



## Circulation Journal Awards of the Year 2009

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 2009.

The aim of these Awards is to recognize papers published in 2009, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 261 original papers published in the Journal in 2009, our 29 Associate Editors selected papers with a high scientific level in their respective fields, and in the second step, the 2 Associate Editor Teams (14 on one team and 15 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 2009, the following 4 papers have been selected for the Circulation Journal Awards.

### <First Place in the Clinical Investigation Section>

#### **Evidence for Rho-Kinase Activation in Patients With Pulmonary Arterial Hypertension**

Zhulanqigige Do.e, Yoshihiro Fukumoto, Aya Takaki, Shunsuke Tawara, Junko Ohashi, Makoto Nakano, Tomohiro Tada, Kenya Saji, Kohichiro Sugimura, Hiroshi Fujita, Yasushi Hoshikawa, Jun Nawata, Takashi Kondo, Hiroaki Shimokawa.

(Department of Cardiovascular Medicine and Department of Thoracic Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan)



**Background:** Direct evidence for Rho-kinase activation in patients with pulmonary hypertension (PH) is still lacking.

**Methods and Results:** Rho-kinase activity in circulating neutrophils was examined by determining the ratio of phosphorylated/total forms of myosin-binding subunit, a substrate of Rho-kinase, in 40 consecutive PH patients and 40 healthy controls. Next, Rho-kinase expression and activity was examined in isolated human lung tissues (5 patients with idiopathic pulmonary arterial hypertension [IPAH], 5 controls) and vascular reactivity of isolated small human pulmonary arteries in vitro (4 IPAH, 4 controls). Rho-kinase activity in circulating neutrophils was significantly increased in the PH patients overall compared with controls ( $P < 0.0001$ ). Significant correlations were noted between Rho-kinase activity and the severity and duration of PAH (all  $P < 0.05$ ). Rho-kinase expression and activity in isolated lung tissues also were significantly increased in the IPAH patients compared with the controls (both  $P < 0.0001$ ). Endothelium-dependent relaxation was markedly impaired and serotonin-induced contraction (in the absence of the endothelium) markedly enhanced in the PAH patients compared with the controls, and the hypercontraction to serotonin was abolished by hydroxyfasudil, a specific Rho-kinase inhibitor.

**Conclusions:** These results provide the first direct evidence for Rho-kinase activation in patients with PAH, suggesting the therapeutic importance of Rho-kinase in the disorder.<sup>1</sup> (*Circ J* 2009; **73**: 1731–1739)

**[Comment]** Pulmonary arterial hypertension (PAH) remains a serious and fatal disorder, for which more effective therapies need to be developed. This study provides for the first time direct evidence for activation of Rho-kinase, a molecule that enhances vascular smooth muscle contraction and arteriosclerosis, in patients with PAH, indicating that Rho-kinase is an important new therapeutic target for the treatment of PAH.

## &lt;Second Place in the Clinical Investigation Section&gt;

**High Ratio of Myeloid Dendritic Cells to Plasmacytoid Dendritic Cells in Blood of Patients With Acute Coronary Syndrome**

Takashi Fukunaga, Hirofumi Soejima, Atsushi Irie, Ryuichiro Fukushima, Yoko Oe, Hiroaki Kawano, Hitoshi Sumida, Koichi Kaikita, Seigo Sugiyama, Yasuharu Nishimura, Hisao Ogawa.

(Department of Cardiovascular Medicine and Department of Immunogenetics, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan)



**Background:** Dendritic cells (DCs) stimulate T-cells to participate in the inflammatory processes that promote the destruction of vulnerable plaques. The relationship between circulating levels of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in patients with acute coronary syndrome (ACS) was evaluated.

**Methods and Results:** Blood samples were obtained from 39 patients with ACS, 41 patients with stable angina pectoris (SAP) and 43 controls. The proportion of mDCs tended to be lower in the ACS group than in the SAP group and controls. Interleukin-12 levels associated with mDCs were significantly higher in the ACS group than in control group. The proportion of pDCs was significantly lower in the ACS groups than in the other two groups. Interferon- $\alpha$  levels secreted by pDCs, however, were not significantly different among the 3 groups. The ratio of mDCs to pDCs  $\geq 4$  is an important value for distinguishing ACS from SAP patients and control patients through receiver operating characteristic analysis (sensitivity; 85.0%, specificity; 83.4%).

**Conclusions:** The ratio of mDCs to pDCs may be a useful marker for detecting ACS and the existence of vulnerable plaques.<sup>2</sup> (*Circ J* 2009; **73**: 1914–1919)

**[Comment]** Dendritic cells (DCs) have recently attracted much attention in the pathogenesis of inflammatory diseases including plaque unstabilization. In this study, the authors examined the relationship between circulating levels of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in patients with acute coronary syndrome (ACS), and found that the ratio of mDCs to pDCs may be a useful marker for detecting ACS and vulnerable plaques.

## &lt;First Place in the Experimental Investigation Section&gt;

**Ischemia Enhances Translocation of Connexin43 and Gap Junction Intercellular Communication, Thereby Propagating Contraction Band Necrosis After Reperfusion**

Kaori Shintani-Ishida, Kana Unuma, Ken-ichi Yoshida.

(Department of Forensic Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan)



**Background:** In ischemia–reperfusion, contraction band necrosis (CBN) is distributed mainly to the lateral border of the risk area and does not spread into the non-risk area beyond the border. It has been suggested that CBN is propagated through gap junctions (GJs), but it is unclear how GJs transmit CBN exclusively in the risk area.

**Methods and Results:** Coronary occlusion for 30 min in rat increased the level of connexin43 (Cx43) protein in the 100,000 $\times$ g pellet fraction to 1.5-fold and decreased that in the 1,000 $\times$ g pellet to half in the risk area compared with the non-risk area. Immunohistochemical analysis showed an increase of Cx43 at intercalated disks in the risk area. A dye transfer assay demonstrated enhancement of GJ intercellular communication (GJIC) in the risk area compared with the non-risk area in the same section. Administration of a GJ blocker, carbenoxolone, at the onset of reperfusion following 30 min of ischemia reduced the CBN area (1/3 vs PBS) in 5 min of reperfusion and limited the infarct size (2/3 vs PBS) in 6 h of reperfusion.

**Conclusions:** These data suggest that ischemia enhances translocation of Cx43 to GJs, thereby promoting propagation of CBN exclusively in the risk area through enhanced GJIC after reperfusion.<sup>3</sup> (*Circ J* 2009; **73**: 1661–1668)

**[Comment]** Myocardial ischemia/reperfusion (I/R) injury is a complex phenomenon that appears to involve several pathological processes. In this study, the authors were able to demonstrate that connexin43, which regulates myocardial gap junctional communication, is activated during myocardial ischemia, and promotes propagating contraction band necrosis after reperfusion, thus demonstrating a novel mechanism involved in myocardial I/R injury.

### <Second Place in the Experimental Investigation Section>

#### Antioxidant, EUK-8, Prevents Murine Dilated Cardiomyopathy

Satoru Kawakami, Akina Matsuda, Tadahiro Sunagawa, Yoshihiro Noda, Takao Kaneko, Shoichi Tahara, Yoshimi Hiraumi, Souichi Adachi, Hiromitsu Matsui, Katsuyuki Ando, Toshiro Fujita, Naoki Maruyama, Takuji Shirasawa, Takahiko Shimizu.

(Molecular Gerontology, Redox Regulation, and Aging Regulation, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan)



**Background:** Mice lacking manganese-superoxide dismutase (Mn-SOD) activity exhibit the typical pathology of dilated cardiomyopathy (DCM). In the present study, presymptomatic and symptomatic mutant mice were treated with the SOD/catalase mimetic, EUK-8.

**Methods and Results:** Presymptomatic heart/muscle-specific Mn-SOD-deficient mice (H/M-*Sod2*<sup>-/-</sup>) were treated with EUK-8 (30 mg·kg<sup>-1</sup>·day<sup>-1</sup>) for 4 weeks, and then cardiac function and the reactive oxygen species (ROS) production in their heart mitochondria were assessed. EUK-8 treatment suppressed the progression of cardiac dysfunction and diminished ROS production and oxidative damage. Furthermore, EUK-8 treatment effectively reversed the cardiac dilatation and dysfunction observed in symptomatic H/M-*Sod2*<sup>-/-</sup> mice. Interestingly, EUK-8 treatment repaired a molecular defect in connexin43.

**Conclusions:** EUK-8 treatment can prevent and cure murine DCM, so SOD/catalase mimetic treatment is proposed as a potential therapy for DCM.<sup>4</sup> (*Circ J* 2009; **73**: 2125–2134)

**[Comment]** Manganese-superoxide dismutase (Mn-SOD) plays an important role in protecting against oxidative stress, and Mn-SOD dysfunction has been implicated in the pathogenesis of dilated cardiomyopathy (DCM). In this study, the authors demonstrated that EUK-8, a SOD/catalase mimetic, ameliorated cardiac dysfunction in heart/muscle-specific Mn-SOD-deficient mice (H/M-*Sod2*<sup>-/-</sup>), suggesting its usefulness for the treatment of DCM in humans.

Awards will be presented to the 4 research groups during the 74<sup>th</sup> 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 2010.

Hiroaki Shimokawa, MD, PhD  
Editor-in-Chief  
*Circulation Journal*

#### References:

1. Doi Z, Fukumoto Y, Takaki A, Tawara S, Ohashi J, Nakano M, et al. Evidence for Rho-kinase activation in patients with pulmonary arterial hypertension. *Circ J* 2009; **73**: 1731–1739.
2. Fukunaga T, Soejima H, Irie A, Fukushima R, Oe Y, Kawano H, et al. High ratio of myeloid dendritic cells to plasmacytoid dendritic cells in blood of patients with acute coronary syndrome. *Circ J* 2009; **73**: 1914–1919.
3. Shintani-Ishida K, Unuma K, Yoshida K. Ischemia enhances translocation of connexin43 and gap junction intercellular communication, thereby propagating contraction band necrosis after reperfusion. *Circ J* 2009; **73**: 1661–1668.
4. Kawakami S, Matsuda A, Sunagawa T, Noda Y, Kaneko T, Tahara S, et al. Antioxidant, EUK-8, prevents murine dilated cardiomyopathy. *Circ J* 2009; **73**: 2125–2134.