



## Circulation Journal Awards for the Year 2011

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 2011.

The aim of these Awards is to recognize papers published in 2011, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 279 original papers published in the Journal in 2011, our 33 Japanese Associate Editors selected papers with a high scientific level in their respective fields, and in the second step, the 2 Associate Editorial Teams (16 on 1 team and 17 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 2011, the following 4 papers have been selected for the *Circulation Journal* Awards.

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

#### **Matrix Metalloproteinase-9 for the Earliest Stage Acute Coronary Syndrome – Comparison With High-Sensitivity Troponin T –**

Nobuaki Kobayashi, Noritake Hata, Noriaki Kume, Shinya Yokoyama, Takuro Shinada, Kazunori Tomita, Mitsunobu Kitamura, Akihiro Shirakabe, Toru Inami, Masanori Yamamoto, Yoshihiko Seino, Kyoichi Mizuno.

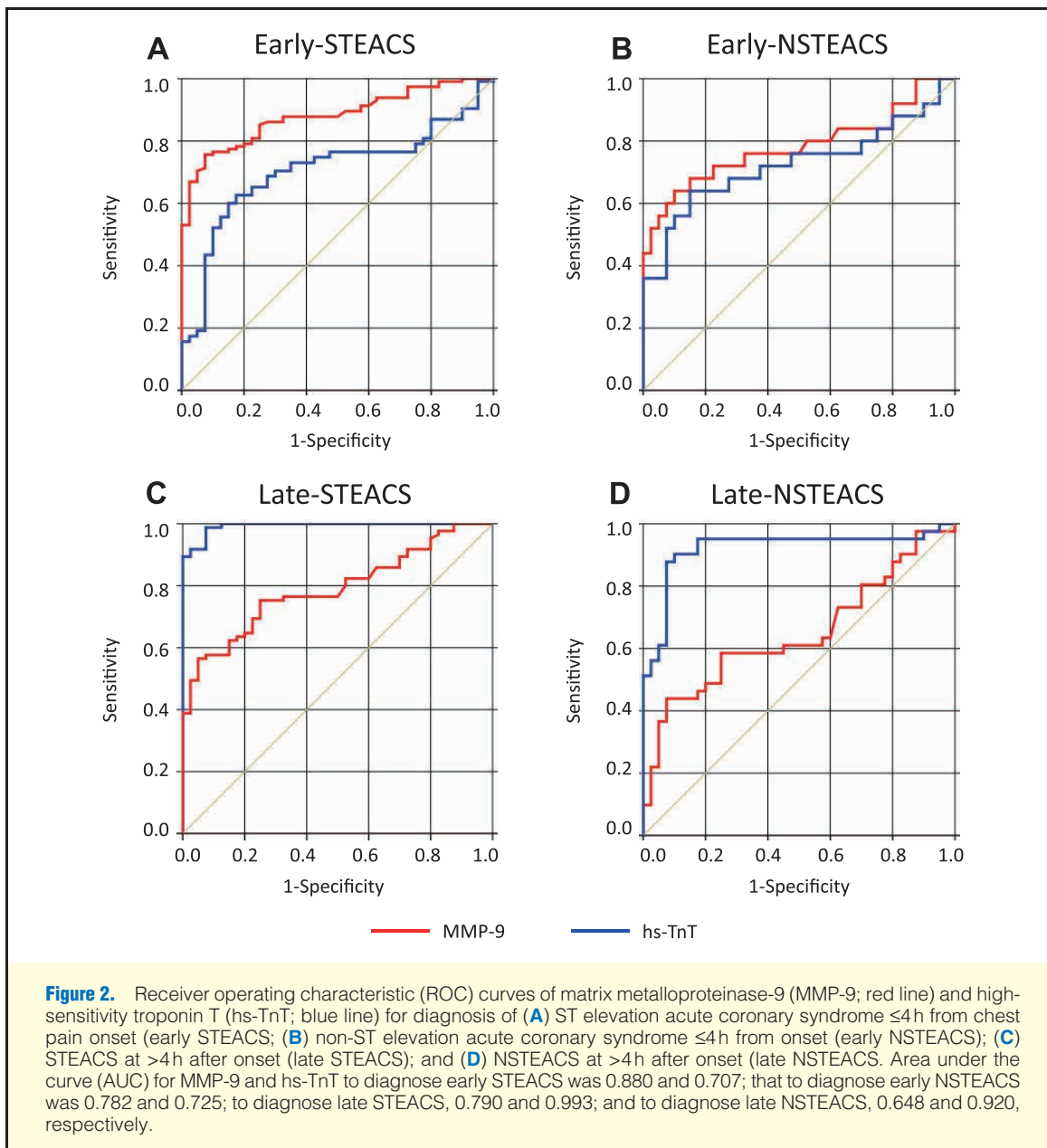
(Division of Intensive Care Unit, Department of Internal Medicine, Chiba Hokusoh Hospital, Nippon Medical School, Chiba; Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto; and Division of Cardiology, Hepatology, Geriatrics and Integrated Medicine, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan)



**Background:** Matrix metalloproteinase-9 (MMP-9) is regarded as a biomarker of plaque rupture or vulnerability and is elevated in patients with acute coronary syndrome (ACS). The aim of the present study was to evaluate the diagnostic value of MMP-9 for early ACS ( $\leq 4$  h of onset) and late ACS ( $> 4$  h after onset), compared with high-sensitivity troponin T (hs-TnT).

**Methods and Results:** MMP-9 and hs-TnT were measured in 200 patients with ST elevation ACS (STEACS; 115 early STEACS and 85 late STEACS patients), and 66 patients with non-ST elevation ACS (NSTEMACS; 25 early NSTEMACS and 41 late NSTEMACS patients). Forty patients with stable angina pectoris (SAP) were enrolled as a control group. MMP-9 levels were significantly higher in patients with early STEACS ( $P < 0.001$ ), early NSTEMACS ( $P < 0.001$ ), late STEACS ( $P < 0.001$ ) and late NSTEMACS ( $P = 0.025$ ) than SAP. MMP-9 levels were significantly higher in patients with early STEACS ( $P = 0.017$ ) and early NSTEMACS ( $P = 0.034$ ) than late STEACS and late NSTEMACS, respectively. Levels of hs-TnT were significantly lower in patients with early STEACS ( $P < 0.001$ ) and early NSTEMACS ( $P = 0.007$ ) than late STEACS and late NSTEMACS, respectively. On receiver operating characteristic curve analysis, area under the curve of early STEACS, early NSTEMACS, late STEACS and late NSTEMACS was 0.880, 0.782, 0.790 and 0.648 for MMP-9, and 0.707, 0.725, 0.993 and 0.920 for hs-TnT, respectively.

**Conclusions:** MMP-9 levels were elevated earlier than hs-TnT and had a higher diagnostic value for early ACS, but not for late ACS, reflecting plaque rupture or vulnerability.<sup>1</sup> (*Circ J* 2011; **75**: 2853–2861)



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

#### Trend of Westernization of Etiology and Clinical Characteristics of Heart Failure Patients in Japan – First Report From the CHART-2 Study –

Nobuyuki Shiba, Kotaro Nochioka, Masanobu Miura, Haruka Kohno, Hiroaki Shimokawa on behalf of the CHART-2 Investigators.

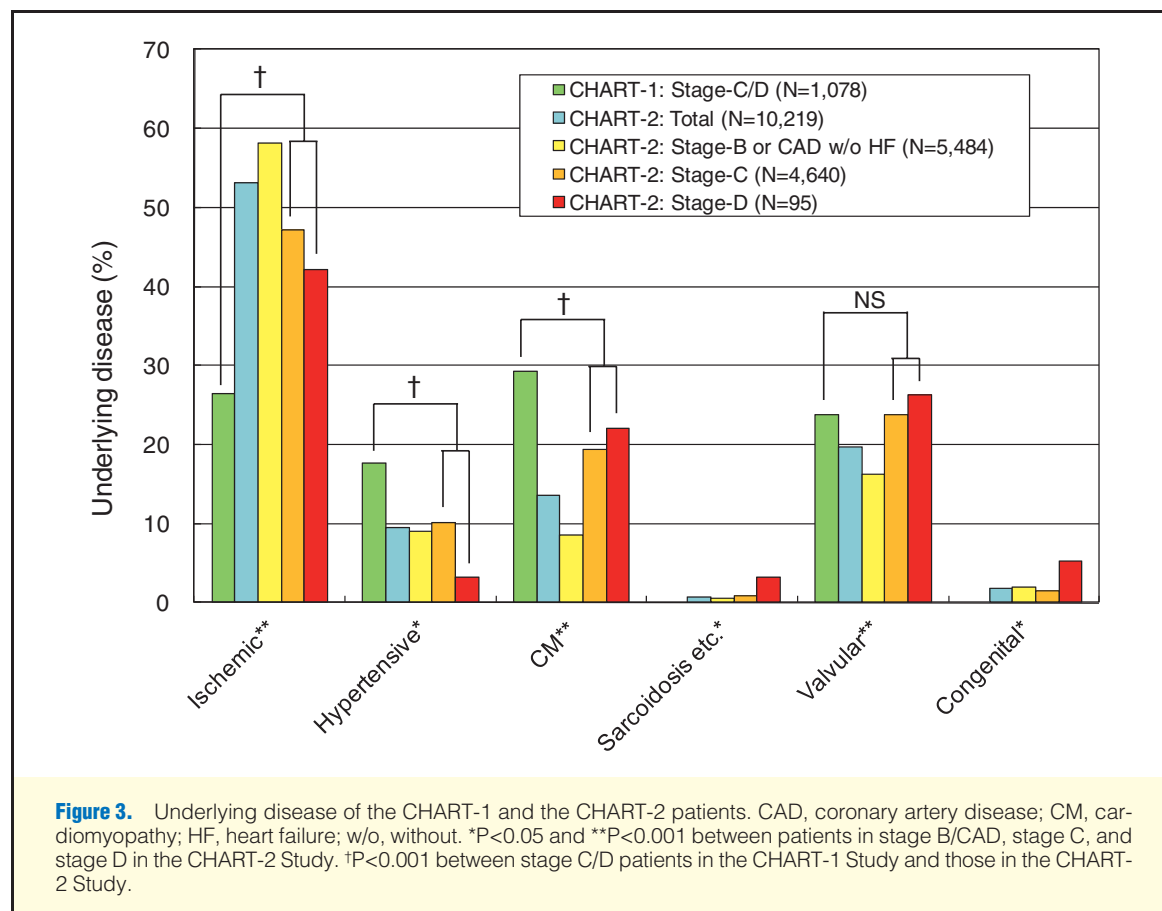
(Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan)



**Background:** Hospitalization due to acute heart failure syndrome (AHFS) is an indicator of worsened prognosis for patients with cardiovascular disease (CVD). The Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study was designed to elucidate characteristics and prognosis of patients at high risk for CVD progression due to AHFS.

**Methods and Results:** The CHART-2 Study is a prospective observational multicenter cohort study. Patients with overt HF, structural cardiac disorder but without HF, or with coronary artery disease (CAD) have been consecutively enrolled from October 2006. As of March 2010, a total of 10,219 patients have been recruited, making the Study the largest multicenter prospective cohort of HF patients in Japan. The mean patient age was  $68.2 \pm 12.3$  years and male patients accounted for 69.8%. Overt HF was observed in 46.3% of patients; and 53.7% did not have HF but were at high risk for AHFS. As HF stage progressed, the prognostic risks (eg, chronic kidney disease, reduced ejection fraction, and increased B-type natriuretic peptide level) became more prominent. Compared with the previous CHART-1 study, the prevalence of ischemic etiology and risk factors (hypertension, diabetes) have increased, as in Western studies.

**Conclusions:** This first report demonstrates the trend of westernization of ischemic etiology and clinical characteristics of HF patients in Japan, indicating the importance of appropriate management and prevention of CAD to prevent AHFS.<sup>2</sup> (*Circ J* 2011; **75**: 823–833)



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

#### Activation of Endothelin-1 Receptor Signaling Pathways Is Associated With Neointima Formation, Neoangiogenesis and Irreversible Pulmonary Artery Hypertension in Patients With Congenital Heart Disease

HaiQiong Huang, Peng Zhang, Zhen Wang, Feng Tang, Zhen Jiang.

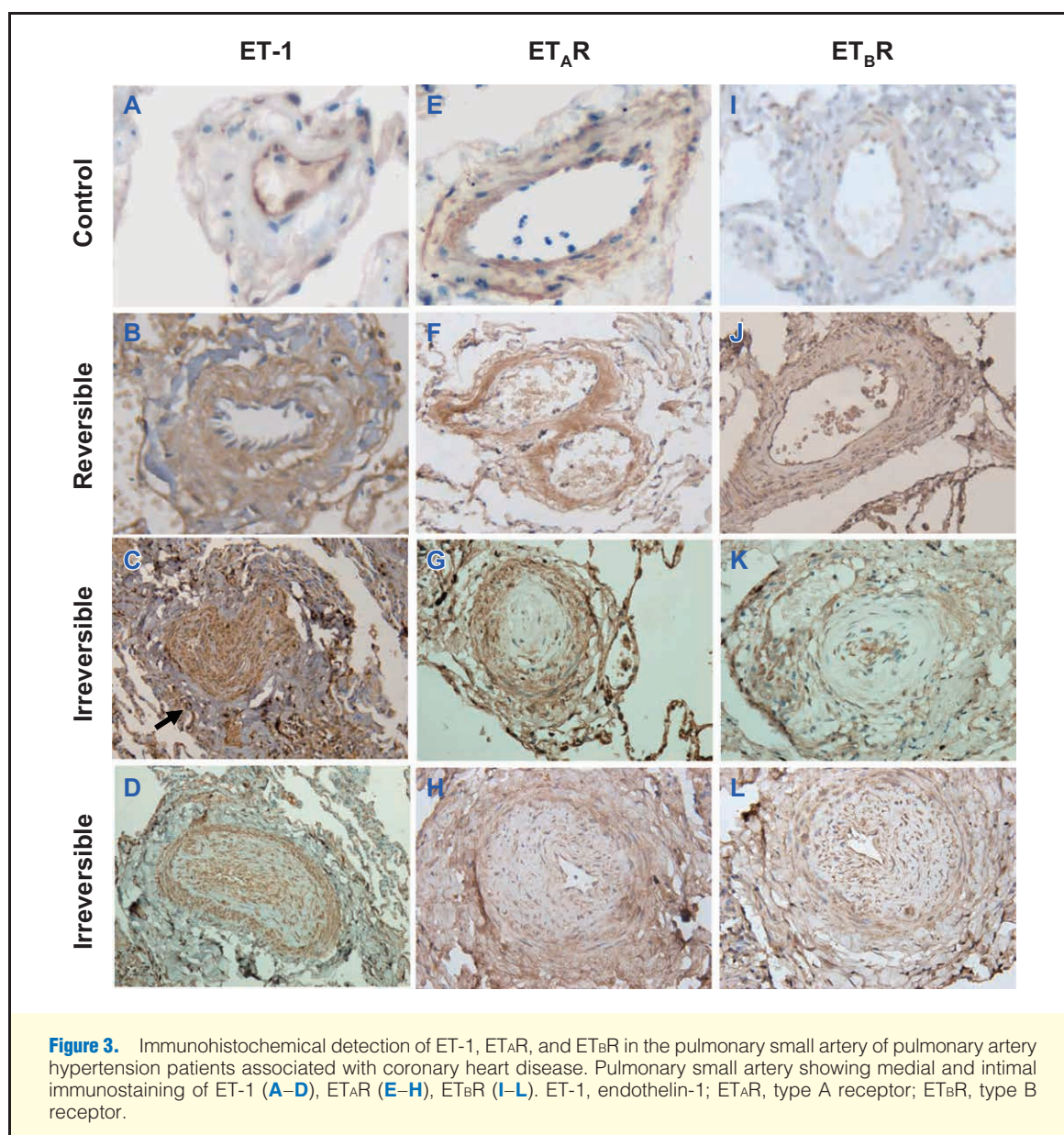
(Department of Anesthesiology, Zhongshan Hospital affiliated with Fudan University, Shanghai; Department of Anesthesiology, Qilu Hospital affiliated with Shandong University, Shandong, China; Department of Molecular Pathology, Cleveland Clinic Pathology & Laboratory Medicine Institute and the Lerner College of Medicine, Cleveland, OH, USA; and Department of Pathology, Huashan Hospital affiliated with Fudan University, Shanghai, China)



**Background:** It is unclear why some patients, who undergo complete repair or palliative surgery for congenital heart disease (CHD), still develop irreversible pulmonary artery hypertension (PAH). There is no consensus to preoperationally assess the reversible and irreversible pulmonary vasculopathy seen in PAH.

**Methods and Results:** The peri-operative pulmonary hemodynamic data of 16 CHD patients (reversible PAH, n=6; irreversible PAH, n=10) were analyzed. The lung biopsies were also performed during surgery for defining histopathological characteristics as well as immunohistochemical expression of endothelin-1 (ET-1), endothelin-1 receptors (ETR), and its downstream signaling markers in the small pulmonary arteries and arterioles. Neointimal formation and neoangiogenesis was characterized by increased intimal layer immunoreactivity for  $\alpha$ -SMA, Factor VIII, CD34, and VEGF. Neointimal formation was found in 90% of patients and neoangiogenesis was found in 80% of patients with irreversible PAH. Neither was present in the reversible PAH group and the control group. Expression of ET-1 and ETR in the neointimal layer of the pulmonary arterioles was upregulated in irreversible PAH, and immunoreactivity of phospho-Akt, phospho-ERK1/2, and phospho-mTOR was also increased in irreversible PAH.

**Conclusions:** Increased expression of ET-1, ETR, and activation of signaling pathways were observed in the pulmonary arteries and arterioles of irreversible PAH patients associated with CHD. Activation of these pathways might in turn lead to neointimal formation and neoangiogenesis and thus might contribute to irreversible pulmonary vascular abnormalities.<sup>3</sup> (*Circ J* 2011; **75**: 1463–1471)

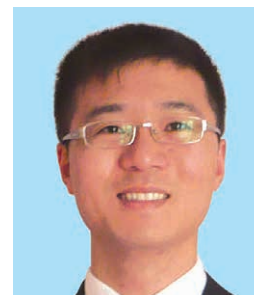




## &lt;Second Place in the Experimental Investigation Section&gt;

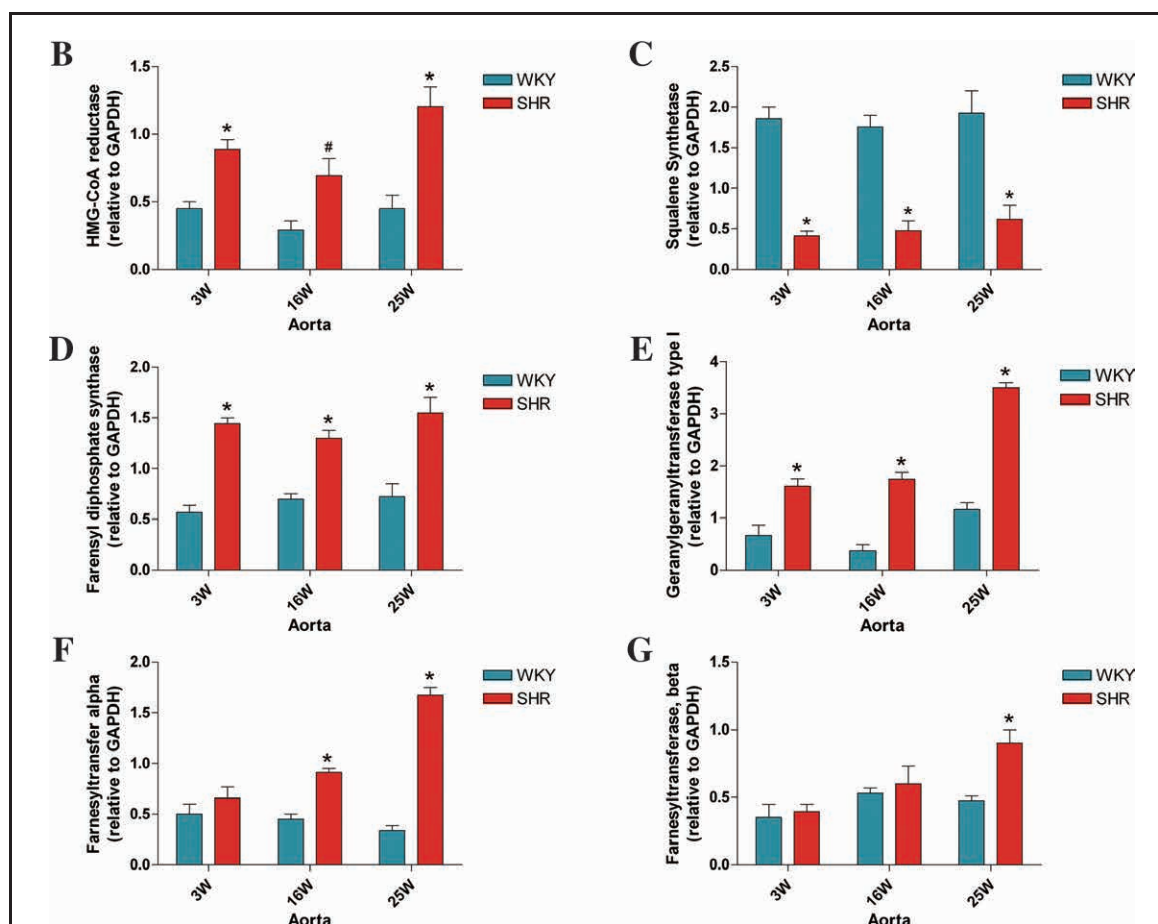
**Alteration of Enzyme Expressions in Mevalonate Pathway – Possible Role for Cardiovascular Remodeling in Spontaneously Hypertensive Rats –**

Jie Han, Dong-Mei Jiang, Chang-Qing Du, Shen-Jiang Hu.

*(Institute of Cardiology, The First Affiliated Hospital, Institute of Cardiology, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang, PR China)*

**Background:** The mevalonate pathway is an important metabolic pathway that plays a key role in multiple cellular processes. The aim of this study was to define whether the enzyme expression in mevalonate pathway changes during cardiovascular remodelling in spontaneously hypertensive rats (SHR).

**Methods and Results:** Hearts and thoracic aortas were removed for the study of cardiovascular remodeling in SHR and Wistar-Kyoto rats (WKY). The protein expression of the enzymes in hearts, aortas and livers was analyzed by western blot. The histological measurements showed that the mass and the size of cardiomyocytes, the media thickness and the media cross-sectional area (MCSA) of the thoracic aorta were all increased in SHR since 3 weeks of age. In the heart, there was overexpression of some enzymes, including 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), farnesyl diphosphate synthase (FDPS), and geranylgeranyltransfer-



**Figure 4.** HMGCR, P-HMGCR, SQS, FDPS, GGTase-I, FNTA and FNTB expressions in aorta quantified by western blot analysis. (B–G) The densitometric average was normalized to the values obtained from the analysis of GAPDH as an internal control. Data are expressed as mean±SEM, n=4. \*P<0.01 vs. age-matched WKY; #P<0.05 vs. age-matched WKY. FDPS, farnesyl diphosphate synthase; FNTA, farnesyltransferase  $\alpha$ ; FNTB, farnesyltransferase  $\beta$ ; GGTase-I, geranylgeranyltransferase type I; HMGCR, 3-hydroxy-3-methylglutaryl CoA reductase; SHR, spontaneously hypertensive rats; SQS, squalene synthase; WKY, Wistar-Kyoto rats.

ase type I (GGTase-I), and downregulation of squalene synthetase (SQS) in SHR since 3 weeks of age. In the aorta, besides similar expressions of HMGR, SQS, FDPS and GGTase-I as in the heart, there was upregulation of farnesyltransferase  $\alpha$  at 16 and 25 weeks of age and of farnesyltransferase  $\beta$  in 25-weeks-old SHR. Western blot demonstrated overexpression of HMGR and downregulation of SQS in SHR livers at all ages tested.

**Conclusions:** The cardiovascular remodeling of SHR preceded the development of hypertension, and altered expression of several key enzymes in the mevalonate pathway may play a potential pathophysiological role in cardiovascular remodeling.<sup>4</sup> (*Circ J* 2011; **75**: 1409–1417)

Awards will be presented to the 5 research groups during the 76th 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 2012.

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

(Released online February 9, 2012)

## References:

1. Kobayashi N, Hata N, Kume N, Yokoyama S, Shinada T, Tomita K, et al. Matrix metalloproteinase-9 for the earliest stage acute coronary syndrome: Comparison with high-sensitivity troponin T. *Circ J* 2011; **75**: 2853–2861.
2. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H; CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the CHART-2 study. *Circ J* 2011; **75**: 823–833.
3. Huang H, Zhang P, Wang Z, Tang F, Jiang Z. Activation of endothelin-1 receptor signaling pathways is associated with neointima formation, neoangiogenesis and irreversible pulmonary artery hypertension in patients with congenital heart disease. *Circ J* 2011; **75**: 1463–1471.
4. Han J, Jiang DM, Du CQ, Hu SJ. Alteration of enzyme expressions in mevalonate pathway: Possible role for cardiovascular remodeling in spontaneously hypertensive rats. *Circ J* 2011; **75**: 1409–1417.