, however, was similar between the high- and low-dose groups (HR, 1.194; 95% CI: 0.789–1.808, $P=0.402$). On multivariable adjustment and inverse probability weighted analysis, the result was the same.

Conclusions: The use of β -blockers in post-AMI patients had significant survival benefit compared with no use of β -blockers. There was no significant additional benefit of high-dose β -blockers compared with low-dose β -blockers, however, in terms of 1-year risk of cardiac death.

Awards will be presented to the 7 research groups during the 84th 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 2020.

Toyooki Murohara, MD, PhD

Editor-in-Chief

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