COVADIS Steering Committee Meeting 2017

(August 30, 2017, Spain, Barcelona)

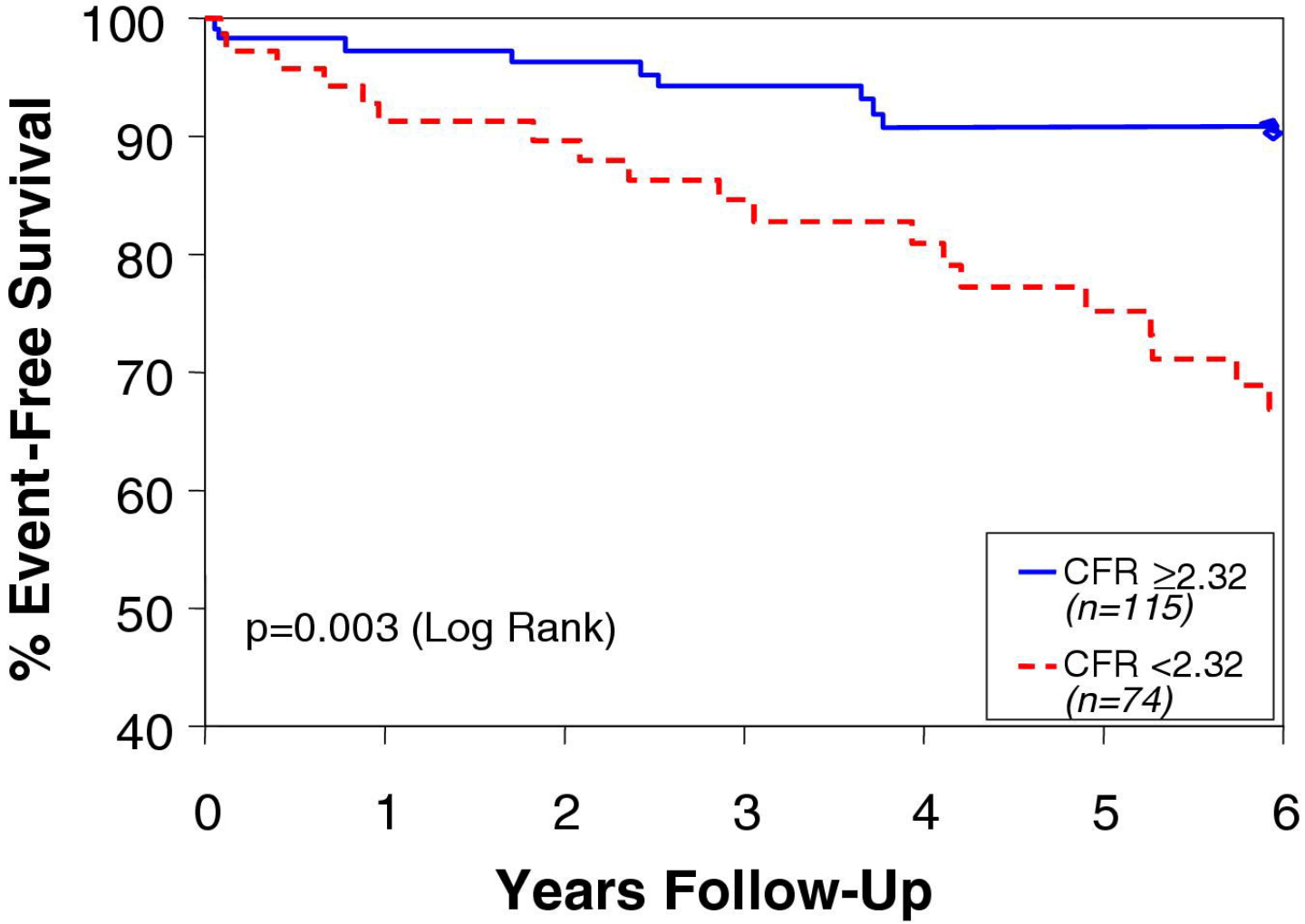
MVA-New Direction in Therapy

Hiroaki Shimokawa, MD, PhD

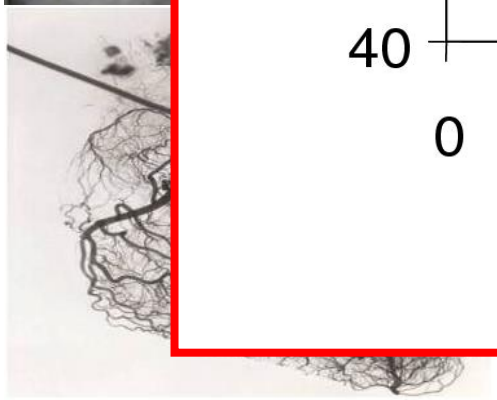
Professor and Chairman
Department of Cardiovascular Medicine,
Tohoku University Graduate School of Medicine,
Sendai, Japan

Fun ation

Poor prognosis of patients with coronary microvascular dysfunction (CMD) (WISE Study)



Pepine CJ, Bairey Merz CN, et al. J Am Coll Cardiol. 2010;55:2825-32.



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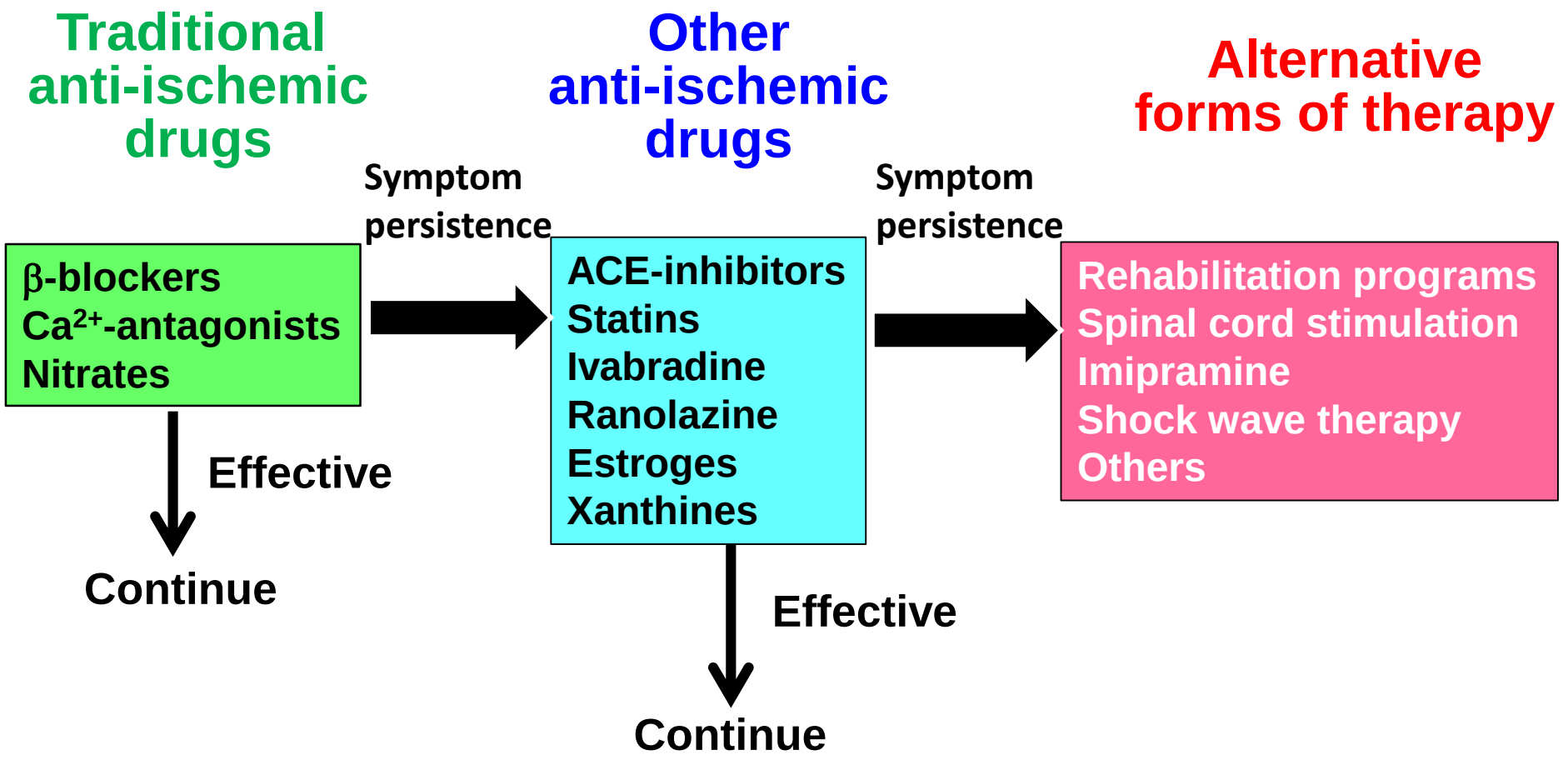
etc.)

s)

(Camici PG, Crea F. *NEJM.* 2007;356:830-40.)

Rational approach to the management of patients with CMD



(Crea F et al., Coronary Microvascular Dysfunction, Springer-Verlag, Italy, 2014.)

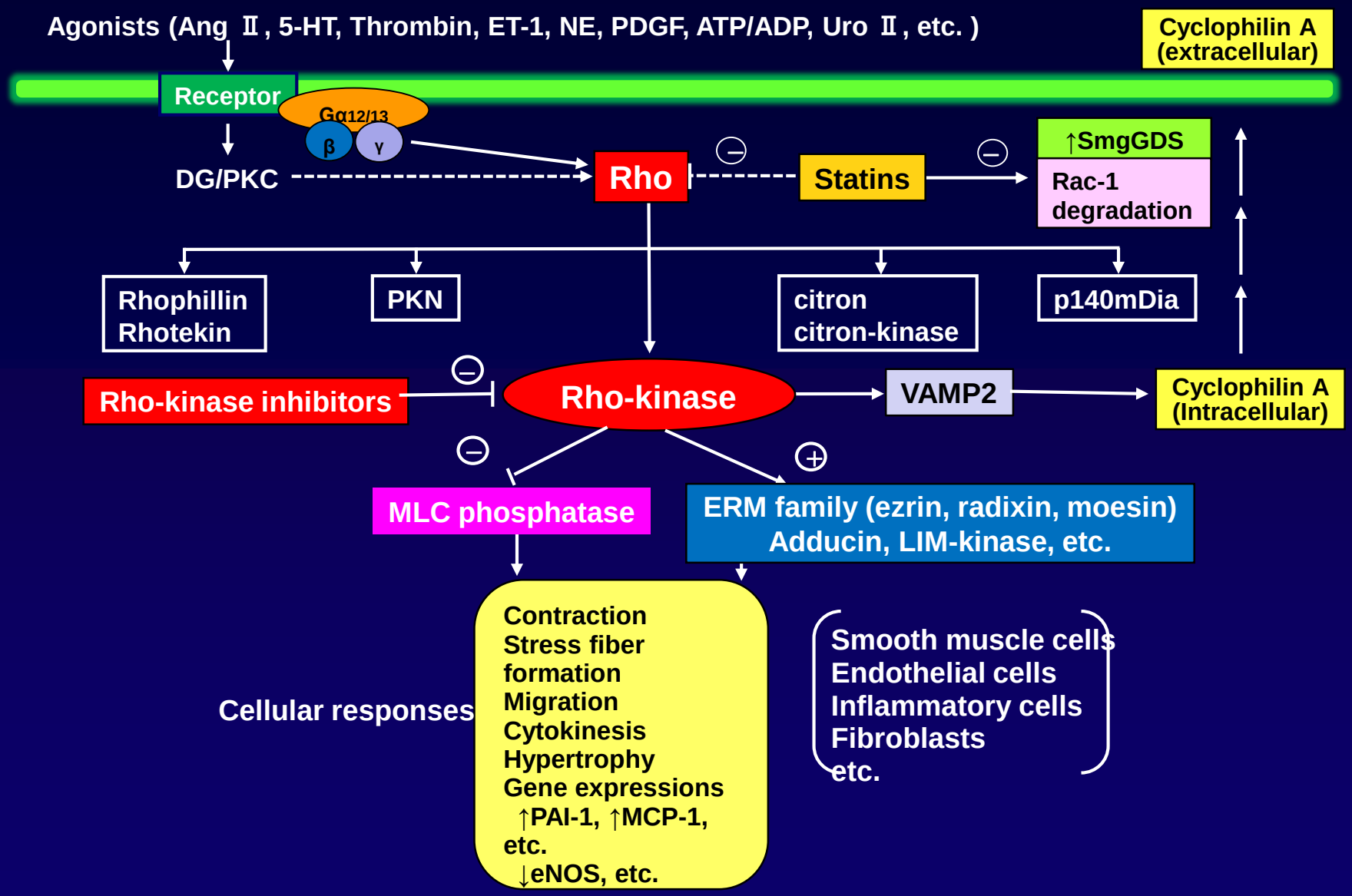
Potential Therapies for CMD

Potential Therapies for CMD

Pharmacologic	Non-pharmacologic
• Nitrates • Statins • ACE-I • ACE-I + Aldosterone blockade • Calcium antagonists • Low-dose tricyclic antidepressants • Estrogens • PDE-5 inhibitors • Exercise • L-arginine • Ranolazine • Ivabradine • Ranolazine + Ivabradine • Metformin • Rho-kinase inhibitors • Endothelin receptor blockers	• Exercise • Cognitive behavioral therapy • Transcendental meditation • Transcutaneous electrical nerve stimulation

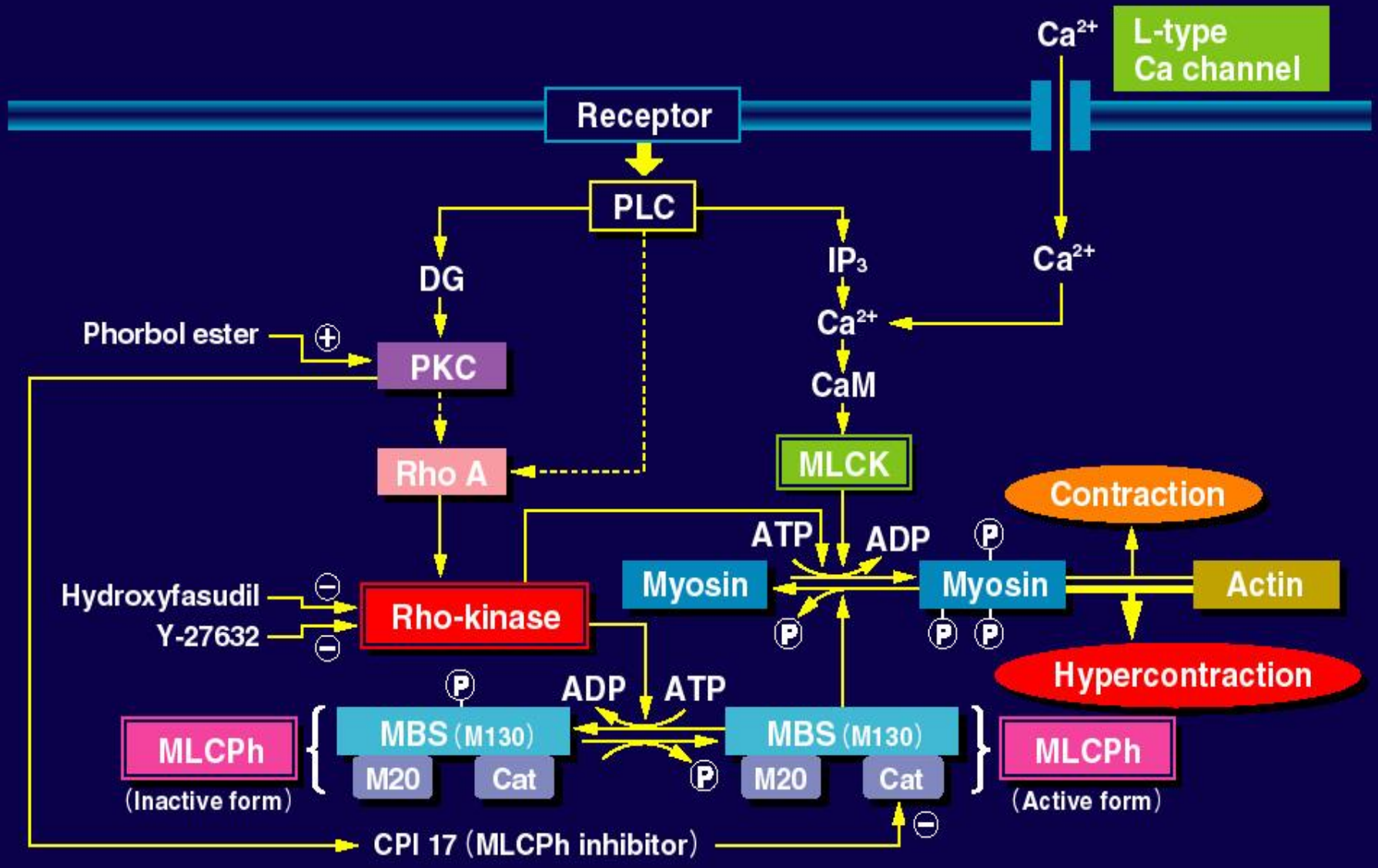
(Merz CNB, Pepine CJ, et al. *Circulation.* 2017;135:1075-1092.)

Roles of Rho-kinase Pathway in the Pathogenesis of CVD



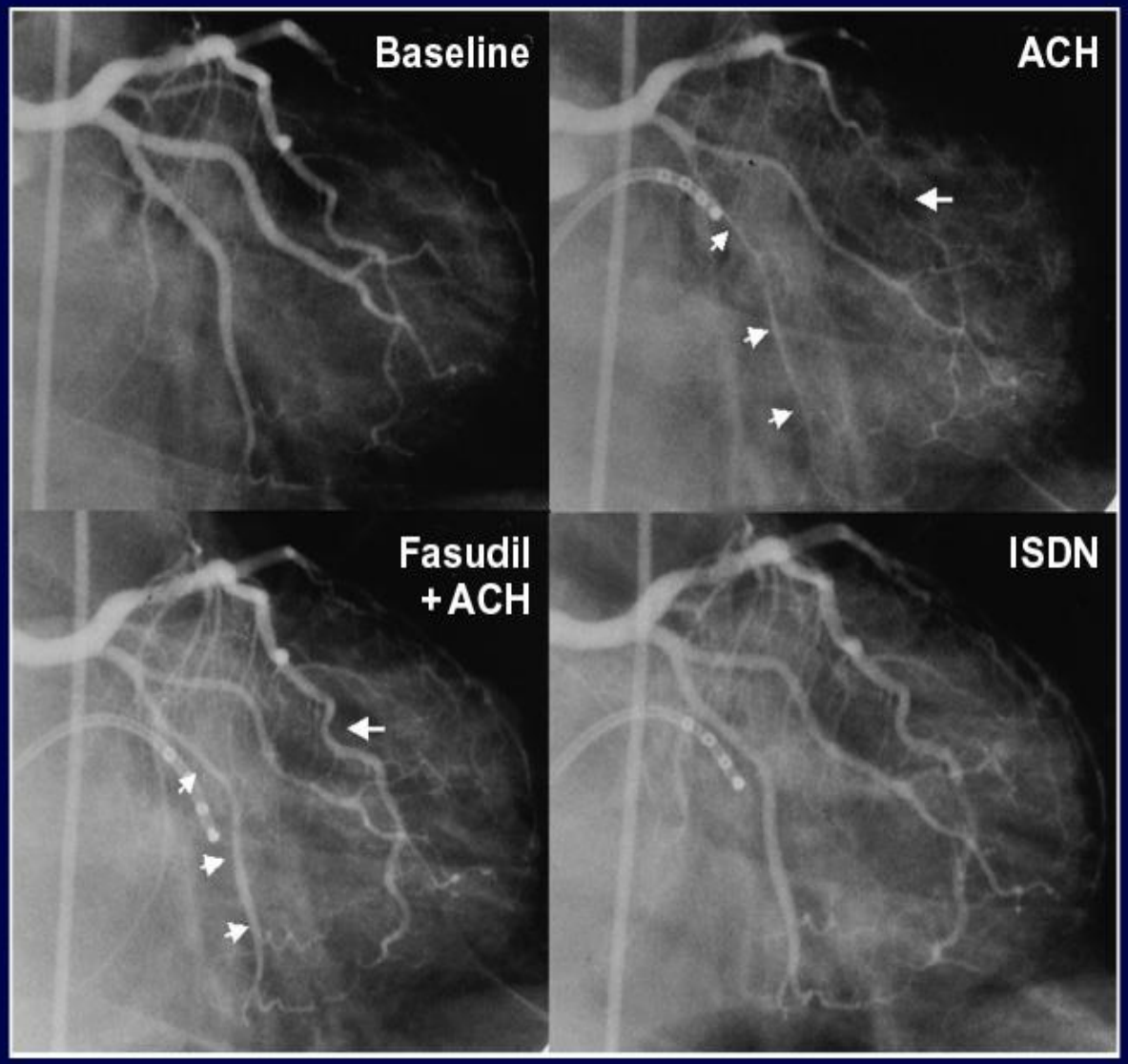
(Shimokawa H. *Eur Heart J*. 2014;35:3180-93.) (Review)
(Shimokawa and Satoh K. *ATVB*. 2015;35:1756-69.) (Review)

Molecular Mechanisms of Coronary Spasm



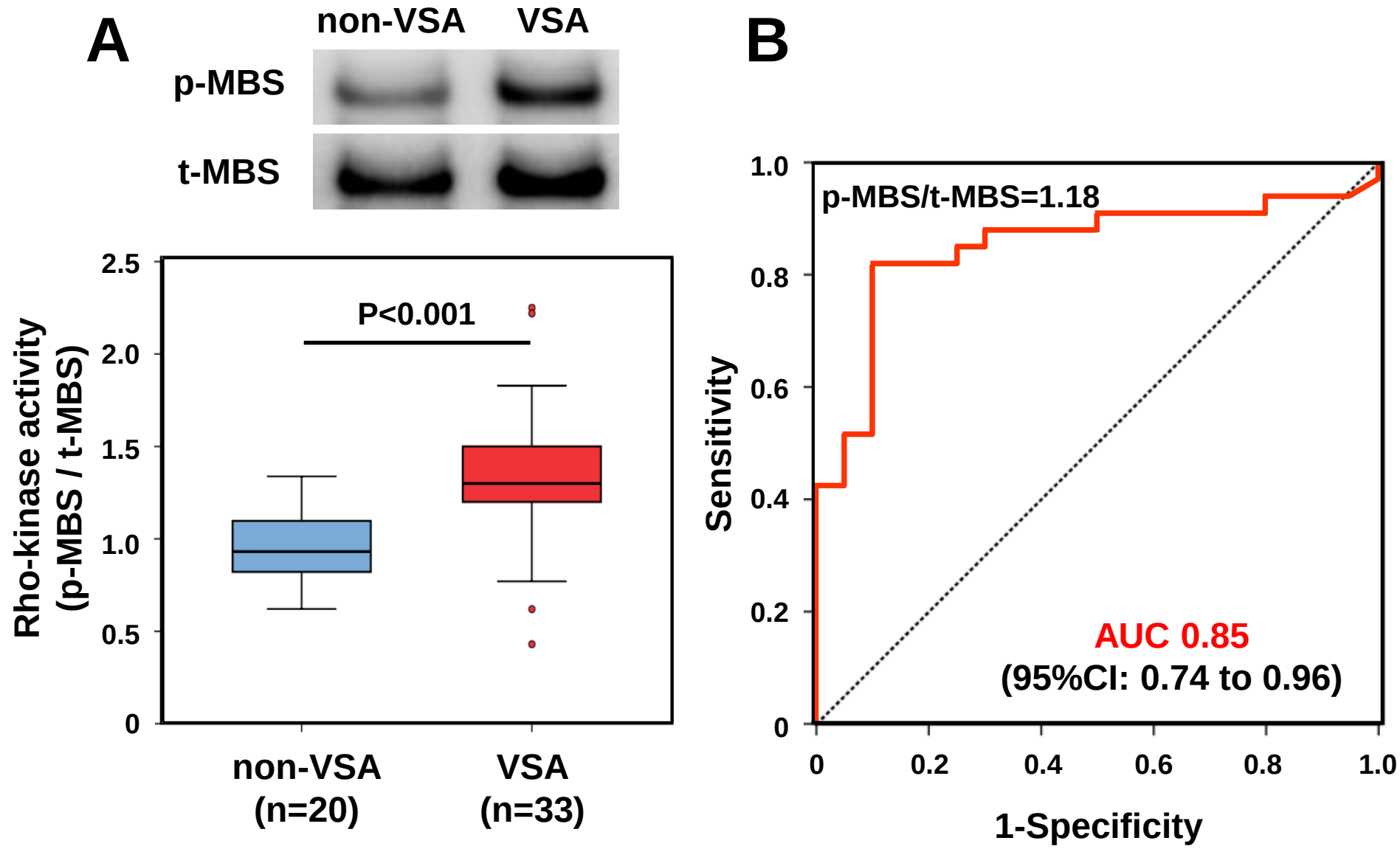
(Shimokawa H. *Eur Heart J*. 2014;35:3180-93.) (Review)
(Shimokawa H. *ATVB*. 2015;35:1756-69.) (Review)
(Shimokawa H, et al. *Circ Res*. 2016;80:352-66.) (Review)

Inhibitory Effects of Fasudil on Multivessel Coronary Spasm



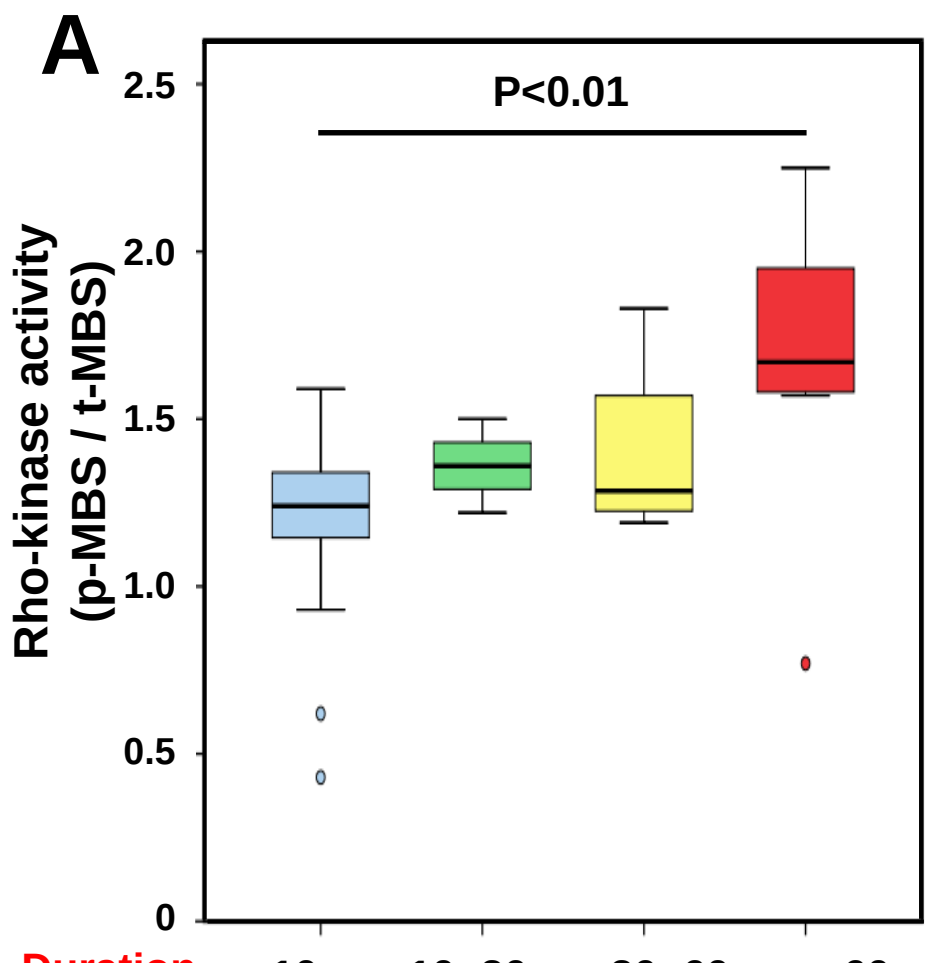
(Masumoto, Mohri, Shimokawa, et al. *Circulation*. 2002;105:1545-7.)

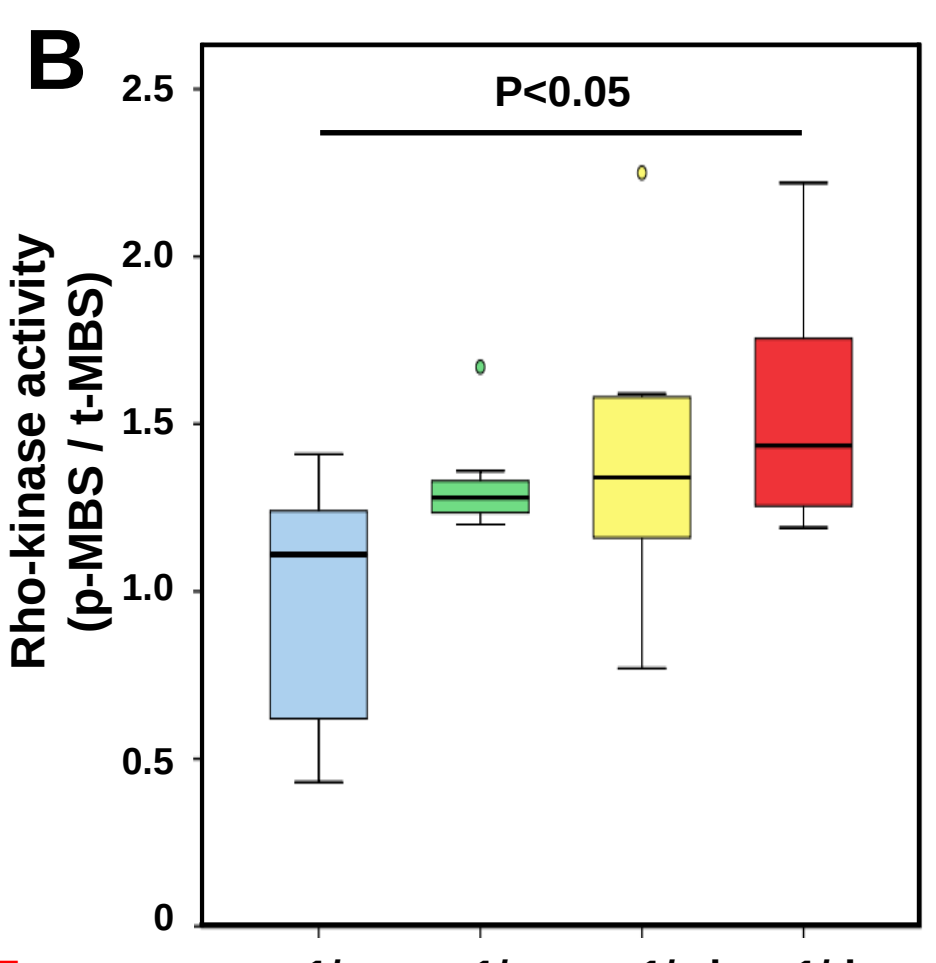
Enhanced Rho-kinase Activity of Circulating Leukocytes in VSA Patients



(Kikuchi, Shimokawa, et al. *JACC.* 2011;58:1231-7.)

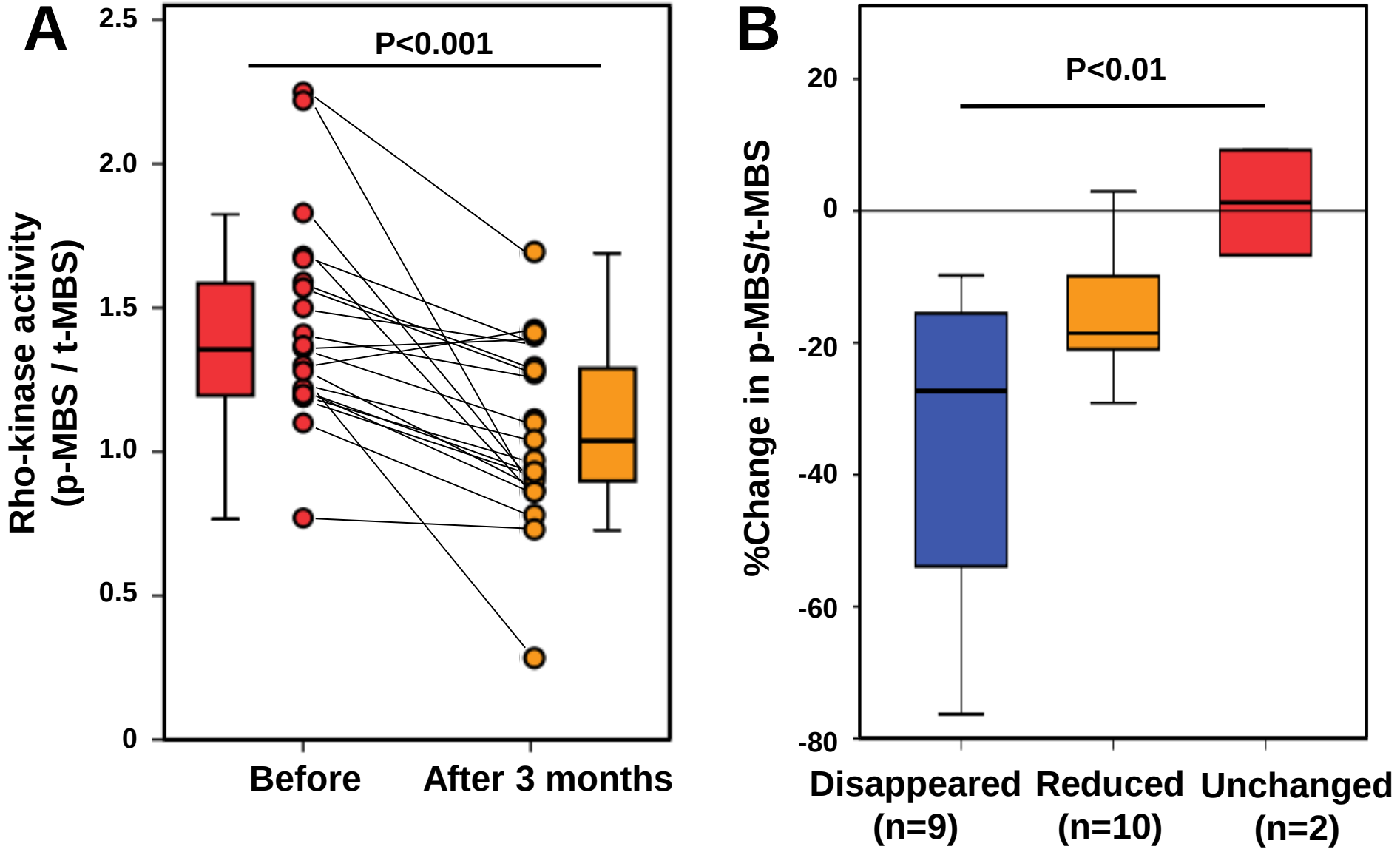
Rho-kinase Activity of Circulating Leukocytes in VSA Patients





(Kikuchi, Shimokawa, et al. *JACC.* 2011;58:1231-7.)

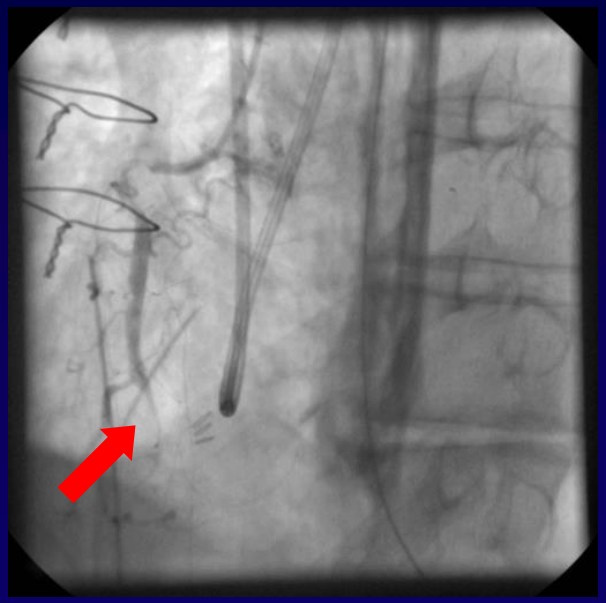
Rho-kinase Activity of Circulating Leukocytes in VSA Patients



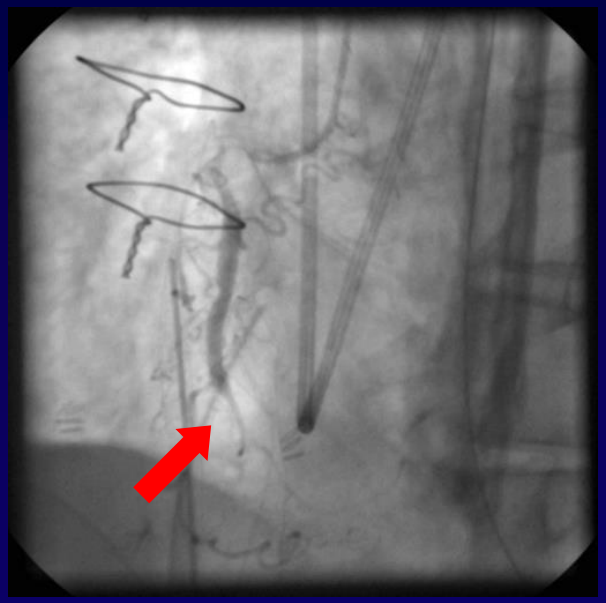
(Kikuchi, Shimokawa, et al. *JACC.* 2011;58:1231-7.)

Inhibitory Effects of Fasudil on Intractable Coronary Spasm

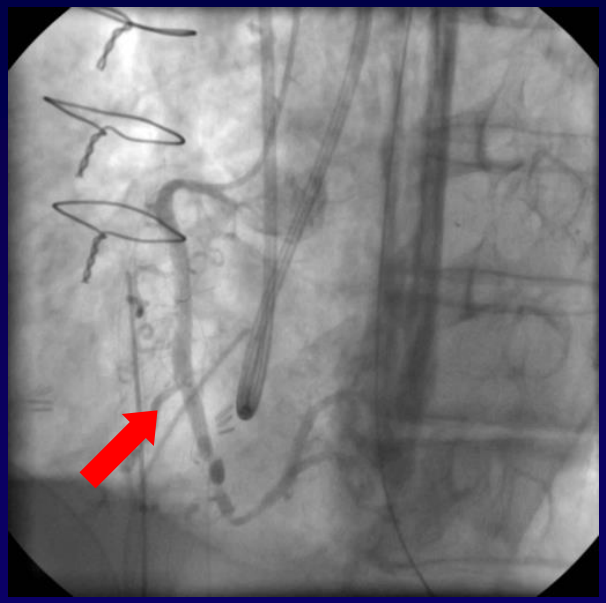
Control



Nirates・CCBs

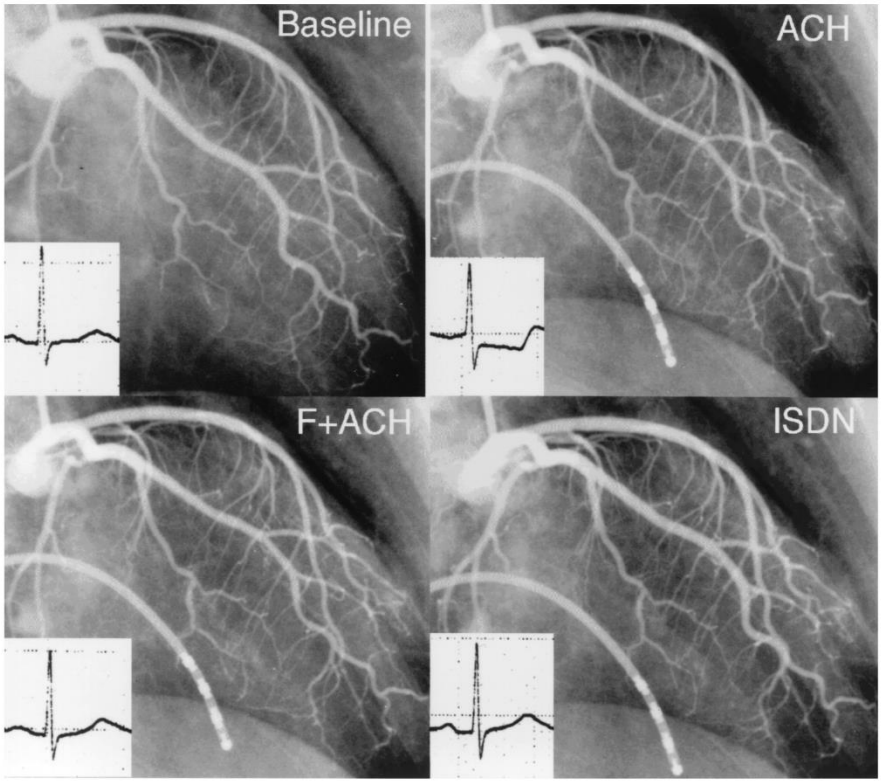


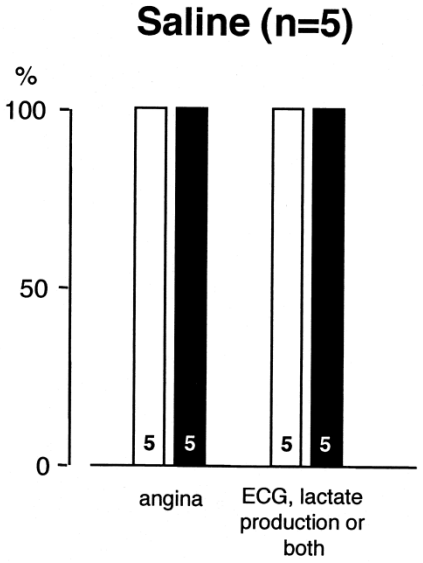
Fasudil

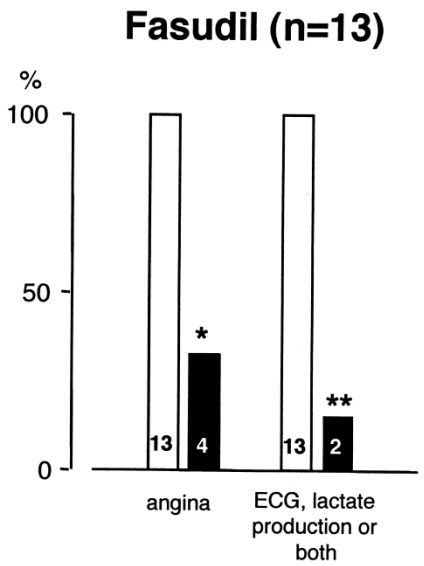


(Ito, Shimokawa et al. *J Cardiovasc Pharmacol*. 2004;44:275-7.)

Rho-kinase inhibition with intracoronary fasudil prevents myocardial ischemia in patients with coronary microvascular spasm







(Mohri M, Shimokawa H et al. *J Am Coll Cardiol*. 2003;41:15-19.)

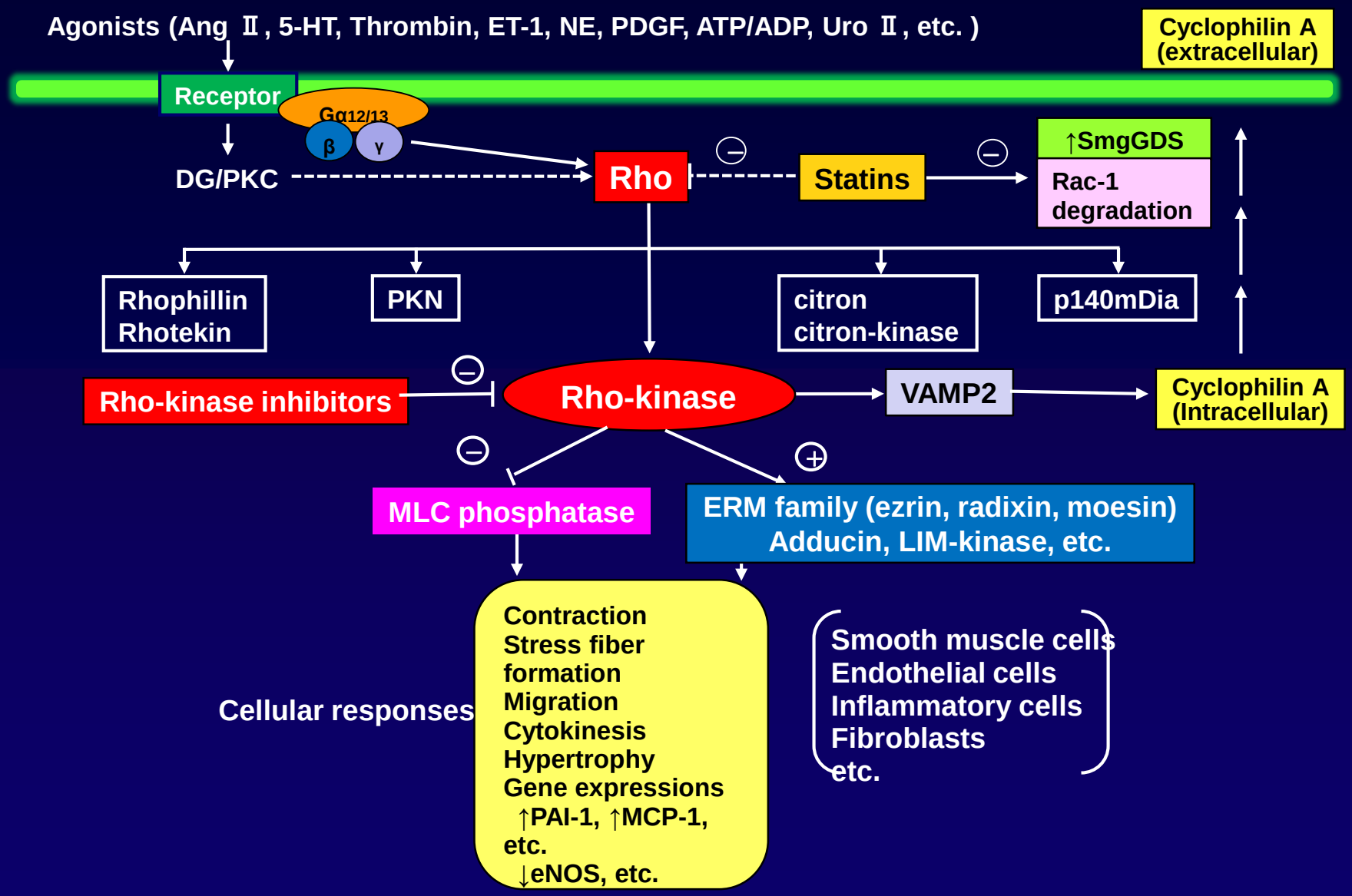
ESC congress 2017
Young Investigator Award
Coronary pathophysiology and microcirculation
(August 27, 2017, Barcelona, Spain)

Important prognostic impact of comorbid coronary microvascular dysfunction in patients with vasospastic angina

Akira Suda, Jun Takahashi, Kiyotaka Hao, Yoku Kikuchi,
Tomohiko Shindo, Masayasu Komatsu, Yuji Odaka, Yasuharu Matsumoto,
Satoshi Miyata, Yasuhiko Sakata, Hiroaki Shimokawa

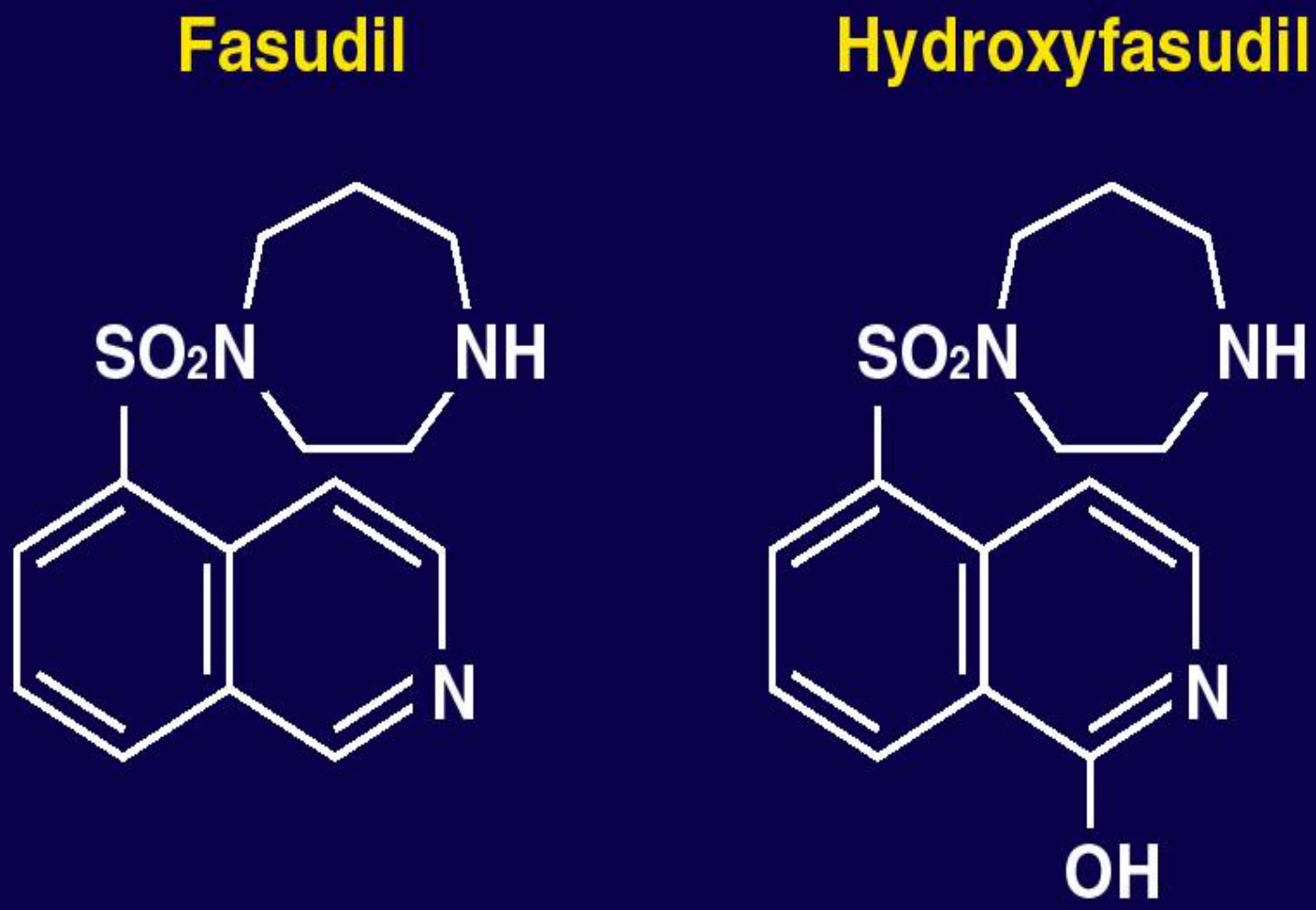
Department of Cardiovascular Medicine,
Tohoku University Graduate School of Medicine, Sendai, Japan

Roles of Rho-kinase Pathway in the Pathogenesis of CVD



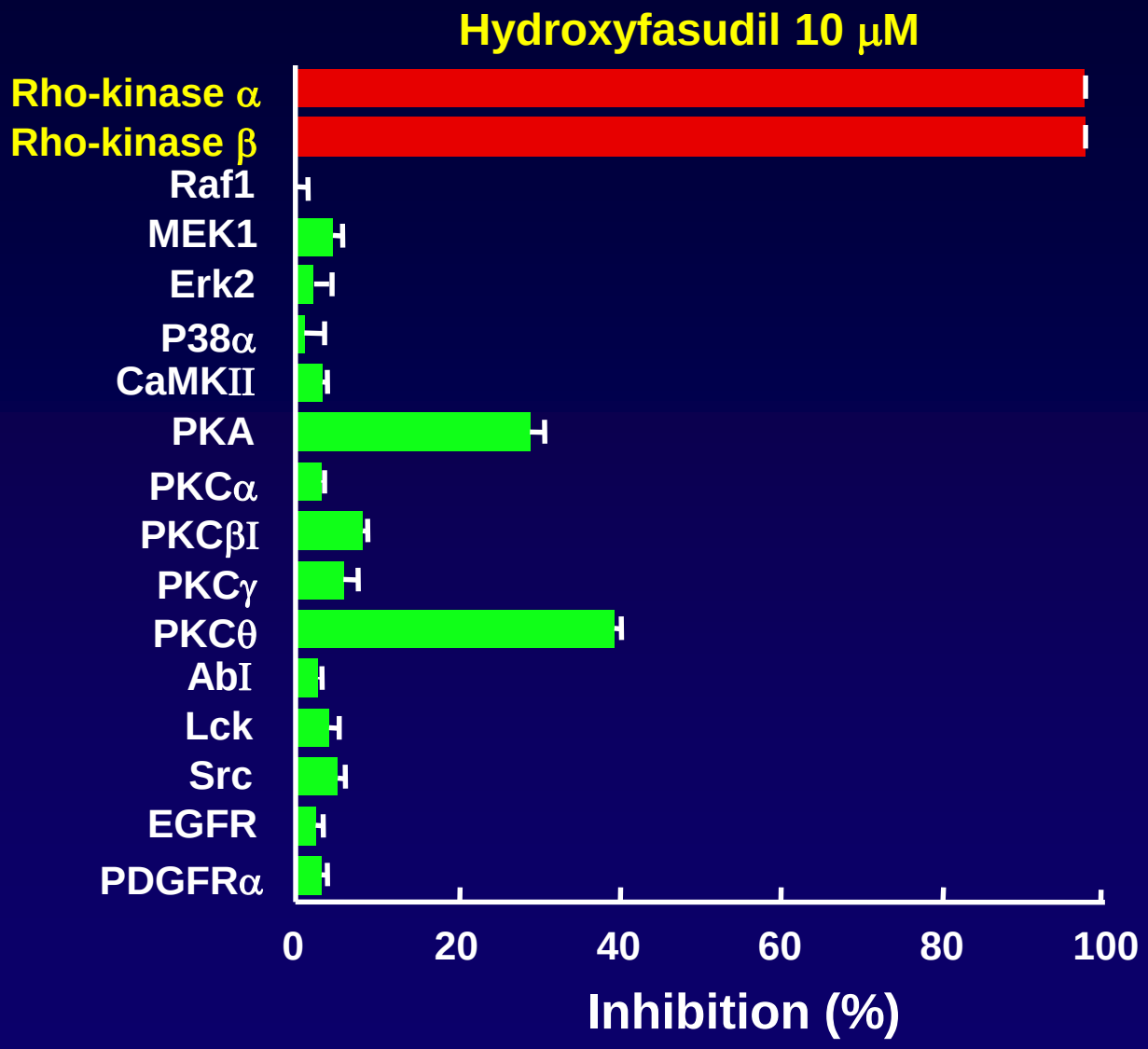
(Shimokawa H. *Eur Heart J*. 2014;35:3180-93.) (Review)
(Shimokawa and Satoh K. *ATVB*. 2015;35:1756-69.) (Review)

Chemical Structure of Fasudil and Hydroxyfasudil



(Shimokawa et al. *Cardiovasc Res*. 1999;43:1138-1141.)

Selective Inhibitory Effects of Hydroxyfasudil on Rho-kinase



(Higashi, Shimokawa, et al. *Circ Res.* 2003;93:767-775.)

Rho-kinase inhibitors

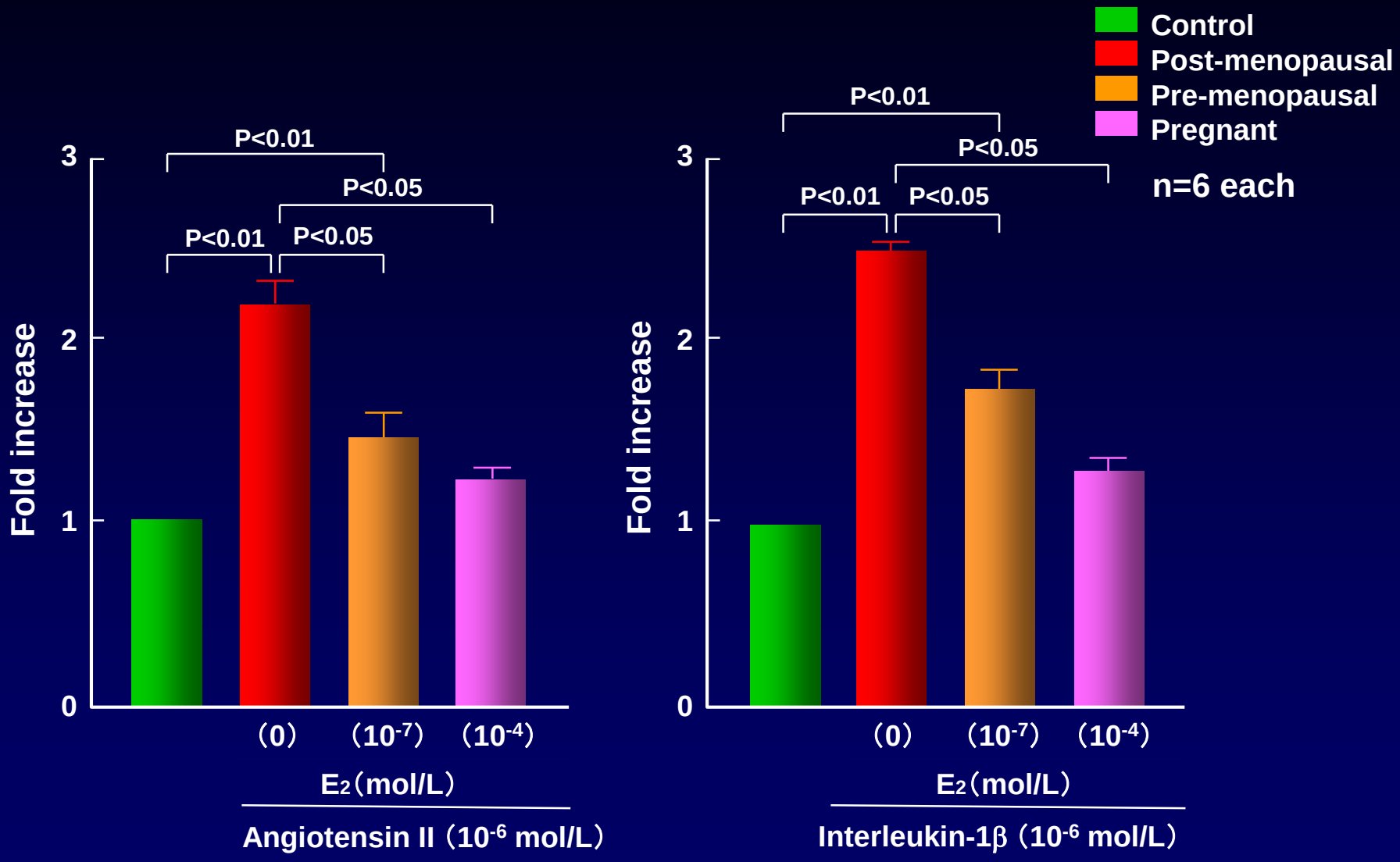
1. Direct inhibitors

- Fasudil (CVR 1999, Circ 2000, Circ Res 2003)
- New drugs (under development)

2. Indirect inhibitors

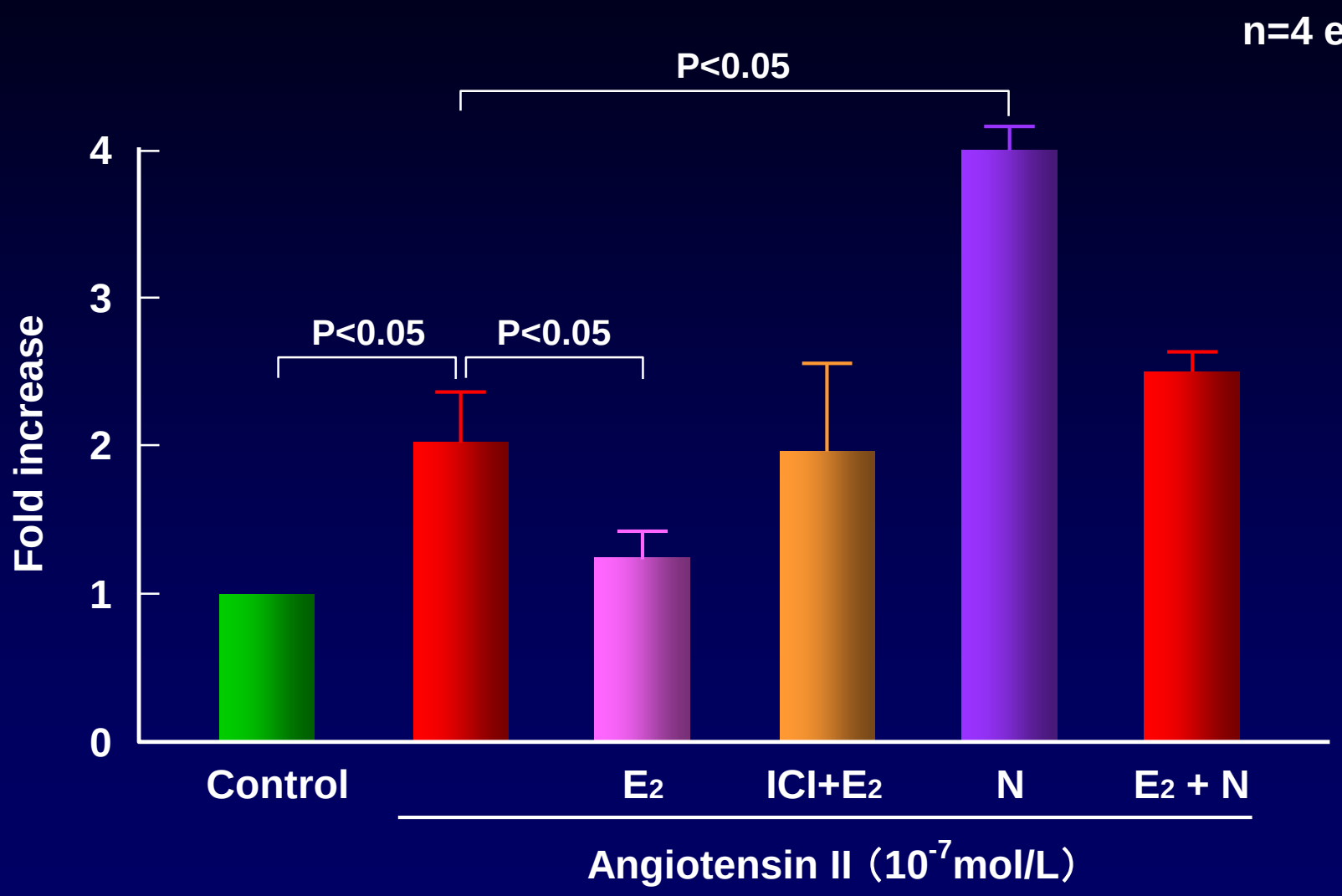
- Estrogen (2004)
- Nifedipine (other CCBs) (EHJ 2012)
- Ezetimibe (Circ J 2012)
- Others

Inhibitory effects of estrogen on Rho-kinase expression
（Human coronary VSMC）



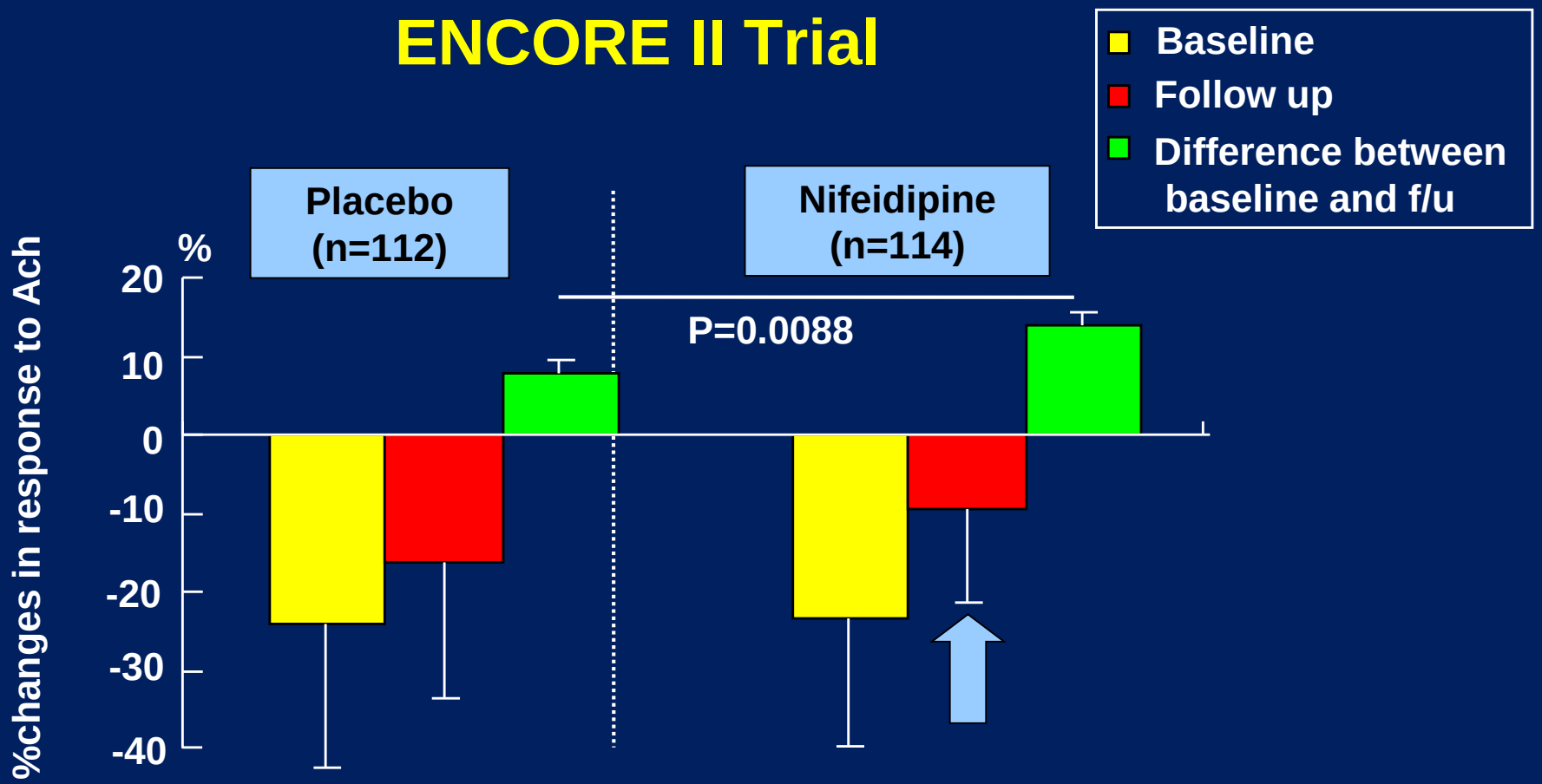
（Hiroki, Shimokawa, et al. *BBRC*. 2004;326:154-159.）

Nicotine abolishes the inhibitory effects of estrogen on Rho-kinase expression (Human coronary VSMC)



（Hiroki, Shimokawa, et al. *BBRC*. 2004;326:154-159.）

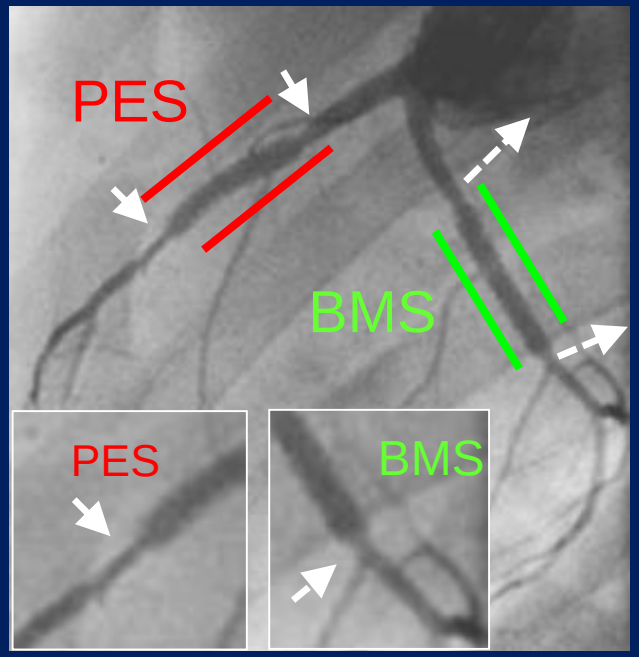
Long-acting nifedipine improves vasomotor function of coronary arteries



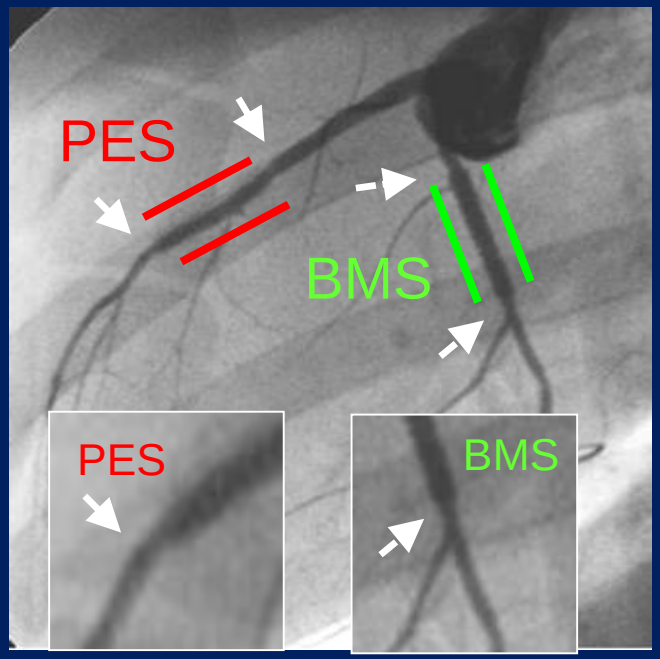
(Luscher TF, et al. *Eur Heart J.* 2009;30:1590-7.)

Long-term treatment with nifedipine suppresses serotonin-induced coronary hyperconstriction at DES sites in pigs in vivo

Control



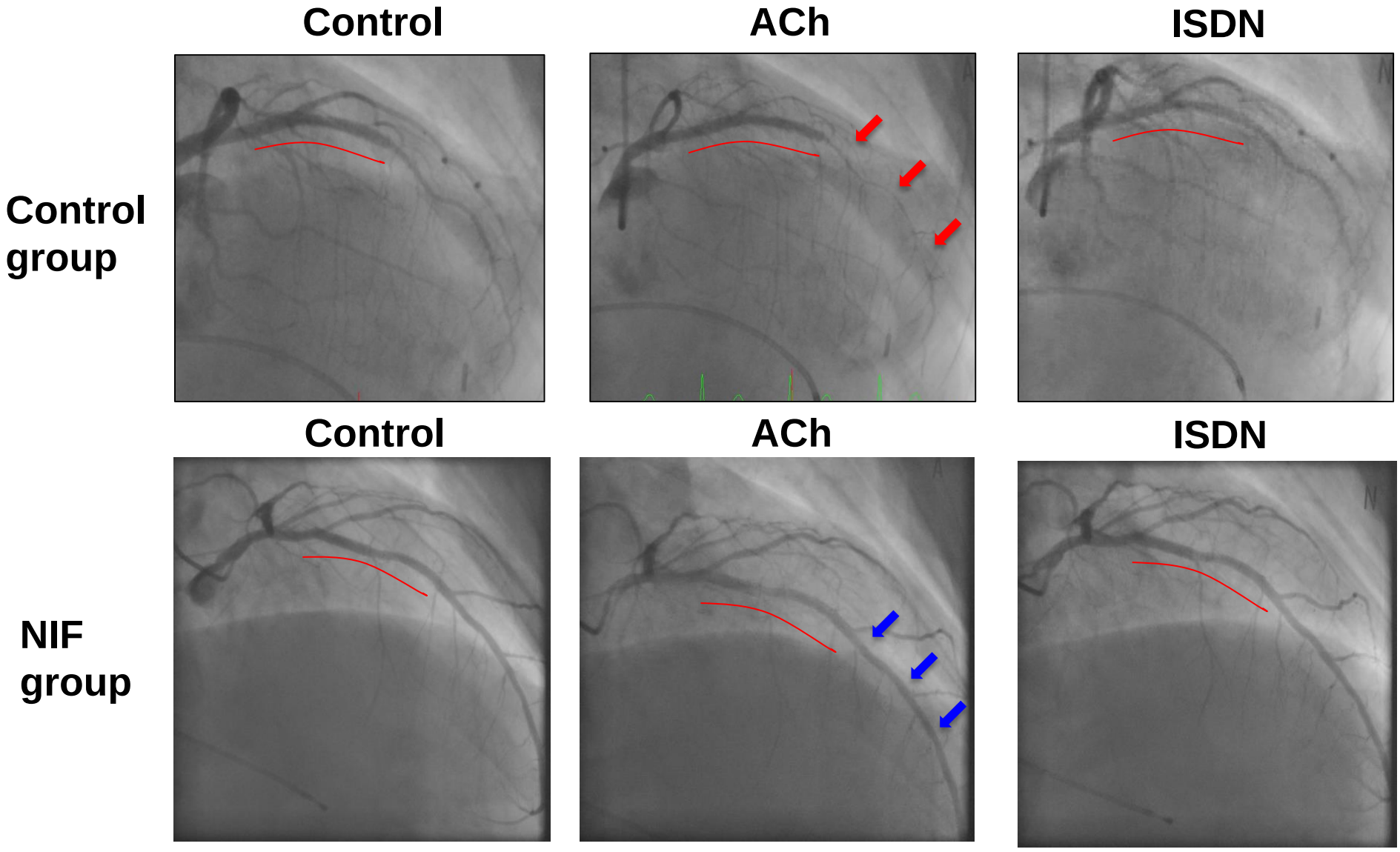
Nifedipine



***NIF was discontinued 24hrs before examination.**

(Tsuburaya, Shimokawa, et al. *Eur Heart J.* 2012;33:791-9.)

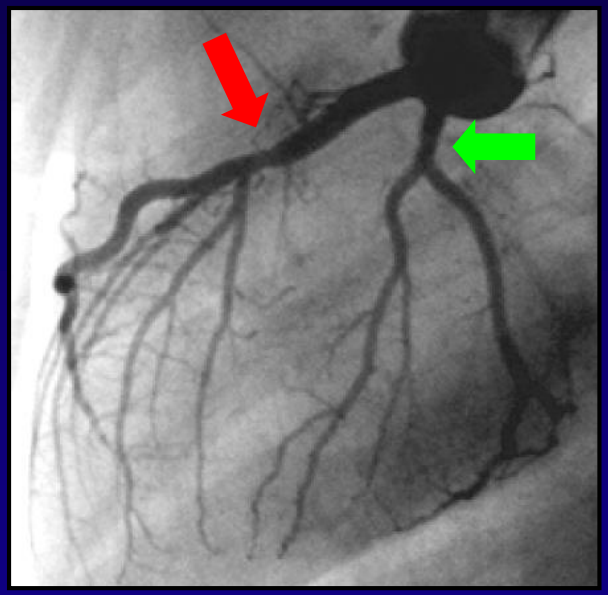
Long-term treatment with nifedipine suppresses DES-induced hyperconstrictng responses in CAD patients



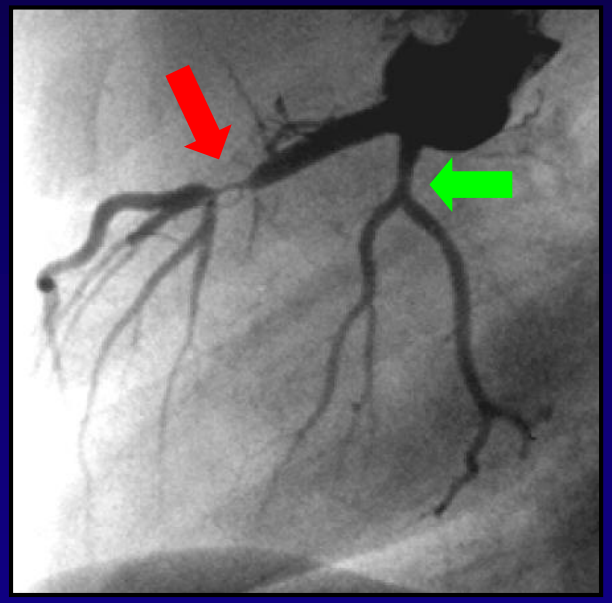
(Tsuburaya, Shimokawa, et al. *Eur Heart J.* 2016;37:2713-21.)

Involvement of Rho-kinase in the effects of remnant-lipoprotein to cause coronary spasm in pigs in vivo

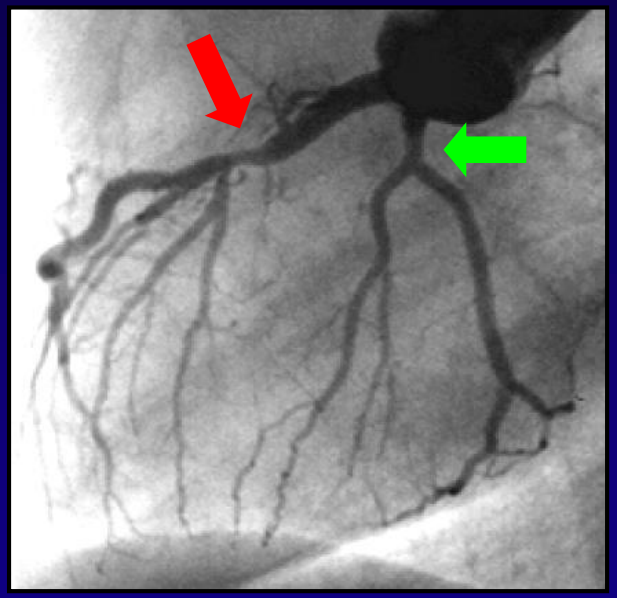
RLP site
non-RLP site



Control



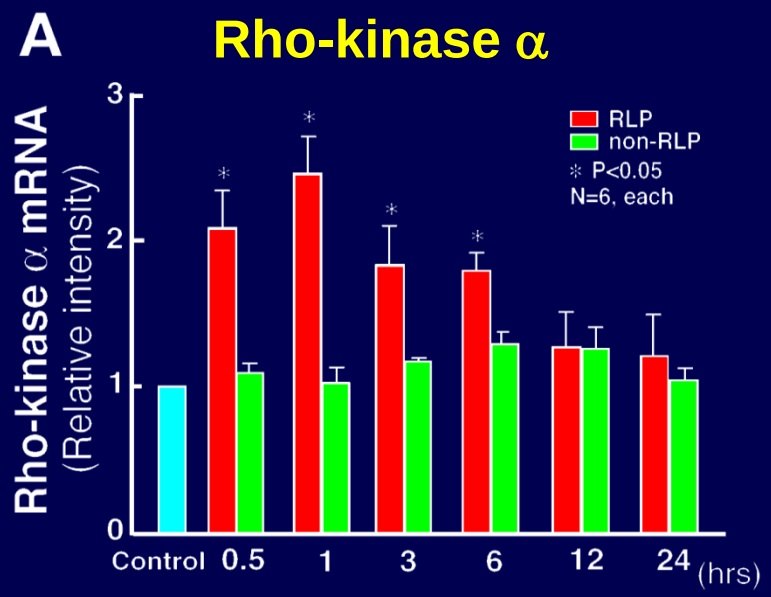
Serotonin

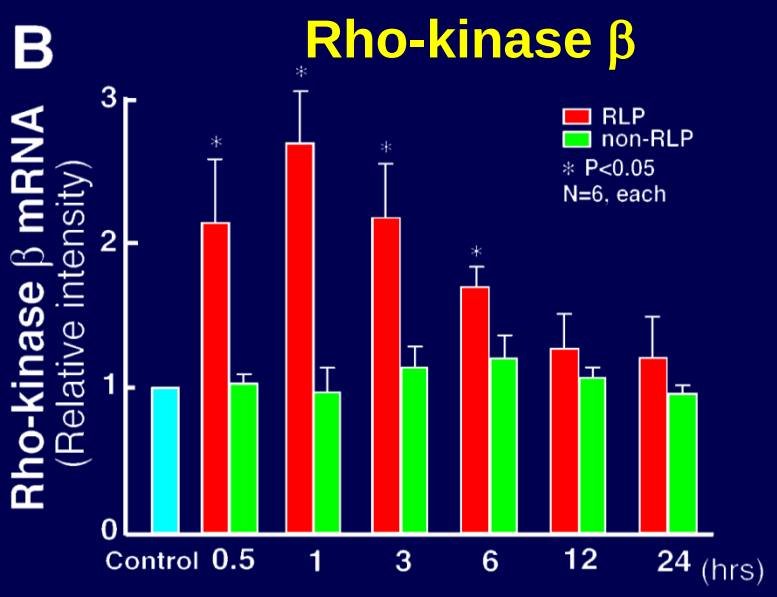


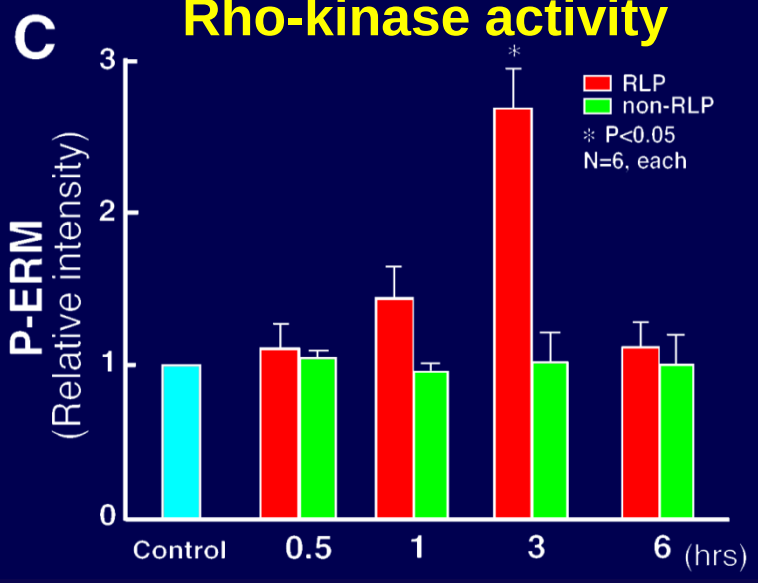
Hydroxyfasudil
+
Serotonin

(Oi, Shimokawa, et al. *ATVB.* 2004;24:918–922.)

Remnant lipoproteins enhances Rho-kinase activity in human coronary VSMC

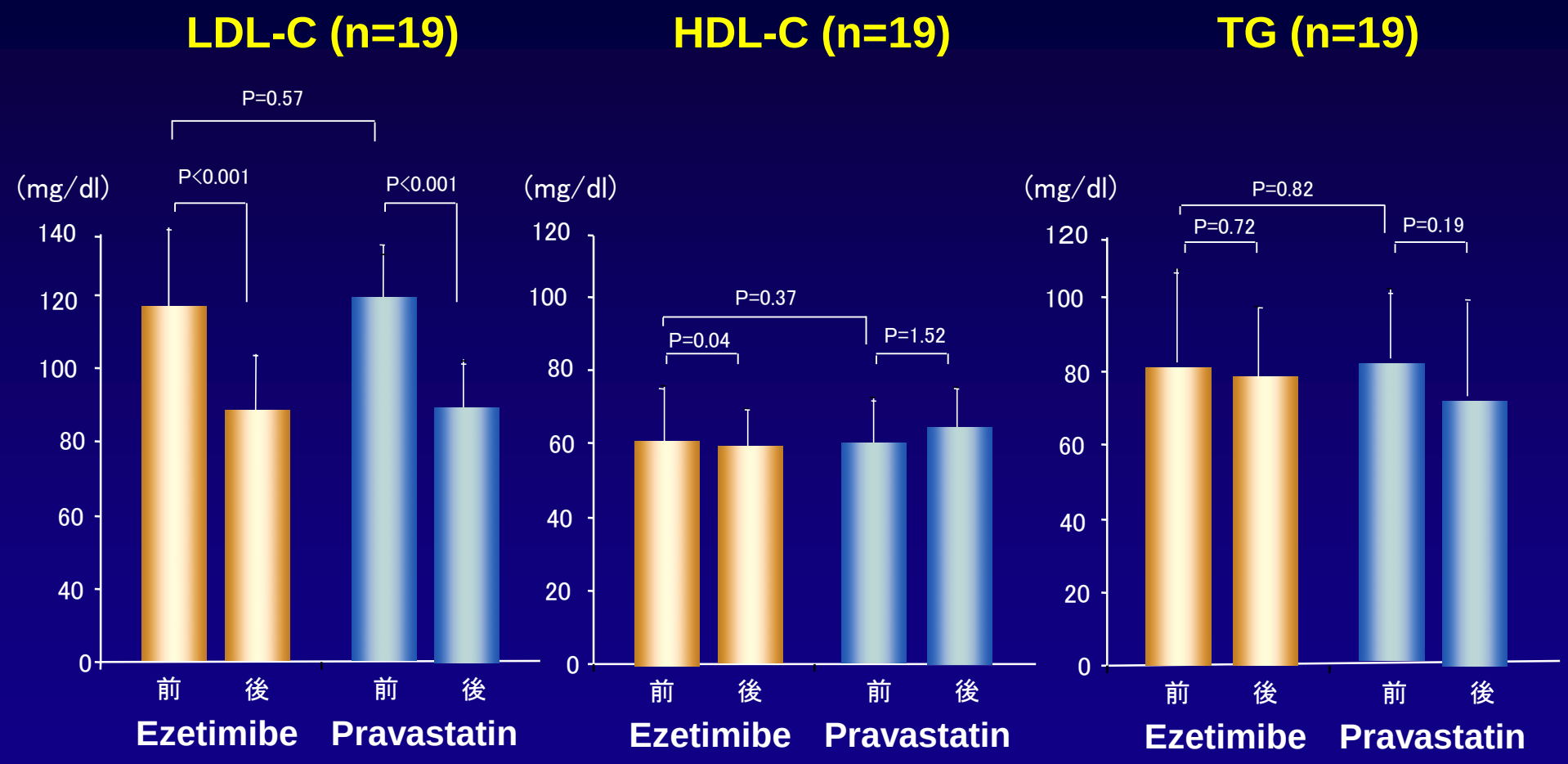






(Oi, Shimokawa, et al. *ATVB.* 2004;24:918–922.)

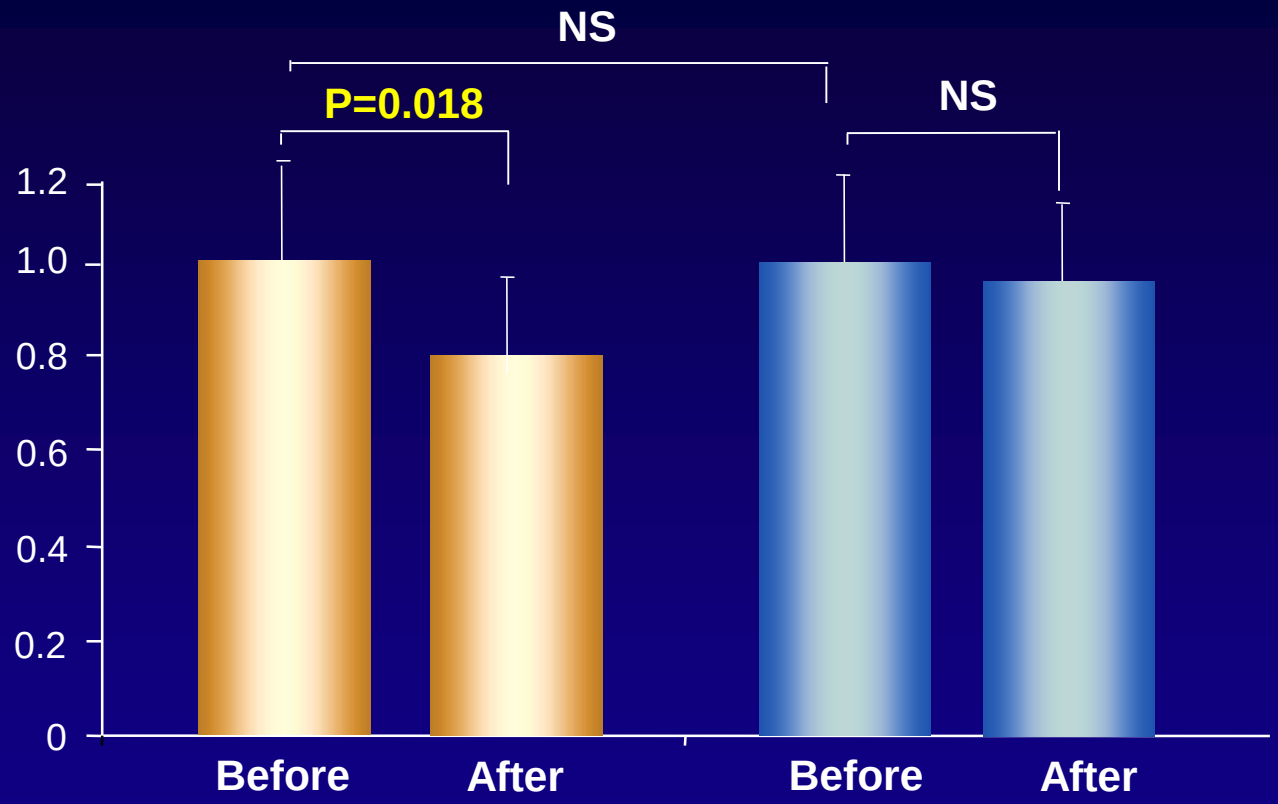
Comparable lipid-lowering effects of ezetimibe and pravasatatin in humans



(Nochioka, Shimokawa, et al. *Circ J*. 2012;76:2023-2030.)

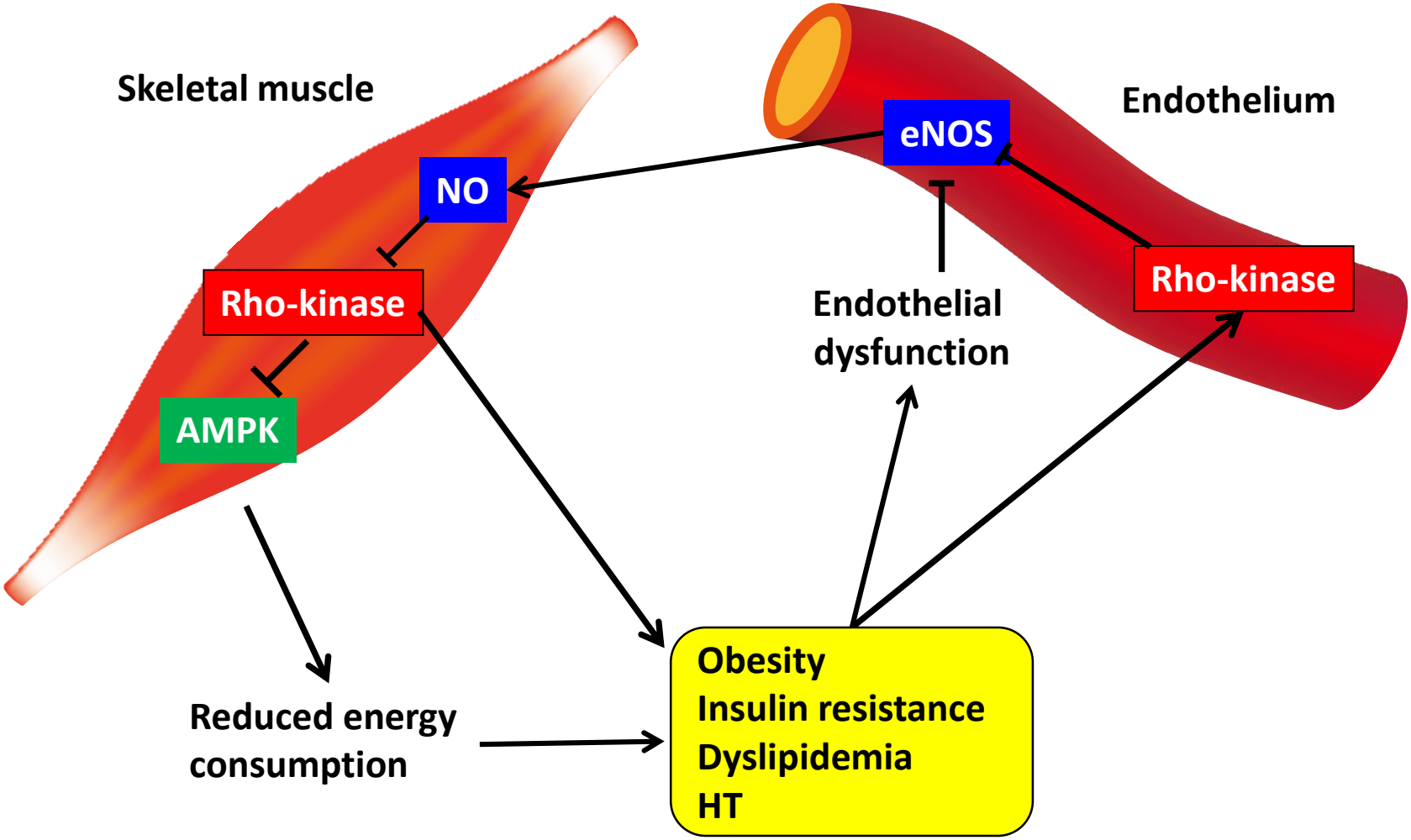
Long-term treatment with ezetimibe suppresses Rho-kinase activity of circulating neutrophils in humans

Rho-kinase activity (pMBS/tMBS ratio)



(Nochioka, Shimokawa, et al. *Circ J*. 2012;76:2023-2030.)

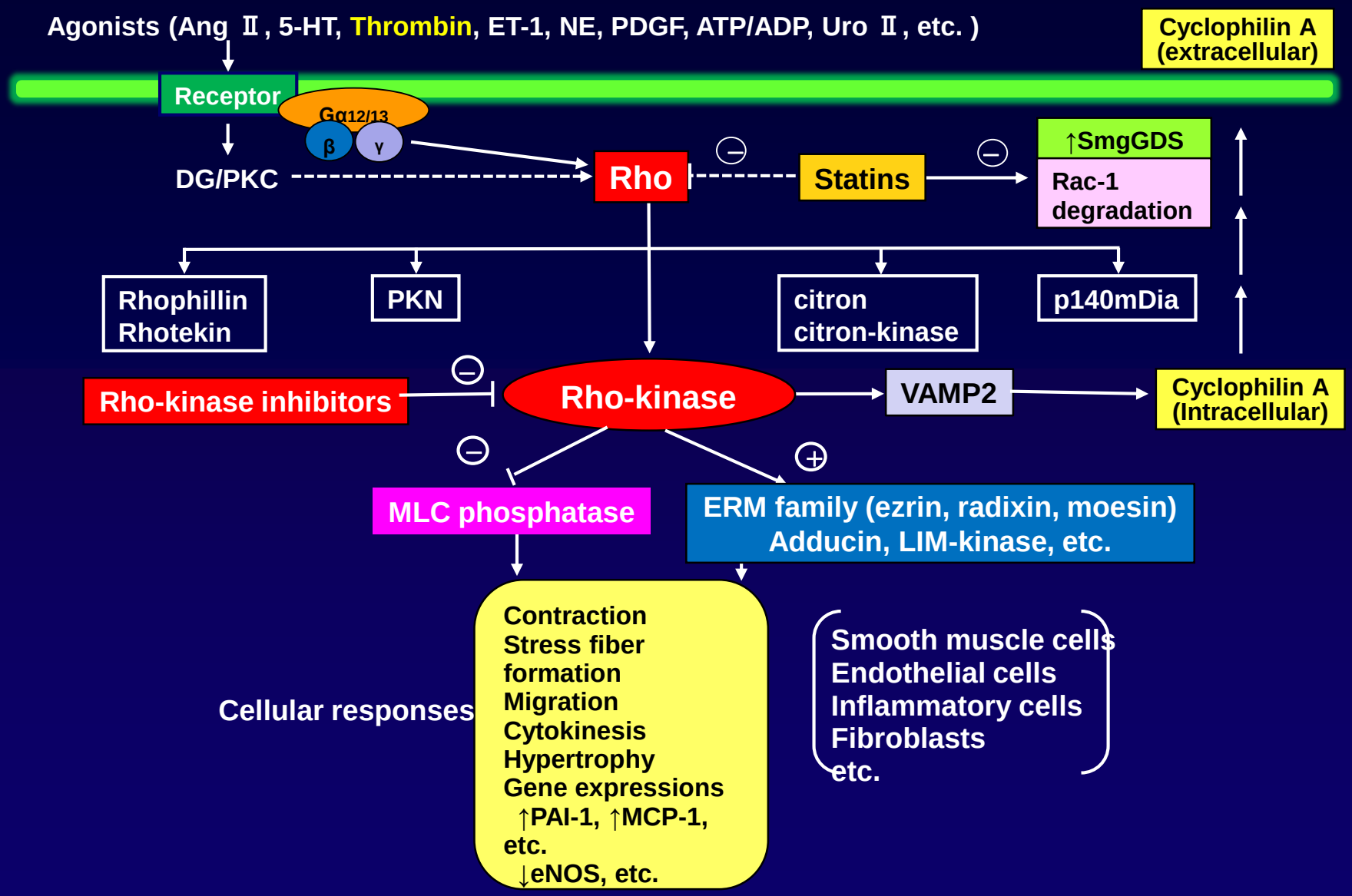
Inhibitory relationship between NO and Rho-kinase



(Noda, Shimokawa, et al. *PloS One*. 2015.)

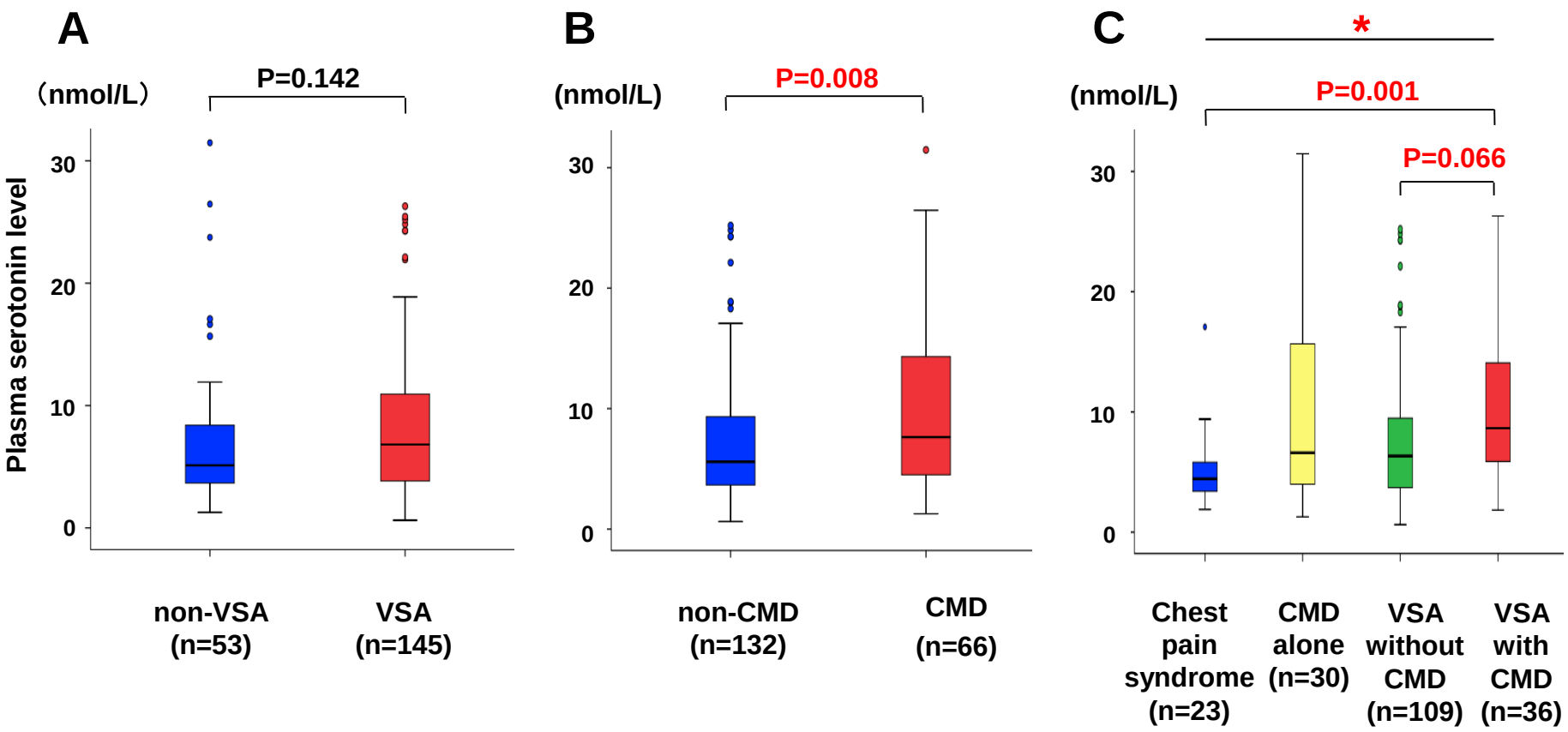
(Shimokawa, et al. *Circ Res*. 2016.) (Review)

Roles of Rho-kinase Pathway in the Pathogenesis of CVD



(Shimokawa H. *Eur Heart J*. 2014;35:3180-93.) (Review)
(Shimokawa and Satoh K. *ATVB*. 2015;35:1756-69.) (Review)

Increased plasma levels of serotonin in patients with CMD



(Odaka, Shimokawa, et al. *Eur Heart J*. 2017;38:489-496.)