Pathogenetic mechanisms of vasospastic angina

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(No COI to disclose)
Important Roles of Coronary Spasm in the Pathogenesis of IHD

Variant angina
Rest angina
Rest & effort angina
Unstable angina
Coronary atherosclerosis

DES-induced spasm
Effort angina
AMI
Post-MI angina
Sudden death

Coronary spasm
Coronary Spasm induced in Atherosclerotic Coronary Artery in Pigs in Vivo

Control
Histamine
Serotonin

(Shimokawa et al. *Science*. 1983;221:560-562.)
Topological Correlation between Spastic Site and Atherosclerotic Site in a Porcine Model of Coronary Spasm

(Shimokawa et al., Science 1983; 221: 560-562.)
Coronary Spasm induced at Inflammatory Coronary Lesion in Pigs in Vivo

Nitroglycerin

Serotonin

Molecular Mechanisms of Coronary Spasm

(Shimokawa H. Trend Pharmacol Sci., 2007;28:296-302.) (Review)
Roles of Rho-kinase Pathway in the Pathogenesis of Cardiovascular Diseases

Agonists (Ang II, 5-HT, Thrombin, ET-1, NE, PDGF, ATP/ADP, Uro II, etc.)

Receptor \( \rightarrow \)  G\( \alpha \)\(_{12/13} \rightarrow \) DG/PKC

\( \rightarrow \) Rho \( \rightarrow \) Statins \( \rightarrow \) Ras

\( \rightarrow \) Rac

Rhophillin Rhotekin \( \rightarrow \) PKN

Rho-kinase inhibitors

Rho-kinase

\( \rightarrow \) Myosin phosphatase

\( \rightarrow \) ERM family (ezrin, radixin, moesin)
Adducin, LIM-kinase, etc.

Contraction
Stress fiber formation
Focal adhesion
Migration
Cytokinesis
Hypertrophy
Gene expression

\( \uparrow \) PAI-1, \( \uparrow \) MCP-1, etc.
\( \downarrow \) eNOS, etc.

Cellular responses

Smooth muscle cells
Endothelial cells
Inflammatory cells
Fibroblasts
etc.

(Shimokawa H. *ATVB*. 2005;25:1767-1775.) (Review)
Chemical Structure of Fasudil and Hydroxyfasudil

(Fasudil)

(SO₂N)₃

(NH)

(Phenanthridine)

(Hydroxyfasudil)

(SO₂N)₃

(NH)

(OH)

(Phenanthridine)

Selective Inhibitory Effects of Hydroxyfasudil on Rho-kinase

(Higashi, Shimokawa, et al. Circ Res. 2003;93:767-775.)
Inhibitory Effects of Fasudil on Multivessel Coronary Spasm

Inhibitory Effects of Fasudil on Intractable Coronary Spasm

Control

Nirates・CCBs

Fasudil

Co-existence of Epicardial and Microvascular Spasm

Baseline

ACh 30 µg

ACh 100 µg

ISDN

Female, 58 yrs.

(Sun, Mohri, Shimokawa et al., J Am Coll Cardiol. 2002;39:847-851.)
Co-existence of Epicardial and Microvascular Spasm

Lactate uptake

Changes in epicardial coronary diameter

(14) (41)

Group 1: MVS+(14)
Group 2: MVS−(41)

(Sun, Mohri, Shimokawa et al., J Am Coll Cardiol. 2002; 39: 847-851.)
Inhibitory Effects of Fasudil on Microvascular Angina

(Mohri, Shimokawa, et al., J Am Coll Cardiol. 2003;41:15-19.)
Inhibitory Effects of Fasudil on Microvascular Angina

Saline (n=5)

- Angina: 5%
- ECG, lactate production or both: 5%

Fasudil (n=13)

- Angina: 13%
- ECG, lactate production or both: 12%

(* indicates statistical significance; ** indicates highly significant difference)

(Mohri, Shimokawa et al., J Am Coll Cardiol. 2003; 41: 15-19.)
Enhanced Rho-kinase Activity of Circulating Leukocytes in VSA Patients

(Kikuchi, Shimokawa, et al. JACC. 2011;58:1231-1237.)
Rho-kinase Activity of Circulating Leukocytes in VSA Patients

(Kikuchi, Shimokawa, et al. JACC. 2011;58:1231-1237.)
Rho-kinase Activity of Circulating Leukocytes in VSA Patients

(Kikuchi, Shimokawa, et al. JACC. 2011;58:1231-1237.)
IVUS Findings of Coronary Spasm

- Thickened sonolucent zone
- Diffuse intimal thickening
- Necrotic core
- Negative remodeling
- Spastic site

Yamagishi M. *JACC*, 1994
Miyano Y. *JACC*, 2000
Hong YJ. *IJC*, 2010

Pre Spasm

IVUS-V
NTG
Spastic site
OCT Findings of Coronary Spasm

Baseline | Provocation | NTG

Intimal bump | Intimal gathering

VSA

Control

(Courtesy by Dr. Atsushi Tanaka)
3D-OCT during Coronary Spasm

(Courtesy by Dr. Atsushi Tanaka)
Intimal Bump / Gathering

VSA
Control

(Intimal bump) 80% vs 0% (P<0.01)
(Intimal gathering) 100% vs 0% (P<0.01)

(Tanaka A, et al. JACC. 2011.)
Problems with Drug-eluting Stents

(1) Long-term prognosis/ Late Thrombosis

- Restenosis: DES 6.7%, BMS 4.5%
- Cardiac death: DES 1.2%, BMS 1.3%
- AMI: DES 1.3%, BMS 1.3%
- Cardiac death/Non-fatal AMI: DES 4.9%, BMS 4.1%

(2) DES-induced coronary spasm

Control

ACh ic後

(Maekawa K. et al. Circulation. 2006;113:e850-851.)


(Pfisterer M. et al. JACC. 2006;48:2584-2591.)
Coronary Hyperconstricting Responses Induced at DES Edges in a Pig in Vivo

Serotonin (100 μg/kg ic)

Hydroxyfasudil + Serotonin

(Shiroto, Shimokawa et al. JACC. 2009;54:2321-2329.)
Pathological Changes at DES Edges in Pigs in Vivo

Microthrombus formation

BMS

PES

Infiltration of inflammatory cells

BMS

PES

(Shiroto, Shimokawa, et al. JACC. 2009;54:2321-2329.)
Up-regulation of Rho-kinase at DES Edges in Pigs in Vivo

Rho-kinase expression

Rho-kinase activity

(Shiroto, Shimokawa, et al. JACC. 2009;54:2321-2329.)
Coronary Spasm induced at a DES Edge in a Patient with CAD

Control

ACh

Fasudil + ACh

NTG

Inhibitory Effects of Long-acting Nifedipine on DES-induced Coronary Changes

Long-acting nifedipine

Inflammation

↑ Rho-kinase express.

↑ Rho-kinase activity

Coronary spasm

(*Shiroto, Shimokawa, et al. JACC. 2009;54:2321-9.)

(Tsuburaya, Shimokawa, et al. EHJ. 2012;33:791-799.)
Japanese Coronary Spasm Association

Foundation: 2006
Participating: 81 hospitals
Secretariat: Tohoku Univ.
Meeting: twice per year
International Collaboration Study on VSA

UK
Prof. Juan Carlos Kaski
(St. George’s University)

Germany
Dr. Peter Ong
Prof. Udo Sechtem (Robert-Bosch-Hospital)

Korea
Prof. Sang Hong Baek
(The Catholic University of Korea)

Italy
Prof. Filippo Crea
(Catholic University of the Sacred Heart)
Prof. Paolo G. Camici
(Vita-Salute San Raffaele University)
Prof. Attilio Maseri
(Heart Care Foundation)

Australia
Prof. John Beltrame
(University of Adelaide)