Dear Colleagues,

On behalf of the Editorial Team of Circulation Journal, I am pleased to announce the Circulation Journal Awards for the Year 2014.

The aim of these Awards is to recognize papers published in 2014, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 256 original papers published in the Journal in 2014, 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 2014, the following 4 papers have been selected for the Circulation Journal Awards.

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

**Histopathological Examination by Lung Biopsy for the Evaluation of Operability and Postoperative Prognosis in Patients With Chronic Thromboembolic Pulmonary Hypertension**

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(*Dr. Yamaki deceased on November 28, 2014.)

**Background:** To evaluate the prognosis after pulmonary thromboendarterectomy (PTE) in patients with chronic thromboembolic pulmonary hypertension (CTEPH), a lung biopsy was performed in 34 patients with central CTEPH and in 7 patients with peripheral CTEPH during PTE.

**Methods and Results:** Postoperative prognosis was classified from A to E based on the postoperative hemodynamic parameters and clinical condition, and was compared with the index of occlusion (IOCTEPH), which indicates the degree of occlusion in the small pulmonary arteries. Criteria of (A–E) were established only for central CTEPH. Category (A) corresponded to an IOCTEPH from 1.0 to 1.4, (B) from 1.5 to 1.7, (C) from 1.8 to 2.0, and (D) from 2.1 to 2.4. One patient with an index of 3.0 was rated as (E). This patient had collateral vessels around the obstructed small pulmonary arteries and died postoperatively. In all 12 patients who underwent PTE after the criteria were established, postoperative hemodynamic parameters and clinical conditions were consistent with the IOCTEPH. One patient with a high degree of medial atrophy in their small pulmonary arteries died after PTE.

**Conclusions:** These results indicate that a lung biopsy during PTE is useful for prognostication in patients with CTEPH.1 (Circ J 2014; 78: 476–482)
< Second Place in the Clinical Investigation Section >

Circadian Variation of Rho-Kinase Activity in Circulating Leukocytes of Patients With Vasospastic Angina

Taro Nihei, Jun Takahashi, Ryuji Tsuburaya, Yoshitaka Ito, Takashi Shiroto, Kiyotaka Hao, Yusuke Takagi, Yasuharu Matsumoto, Masaharu Nakayama, Satoshi Miyata, Yasuhiko Sakata, Kenta Ito, Hiroaki Shimokawa

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Background: Vasospastic angina (VSA) is known to exhibit circadian variation with an early morning peak. We examined whether Rho-kinase activity in circulating leukocytes, which is a useful biomarker for disease activity assessment of VSA, exhibits circadian variation in patients with VSA.

Methods and Results: In consecutive 31 VSA patients (M/F 23/8, 57±13 [SD] years) and 18 non-VSA patients (M/F 8/10, 57±14 years), we measured Rho-kinase activity in circulating leukocytes at 6:00, 12:00 and 21:00. We also examined the relationship between the Rho-kinase activity and coronary vasomotor responses during provocation test. Rho-kinase activity was significantly higher in VSA patients than in non-VSA patients at 6:00 (1.17±0.17 vs. 0.92±0.22, P<0.001), and showed a significant circadian variation with a peak at 6:00 (1.00±0.15 at 21:00, 1.17±0.17 at 6:00 and 1.12±0.22 at 12:00, P<0.001) in VSA patients, whereas no such variation was noted in non-VSA patients. Importantly, Rho-kinase activity at spasm provocation test was significantly correlated with basal coronary tone defined by vasodilating responses to intracoronary nitrate (r=0.40, P<0.05) and coronary vasoconstricting responses to acetylcholine (r=0.44, P<0.05) in VSA patients. Furthermore, their Rho-kinase activity at 6:00 was positively correlated with nocturnal parasympathetic activity as evaluated by heart rate variability in Holter monitoring (r=0.48, P<0.05).

**Circadian variation of spontaneous attacks and Rho-kinase activity in circulating leukocytes. (A) Circadian variation of spontaneous attacks in all subjects. (B) Diurnal fluctuation of Rho-kinase activity in circulating leukocytes. Results are expressed as mean ± standard deviation. (C, D) Individual circadian variation of Rho-kinase activity in non-VSA patients (C) and VSA patients (D). *P<0.001 for the differences in Rho-kinase activity between the non-VSA and the VSA groups. VSA, vasospastic angina. MBS, myosin-binding subunit; p-/t-, phosphorylated/total form.**

**Microtubule Disorganization Affects the Mitochondrial Permeability Transition Pore in Cardiac Myocytes**

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**Background:** Microtubule (MT) disorganization is related to cardiac disorders. To elucidate the mechanism by which disorganization of the MT network deteriorates cardiac function, the relationship between MT disorganization and mitochondrial permeability transition pore (mPTP) in cardiac myocytes was investigated.

**Methods and Results:** The effects of MT stabilization (by paclitaxel) and MT disruption (by nocodazole) on mitochondrial membrane potential (ΔΨm) and the opening of mPTP were measured in permeabilized Sprague-Dawley rat myocytes.
Both paclitaxel and nocodazole depolarized $\Delta \Psi_m$ and opened mPTP. When isolated mitochondria were exposed to paclitaxel or nocodazole, there were no changes in $\Delta \Psi_m$. The effects of paclitaxel or nocodazole on $\Delta \Psi_m$ depolarization and mPTP were inhibited by cyclosporin A. Treatment of myocytes with 0Ca+BAPTA or inhibition of sarcoplasmic reticulum (SR) $\text{Ca}^{2+}$ uptake by thapsigargin prevented the effect of paclitaxel on mPTP, but not that of nocodazole. Inhibition of the mitochondrial $\text{Ca}^{2+}$ uniporter by Ru360 did not alter the effect of paclitaxel on mPTP. Paclitaxel reduced the expression of the mitochondrial fusion protein, mitofusin-2, and induced mitochondrial fragmentation.

**Conclusions:** Disruption of the MT network by nocodazole might destroy the MT-mitochondria connection and alter mitochondrial function. MT disorganization by paclitaxel could regulate mPTP through the outer mitochondrial membrane complex and the $\text{Ca}^{2+}$-sensitive signaling pathway, which also interacts with the mitochondrial fusion protein, mitofusin-2.3 (Circ J 2014; 78: 1206–1215)
< First Place in the Experimental Investigation Section >

DNA Methylation of Human Telomerase Reverse Transcriptase Associated With Leukocyte Telomere Length Shortening in Hyperhomocysteinemia-Type Hypertension in Humans and in a Rat Model
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**Background:** Elevated homocysteine (Hcy) levels might play a role in the development of essential hypertension (EH). Telomere dynamics provide valuable insight into the pathogenesis of age-related diseases. The contribution of Hcy to leukocyte telomere length (LTL) shortening in EH and the underlying mechanism was examined.

**Methods and Results:** LTL (ratio of the copy number of telomere [T] repeats to that of a single [S] gene, T/S ratio) was inversely associated with age in patients with EH (n=258) and healthy controls (n=137), but significantly decreased...
with the Hcy level only in patients with hypertension after adjustment for age and sex. Age, hypertension and levels of Hcy and low-density lipoprotein combined contributed to LTL shortening; an increased serum folate level could reverse the Hcy effect seen on multivariate regression analysis. In addition, qPCR and methylation-specific PCR assay revealed that LTL shortening and mRNA expression and the methylation ratio of human telomerase reverse transcriptase (hTERT) were lower in patients with EH than in controls, and gradually decreased with increasing Hcy level, but not with blood pressure, in EH patients (P trend <0.0001, 0.004 and 0.012, respectively). Furthermore, Hyperhomocysteinemia, but not hypertension, promoted telomerase reverse transcriptase DNA hypomethylation and reduced mRNA levels, which contributed to shortened LTL in the hypertension rat model.

Conclusions: Elevated Hcy but not hypertension was related to hTERT DNA hypomethylation and reduced mRNA level, thus contributing to the shortening of LTL hypertension. (Circ J 2014; 78: 1915–1923)

Awards will be presented to the 4 research groups during the 79th 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 2015.

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References: