用することが基本であるため，いかに総虚血時間を2時間以内にするかが課題である．重症例（Killip3，4型）や発症から3時間以上経過した例では，PCIが優先される．

プレホスピタルにおける12誘導によるSTEMIあるいは非ST上昇MI（non-ST elevation MI，NSTEMI）の診断ができれば，今後の課題として早期の再灌流を得るため，抗血栓薬（抗血小板薬，抗トロンビン薬，低分子ヘパリンなど）のプレホスピタルから救急室間での使用がある．我が国では，これらの抗血栓薬の多くが急性冠症候群への認可を得ていないため，今後の適用拡大が望まれている．

5. 救急部での今後の課題

ACSのうちSTEMIについては早期再灌流療法が勧告されているため，12誘導心電図診断により比較的診断は容易である（図4）．MIの診断基準が変更され，従来の診断基準に用いられてきた心筋逸脱酵素であるCPK（creatine phosphokinase）やMB-CPKによる診断ではなく，心筋壊死に特異的な心筋マーカーであるトロポニンの適用が勧告されている[6]．また，ST上昇発作でも早期再灌流により梗塞に至らないものをaborted myocardial infarctionとして分類されている．またNSTEMIや不安定狭心症の診断は，心電図や心筋マーカー値が正常な場合には困難な場合が多く，米国では胸痛ユニットなどで心電図モニターをしながら心筋マーカー再測定で経過観察を行うことが勧告されている．経過観察で異常所見がない場合には，ACS軽症例を正常例と選別し無用な入院を避けるため，運動負荷試験や冠動脈CT（computed tomography），負荷心エコー図，負荷SPECT（single photon emission computed tomography）などの非侵襲的検査の有用性が報告されている．

ACSが確定的である場合には，トロポニン測定も加味して重症度を評価し，ハイリスク例は早期入院後に早期侵襲的治療が勧告されている．重症度判定として，TIMI（Thrombolysis in Myocardial Infarction）リスクスコア[7]やGRACE（Global Registry of Acute Coronary Events）スコア[8]が提唱されている．前者は，65歳以上，冠危険因子3項目以上，50％以上の冠動脈狭窄の既往，ST変化，24時間以内の症状，7日以内のアスピリン使用，心筋マーカー陽性の1点ずつ7項目からなり，点数が増えるほど14日以内の心事故発生率が高いとされる．後者は，年齢，心不全や心筋梗塞既往，心拍数，収縮期血圧，ST低下，クレアチニン値，心筋マーカー，PCI未施行に重み点数をつけ，評価を行うもので，6カ月以内の心事故発生を予測するものである．これらのリスク評価をプレホスピタルで実施するか今後の検討課題である．

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日本における心臓突然死の現状

野々木 宏*

abstract

救急隊により応急処置を受けた病院外での突然の心停止について全国登録が開始され，年間で10万人以上が院外心停止を生じ，その救命率はなお低いことが明らかとなっている．これらは突然死であり，実態が明らかとされず，対策も十分とはいえない状況である．突然死の定義で使用されてきたのはICD-9での「発症から24時間以内の予期せぬ内因性死亡」である．この定義を用いたこれまでの疫学調査あるいは病理解剖による調査から，突然死の原因は心臓性が約6割，大血管や脳血管疾患を含めた循環器疾患は約8割であった．病理解剖を実施した報告から，最大原因は急性心筋梗塞であり，突然死例の約1/3であった．全国的な急性心筋梗塞の発症登録から，院外心停止例を含めると死亡率は20%以上と高率であり，救命対策を検討するうえで，原因不明の突然死に対して病理解剖や登録が可能となるシステムが必要と考えられる点である．

I 突然死の定義と原因疾患

突然死の定義は種々あり，その原因あるいは発生頻度を検討する場合には，用いられている定義に注意を要する．WHOの国際疾病分類(ICD)-9では，「発症から24時間以内の予期せぬ内因性死亡」との定義が用いられていた．わが国では，これまでこの定義に基づいて死亡診断を行っていた．この定義を用いたわが国の地域疫学調査9報告[1]では，突然の自然死は約2万9千例で，10万人あたり80例となり，そのうち心臓・大血管系疾患の割合は約6割，脳血管疾患まで含めると約8割が循環器疾患である（図1）．ただし，そのうち急性心筋梗塞の占める割合は不明である．ICD-10からは，時間の規定がなくなったため，今後同様の検討をする場合には留意が必要である．

病理解剖での急性心筋梗塞の診断には，冠動脈血栓像とプラーク破綻像の証明，またnitro-blue-tetrazolium染色による梗塞像の証明が有用である．この方法を用いて，東海林らは心停止により搬入され死亡した成人症例の病理解剖により原因を検討した[2]．内因性心停止593例の34%が急性心筋梗塞で

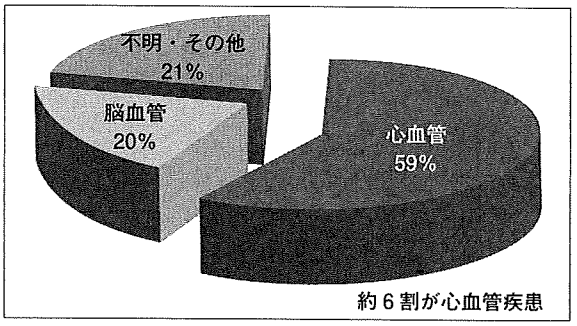

図1 突然死の疫学調査 死因の内訳
24時間以内の急死，自然死（国際疾病分類ICD-9）
全国9地域の死亡診断書報告 N=28,923
10万人あたり80件（心血管45件）
年間約10万件／全国

〔参考文献1)より改変〕

* 国立循環器病センター心臓血管内科部長

最多であり，その他の心疾患（陳旧性心筋梗塞，冠攣縮性狭心症，致死性不整脈，心筋症，弁膜症，先天性心疾患，心タンポナーデが含まれる）が18%，大動脈瘤破裂と急性大動脈解離などの大動脈病変12%，くも膜下出血14%，その他（急性呼吸不全，肺塞栓，アルコール中毒，消化管出血，脳神経筋疾患，癌末期など）22%であった（図2）．その結果，心臓性が52%であり，また脳血管と大血管疾患を含めた循環器疾患が78%と高率であることが判明した．疫学データと酷似した結果である．これで明らかとなったことは，搬入時に急性心不全による心停止と判断された症例のうち半数が急性心筋梗塞であった点である．また，その他の心疾患に心筋症や不整脈が含まれている．近年，若年者のスポーツ時の急死例や中年男性での急死例が注目されており[3]，肥大型心筋症や先天性心疾患，QT延長症候群，Brugada 症候群，心臓震盪などの原因が考えられる[4]．原因不明の突然死に対して病理解剖や登録が可能となるシステムが必要と考えられる点である．

院外心停止の最大原因である急性心筋梗塞の致命率について厚生労働省循環器病委託研究班による調査が実施された．23地域の全病院（約1,300万人，954病院）に対して1カ月間の急性心筋梗塞と院外心停止例を調査した[5]．心筋梗塞540症例，内因性心停止例230例の報告があり，院外心停止の1/3を急性心筋梗塞とすると10万人あたり年間57例の急性心筋梗塞発症となった．院内死亡率は10%で，院外心停止を加味すると死亡率は21%であった．急性心筋梗塞の予後をさらに改善するには，プレホスピタルの救急システムへの対策が必要である．

II ウツタイン様式による院外心停止登録

近年では院外心停止に対する救命対策のため，臨床疫学の立場から院外心停止が定義されている．その様式は最初の会議の開催地の名前にちなんでウツタイン様式とよばれている[6]．ウツタイン様式による心停止とは「脈拍が触知できない，反応がない，無呼吸で確認される心臓の機械的な活動の停止」と定義され，心原性と推測できるものと非心原性に分けられ，原因が不明な場合には除外診断に基づき心

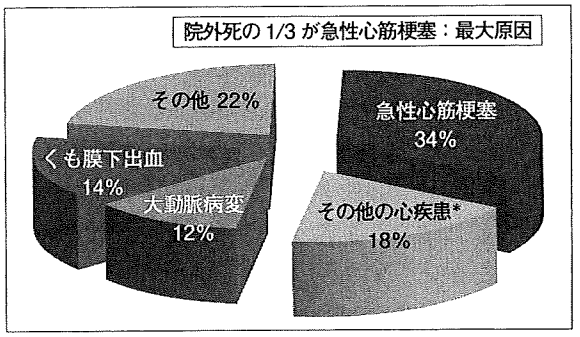

図2　内因性院外死の原因疾患：病理解剖
外傷を除いた院外での突然死は8割が循環器疾患
＊危険な不整脈，その他の虚血性心疾患，心筋症など
〔参考文献2）より改変〕

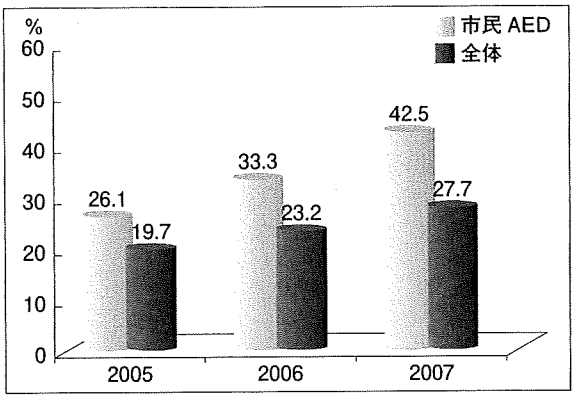

図3　心原性で目撃のある心室細動１カ月生存
〔総務省消防庁による全国院外心停止登録ウツタイン様式オンライン入力データより〕

原性と扱われている．非心原性には，乳児突然死症候群，急性薬物中毒，自殺，溺死，出血，脳血管障害（くも膜下出血を含む），外傷が分類される．ウツタイン様式では，心停止が予期せぬか否かは問題ではなく，また原因が不明の場合は心原性と分類されている．その点が限界ではあるが，この様式では救命の対象となることが重要であり，国際的な比較や地域比較が可能となり，救急体制の対策も検討可能となることが特徴である．

総務省による全国ウツタイン様式による院外心停止データ登録が平成17年から開始されており，わが国の心原性院外心停止例での心室細動率は約20%と低率であることが判明した．院外心停止の救命率が高い米国・シアトル市では，目撃のある心原性心停止例での初期調律は心室細動が最多であり，45%と高率である[7]．この原因は，心停止から心電図記録までの時間が3分以内の場合には50～60%と高率に心

室細動が観察されるという東京都の長尾らの報告[8]から考えると，記録までの時間が長いこと，市民のCPR率が低いことが大きな因子であると考えられる．心原性心停止で目撃がある心室細動例の救命率は，図3のように徐々に改善し，特に市民が自動体外式除細動器（AED）を用いた場合には救命率が40%を超えるようになった．市民によるCPR実施率とAED適用率の向上がさらに望まれる．

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Usefulness of Varying ST changes in transmitted 12-lead electrocardiogram from a moving ambulance with the Mobile Telemedicine System in a patient with acute myocardial infarction

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Abstract : Mobile telemedicine is a wireless communicating system between doctors at a hospital and Emergency Medical Technicians on an ambulance, and enables us to transmit a patient's living body information, such as 12-Lead electrocardiogram (ECG), blood pressure, oxygen saturation, breathing rate, and so on to a hospital in real time during an ambulance ride by using mounted cameras and monitoring systems. The patient was a 71-year-old man having severe chest pain. His initial ECG transmitted from the ambulance showed ST elevation in the II III aVF and precardial leads indicating ST elevated myocardial infarction. Though, his final ECG on arrival did not show any ST elevations but the chest pain continued. We therefore performed immediate coronary arteriography and carried out interventions to segment 6 and 13. Using 12-Lead ECG before admission, we were able to diagnose ST elevation acute coronary syndrome during the transfer and useful for preparation for acceptance. This may be the first report of live-ECGs showing the usefulness of varying ST changes transmitted from a moving ambulance.

Key Words : Mobile telemedicine, 12-Lead electrocardiogram, acute myocardial infarction

1. Introduction

In the past, there used to be a variety of monitoring systems to observe patients during ambulance transfers; however, the information was sometimes not precise enough to assess cardiac patients[1)2)]. Recently, the quality of transmitted images has remarkably improved.

Mobile telemedicine is a wireless communicating system introduced by the National Cardiovascular Center, Japan [3)-5)]. The system provides a wireless link between physicians at a hospital and paramedics on an ambulance and enables us to transmit a patient's vital signs information, such as 12 lead electrocardiogram (ECG), blood pressure, oxygen saturation, breathing rate, and so on to a hospital in real time during an ambulance ride by using mounted cameras and monitoring systems.

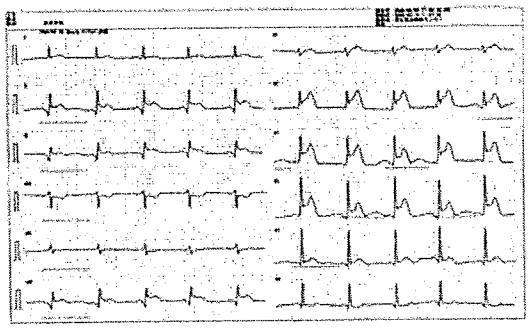
2. Case

The attached figures show live ECGs taken on a moving ambulance and transmitted to our emergency and critical care center via the Mobile telemedicine system. The patient was a 71-year-old man, with a very long history of irregular chest pain. One day he had a severe chest pain while walking and called for an ambulance.

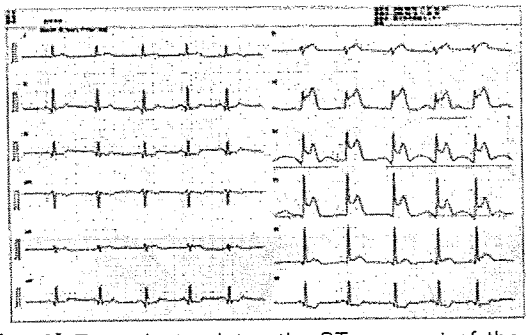
His initial ECG showing ST elevation in the II III aVF and precardial leads indicating ST elevated myocardial infarction [Fig.1] .

On his way to our hospital, his ST segment showed some fluctuations [Fig.2-4] . His final ECG on arrival did not show any ST elevations but the chest pain continued [Fig.5] .

We therefore performed emergency coronary angiography and carried out interventions to left anterior descending artery and left circumflex artery using coronary stenting right after thrombo absorbsion [Fig.6] . Max Creatinine kinase was elevated to 1394 IU/L. ECG on chronic state showed no Q waves.



[Fig.1] The patient's initial ECG, showing ST elevation in the II III aVF and precardial leads.

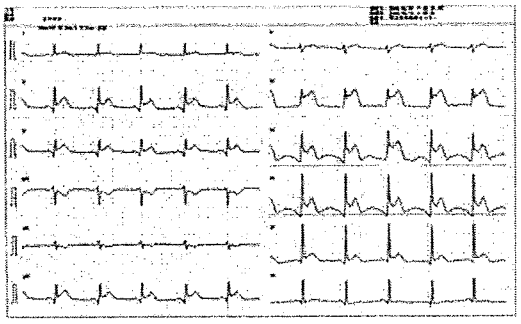


[Fig.2] Two minutes later, the ST segment of the II III aVF leads has returned to the baseline.

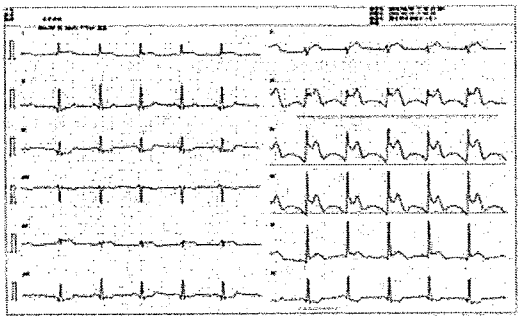
3. Discusion

Although there had been ST elevation during the transfer in real-time fashion, we didn't see any ST elevation at his arrival. Before admission, we prepared the emergency catheterization due to the information of ST elevation ECG. As thrombus and

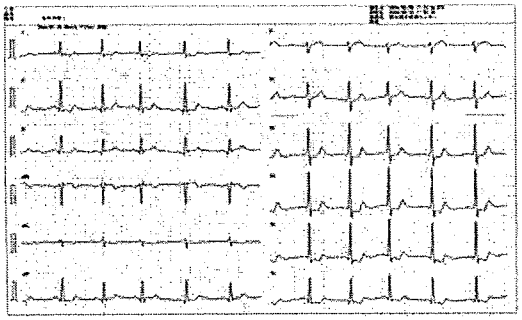
subtotal stenosis were seen in segment 6 and 13, we performed PCI successfully.
We are able to diagnose acute myocardial infarction during the transfer and useful for preparation for acceptance.
Only 12-lead ECG detects the precardial leads' ST elevation and its change.
At the arrival, ST returned to the baseline: it would have been difficult to diagnose ST-elevation acute coronary syndrome with high-risk by only seeing the last ECG. After admission without prehospital continuous 12-lead ECG, this patient will be stratified into no ST change with low-risk and without emergency coronary angiography. These observations will show the new concept for the risk stratification for ACS, because standard stratification is performed using ECG changes in emergency department or after admission.
Thus, the continuous 12-lead ECG transmission using the mobile telemedicine is useful for the management of acute coronary syndrome in the emergency system.
AHA/ACC guidelines recommend routine use of 12-lead ECG and advance notification for patients with acute coronary syndrome [6].



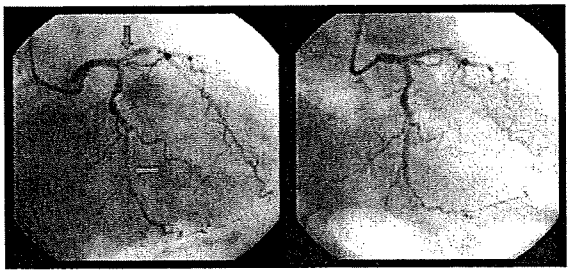
【Fig.3】 Three minutes later, the ST segment of the II III aVF leads has re-elevated.



【Fig.4】 Four minutes later, the ST segment of the II III aVF leads has returned once more to the baseline.



【Fig.5】 Seven minutes later, the ST segment of the precardial leads has returned to the baseline.



【Fig.6】 Emergency coronary angiography was performed (left). As thrombus and severe stenosis were seen in segment 6 and 13 (arrows), we performed intervention using coronary stenting to those sites (right).

4. Conclusion

This may be the first report of live-ECGs showing varying ST changes transmitted from a moving ambulance. Mobile doctor car and helicopter will surely play a significant role as virtual-doctor mobile in future.

5. Sources of Funding

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PRE-CLINICAL RESEARCH

Role of Rho-Kinase in the Pathogenesis of Coronary Hyperconstricting Responses Induced by Drug-Eluting Stents in Pigs In Vivo

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Objectives This study examined whether the Rho-kinase pathway is involved in the pathogenesis of coronary hyperconstricting responses induced by drug-eluting stents (DES) in pigs in vivo.

Background Recent studies showed that coronary vasoconstricting responses are enhanced at the edge of coronary segments implanted with DES compared with bare-metal stents (BMS) in humans. We have previously shown that the activated Rho-kinase pathway plays a central role in the molecular mechanism of coronary vasospasm in animals and humans.

Methods Human coronary artery smooth muscle cells (hCASMCs) were coincubated with various concentrations of paclitaxel (10^{-9} to 10^{-6} mol/l, corresponding levels reported in DES-implanted arterial tissue) for 24 h. A paclitaxel-eluting stent (PES), sirolimus-eluting stent (SES), and BMS were randomly implanted in the left coronary arteries in pigs for 4 weeks.

Results In hCASMCs, paclitaxel significantly enhanced Rho-kinase expression and activity. In a porcine model, coronary vasoconstricting responses to serotonin (10 and 100 μg/kg intracoronary administration) were significantly enhanced at the PES site compared with the BMS site (45 ± 4% vs. 30 ± 3%; $p < 0.01$; $n = 12$ each), and were abolished by hydroxyfasudil (90 and 300 μg/kg intracoronary administration), a selective Rho-kinase inhibitor. The PES enhanced inflammatory responses and microthrombus formation at the stent edge, where immunoreactivities for Rho-kinase expression and activity were increased. In organ chamber experiments, serotonin-induced contractions were significantly enhanced in rings from the PES edge site compared with the BMS edge site. The SES also caused similar coronary hyperconstricting responses to serotonin in vivo.

Conclusions These results suggest that the Rho-kinase pathway plays an important role in the pathogenesis of DES-induced coronary hyperconstricting responses. (J Am Coll Cardiol 2009;54:2321–9) © 2009 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have dramatically reduced the rate of restenosis after percutaneous coronary intervention, revolutionizing interventional cardiology (1,2). However, DES have also been shown not to improve patient survival compared with bare-metal stents (BMS) (3). Indeed, recent studies suggest that the early benefits of DES are offset by an increased risk of late stent thrombosis, a potentially fatal complication (4). The DES-induced impairment of coronary vasomotion is another concern regarding the long-term safety of DES (5–10). Enhanced vasoconstriction in response to acetylcholine (5–8) or exercise (9) was shown in the coronary segments adjacent to DES, but not in those adjacent to BMS, and even death was reported among patients with severe coronary vasospasm after DES implantation (10). However, the underlying molecular mechanism for the DES-induced coronary hyperconstriction remains to be elucidated.

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Rho-kinase is one of the down-stream effectors of the small GTP-binding protein Rho and consists of 2 isoforms, Rho-kinase beta (ROCK1) and Rho-kinase alpha (ROCK2)

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CAG = coronary angiography
DES = drug-eluting stent(s)
ERM = ezrin/radixin/moesin
hCASMC = human coronary artery smooth muscle cell
IC = intracoronary administration
MYPT1 = myosin phosphatase target subunit 1
PES = paclitaxel-eluting stent(s)
RNA = ribonucleic acid
ROCK1 = Rho-kinase beta
ROCK2 = Rho-kinase alpha
SES = sirolimus-eluting stent(s)
VSMC = vascular smooth muscle cell

(11,12). We have previously shown that activation of Rho-kinase plays a central role in the molecular mechanism of coronary vasospasm through vascular smooth muscle cell (VSMC) hypercontraction and down-regulation of endothelial nitric oxide synthase in endothelial cells (13–21).

In the present study, we thus examined whether the Rho-kinase pathway is also involved in the pathogenesis of DES-induced coronary hyperconstriction.

Methods

All procedures were performed according to the protocols approved by the Institutional Committee for Use and Care of Laboratory Animals of Tohoku University (20MdA-47).

Cell culture. Human coronary artery smooth muscle cells (hCASMCs) (Lonza, Walkersville, Maryland; passages 4 through 10) were seeded in a growth medium (SmGM-2 Bullet Kit, Lonza) for 24 h and then growth-arrested in a Dulbecco modified Eagle medium (Sigma Aldrich, St. Louis, Missouri) supplemented with 0.1% bovine serum albumin, 100 IU/ml penicillin, and 100 μg/ml streptomycin for 24 h, and used for the experiments.

Real-time polymerase chain reaction for ROCK1 and ROCK2 messenger ribonucleic acid (RNA) expression. The hCASMCs (1×10^5) were coincubated with 10^{-9} to 10^{-6} mol/l paclitaxel for 24 h (n = 9) (22). Cells were lysed, and total RNA was extracted using the RNeasy Micro Kit (Qiagen, Hilden, Germany). Total RNA (600 ng) was reverse-transcribed using a QuantiTect Reverse Transcription Kit (Qiagen). Real-time polymerase chain reaction was performed using the Real-Time Detection System (Bio-Rad Laboratories, Hercules, Califomia). Sequences of the primers were (forward, reverse) 5′-CTGCAACTGGAACTCAACCAAGAA-3′, 5′-TTAGCACGCAATTGCTCAATATCAC-3′ for ROCK1, 5′-TGCTTTAAATTTGCTGGCTACCCTA-3′, 5′-CACACAGCTGCATGTCTGAGGA-3′ for ROCK2, and 5′-TGGCACCCAGCACAATGAA-3′, 5′-CTAAGTC-ATAGTCCGCCTAGAAGCA-3′ for beta-actin, all of which were designed by the Perfect Real Time Support System (Takara Bio Inc., Shiga, Japan). The beta-actin was used as an internal control; SYBR Premix Ex Taq I and II (Takara Bio Inc.) were used for the detection of ROCK1 and ROCK2 cDNA, respectively.

Western blotting for Rho-kinase activity. The hCASMCs (1×10^5) were coincubated with 10^{-8} mol/l paclitaxel, a comparable concentration in the DES-implanted coronary arteries in pigs (n = 6) for 24 h (23). Western blot analysis was performed for Rho-kinase activity, which was expressed as the extent of phosphorylated ezrin/radixin/moesin (ERM) family, substrates of Rho-kinase, compared with that of total ERM, as previously reported (24).

In vivo study. Domestic male pigs (2 to 3 months old and weighing 20 to 30 kg) were pre-treated orally with aspirin (300 mg/day) and clopidogrel (150 mg/day) for 2 days before stent implantation. After sedation with ketamine hydrochloride (15 mg/kg intramuscularly) and anesthesia with inhaled 2% to 5% sevoflurane and heparinization (5,000 U intravenously), we randomly implanted a paclitaxel-eluting stent (PES) (Taxus Express 2, Boston Scientific, Natick, Massachusetts) and a BMS (Express 2, Boston Scientific) in the left anterior descending and circumflex coronary arteries in the same pig (n = 8). In an additional experiment, another set of comparisons between a sirolimus-eluting stent (SES) (Cypher, Johnson & Johnson, New Brunswick, New Jersey) and a BMS (Velocity, Johnson & Johnson) was performed (n = 6). We defined the control sites as those at 10 to 20 mm proximal and distal to the stent edges, and calculated overstretch ratio of stent diameter by dividing a control vessel diameter (25). The antiplatelet therapy with aspirin and clopidogrel was continued after the stent implantation for 4 weeks.

Four weeks after the stent implantation, we performed coronary angiography (CAG) to examine coronary vasomotion (26). Briefly, after the baseline CAG, we examined coronary responses to serotonin (10 and 100 μg/kg intracoronary administration [IC]) and then to bradykinin (0.1 μg/kg IC). We re-examined the responses to serotonin after hydroxyfasudil (30 and 100 μg/kg/min IC infusion for 3 min), a specific Rho-kinase inhibitor (11), then those to bradykinin after intracoronary infusion of N^G-monomethyl-L-arginine (1 mg/kg for 10 min) (27), and finally those to nitroglycerin (10 μg/kg IC). We performed each protocol at a 30-min interval (26). Quantitative CAG (DFP-2000A, Toshiba Medical, Tokyo, Japan) was performed in a blind manner as previously reported (13,15). For clarity of the data, the mean value of the vasomotor responses of the proximal and the distal stent edges is presented. In the PES protocol, 2 animals were excluded because of >50% coronary restenosis (n = 1) and severe infection (n = 1).

Histological analysis. After the CAG study, animals were euthanized with a lethal dose of sodium pentobarbital (40 mg/kg intravenously), and histological analysis was performed as previously reported (28). The extent of microthrombus formation was assessed semiquantitatively by using the following scale: 0 = none; 1 = minute thrombus peristent; 2 = thrombus <50% circular area of peristent; and 3 = thrombus all around stent strut. The extent of inflammatory responses, including peristent leukocyte and macrophage infiltration and adventitial inflammatory changes, was also assessed by using the following scale: 0 = none; 1 = fewer than 5 inflammatory cells; 2 = fewer than 20 inflammatory cells; and 3 = more than 20 inflammatory cells.

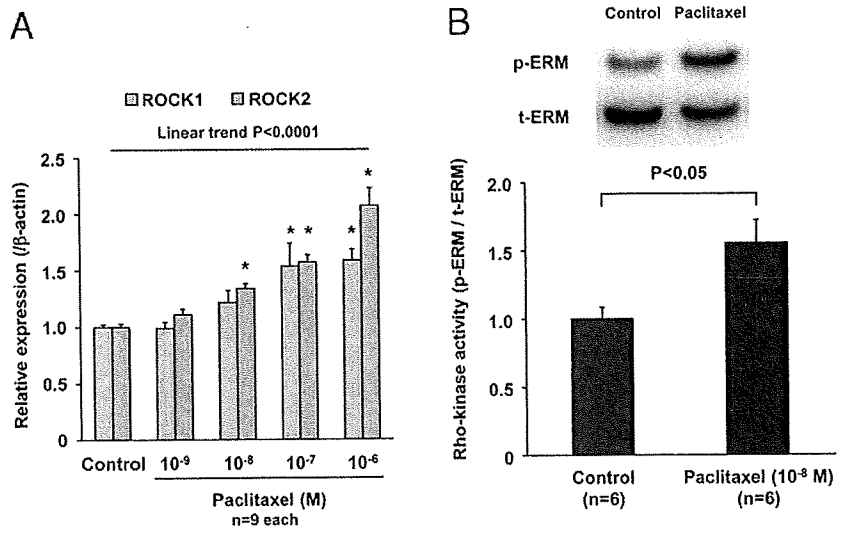

Figure 1 **Paclitaxel Increases Rho-Kinase Expression and Activity In Vitro**

(A) Paclitaxel significantly enhanced messenger ribonucleic acid expression of Rho-kinase beta (ROCK1) and Rho-kinase alpha (ROCK2) in a concentration-dependent manner. *p < 0.05 versus control. **(B)** Rho-kinase activity, as evaluated by the extent of ezrin/radixin/moesin phosphorylation, was significantly increased after 24-h coincubation with paclitaxel (10^{-8} mol/l). p-ERM = phosphorylated ezrin/radixin/moesin; t-ERM = total ezrin/radixin/moesin.

Immunohistological analysis. Immunohistochemical staining was performed using mouse antihuman ROCK1 antibody (1:50, BD Biosciences, San Jose, California), mouse antihuman ROCK2 antibody (1:50, BD Biosciences), and rabbit antihuman phosphorylated myosin phosphatase target subunit 1 (phospho-MYPT1, Thr696) (1:50, Upstate, Billerica, Massachusetts), substrates of Rho-kinase (29). Nonimmune mouse or rabbit immunoglobulin G was used as negative control. We semiquantitatively assessed the extent of ROCK1, ROCK2, and phosphorylated MYPT1 using the following scale: 0 = none; 1 = slight; 2 = moderate; and 3 = high (30).

Organ chamber experiments. Organ chamber experiments were performed (n = 8) at 4 weeks after the stent implantation (15,26). Briefly, the coronary segments just adjacent to the proximal and distal edges of the stent (4-mm-long rings) were removed by gentle rubbing of the luminal surface with a cotton swab. The coronary segment at 20 mm distal to the stent edge was used as a control. The contractions to serotonin (10^{-9} to 3×10^{-6} mol/l) were examined and were expressed as a percentage to the average value of the 3-time pre-contractions to 62 mmol/l KCl (15,26).

Statistical analysis. All results are expressed as mean ± SEM. The results of reverse-transcriptase polymerase chain reaction were analyzed by 1-way analysis of variance followed by the Dunnett test, and the dose-dependent linear trend was also assessed. The results of Western blotting and angiographical data were analyzed by unpaired Student *t* test. The results of organ chamber experiments were analyzed by 2-way analysis of variance followed by a Bonferroni test. The results of histological studies and immunohistological studies were analyzed by Mann-Whitney *U* test. A value of $p < 0.05$ was considered to be statistically significant.

Results

Paclitaxel increases Rho-kinase expression and activity in vitro. In cultured hCASMCs, paclitaxel (10^{-9} to 10^{-6} mol/l for 24 h) increased messenger RNA expression of both ROCK1 and ROCK2 in a concentration-dependent manner (both $p < 0.0001$ for linear trend) (Fig. 1A). Paclitaxel (10^{-8} mol/l for 24 h) also significantly increased the extent of ERM phosphorylation, a marker of Rho-kinase activity (Fig. 1B).

PES induces hydroxyfasudil-sensitive coronary hyperconstricting responses in vivo. In the stent implantation procedure, there was no significant difference in the procedures between the BMS and the PES sites (Table 1). Four weeks after the stent implantation, intracoronary serotonin

Table 1 **Procedural and Angiographic Findings, Comparison Between BMS and PES**

	BMS	PES	p Value
Control vessel diameter (mm)	2.55 ± 0.08	2.48 ± 0.07	0.54
Stent diameter (mm)	2.72 ± 0.09	2.58 ± 0.08	0.26
Stent length (mm)	16.0 ± 0.0	16.0 ± 0.0	N/A
Overstretch ratio	1.06 ± 0.04	1.04 ± 0.4	0.73
Maximum inflation pressure (atm)	10.7 ± 1.28	8.7 ± 0.42	0.19

Values are expressed as mean ± SEM (n = 6 each). Stent diameter was calculated by averaging the diameters at the proximal edge, mid portion, and distal edge of the stented coronary artery. Overstretch ratio is the stent diameter divided by the control vessel diameter. Nominal pressure was 9 atm for both BMS (Express 2, Boston Scientific, Natick, Massachusetts) and PES.
BMS = bare-metal stent(s); PES = paclitaxel-eluting stent(s); N/A = not available.

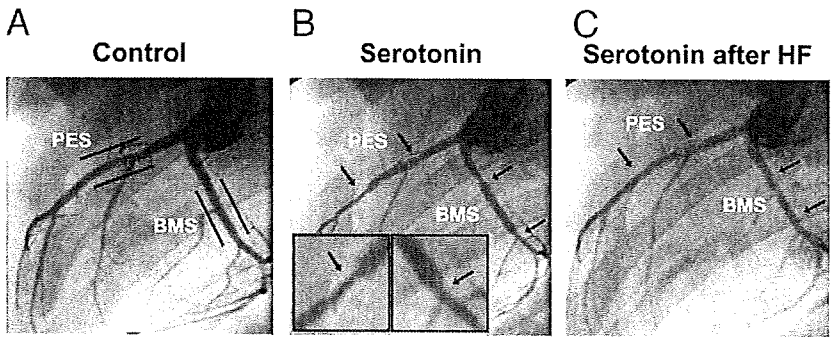

Figure 2 PES Enhances Coronary Vasoconstricting Responses in Pigs In Vivo

Representative left coronary angiograms under control condition **(A)**, after intracoronary serotonin (100 μg/kg intracoronary administration) without **(B)** and with **(C)** hydroxyfasudil (HF) (300 μg/kg intracoronary administration). The **red lines** indicate the site of paclitaxel-eluting stent (PES) implantation, and **blue lines** indicate the site of bare-metal stent (BMS) implantation. **Red arrows** indicate the proximal and distal edges of PES, and **blue arrows** indicate those of BMS. Magnified images of the distal edge of PES and BMS are shown in the **boxes (B)**.

caused hyperconstriction at the proximal and distal edge segments of the PES site as compared with the BMS site, which was abolished by intracoronary pre-treatment with hydroxyfasudil, a selective Rho-kinase inhibitor (Fig. 2). Quantitative analysis showed that the responses of the stent edges were significantly enhanced at the PES site compared with the BMS site and were abolished by hydroxyfasudil (Fig. 3A). In contrast, the vasoconstricting responses to serotonin were comparable in the control (nonstented) sites between the BMS and the PES sites (Fig. 3B).

Coronary vasodilating responses to bradykinin did not differ significantly between the PES and the BMS sites (PES 1.6 ± 1.1%, BMS 1.4 ± 0.6% from baseline) and were equally impaired as compared with the control sites (PES 5.8 ± 1.3%, BMS 6.0 ± 0.9%, both $p < 0.01$). Moreover, responses to bradykinin with and without pre-treatment of N^G-monomethyl-L-arginine did not differ significantly between the BMS and the PES sites. Coronary vasodilating responses to nitroglycerin were comparable between the 2 stent sites (PES 3.5 ± 1.4%, BMS 3.9 ±

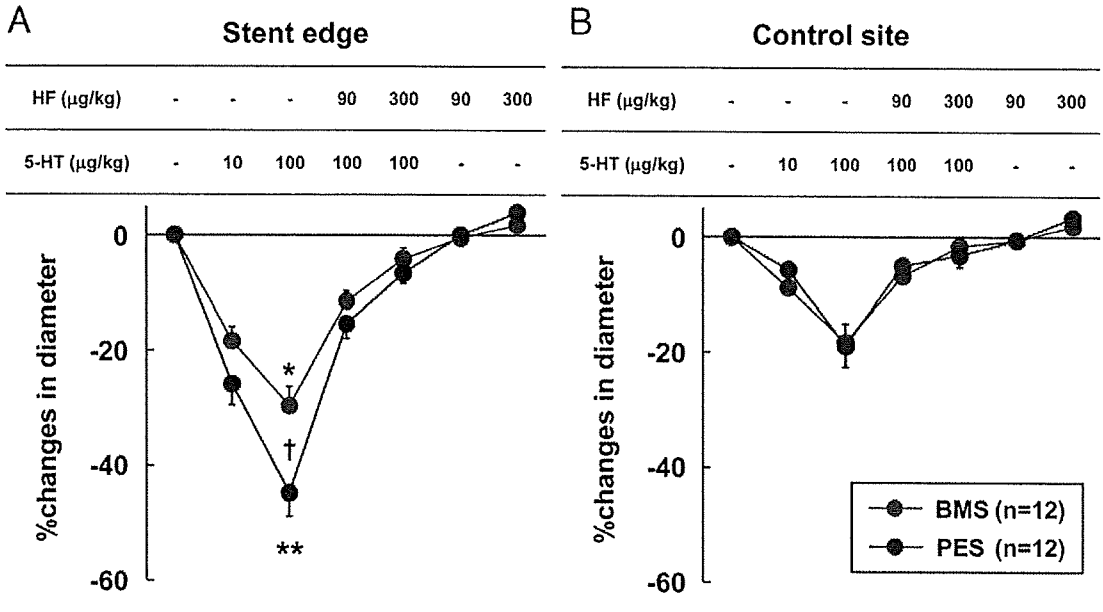

Figure 3 PES Enhances Coronary Vasoconstricting Responses in Pigs In Vivo

Coronary vasoconstricting responses to intracoronary serotonin (5-HT) before and after the pre-treatment with HF in the stent edges **(A)** and the control sites **(B)**. The vasoconstricting responses are expressed as percent changes in diameter from the level with nitroglycerin (10 μg/kg intracoronary administration). Results are expressed as mean ± SEM. *$p < 0.05$ versus control site. †$p < 0.01$ versus BMS. **$p < 0.01$ versus control site. Abbreviations as in Figure 2.

1.5%) with no significant difference with the control sites (PES 9.0 ± 2.0%, BMS 6.9 ± 1.2%).

PES enhances coronary microthrombus formation and inflammatory responses in vivo. Histological analysis showed that neointimal formation of the coronary artery was significantly suppressed in the PES site compared with the BMS site (Figs. 4A to 4C). However, the extent of peristent microthrombus formation (Figs. 4D to 4F) and that of inflammatory responses (Figs. 4G to 4I) were significantly enhanced at the PES site compared with the BMS site.

PES enhances coronary Rho-kinase expression and Rho-kinase activity. Immunohistological analysis showed that ROCK1 (Figs. 5A to 5D), ROCK2 (Figs. 5E to 5H), and phospho-MYPT1 (Figs. 5I to 5L) were highly expressed in the PES as compared with the BMS site.

PES enhances contractions to serotonin of isolated coronary arteries. In organ chamber experiments, serotonin caused concentration-dependent contractions of coronary rings without endothelium. The extent of the contractions at the stent edge segments was significantly greater at the PES site compared with the BMS site (Fig. 6A). In contrast, the extent of the contractions at the control sites was comparable between the BMS and the PES sites (Fig. 6B).

SES induces coronary hyperconstricting responses similar to those of PES in vivo. In an additional experiment, we performed a similar in vivo protocol with SES to examine whether other DES also cause coronary hyperconstricting responses. The stent implantation procedures were comparable between the BMS (Velocity) and the SES sites (Table 2). Coronary hyperconstricting responses to serotonin were also noted at the proximal and distal edge segments of the SES site as compared with the BMS site, which was abolished by intracoronary pre-treatment with hydroxyfasudil (Figs. 7 and 8). The histological analysis showed the higher score of microthrombus formation (SES 2.33 ± 0.33, BMS 0.75 ± 0.28) and of inflammatory responses (SES 5.00 ± 1.30, BMS 0.70 ± 0.12) in SES sites than in BMS sites (both $p < 0.01$).

Discussion

The major findings of this study were: 1) paclitaxel increased Rho-kinase expression and activity in hCASMCs

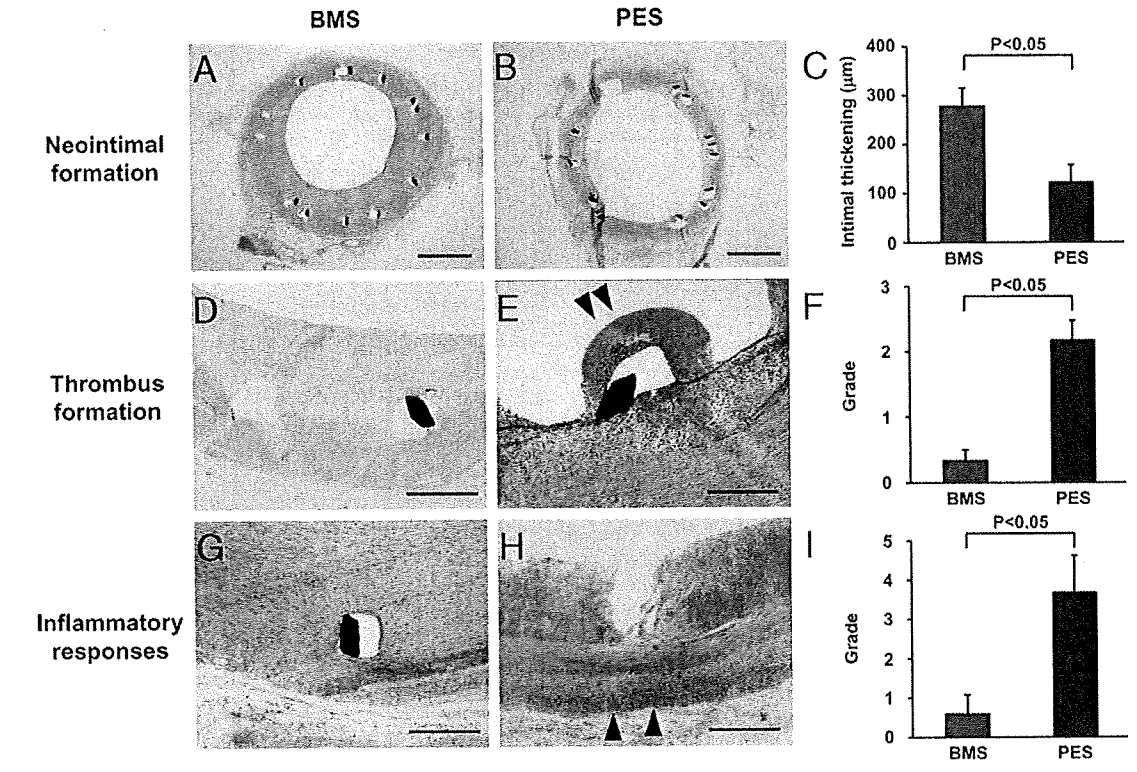

Figure 4 PES Enhances Coronary Microthrombus Formation and Inflammatory Responses in Pigs In Vivo

Representative photomicrographs of BMS-treated arteries **(A, D, G)** and PES-treated arteries **(B, E, H)**. Scale bars represent 1 mm **(A, B)** and 200 μm **(D, E, G, H)**, respectively. Semiquantitative analysis showed that although neointimal formation was significantly suppressed in the PES site **(C)**, peristent microthrombus formation **(arrowheads in E, panel F)** and inflammatory responses **(arrowheads in H, panel I)** were significantly enhanced at the PES site compared with the BMS site (n = 6 each). Abbreviations as in Figure 2.

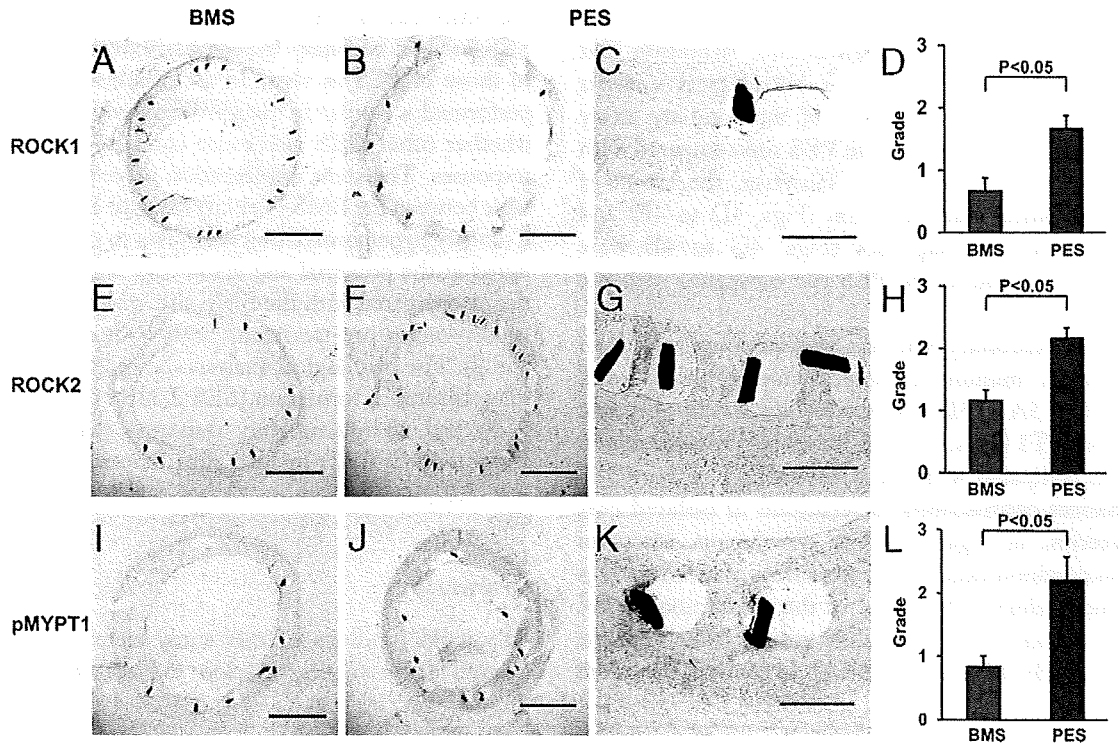

Figure 5 PES Enhances Coronary Rho-Kinase Expression and Activity in Pigs In Vivo

Representative immunostainings of BMS-treated arteries **(A, E, I)**, PES-treated arteries **(B, F, J)**, and magnified images of the PES-treated arteries **(C, G, K)**. Scale bars represent 1 mm **(A, B, E, F, I, J)** and 200 μm **(C, G, K)**, respectively. Semiquantitative analysis showed that ROCK1 **(D)**, ROCK2 **(H)**, and phosphorylated myosin phosphatase target subunit 1 (pMYPT1) **(L)** were expressed to a greater extent in the PES site compared with the BMS site (n = 6 each). Abbreviations as in Figures 1 and 2.

in vitro; 2) PES enhanced coronary vasoconstricting responses to serotonin as compared with BMS in pigs both in vivo and in vitro; 3) the hyperconstrictive responses were abolished by hydroxyfasudil, a selective Rho-kinase inhibitor; 4) those functional alterations of the coronary arteries were associated with enhanced microthrombus formation and inflammatory cell infiltration, where immunoreactivities for ROCK1, ROCK2,

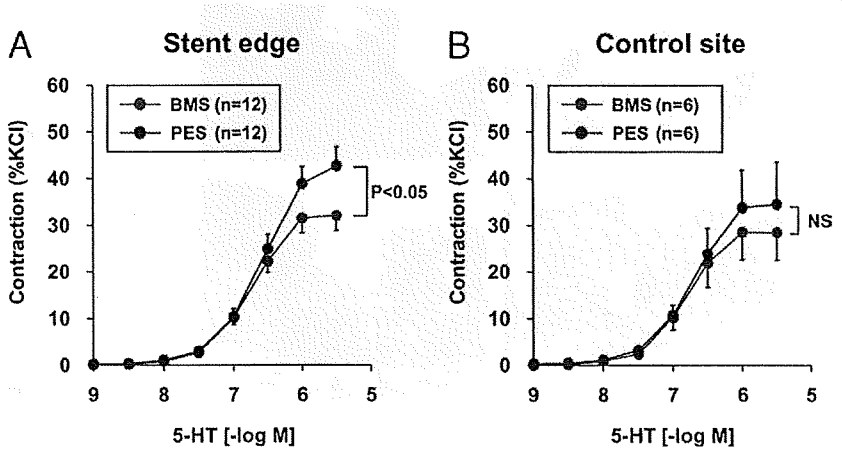

Figure 6 PES Causes Hypercontractions of Porcine Coronary Arteries In Vitro

Serotonin-induced contractions of isolated coronary rings without endothelium, when expressed as percent contraction to 62 mmol/l KCl, were significantly enhanced at the edge of the PES site compared with the BMS site **(A)**. In contrast, no difference was noted at the control site **(B)**. Results are expressed as mean ± SEM. NS = not significant; other abbreviations as in Figure 2.

Table 2 Procedural and Angiographic Findings, Comparison Between BMS and SES

	BMS	SES	p Value
Control vessel diameter (mm)	2.69 ± 0.12	2.58 ± 0.24	0.24
Stent diameter (mm)	2.62 ± 0.21	2.70 ± 0.18	0.49
Stent length (mm)	19.7 ± 1.1	19.2 ± 1.3	0.77
Overstretch ratio	0.97 ± 0.08	1.03 ± 0.07	0.21
Maximum inflation pressure (atm)	10.8 ± 1.1	12.0 ± 0.0	0.15

Values are expressed as mean ± SEM (n = 6 each). Stent diameter was calculated by averaging the diameters at the proximal edge, mid portion, and distal edge of the stented coronary artery. Overstretch ratio is the stent diameter divided by the control vessel diameter. Nominal pressure was 8 atm for bare-metal stents (BMS) (Velocity, Johnson & Johnson, New Brunswick, New Jersey) and 12 atm for sirolimus-eluting stents (SES), respectively.

and Rho-kinase activity (phospho-MYPT1) were increased; and 5) SES also caused similar coronary hyperconstricting responses in vivo as did PES.

DES and Rho-kinase. Paclitaxel, a tubulin polymerizing agent (31), is now widely used for the pharmacologic component of DES because it inhibits VSMC proliferation and migration in vitro (22) and suppresses neointimal thickening in animal models in vivo (32). The present result with hCASMCs provides new findings that paclitaxel significantly enhances ROCK1 and ROCK2 messenger RNA expression and Rho-kinase activity at its clinically relevant concentration. The previous studies showed that Rho guanine triphosphatases control organization of the actin cytoskeleton (33) and that Rho could be activated by paclitaxel, possibly through interfering with microtubules or actin polymerization (34), suggesting that paclitaxel may activate Rho-kinase in part by cytoskeletal reorganization.

Enhanced Rho-kinase activity plays a central role in the pathogenesis of coronary vasospasm (11). Intracoronary administration of fasudil or hydroxyfasudil (11), selective Rho-kinase inhibitors, markedly inhibits coronary vasospasm in porcine models with various inflammatory stimuli in vivo (13–18) and in humans (19,20). In the present porcine model, serotonin-induced coronary hyperconstriction was significantly enhanced at the PES as well as the SES site as compared with the BMS site. This finding was duplicated in organ chamber experiments using coronary rings without endothelium. Endothelial function was equally but modestly reduced at the PES and BMS sites in vivo. The previous study reported that paclitaxel did not impair endothelium nitric oxide synthase activity or nitric oxide release from coronary artery endothelial cells (35). Thus, in the present porcine model, the coronary hyperconstricting responses are mainly caused by VSMC hypercontraction through a Rho-kinase–mediated mechanism rather than endothelial dysfunction, a finding consistent with the previous studies (27,36).

Mechanisms of DES-induced Rho-kinase activation. A DES consists of 3 distinct components, including platform, drug, and polymer. In the present study, a possible adverse effect of platform can be excluded because we used the same platform and the procedural data were well comparable between the 2 stent sites. In the present study, neointimal formation was more suppressed and peristent microthrombus formation was more enhanced at the DES site. These histological findings reflect antiproliferative effects of paclitaxel on both VSMC and endothelial cells, leading to delayed re-endothelialization and resultant thrombus formation (37). Activated platelets may be involved in the thrombus formation through Rho/Rho-kinase pathways by releasing serotonin and platelet-derived growth factors (11) and interactions with thrombin (38).

The present study also showed that inflammatory responses were accelerated at the DES site. These changes could be caused by a local hypersensitivity reaction to the nonbioabsorbing polymer used in DES (37). Indeed, we have previously shown that the expression of Rho-kinase

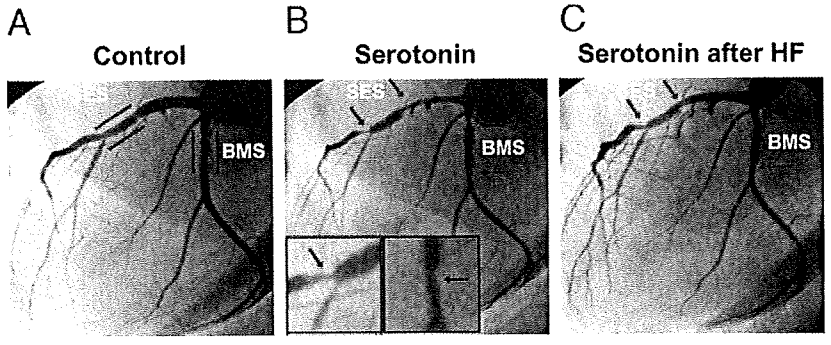

Figure 7 SES Enhances Coronary Vasoconstricting Responses in Pigs In Vivo

Representative left coronary angiograms under control condition **(A)**, after intracoronary serotonin (100 μg/kg intracoronary administration) **(B)**, and after intracoronary serotonin with HF (300 μg/kg intracoronary administration) **(C)**. **Pink lines** indicate the site of sirolimus-eluting stent (SES) implantation, and **blue lines** indicate the site of BMS implantation. **Pink arrows** indicate the proximal and distal edges of SES, and **blue arrows** indicate those of BMS. Magnified images of the distal edge of SES and BMS are shown in the **boxes (B)**. Abbreviations as in Figure 2.

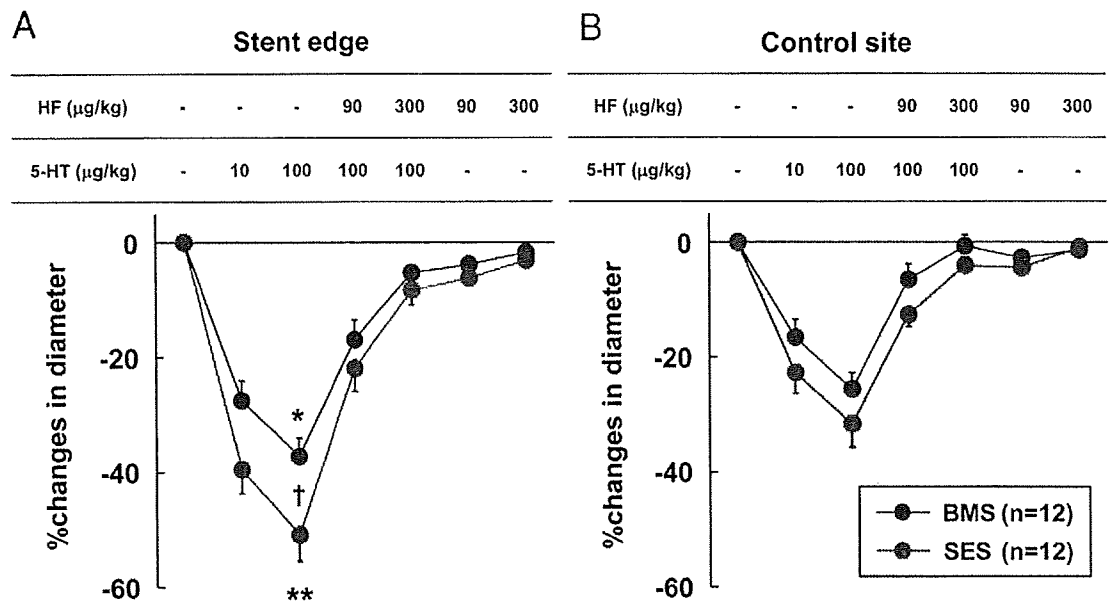

Figure 8 **SES Enhances Coronary Vasoconstricting Responses in Pigs In Vivo**

Coronary vasoconstricting responses to intracoronary serotonin (5-HT) before and after the pre-treatment with HF, a selective Rho-kinase inhibitor, in the stent edges **(A)** and the control sites **(B)**. The vasoconstricting responses are expressed as percent changes in diameter from the level with nitroglycerin (10 μg/kg intracoronary administration). Results are expressed as mean ± SEM. *$p < 0.05$ versus control site. †$p < 0.05$ versus BMS. **$p < 0.01$ versus control site. SES = sirolimus-eluting stents; other abbreviations as in Figure 2.

itself is accelerated by inflammatory stimuli, such as angiotensin II and interleukin-1 beta, through protein kinase C/nuclear factor kappa beta pathway (39). Thus, it is conceivable that DES-induced inflammatory responses also enhance Rho-kinase activity with a resultant coronary hyperconstricting response and thrombus formation. Indeed, in association with those changes, immunoreactivities of ROCK1, ROCK2, and phospho-MYPT1, a reliable marker of Rho-kinase activity (29), were enhanced.

Study limitations. First, we were unable to dissect the roles of ROCK1 and ROCK2. Recently, it was reported that ROCK isoforms may have different roles in neointimal formation (40). Furthermore, the localization of Rho-kinase activation and the role of other G-proteins (e.g., Rac-1) remain to be examined in future studies. Second, the present study was performed in normal juvenile pigs without preexisting atherosclerotic coronary lesions. This might explain, at least in part, the discrepancy between the present animal study (normal vascular function at the distal segment) and the previous clinical study (coronary hyperconstricting responses even at the distal segment of DES-implanted arteries) (6). Finally, in the present study, we used intracoronary serotonin administration to examine coronary vasomotor responses. In the clinical setting, acetylcholine is now frequently used to provoke coronary spasm. However, it has been reported that serotonin better mimics spontaneous vasospasm in humans than acetylcholine (41).

Conclusions

The present study suggests that the activated Rho-kinase pathway plays an important pathogenetic role in the DES-induced coronary hyperconstricting responses. Use of Rho-kinase inhibitors and other vasculoprotective agents (e.g., calcium-channel blockers and statins), in addition to developing innovative devices, may help to optimize the efficacy and safety of DES.

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Key Words: vasoconstriction ■ stents ■ smooth muscle ■ inflammation.

Circ J 2009; **73:** 767–769

Importance of Dual Induction Tests for Coronary Vasospasm and Ventricular Fibrillation in Patients Surviving Out-of-Hospital Cardiac Arrest

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Background: The pathogenesis of out-of-hospital cardiac arrest (OHCA) without organic heart disease has not been fully investigated.

Methods and Results: Induction tests were performed in 12 consecutive patients with OHCA for both coronary vasospasm with intracoronary acetylcholine and ventricular fibrillation (VF) with programmed stimulation at 1 month after the event. All patients were positive for 1 of the tests: coronary vasospasm alone in 3, VF alone in 2, and both in 7. All patients underwent implantable cardioverter defibrillator (ICD) implantation and appropriate ICD shock was documented in 1 patient.

Conclusions: OHCA has a heterogeneous pathogenesis and so dual induction tests are necessary. (*Circ J* 2009; **73:** 767–769)

Key Words: Coronary vasospasm; Electrophysiology; Sudden cardiac death

The widespread implementation of defibrillation programs has saved many patients with out-of-hospital cardiac arrest (OHCA), making subsequent care of these patients more important than ever! Although structural heart diseases (eg, acute myocardial infarction) are the major underlying causes of OHCA,[2] accumulating evidence indicates that cardiac arrest in the absence of structural heart disease is more common than previously expected.[3] Sudden death in the absence of organic heart disease is termed "Pokkuri disease" in Japan, where both coronary vasospasm and ventricular fibrillation (VF) may play an important role in pathogenesis, although this has not yet been fully investigated. In the present study, we examined the prevalence of these 2 factors in OHCA survivors by performing induction tests for both coronary vasospasm and VF.

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Methods

The present study was approved by the Ethical Committee of Tohoku University, and informed consent was given by each patient.

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Study Patients

We examined 12 consecutive patients without organic heart disease who had survived an OHCA (M/F, 11/1; age, 44±12 [SD] years) between December 2004 and December 2008 (**Table**). The diagnosis of organic heart disease was made by physical examination, laboratory tests, 12-lead ECG, chest X-ray, 2-dimensional and color-flow-Doppler echocardiography, left ventriculography and coronary angiography. The induction tests for coronary vasospasm with intracoronary acetylcholine (ACh) and VF with programmed stimulation were performed after full recovery from the OHCA event (15–58 days, mean 31 days).

Acetylcholine Provocation Test for Coronary Vasospasm

The protocol has been described previously.[4] Briefly, following control coronary angiography, ACh was administrated into the coronary artery (12.5, 25, 50, and 100μg). A positive response was defined as the development of >90% stenosis accompanied by chest pain and/or ischemic ECG changes. The type of coronary spasm was classified as focal or diffuse.[5]

Electrophysiological Study for VF

We performed the electrophysiological study (EPS) after the ACh provocation test (0–19 days, mean 9 days). All patients with a positive response to the ACh provocation test were treated with a calcium-channel blocker (CCB) when undergoing the EPS. The programmed stimulation protocol included a minimum of 2 basic pacing cycle lengths (600 and 400 ms) with single, double or triple extra-stimuli at the right ventricular apex. If VF was not induced, the same protocol was repeated under isoproterenol stimulation and/or pacing in the right ventricular outflow. Drug challenge test using intravenous flecainide (2 mg/kg) or pilsicainide (1 mg/kg) was also performed to diagnose Brugada syndrome.[6]

Table. Patient Characteristics and Results of Dual Induction Tests

Patient no.	Age (years)/ sex	Coronary risk factors	Rhythm at cardiac arrest	Bystnder CPR	Therapeutic hypothermia	LVEF (%)	Acetylcholine provocation	VF induction	Drug challenge test	Late potential	CCB (daily dose)	ICD implantation	Follow-up (months)	ICD shocks
1	54/M	S, HL	VF	+	–	60	+ (F)	–	NA	–	Amlodipine/5 mg	+	48	0
2	32/M	–	VF	+	–	72	+ (D)	+	–	–	Benidipine/2 mg	+	28	0
3	57/M	S	VF	+	–	59	+ (D)	+	+	+	Benidipine/2 mg	+	25	3
4	41/M	S	VF	+	+	70	+ (D)	–	–	–	Benidipine/8 mg, Diltiazem/200 mg	+	21	0
5	60/M	S	VF	+	+	78	+ (F)	–	–	–	Benidipine/4 mg	+	21	0
6	41/M	S	VF	+	–	61	–	+	+	+	–	+	20	0
7	22/M	S	VF	–	+	64	+ (D)	+	–	–	Benidipine/8 mg, Diltiazem/200 mg	+	18	0
8	47/F	–	VF	+	–	74	+ (D)	+	–	–	Benidipine/4 mg	+	18	0
9	31/M	S	VF	+	–	55	–	+	–	–	–	+	15	0
10	39/M	S	VF	+	+	75	+ (D)	+	+	+	Diltiazem/200 mg	+	7	0
11	59/M	–	VF	+	+	72	+ (D)	+	–	+	Benidipine/8 mg	+	7	0
12	56/M	S	VF	–	+	56	+ (D)	+	–	–	Benidipine/8 mg	+	1	0

CPR, cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; CCB, calcium-channel blocker; ICD, implantable cardioverter defibrillator; S, smoking; HL, hyperlipidemia; F, focal vasospasm; D, diffuse vasospasm; NA, not available.

Results

OHCA had occurred between midnight and early morning in 10 patients (83%) and VF had been documented as the initial rhythm at cardiac arrest in all patients (**Table**). The prevalence of coronary risk factors was relatively low, except for smoking habit (**Table**). Bystander cardiopulmonary resuscitation had been performed in 10 patients and therapeutic mild hypothermia in 6 (**Table**). The left ventricular ejection fraction was fairly well preserved (66±7%).

All patients were positive for 1 of the 2 tests: coronary spasm alone in 3, VF alone in 2, and both in 7 (**Table**). ECG changes typical of Brugada syndrome was induced by pilsicainide in 1 patient with VF alone and in 2 patients with both coronary spasm and VF (**Table**). Importantly, 7 of the 10 patients with coronary spasm also had inducible VF, even under intensive medical therapy with CCBs, and all of them had the diffuse type of spasm (**Table**).

All patients subsequently underwent ICD implantation. During the follow-up period (1–48 months, mean 19 months), none had chest pain or syncope. However, appropriate ICD shock for VF was documented in 1 patient with both coronary spasm and Brugada syndrome (**Figure**).

Discussion

The major finding of the present study is that the patients surviving an OHCA without organic heart diseases were positive for either coronary vasospasm or VF, suggesting heterogeneity of the pathogenesis of OHCA and the importance of performing the induction tests for both of the disorders that could cause OHCA.

The survival rate of OHCA, especially in witnessed cases of VF or pulseless VT, is increasing in association with the decrease in the time interval from ambulance call to electrical shock[1] Among OHCA survivors, a number of patients have not had apparent structural cardiac abnormalities, indicating a potential role of functional cardiac impairment in the pathogenesis of OHCA[3] In the present study, all the OHCA survivors were positive for either coronary spasm or VF, and 50% were positive for both tests, indicating the importance of performing both inductions and subsequent medical therapy based on the results of the provocation tests. It remains to be examined in future studies whether coronary microvascular impairment is also involved in patients with both coronary spasm and VF[5]

ICD implantation is a useful therapy for OHCA survivors with induced VF and/or Brugada syndrome diagnosed by EPS[7] but it is still controversial whether ICD is also effective for secondary prevention of sudden cardiac death caused by coronary spasm. Meisel et al previously reported both the efficacy and limitation of ICD therapy in patients with refractory variant angina[8] In their 7 patients with variant angina complicated by VF, appropriate ICD shocks were documented in 4 patients, but 1 patient died of electromechanical dissociation even under intensive medical treatment with CCBs[8] In clinical practice, the efficacy of medication for preventing coronary vasospasm is assessed on the basis of symptoms; however, it is also known that silent myocardial ischemia because of coronary vasospasm can initiate fatal arrhythmias[9] and that coronary vasospasm could be induced despite a fair clinical course with CCBs[10] Therefore, it remains to be examined in a future multicenter study whether ICD therapy can improve the prognosis of OHCA survivors with coronary vasospasm.

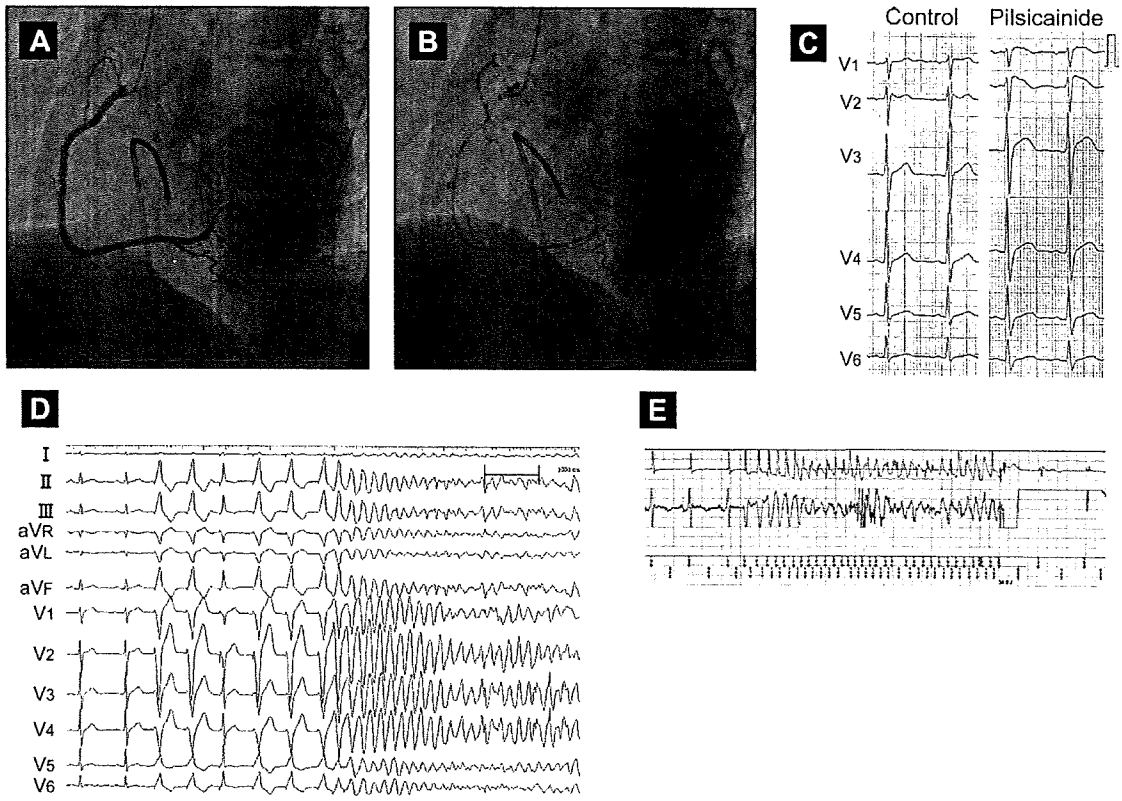

Figure. Representative case of out-of-hospital cardiac arrest (OHCA) with both coronary spasm and ventricular fibrillation (VF). In this 57 year-old male patient, coronary angiography (CAG) was performed 19 days after the onset of an OHCA. Although no significant coronary stenosis was found in control CAG (**A**), severe and diffuse coronary spasm was induced by intracoronary acetylcholine (**B**). Drug challenge test with 1 mg/kg pilsicainide demonstrated ECG changes typical for Brugada syndrome (**C**), and in the electrophysiological study performed under medication with calcium-channel blocker (CCB) 10 days after the CAG study, VF was induced by programmed stimulation (**D**). At 593 days after the onset of the OHCA, despite treatment with CCBs, recurrent VF (without proceeding ST-T changes) and an appropriate ICD shock was documented (**E**).

In conclusion, it is important that the induction tests for both coronary vasospasm and VF are performed in patients surviving a OHCA without organic heart disease.

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ORIGINAL ARTICLE
Epidemiology

Trends in Acute Myocardial Infarction Incidence and Mortality Over 30 Years in Japan:

Report From the MIYAGI-AMI Registry Study

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Background: Worldwide, the rate of aging is highest in Japan, especially the female population. To explore the trends for acute myocardial infarction (AMI) in Japan, the MIYAGI-AMI Registry Study has been conducted for 30 years since 1979, whereby all AMI patients in the Miyagi prefecture are prospectively registered.

Methods and Results: In 1979–2008, 22,551 AMI patients (male/female 16,238/6,313) were registered from 43 hospitals. The age-adjusted incidence of AMI (/100,000 persons/year) increased from 7.4 in 1979 to 27.0 in 2008 (P<0.001). Although control of coronary risk factors remained insufficient, the rates of ambulance use and primary percutaneous coronary intervention (PCI) have increased, and the overall in-hospital mortality (age-adjusted) has decreased from 20.0% in 1979 to 7.8% in 2008 (P<0.0001). However, the in-hospital mortality remains relatively higher in female than in male patients (12.2% vs 6.3% in 2008). Female patients were characterized by higher age and lower PCI rate.

Conclusions: The MIYAGI-AMI Registry Study demonstrates the steady trend of an increasing incidence, but decreasing mortality, for AMI in Japan over the past 30 years, although the female population still remains at higher risk for in-hospital death, despite improvements in the use of ambulances and primary PCI. (*Circ J* 2010; **74:** 93–100)

Key Words: Acute myocardial infarction; Aging; Gender; Risk factors

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. In the United States, nearly 1 million patients suffer from AMI each year.[1] In the past decades, industrialization, urbanization, and associated life-style changes have taken place worldwide as the population grows older in association with the epidemics of obesity and metabolic syndrome. Especially in Japan, these changes have become more evident because the rate of aging is the highest in the world and the westernization of lifestyle has progressed rapidly.[2] In order to estimate the trends in the burden of disease, particularly that of AMI, it is important to monitor and track the incidence and mortality of AMI in the same community for a long time. Indeed, the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO-MONICA) project reported the prevalence and case-fatality rate in 21 countries,[3] but Japan was not included. Moreover, in Japan, there have been few studies specifically for AMI and most of them have included a small number of annual events with a relatively short monitoring period.[4–7]

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To explore the actual trend for AMI reflecting "real-world" practice in Japan, we have been conducting the MIYAGI-AMI Registry Study for 30 years since 1979, whereby all AMI patients in the Miyagi prefecture have been prospectively registered and there has been a relatively stable population over those years.[8,9]

Methods

The MIYAGI-AMI Registry Study

The Miyagi prefecture is located in northeastern Japan and has had a relatively stable population of approximately 2 million over the last 30 years (2,054,000 in 1979 and

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