



Circulation Journal Awards for the Year 2012

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 2012.

The aim of these Awards is to recognize papers published in 2012, both clinical and experimental studies, that were highly appreciated by the Editorial Team. The selection process comprises 2 steps. In the first step, from 290 original papers published in the Journal in 2012, 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 2012, the following 4 papers have been selected for the *Circulation Journal* Awards.

< First Place in the Clinical Investigation Section >

Neurological Benefit of Therapeutic Hypothermia Following Return of Spontaneous Circulation for Out-of-Hospital Non-Shockable Cardiac Arrest

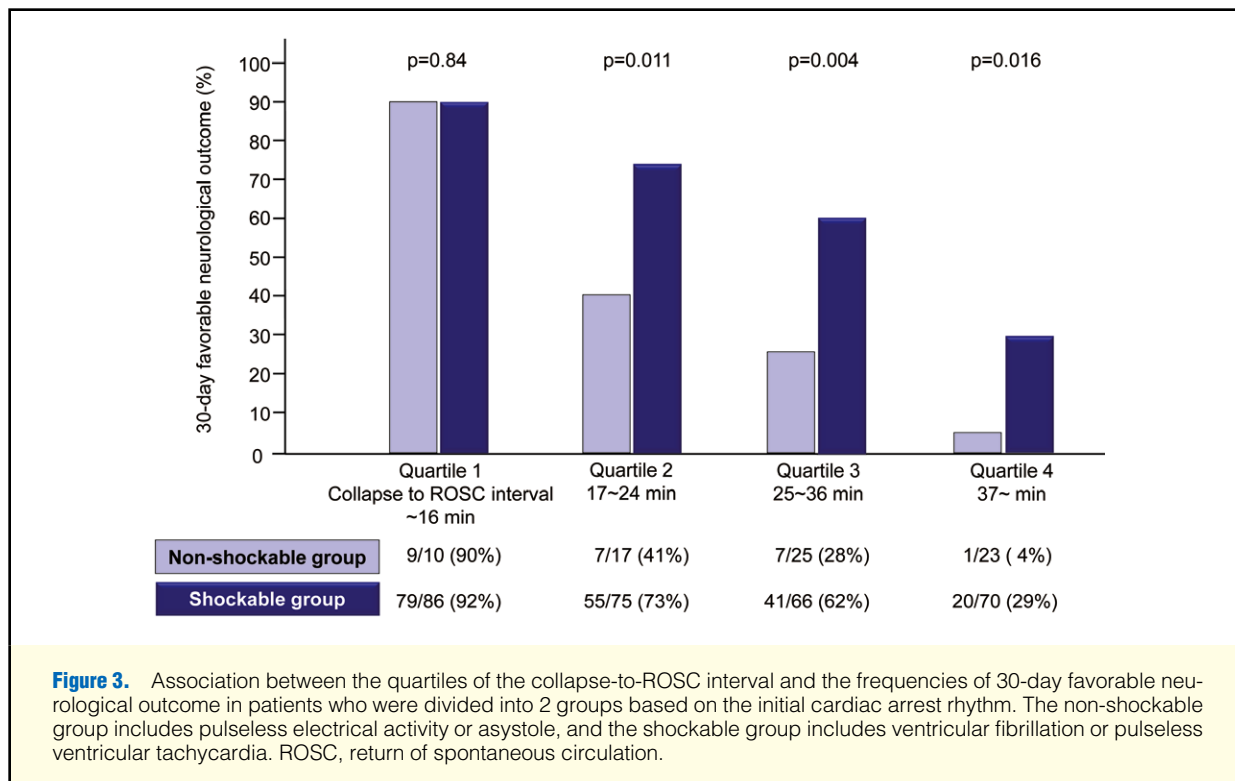
Taketomo Soga, Ken Nagao, Hirotaka Sawano, Hiroyuki Yokoyama, Yoshio Tahara, Mamoru Hase, Takayuki Otani, Shinichi Shirai, Hiroshi Hazui, Hideki Arimoto, Kazunori Kashiwase, Shunji Kasaoka, Tomokazu Motomura, Yasuhiro Kuroda, Yuji Yasuga, Naohiro Yonemoto, Hiroshi Nonogi for the J-PULSE-Hypo Investigators

(Department of Cardiology, Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Surugadai Nihon University Hospital, Tokyo; Senri Critical Care Medical Center, Saiseikai Senri Hospital, Suita; National Cerebral and Cardiovascular Center, Suita; Critical Care and Emergency Medical Center, Yokohama City University Medical Center, Yokohama; Emergency and Critical Care Center, Sapporo City University Hospital, Sapporo; Hiroshima City Hospital, Hiroshima; Division of Cardiology, Kokura Memorial Hospital, Kokura; Emergency Medicine, Osaka Mishima Emergency and Critical Care Center, Osaka; Emergency and Critical Care Medical Center, Osaka City General Hospital, Osaka; Division of Cardiology, Osaka Police Hospital, Osaka; Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, Ube; Department of Emergency Medicine, Saga University Hospital, Saga; Emergency and Critical Care Center, Kagawa University Hospital, Kagawa; Department of Cardiology, Sumitomo Hospital, Osaka; and Department of Epidemiology and Biostatistics, National Center of Neurology and Psychiatry, Tokyo, Japan)



Background: Although therapeutic hypothermia is an effective therapy for comatose adults experiencing out-of-hospital shockable cardiac arrest, there is insufficient evidence that is also applicable for those with out-of-hospital non-shockable cardiac arrest.

Methods and Results: Of 452 comatose adults treated with therapeutic hypothermia after return of spontaneous circulation (ROSC) subsequent to an out-of-hospital cardiac arrest of cardiac etiology, 372 who had a bystander-witnessed cardiac arrest, target core temperature of 32–34°C and cooling duration of 12–72 h were eligible for this study (75 cases of non-shockable cardiac arrest, 297 cases of shockable cardiac arrest). The median collapse-to-ROSC interval was significantly longer in the non-shockable group than in the shockable group (30 min vs. 22 min, $P=0.008$), resulting in a significantly lower frequency of 30-day favorable neurological outcome in the non-shockable group compared with the shockable group (32% vs. 66%, $P<0.001$). However, an analysis of data in quartiles assigned to varying lengths of



collapse-to-ROSC interval revealed a similar frequency of 30-day favorable neurological outcome among both groups when the collapse-to-ROSC interval was ≤ 16 min (90% non-shockable group vs. 92% shockable group; odds ratio 0.80, 95% confidence interval 0.09–7.24, $P=0.84$).

Conclusions: Post-ROSC cooling is an effective treatment for patients with non-shockable cardiac arrest when the time interval from collapse to ROSC is short.¹ (*Circ J* 2012; **76**: 2579–2585)

< Second Place in the Clinical Investigation Section >

Genetic Analysis of Essential Cardiac Transcription Factors in 256 Patients With Non-Syndromic Congenital Heart Defects

Kazuki Kodo, Tsutomu Nishizawa, Michiko Furutani, Shoichi Arai, Kazuaki Ishihara, Mayumi Oda, Shinji Makino, Keiichi Fukuda, Takao Takahashi, Rumiko Matsuoka, Toshio Nakanishi, Hiroyuki Yamagishi

(Department of Pediatrics, Division of Pediatric Cardiology, Department of Cardiology, and Center for Integrated Medical Research, Keio University School of Medicine, Tokyo; International Research and Educational Institute for Integrated Medical Sciences (IREIIMS), Division of Pediatric Cardiology and Division of Cardiovascular Surgery, Tokyo Women's Medical University, Tokyo, Japan)



Background: The genetic basis of most congenital heart defects (CHDs), especially non-syndromic and non-familial conditions, remains largely unknown.

Methods and Results: DNA samples were collected from immortalized cell lines and original genomes of 256 non-syndromic, non-familial patients with cardiac outflow tract (OFT) defects. Genes encoding NKX2.5, GATA4, GATA6, MEF2C, and ISL1, essential for heart development, were analyzed using PCR-based bidirectional sequencing. The transcriptional activity of proteins with identified sequence variations was analyzed using a luciferase assay. A novel sequence variant (A103V in *MEF2C*) was identified, in addition to 4 unreported non-synonymous sequence variants in 3 known causative genes (A6V in *NKX2.5*, T330R and S339R in *GATA4*, and E142K in *GATA6*) in 5 individuals.

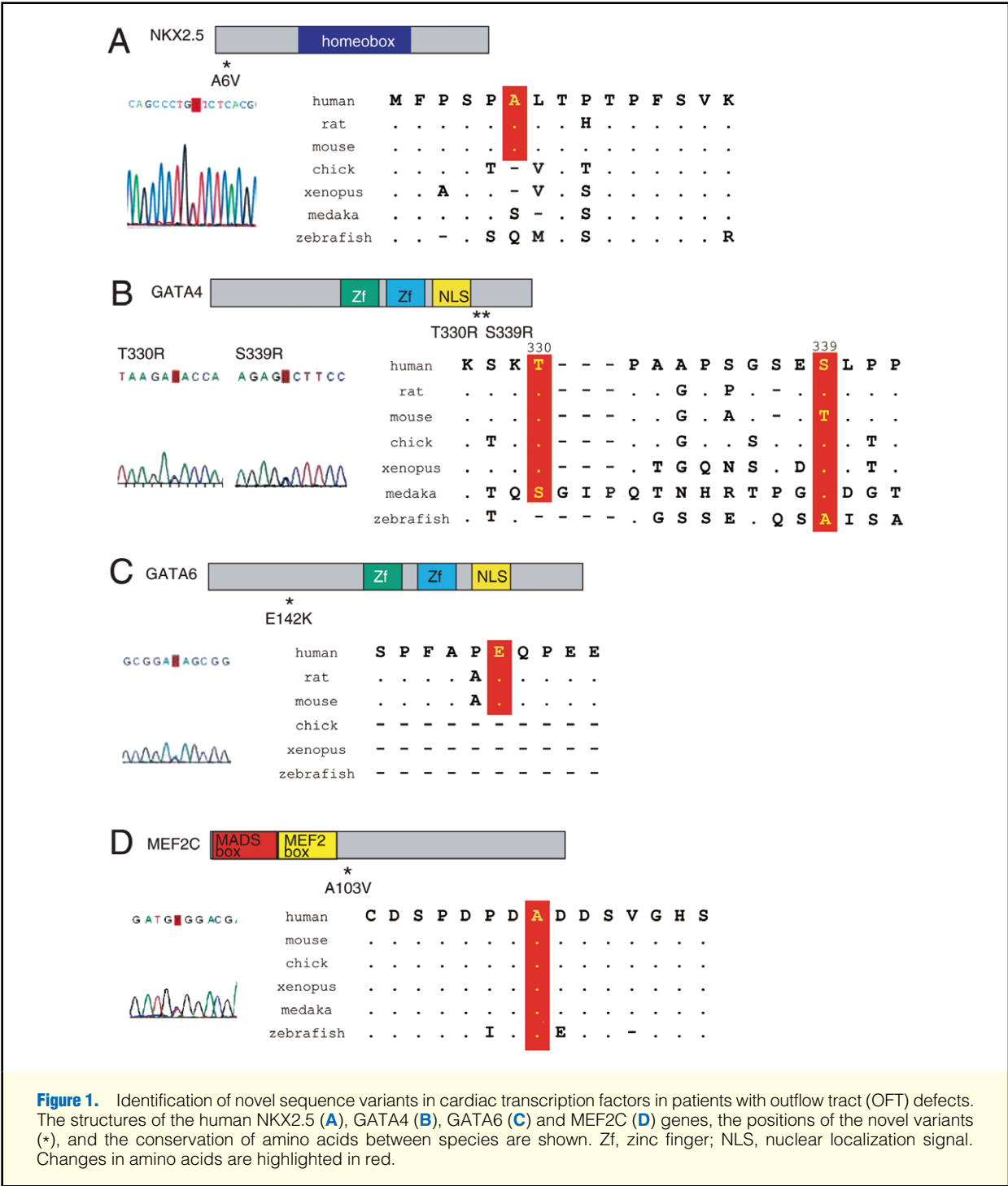


Figure 1. Identification of novel sequence variants in cardiac transcription factors in patients with outflow tract (OFT) defects. The structures of the human NKX2.5 (A), GATA4 (B), GATA6 (C) and MEF2C (D) genes, the positions of the novel variants (*), and the conservation of amino acids between species are shown. Zf, zinc finger; NLS, nuclear localization signal. Changes in amino acids are highlighted in red.

None of these was found in 500 controls without CHDs. In vitro functional assay showed that all proteins with identified sequence variations exhibited significant changes in transcriptional activity and/or synergistic activity with other transcription factors. Furthermore, overexpression of the A103V MEF2C variant in a fish system disturbed early cardiac development.

Conclusions: New mutations in the transcription factors NKX2.5, GATA4, GATA6, and MEF2C that affect their protein function were identified in 2.3% (6/256) of patients with OFT defects. Our results provide the first demonstration of MEF2C mutation and suggest that disturbances in the regulatory circuits involving these cardiac transcription factors may cause a subset of non-syndromic and non-familial CHDs.² (Circ J 2012; 76: 1703–1711)

< First Place in the Experimental Investigation Section >

Electrophysiological Properties of Prion-Positive Cardiac Progenitors Derived From Murine Embryonic Stem Cells

Hiroshi Fujii, Yu Ikeuchi, Yasutaka Kurata, Nobuhito Ikeda, Udin Bahrudin, Peili Li, Yuji Nakayama, Ryo Endo, Akira Hasegawa, Kumi Morikawa, Junichiro Miake, Akio Yoshida, Kyoko Hidaka, Takayuki Morisaki, Haruaki Ninomiya, Yasuaki Shirayoshi, Kazuhiro Yamamoto, Ichiro Hisatome

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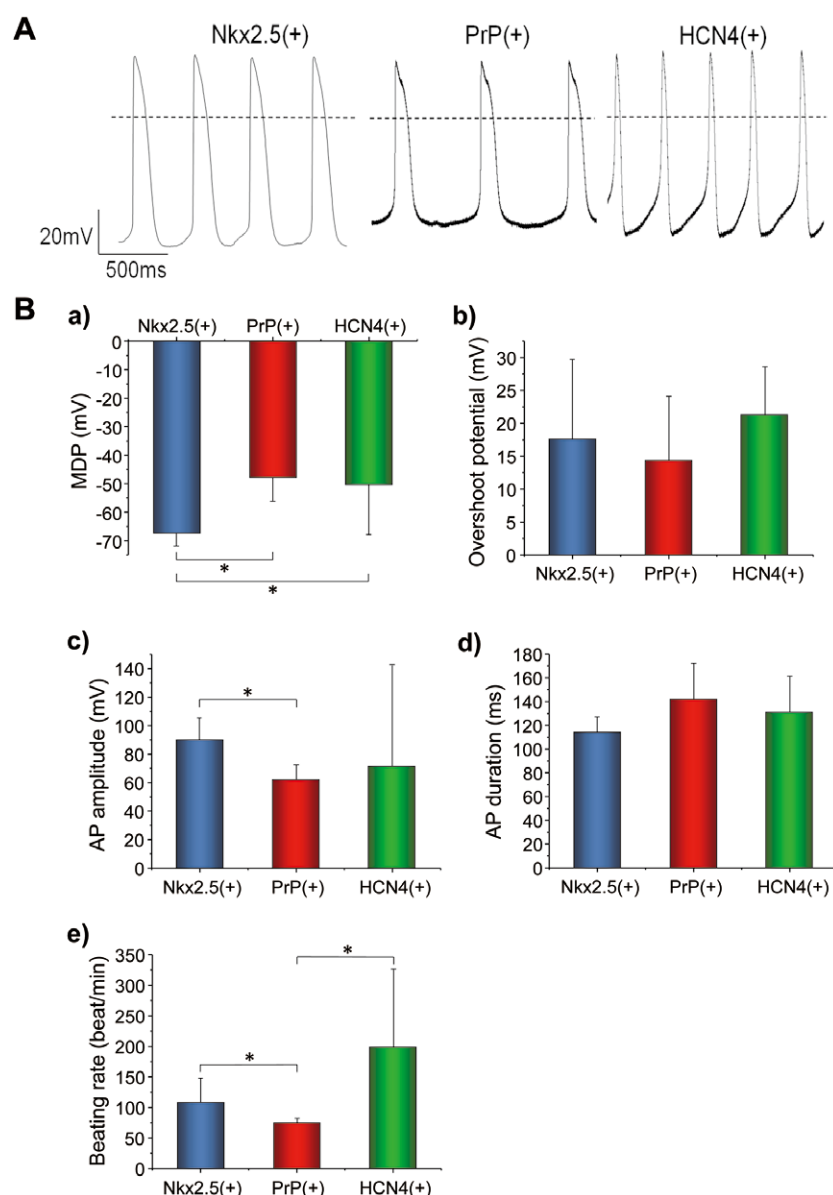


Figure 6. Comparison of electrophysiological properties during spontaneous firings of prion protein (PrP)-positive cells with those of Nkx2.5-positive cells and HCN4-positive cells. (A) Representative action potentials (APs) of (Left) an Nkx2.5-GFP-positive, (Middle) PrP-positive, and (Right) HCN4-GFP-positive cell with automaticity derived from hcgp7, AB1, and HCN4p-EGFP embryonic stem (ES) cells, respectively, on day 14 of their differentiation. (B) Comparisons of (a) averaged maximum diastolic potential (MDP), (b) overshoot potential, (c) AP amplitude, (d) AP duration at 50% repolarization (APD₅₀), and (e) beating rate in 16 Nkx2.5-positive, 7 PrP-positive, and 8 HCN4-positive cells with automaticity on day 14 of their differentiation. *P<0.05.

Background: The prion protein (PrP) has been reported to serve as a surface marker for isolation of cardiomyogenic progenitors from murine embryonic stem (ES) cells. Although PrP-positive cells exhibited automaticity, their electrophysiological characteristics remain unresolved. The aim of the present study was therefore to investigate the electrophysiological properties of PrP-positive cells in comparison with those of HCN4p- or Nkx2.5-positive cells.

Methods and Results: Differentiation of AB1, HCN5p-EGFP and hcg7 ES cells into cardiac progenitors was induced by embryoid body (EB) formation. EBs were dissociated and cells expressing PrP, HCN4-EGFP and/or Nkx2.5-GFP were collected via flow cytometry. Sorted cells were subjected to reverse transcriptase-polymerase chain reaction, immunostaining and patch-clamp experiments. PrP-positive cells expressed mRNA of undifferentiation markers, first and second heart field markers, and cardiac-specific genes and ion channels, indicating their commitment to cardiomyogenic progenitors. PrP-positive cells with automaticity showed positive and negative chronotropic responses to isoproterenol and carbamylcholine, respectively. Hyperpolarization-activated cation current (I_h) was barely detectable, whereas Na^+ and L-type Ca^{2+} channel currents were frequently observed. Their spontaneous activity was slowed by inhibition of sarcoplasmic reticulum Ca^{2+} uptake and release but not by blocking I_h . The maximum diastolic potential of their spontaneous firings was more depolarized than that of Nkx2.5-GFP-positive cells.

Conclusions: PrP-positive cells contained cardiac progenitors that separated from the lineage of sinoatrial node cells. PrP can be used as a marker to enrich nascent cardiac progenitors.³ (*Circ J* 2012; **76**: 2875–2883)

< Second Place in the Experimental Investigation Section >

Waon Therapy Upregulates Hsp90 and Leads to Angiogenesis Through the Akt-Endothelial Nitric Oxide Synthase Pathway in Mouse Hindlimb Ischemia

Takahiro Miyauchi, Masaaki Miyata, Yoshiyuki Ikeda, Yuichi Akasaki, Narisato Hamada, Takahiro Shirasawa, Yuko Furusho, Chuwa Tei

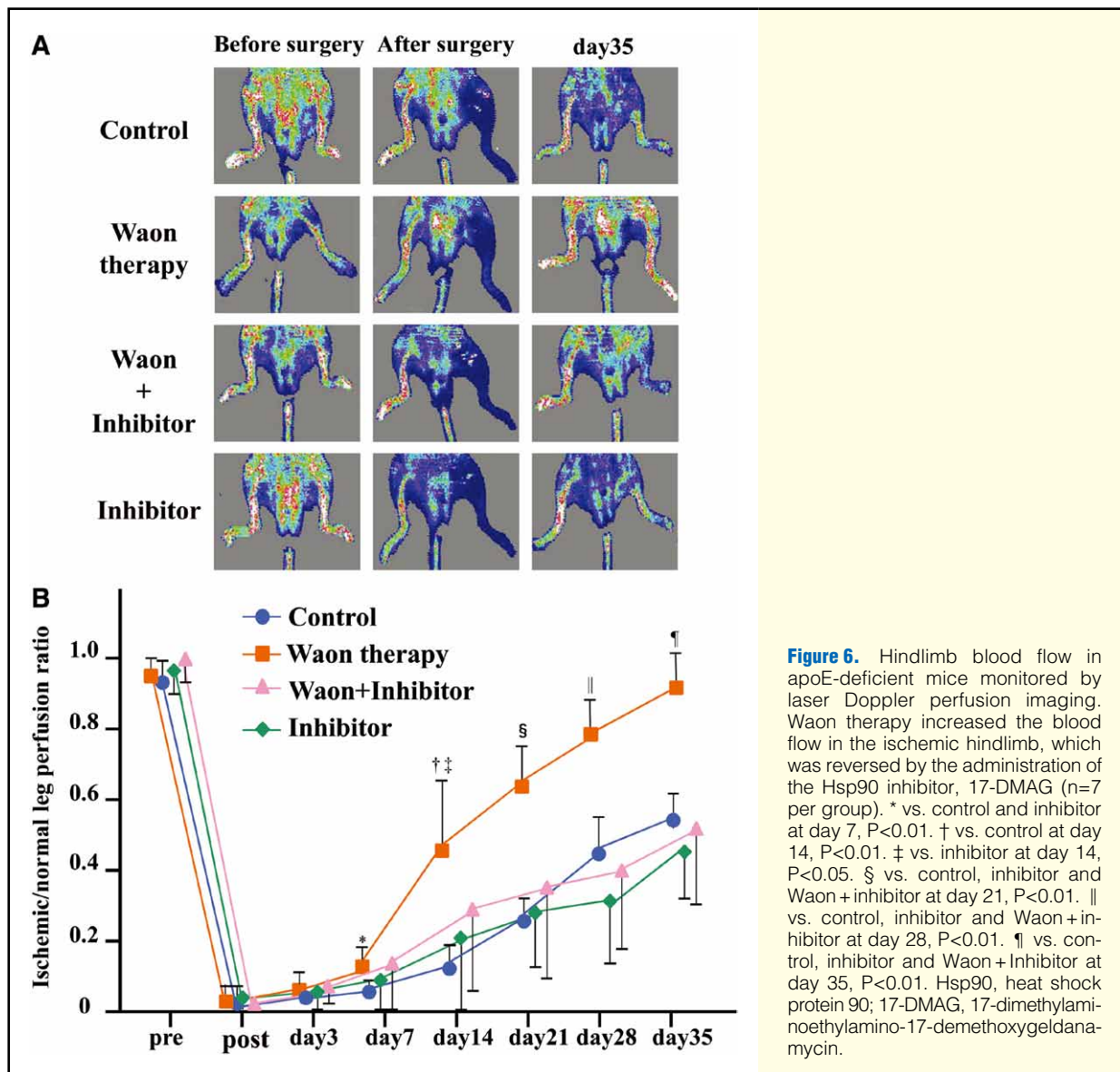
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Background: Thermal therapy, namely Waon therapy, has previously been reported to regulate nitric oxide (NO) and endothelial NO synthase (eNOS) and augment ischemia-induced angiogenesis in mice and improve limb ischemia in patients with peripheral artery disease. The aim of this study was to clarify the precise mechanism by which Waon therapy augments angiogenesis in mice with hindlimb ischemia.

Methods and Results: Unilateral hindlimb ischemia was induced in apolipoprotein E-deficient mice and Waon therapy was performed for 5 weeks. Heat shock protein 90 (Hsp90), phosphorylated-Akt, and phosphorylated-eNOS were detected in arterial endothelial cells of ischemic hindlimbs and all were upregulated by Waon therapy compared to controls. Waon therapy also increased serum concentrations of nitrite and nitrate. Capillary density and the ischemic limb/normal side blood perfusion ratio monitored by laser Doppler perfusion imaging in the Waon therapy group were significantly increased beyond those in the control group. The effect of Waon therapy on angiogenesis through the activation of the Hsp90/Akt/eNOS pathway was attenuated by the administration of a Hsp90 inhibitor.

Conclusions: It is suggested that Waon therapy upregulates Hsp90, which contributes to the activation of the Akt/eNOS/NO pathway, and induces angiogenesis in mice with hindlimb ischemia.⁴ (*Circ J* 2012; **76**: 1712–1721)



Awards will be presented to the 4 research groups during the 77th 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 2013.

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Editor-in-Chief
Circulation Journal

(Released online February 9, 2013)

References:

1. Soga T, Nagao K, Sawano H, Yokoyama H, Tahara Y, Hase M, et al; for the J-PULSE-Hypo Investigators. Neurological benefit of therapeutic hypothermia following return of spontaneous circulation for out-of-hospital non-shockable cardiac arrest. *Circ J* 2012; **76**: 2579–2585.
2. Kodo K, Nishizawa T, Furutani M, Arai S, Ishihara K, Oda M, et al. Genetic analysis of essential cardiac transcription factors in 256 patients with non-syndromic congenital heart defects. *Circ J* 2012; **76**: 1703–1711.
3. Fujii H, Ikeuchi Y, Kurata Y, Ikeda N, Bahrudin U, Li P, et al. Electrophysiological properties of prion-positive cardiac progenitors derived from murine embryonic stem cells. *Circ J* 2012; **76**: 2875–2883.
4. Miyauchi T, Miyata M, Ikeda Y, Akasaki Y, Hamada N, Shirasawa T, et al. Waon therapy upregulates Hsp90 and leads to angiogenesis through the Akt-endothelial nitric oxide synthase pathway in mouse hindlimb ischemia. *Circ J* 2012; **76**: 1712–1721.