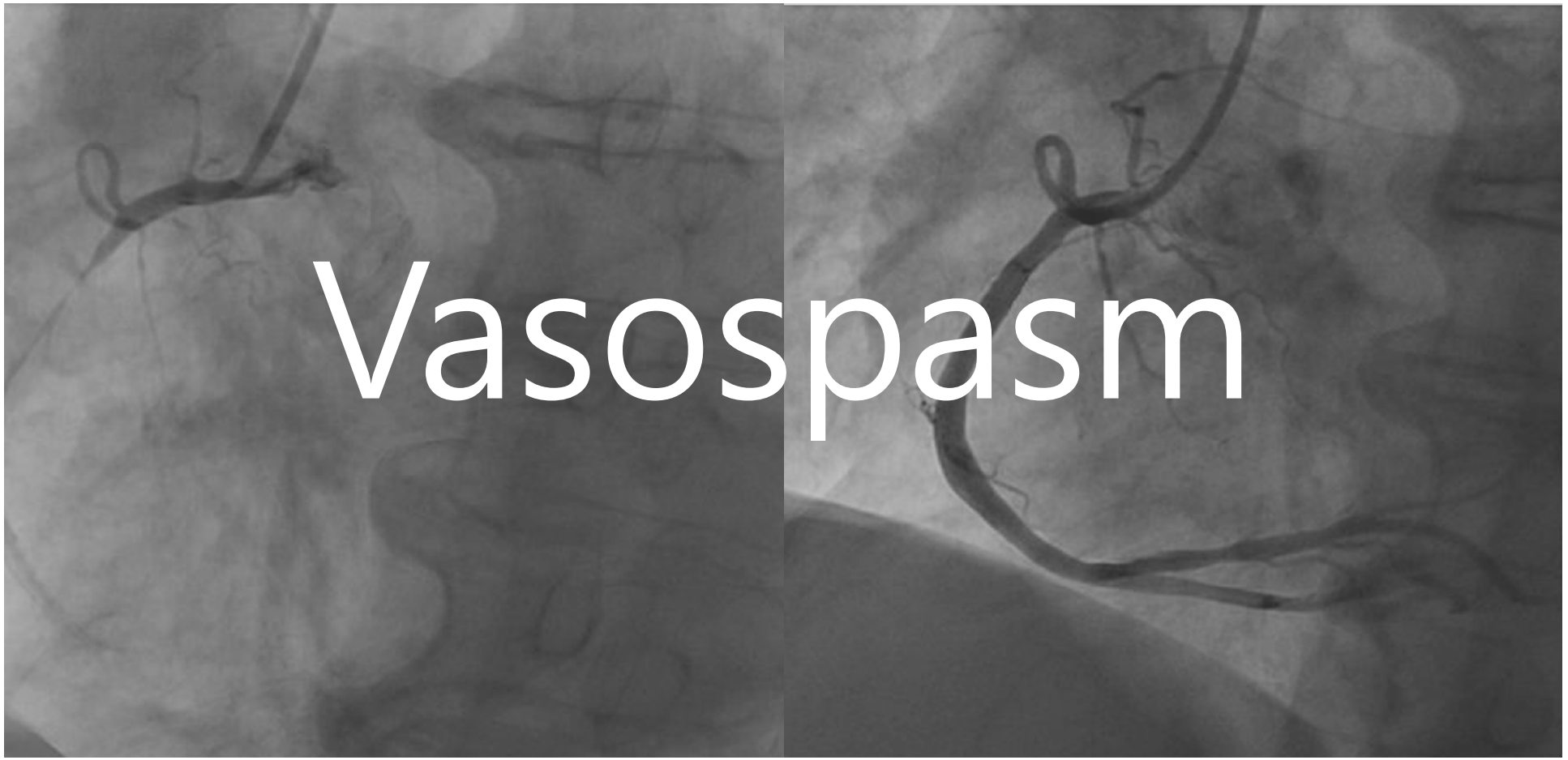


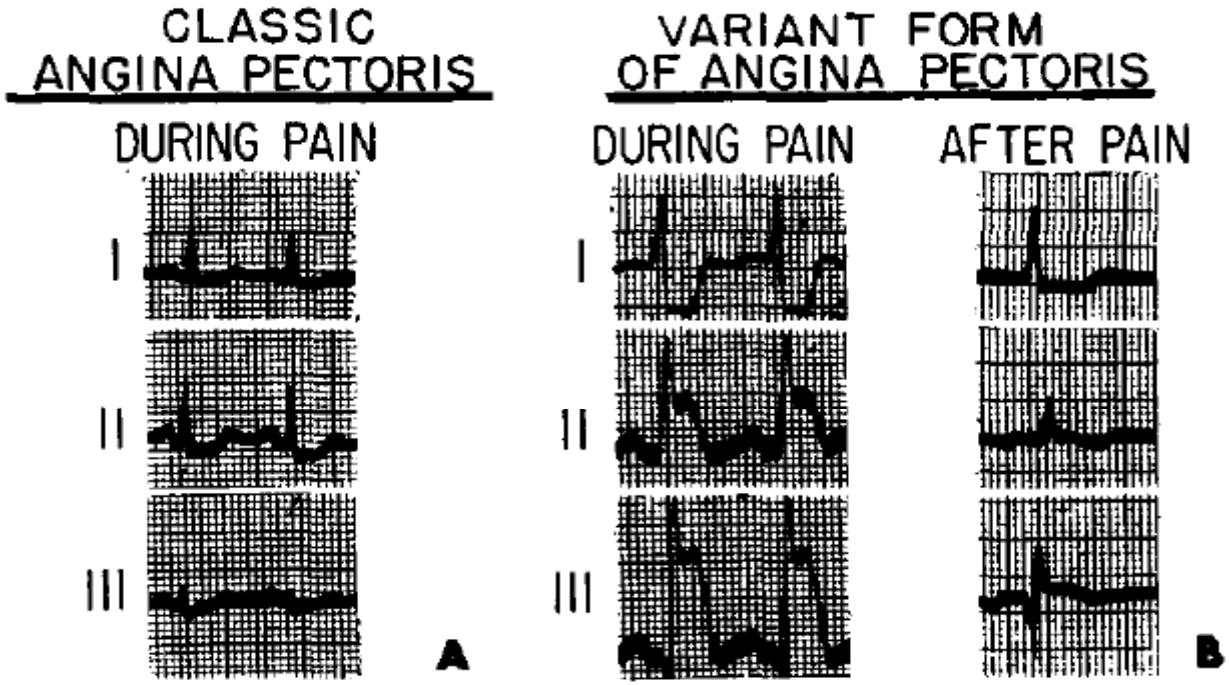
한림의대
조상호

Angina Pectoris*
I. A Variant Form of Angina Pectoris

Preliminary Report

MYRON PRINZMETAL, M.D., REXFORD KENNAMER, M.D., REUBEN MERLISS, M.D.,
TAKASHI WADA, M.D. *and* NACI BOR, M.D.
Los Angeles, California

"increased tonus at the site of an atherosclerotic plaque"



Prinzmetal. AJM 1959

Variant angina (VA)

- Young, male
- Diurnal variation
- Resting pain
- Myocardial infarction (MI),
  life-threatening ventricular arrhythmias,
  sudden death
- 32.3% with ACh, 29% with EG test in Japan
- 12.3% in France, 4% in north America

Variant angina is decreasing

Time Period	Diagnostic CAG, No.	SSPT, No.	CSA, No.	Variant, No.	CSA/CAG, %	CSA/SSPT, %	Variant/ CSA, %
1991–1993	605	493	89	28	14.7†	18.1	31.5†
1994–1996	948	492	120	33	12.7	24.3	27.5†
1997–1999	725	200	63	9	8.7	31.5	14.3
2000–2002	870	330	77	4	8.4	23.3	5.2
Totals	3,148	1,515	349	74	11.1‡	22.9§	21.2‖

Because of wide use of calcium channel blocker ? : Medication before hospital admission in patients with coronary spasm

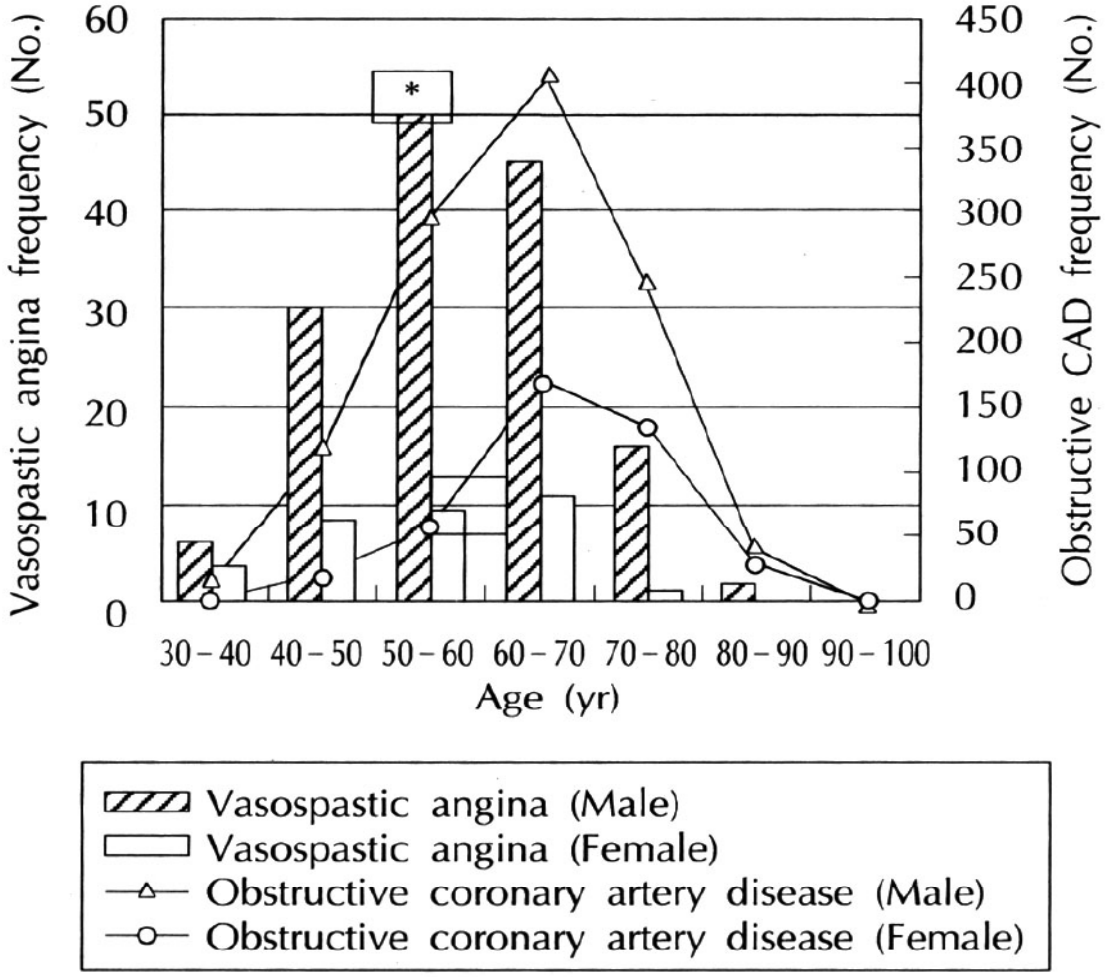
Time Periods	CA	ISDN/Nicorandil	Both	S-CAs	L-CAs
1991–1993 (n = 89)	29 (32.6)	24 (27.0)	22 (24.7)	23 (79.3)	6 (20.7)
1994–1996 (n = 120)	33 (27.5)	35 (29.2)	28 (23.3)	13 (39.4)	20 (60.6)
1997–1999 (n = 63)	30 (47.6)	29 (46.0)	24 (38.1)	1 (3.3)	29 (96.7)
2000–2002 (n = 77)	38 (49.4)†	18 (23.4)	9 (11.7)	3 (7.9)‡	35 (92.1)‡
Nonvariant (n = 275)	111 (40.4)	92 (33.5)	71 (25.8)	28 (10.2)	83 (30.2)
Variant (n = 74)	19 (25.7)	12 (16.2)	12 (16.2)	12 (16.2)	7 (9.5)
Total (n = 349)	130 (37.2)	106 (30.4)	83 (23.8)	40 (11.5)	90 (25.8)

Characteristics of VA in Korea

	Vasospastic angina (181 Cases)	Obstructive coronary artery disease (1533 Cases)	Normal control (455 Cases)
Sex			
Male (%)	149 (82.3)*	1122 (73.2)	378 (82.3)
Female (%)	32 (17.7)	411 (26.8)	77 (17.7)
Age			
Mean age (years)	52.2±10.7†	59.0±10.6	52.5±10.7

Korean Circulation J 2002;32:224-232

Age and sex distribution in VA and CAD



Korean Circulation J 2002;32:224-232

Variant angina

- 88% cases spasm causing ischemia was localized to the site of an organic lesion :

  by *Prinzmetal*

- Anatomy: normal coronary arteries varies from 30% to 64%

- 0.5-0.8% of patients could show evidence of coronary artery spasm stimulated either by the tip of the catheter or contrast medium

Korean VA, 256 patients, (1996-2006 retrospective study)

Results	N (%)
Single vs. multivessels spasm	
Single vessel spasm	223 (97.1)
Multivessels spasm	33 (12.9)
Pure vs. mixed angina	
Pure vasospastic angina	206 (80.5)
Mixed angina	50 (19.5)
Spasm site	
LAD only	92 (35.9)
LCX, only	24 (9.4)
RCA, only	107 (41.8)
LAD, LCX	9 (3.5)
LCX, RCA	4 (1.6)
RCA, LAD	15 (5.9)
LAD, LCX, RCA	5 (2.0)
Spasm artery	
LAD	121 (41.2)
LCX	42 (14.3)
RCA	131 (44.6)

Results	N (%)
No significa	06 (80.5)
Significant f	50 (19.5)
One vesse	38 (14.8)
Two vesse	12 (4.7)
Triple ves	0 (0)
Left main	0 (0)
Percutaneou	18 (7.0)

유상용등 Korean Circ J 2008;38:651-658

VA characteristics

Variables	Subsets	No. of patients	%
Coronary artery disease	No stenosis >75%	97	40
	One-vessel disease	108	44
	Multivessel disease	40	16
Calcium antagonist	Yes	176	72
	No	69	28
Site of ST elevation	Anterior	124	51
	Inferior	94	38
	Both	27	11
Disease activity	Spontaneous attacks	211	86
	Provoked attacks only	34	14
Left ventricular function	Normal	230	94
	Abnormal	15	6
Smoking	Yes	79	34
	No	154	66
Alcohol	Yes	128	55
	No	105	45
Coronary artery bypass surgery	Yes	34	14
	No	211	86

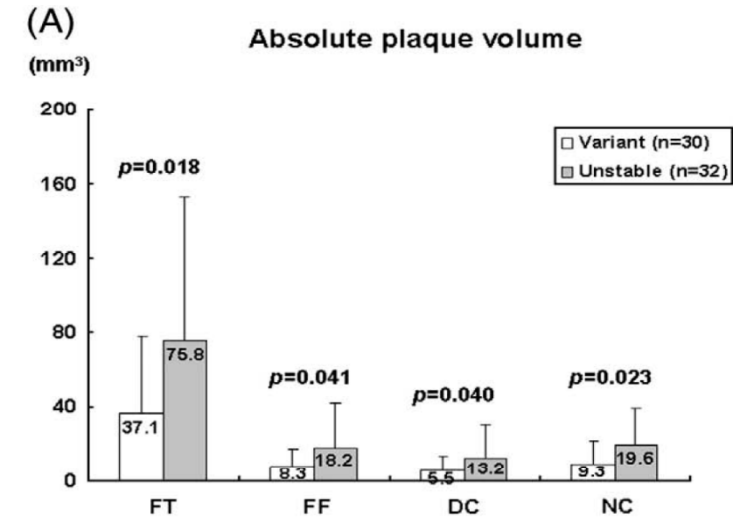
Circulation 1988;78:1-9

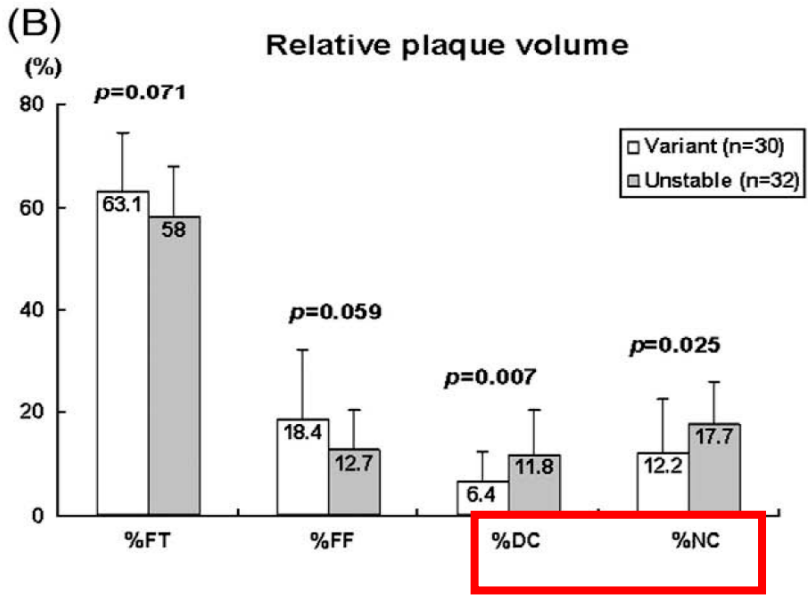
Histology of VA from directional coronary atherectomy

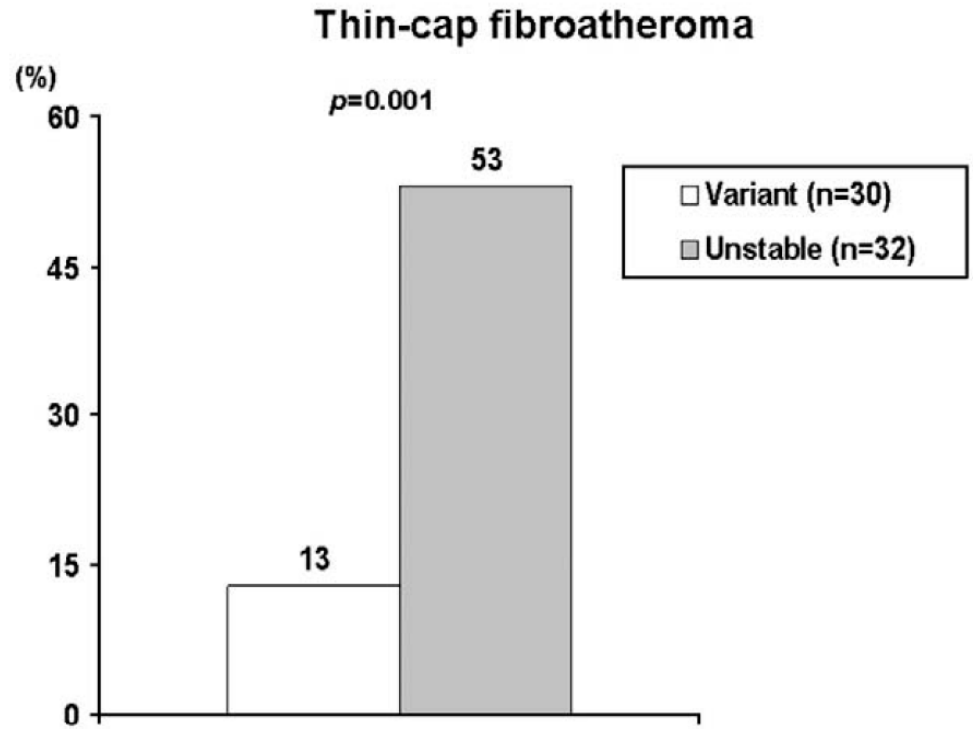
	VAP (n = 22)	SAP (n = 100)	Restenosis (n = 80)
Fibro-atheromatous plaque (n)	32% (7)*	92% (92)	10% (8)*
Neointimal hyperplasia (n)	68% (15)*	8% (8)	90% (78)*
Thrombus (n)	10% (2)	6% (6)	9% (11)
Intimal hemorrhage (n)	14% (3)	4% (4)	8% (6)
Calcification (n)	10% (2)	11% (11)	11% (9)

J Am Coll Cardiol 1999;33:198 –205

Plaque components at coronary sites with focal spasm in patients with VA: **more stable plaque than in UAP**

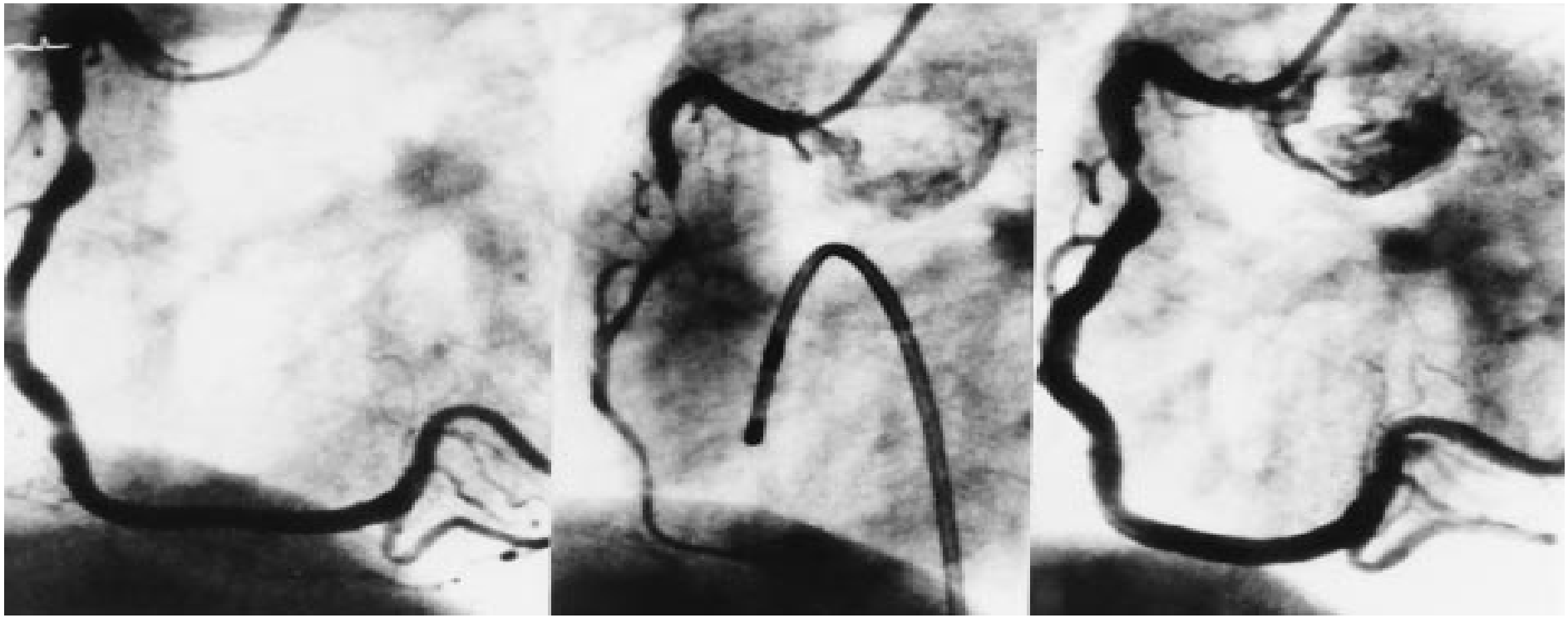






YJ Hong et al, IJC 2009

Combination of fixed lesion and spasm



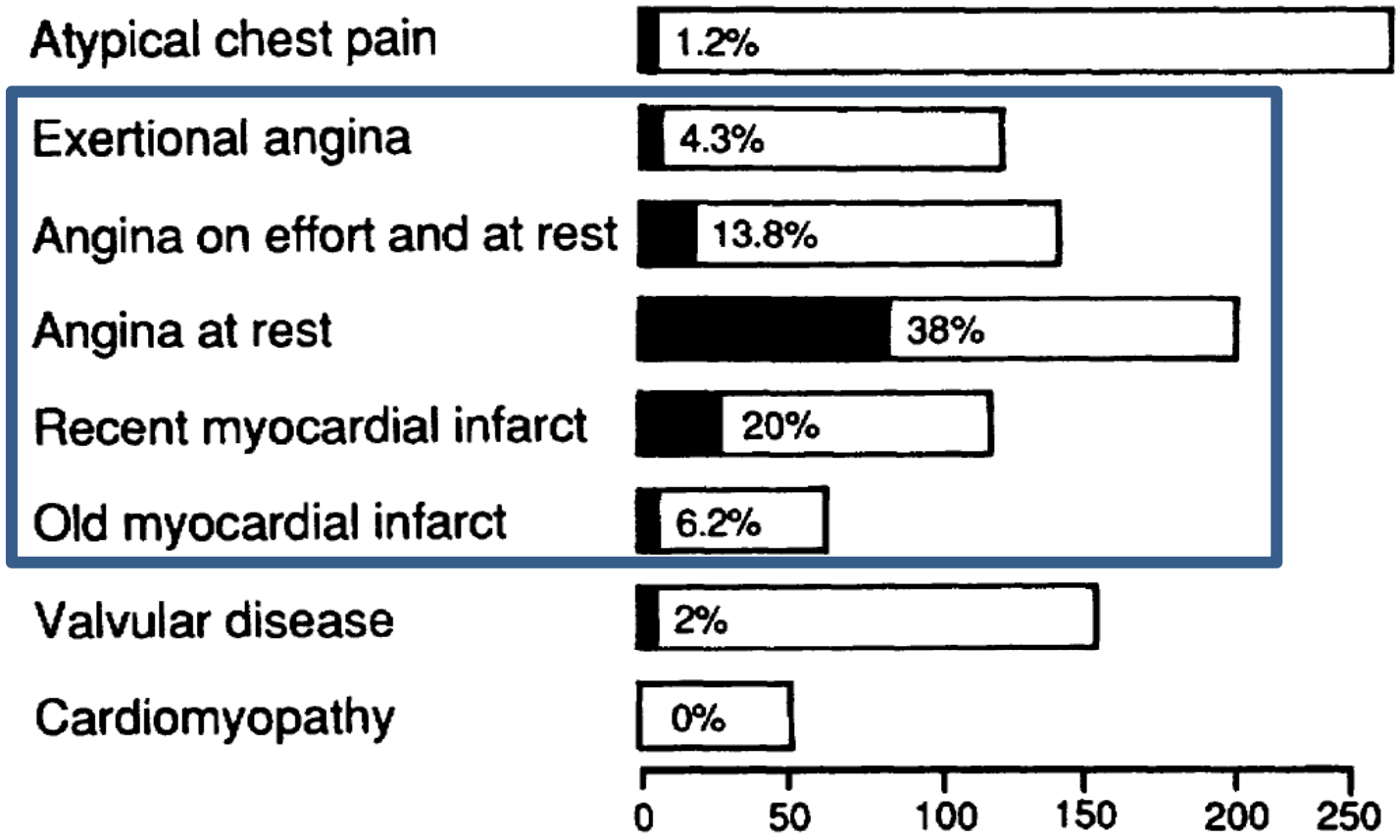
Inducible coronary spasm in post MI patients

Study	Provocative Agent	Myocardial Infarct Patients			Control Patients	
		n	Days Post-MI	Spasm	n	Spasm
Recent myocardial infarct						
Caucasian patients						
Bertrand et al. (79)	Methylergonovine	131	< 42	21%	353	9%
Mongiardo et al. (80)	Serotonin	24	6–12	11%		
Pristipino et al. (5)	Acetylcholine	19	7–10	37%		
Japanese patients						
Okumura et al. (81)	Acetylcholine	16	25–725	69%	16	21%
Pristipino et al. (5)	Acetylcholine	15	7–10	80%		
Remote myocardial infarct						
Caucasian patients						
Bertrand et al. (82)	Methylergonovine	64	> 6 weeks	6%	248	1%
Japanese patients						
Nosaka et al. (83)	Ergonovine	398		23%	648	1%

More inducible spasm in oriental than western in post MI patients

Study	Patient race	Provocative agent	MI		Stable CAD	
			n	Spasm	n	Spasm
Recent MI						
Bertrand[50]	Caucasian	Methylergonovine	131	21%	353	9%
Pristipino[25]	Caucasian	Acetylcholine	19	37%		
Pristipino[25]	Japanese	Acetylcholine	15	80%		
Okumura[51]	Japanese	Acetylcholine	16	69%	16	21%
Remote MI (>6 weeks)						
Bertrand[24]	Caucasian	Methylergonovine	64	6%	248	1%
Nosaka[52]	Japanese	Ergonovine	398	23%	648	1%

Provoked coronary spasm in various situation



Circulation. 1990; 81: 1983–1991

VA and ACS

- Causality?

- Spasm → ACS
  vs. ACS → Endothelial dysfunction → Spasm

*Histology and IVUS+VH study
* Spasm test in ACS?
* CCB or nitrate in spasm + ACS ?

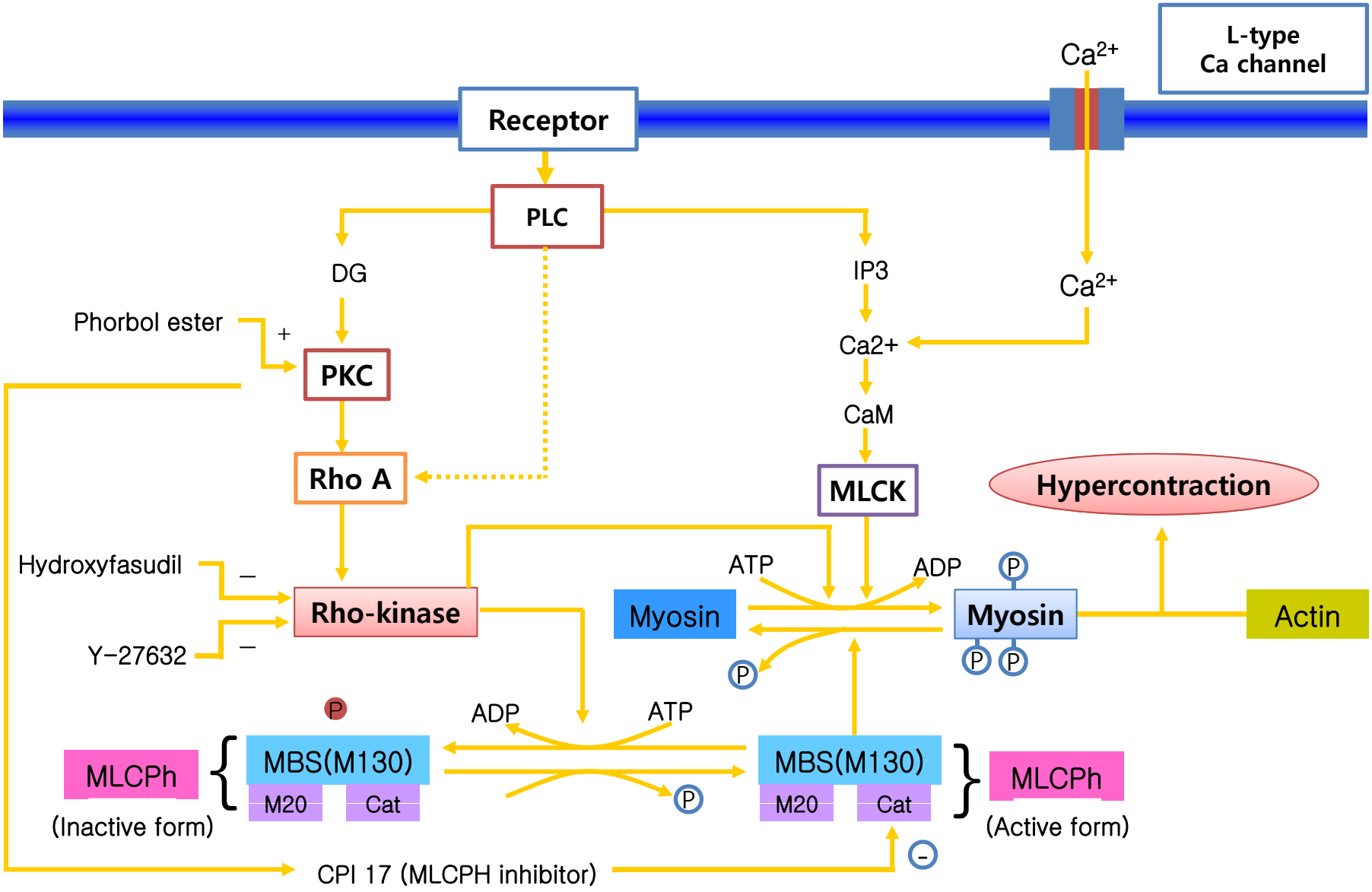
Coronary arteries of patients with spasm

- Vasomotor tone
- Endothelial dysfunction

- Vagal withdrwal
- Sympathetic activity
- Smooth muscle contraction
- Nitric oxide release

- Genetic background
- Smoking
- K_{ATP} channel in smooth muscle cell (SMC)

Molecular Mechanisms for Coronary Spasm



Shimokawa H. *J Cardiovasc Pharmacol.* 2002, 39:319–327

VA and inflammation from biomarker study

Variables	χ^2 test	*P* value	Odds ratio	95% confidence interval
Smoking	4.187	0.052	1.461	1.092–1.844
WBC	4.562	0.041	1.629	1.138–2.040
PMC	5.309	0.006	1.821	1.192–2.108
CRP	6.482	0.001	2.034	1.263–3.378
IL-6	4.880	0.004	1.921	1.196–2.273

CRP, C-reactive protein; IL-6, interleukin-6; PMC, peripheral monocyte count; WBC, white blood count.

Quartile	χ^2 test	*P* value	Odds ratio	95% confidence interval
1st ($\leq$ 1 mg/l)			1.000	
2nd (1–3 mg/l)	1.842	0.249	2.183	0.948–4.135
3rd ($\geq$ 3 mg/l)	6.351	0.002	4.982	1.503–8.927

Coronary Artery Disease 2008, 19:293–297

Low HDL, risk factor of VA by Multivariate analysis

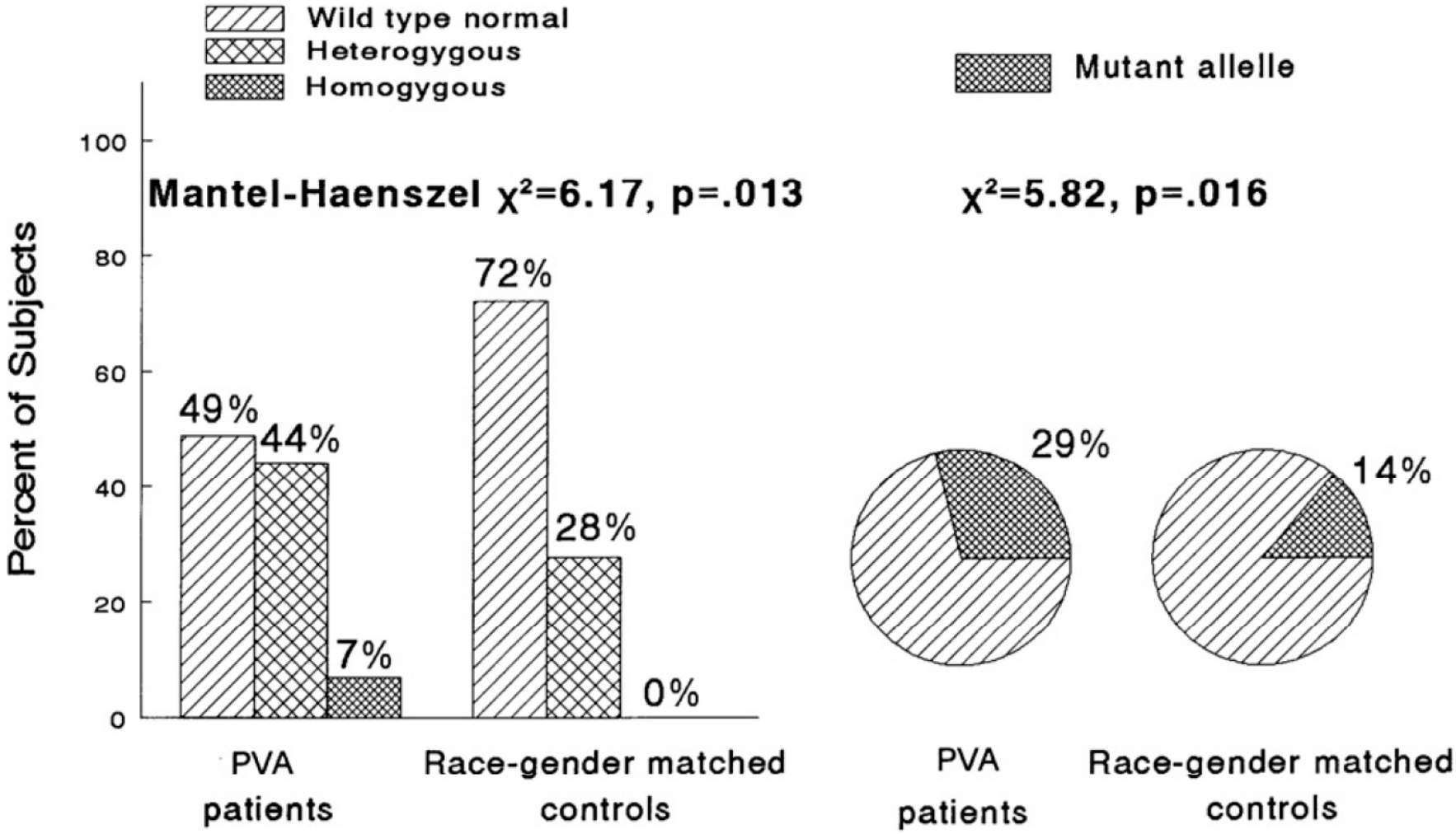
		Univariate			Multivariate		
	n	OR	95% CI	*P*	OR	95% CI	*P*
Age ≥65 years	48	1.55	0.77–3.11	0.218	2.11	0.96–4.62	0.062
Male sex	100	1.31	0.71–2.42	0.382			
Smoking	53	2.48	1.22–5.03	0.023	2.68	1.23–5.83	0.013
Alcohol	77	1.33	0.72–2.46	0.367			
Hypertension	57	1.15	0.60–2.19	0.679			
BMI ≥25 kg/m^2	58	1.20	0.63–2.28	0.586			
Impaired fasting glucose/DM	38	2.70	1.19–6.13	0.018	2.47	1.06–5.83	0.037
Lowest HDL-C quartile	40	4.31	1.78–10.43	0.001	3.39	1.34–8.54	0.010
Highest LDL-C quartile	45	0.92	0.46–1.84	0.822			

Racial differences

- Japanese patients – diffusely, multivessel spasm

- endothelial nitric oxide synthetase(eNOS) gene (resulting in deficient nitric oxide production)- 69% and 75%, respectively, incidence of coronary spasm

eNOS T-786C genotypes and mutant allele frequency in 43 patients with VA



Oxidative stress and spasm: RR homozygote of paraoxonase Q192R polymorphism are associated with variant angina

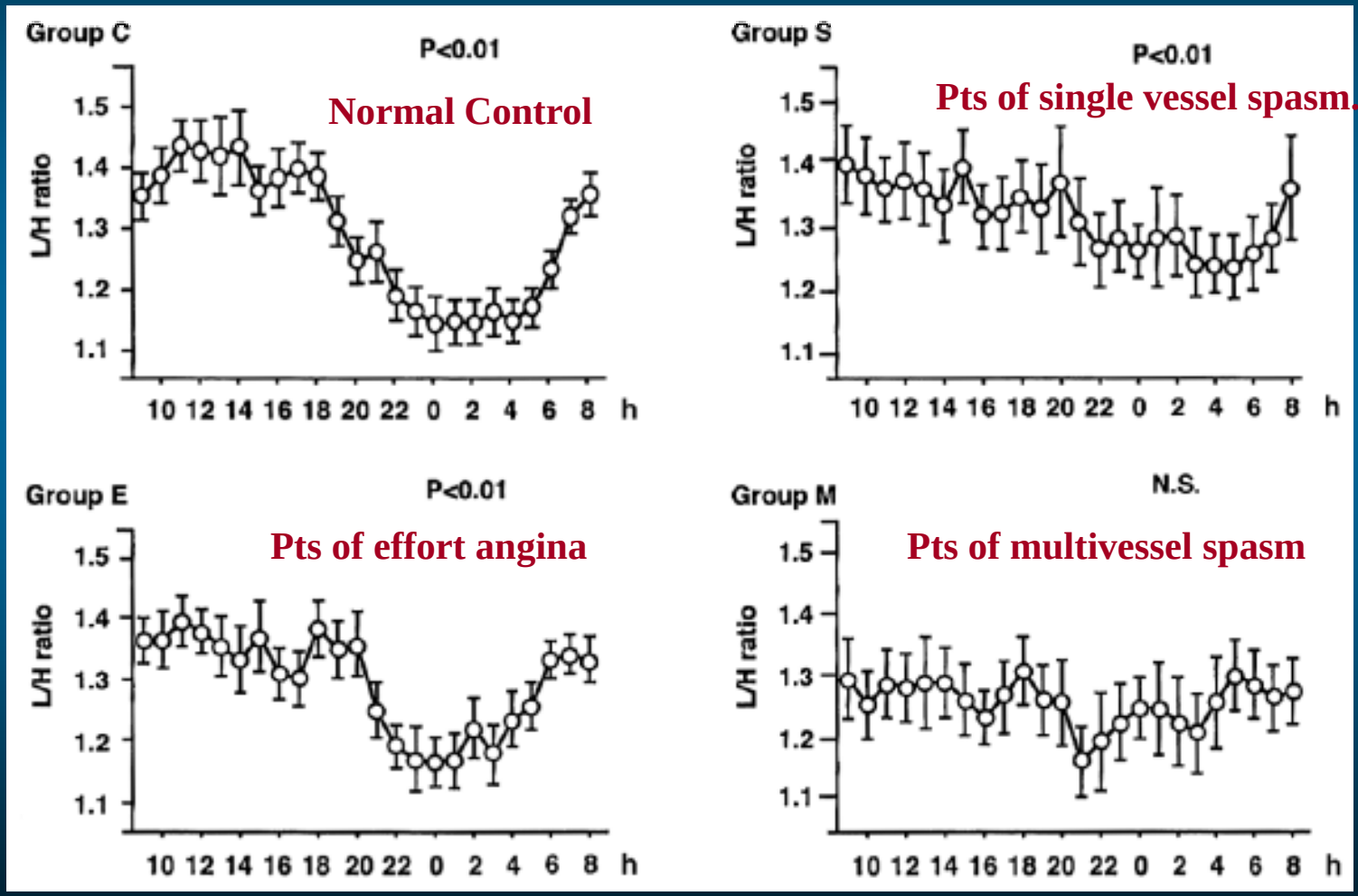
	OR	95% CI	p
Variant angina			
Smoking (current- or ex-)	3.392	1.777−6.476	<0.001
RR homozygote	2.240	1.012−4.956	0.047

YS Cho, HS Kim et al Korean Circulation J 2003;33:104-112)

Circardian Variation of Autonomic Nervous Activity in Patients With Multivessel Coronary Spasm

Sympathetic nervous activity was enhanced in the nighttime in pts with multivessel spasm.

Sympathovagal balance at HR variability test



Jpn Circ J 2001;65:593-598

Adrenergic Receptor

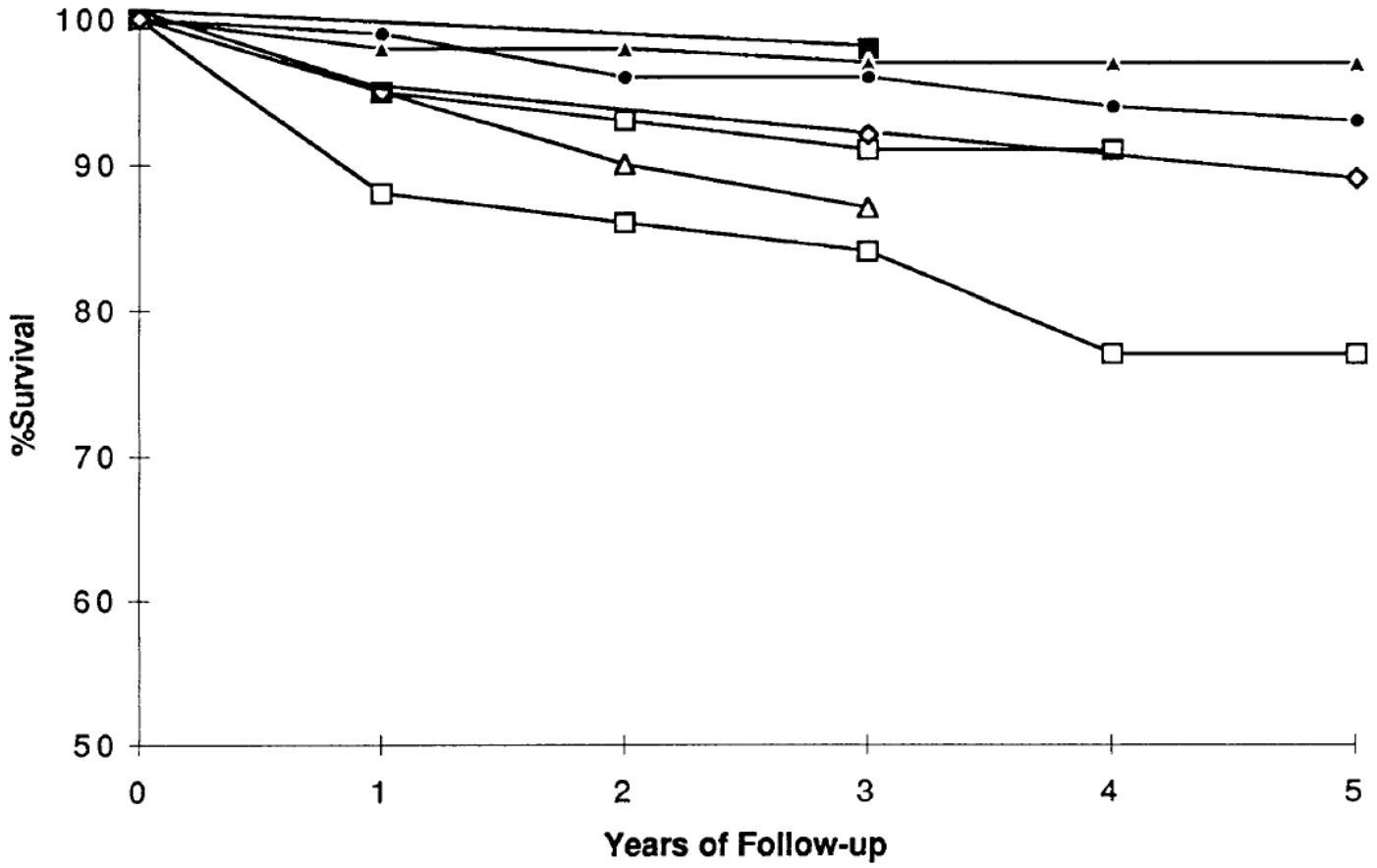
- α_2 adrenergic receptor : vasoconstriction
- β_2-adrenergic receptor : vasodilation
- β_1-adrenergic receptor : chronotrophic, inotrophic changes

VA clinical parameters and AR genotypes in multiple logistic regression analysis

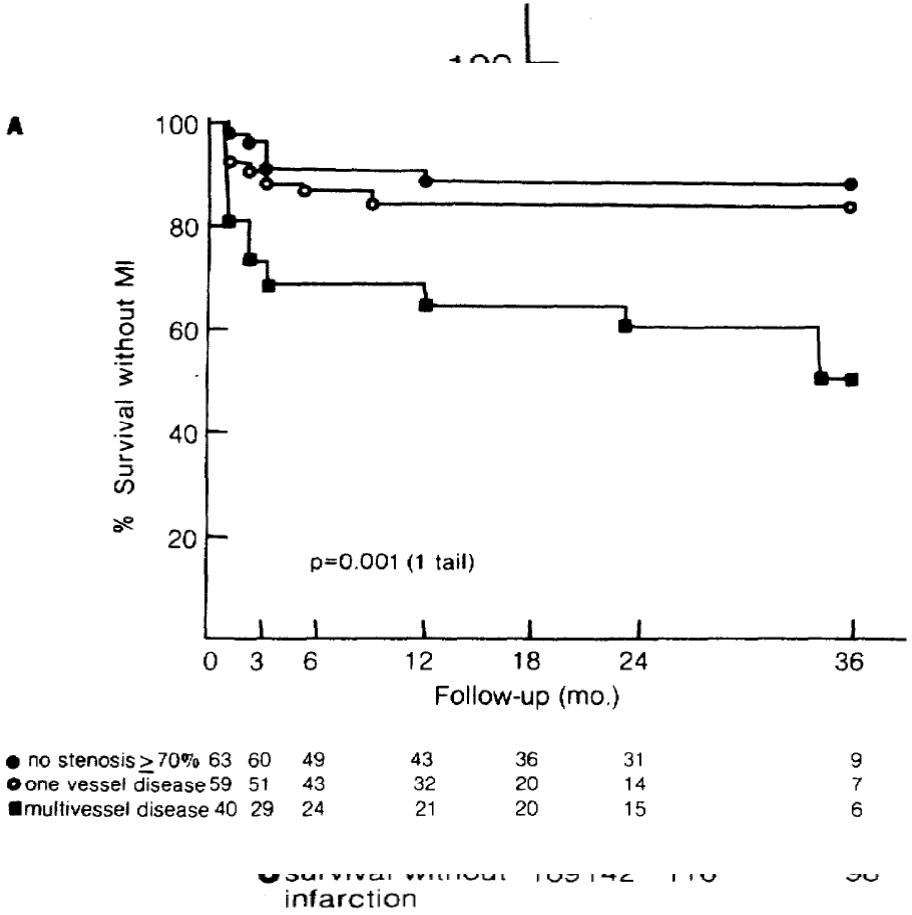
	OR	95% CI	P
α_{2C}Del322-325 allele carrier	5.132	2.094-12.578	.0003
β_2Gln27 homozygote	3.152	1.364-7.285	.0072
Smoking	4.902	2.105-11.416	.0002
Male sex	1.348	0.570-3.186	NS
Age (1 y)	1.089	1.046-1.135	<.0001
Diabetes	4.103	0.836-20.131	NS
Hypertension	0.434	0.184-1.024	NS
Dyslipidemia	1.869	0.541-6.457	NS

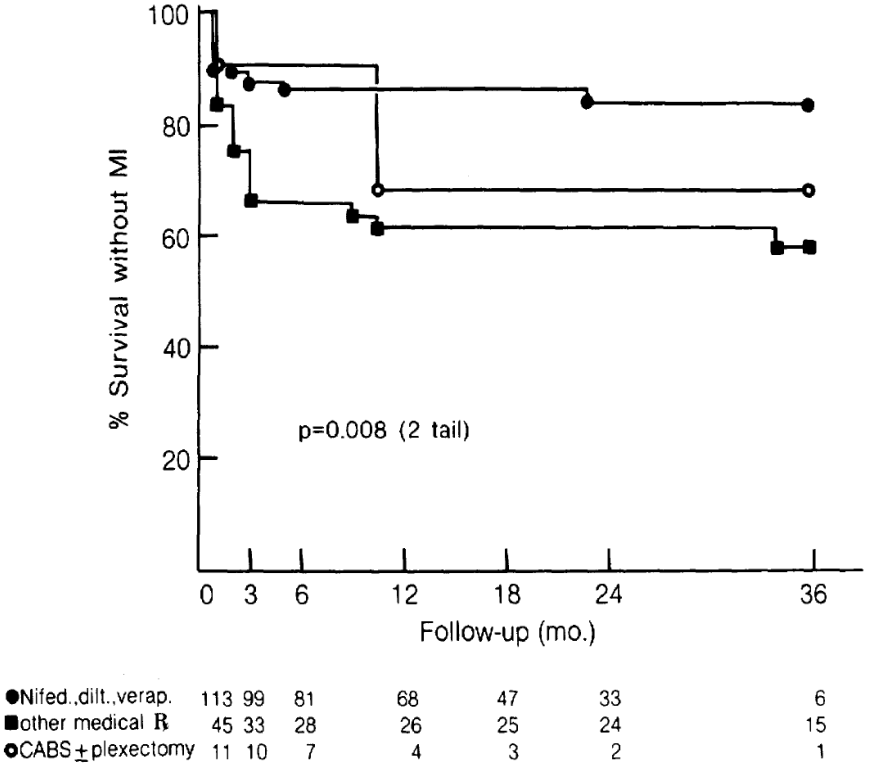
JS Park, SH Jo.. et al. Am Heart J 2006;151:864- 9

Survival in VA patients is good and better in Oriental than in the West



Prognosis of VA





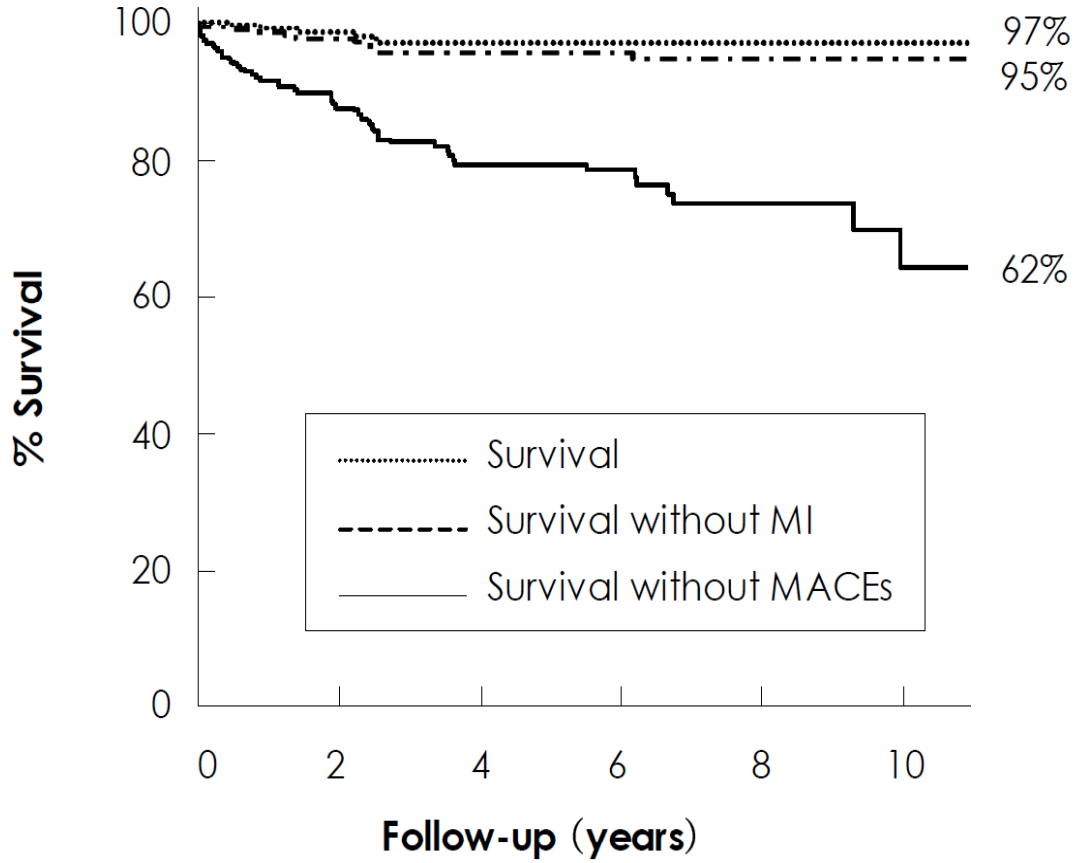
Circulation 1983:68,258-265

Predictor of survival of VA

Variable	Survival		Survival without infarction	
	χ^2	p value	χ^2	p value
Coronary artery disease	14.7	.0003	13.4	.001
Disease activity	5.7	.03	9.6	.004
Left ventricular function	3.0	.04	5.6	.02
Initial treatment	0.89	NS	9.7	.008
Age	2.9	NS	1.0	NS
Duration of rest angina	0.81	NS	2.2	NS
Site of ST elevation	0.17	NS	1.5	NS

Circulation 1983:68,258-265

Survival in Korean VA -97%



Number at risk						
Survival	256	182	134	95	34	14
Survival without MI	256	180	131	91	33	13
Survival without MACEs	256	163	110	74	27	10

유상용등 Korean Circ J 2008;38:651-658

202 patients with VA, Repeated angina attack - From Japan data

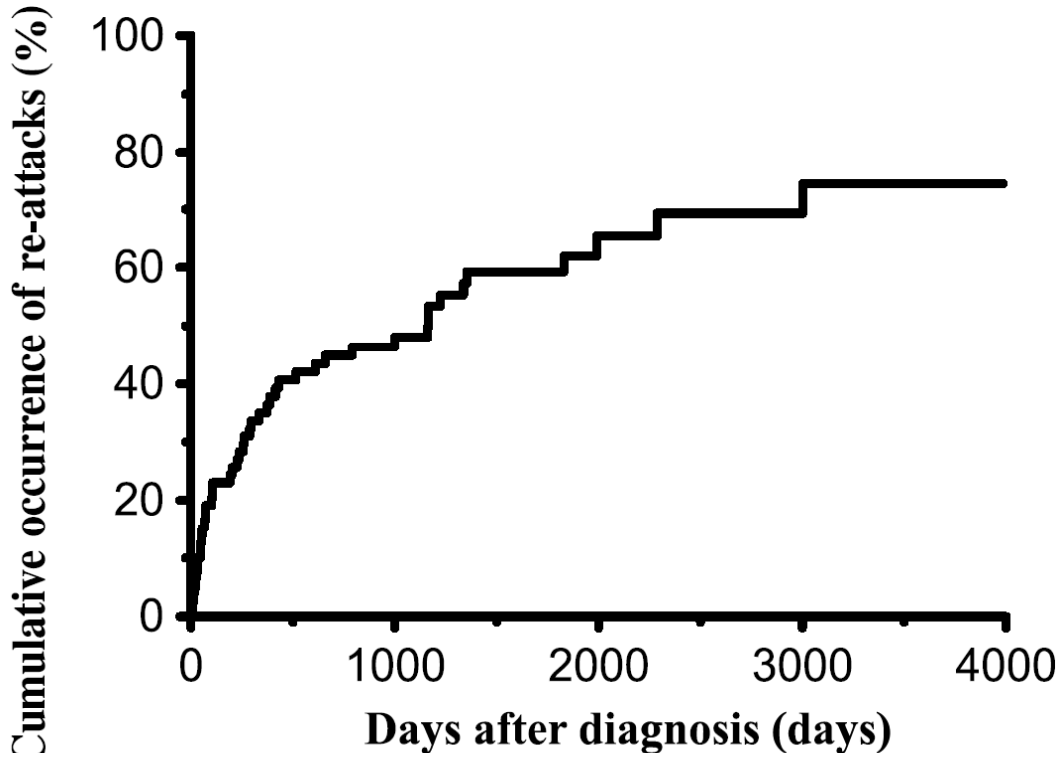


Table 2. Results of Follow-up (n=80)

Follow-up period	1,796±1,169 days
Deaths	0 (0%)
Chest symptoms	46 (57.5%)
Re-hospitalization for angina attack	2 (2.5%)
Non-Q myocardial infarction	1 (1.3%)

Circ J 2009; 73: 512 – 515

Diagnostic Options in CAS

- Electrocardiogram
- Holter monitoring
- Coronary angiography with ergonovine, Ach
- Ergonovine stress echocardiography

Variant angina diagnosis by coronary angiography (CAG)

- Intravenous(IV) or intracoronary(IC) ergot alkaloid (ergonovine maleate, EG) or acetylcholine (ACh)

- angiographically defined total vessel occlusion or subtotal occlusion with or without organic stenosis (100%, 99%, 75%)

- spasm in angiography
- chest pain
- ECG changes

- Physiological Coronary Constriction - Reduction in epicardial coronary artery diameter in response to ergonovine is usually diffuse and quite mild, not exceeding 30%

Ach is comparable to EG
and comfortable in detecting multivessel spasm

PATHOPHYSIOLOGY AND NATURAL HISTORY
VARIANT ANGINA

Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm

HIROFUMI YASUE, M.D., YUTAKA HORIO, M.D., NATUSUKI NAKAMURA, M.D., HIROMI FUJII, M.D., NOBUYA IMOTO, M.D., RYUJI SONODA, M.D., KIYOTAKA KUGIYAMA, M.D., KENJI OBATA, M.D., YASUHIRO MORIKAMI, M.D., AND TADASHI KIMURA, M.D.

ABSTRACT We injected acetylcholine (ACh), the neurotransmitter of the parasympathetic nervous system, into the coronary arteries of 28 patients with variant angina. Injection of 10 to 80 μg ACh into the coronary artery responsible for the attack induced spasm together with chest pain and ST segment elevation or depression on the electrocardiogram in 30 of the 32 arteries of 25 of the 27 patients. The injection of 20 to 100 μg ACh into the coronary artery not responsible for the attack in 18 patients resulted in various degrees of constriction in most of them, but no spasm in any of them. After intravenous injection of 1.0 to 1.5 mg atropine sulfate, the injection of ACh into the coronary artery responsible for the attack did not induce spasm or attack in any of the nine coronary arteries injected in eight patients. We conclude that the intracoronary injection of ACh induces coronary spasm and attack in patients with variant angina and that the activity of the parasympathetic nervous system may play a role in the pathogenesis of coronary spasm. We also conclude that the intracoronary injection of ACh is a useful test for provocation of coronary spasm.
Circulation 74, No. 5, 955–963, 1986.

Other provocative tests

- Serotonin, histamine, dopamine
- Exercise, cold pressor tests, hyperventilation

- ergon
- Hyper

Ergonovine stress echo
Hyperventilation echo

- Histamine 47%,
- exercise in 46%,
- cold pressor 11%
- handgrip tests 7%

Comparison of Potential Advantages and Disadvantages of Ergonovine Echocardiography Versus Invasive Spasm Provocation Test

		Invasive (+)	Provocation (−)
Ergonovine Echocardiography	(+)	142	6
	(−)	10	60

Sensitivity: 93%; specificity: 91%; (+) predictive value: 96%; (−) predictive value: 86%.

	Advantage	Disadvantage
Invasive provocation during angiography	Angiogram Intracoronary nitroglycerin Temporary pacemaker backup	Relatively late and insensitive ischemic markers (chest pain, electrocardiogram changes) Invasive, perturbing vasomotor tone Injection contrast agent into coronary circulation Continuous monitoring of ischemic process impossible
Ergonovine echocardiography	Regional wall motion abnormalities-sensitive & specific; early detection and termination Noninvasive, not perturbing vasomotor tone Repeat and follow-up studies	Intracoronary injection of nitroglycerin impossible Temporary pacemaker backup impossible Dependent on acoustic window

Song JK et al J Am Coll Cardiol 2000;35: 1850–6

Case Reports Korean Circulation J 2002;32(4):359-362

Ergonovine 부하 심초음파 검사중 발생한 심정지 1예

동아대학교 의과대학 순환기내과학교실
박태호 · 김무현 · 장세준 · 김성근 · 양두경
오일환 · 차광수 · 김영대 · 김종성

Heart Arrest Caused by Ergonovine Stress Echocardiography

Tae Ho Park, MD, Moo Hyun Kim, MD, Se Jun Jang, MD,
Seong Geun Kim, MD, Doo Kyung Yang, MD, Ill Hwan Oh, MD,
Kwang Soo Cha, MD, Young Dae Kim, MD and Jong Seong Kim, MD
Division of Cardiology, Dong-A Medical College, Pusan, Korea

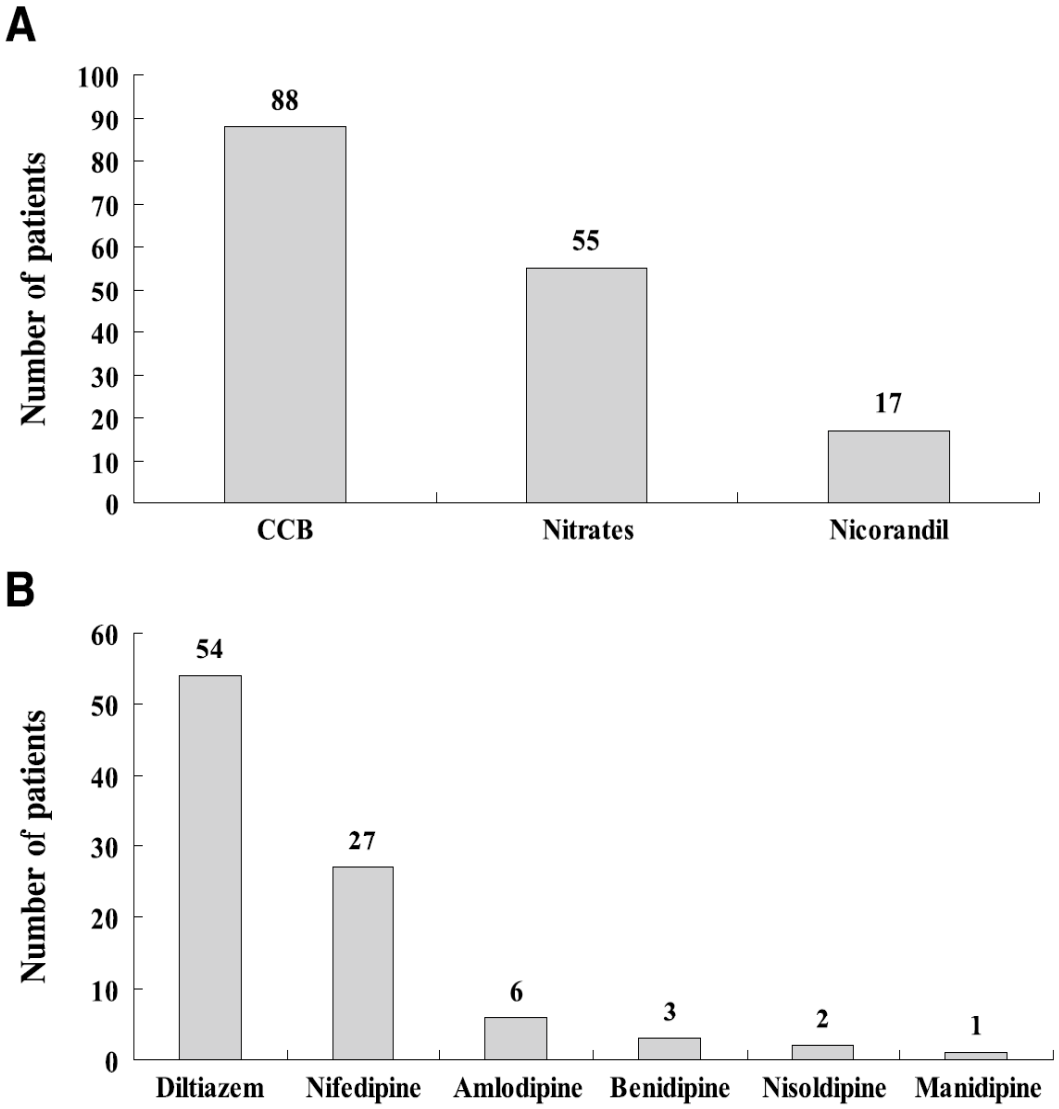
(Korean Circulation J 2002;32(4):359-362

Management

- Stop smoking
- Calcium channel blocker
- Nitrate

- Nicorandil (K_{ATP} channel, SUR-/- mouse), prazosin, steroids, ketanserin, denopamine (adrenergic beta-1 agonist), angiotensin converting enzyme inhibitors, amiodarone

Medications at diagnosis (n=90) and types calcium channel blockers (CCBs) at diagnosis.



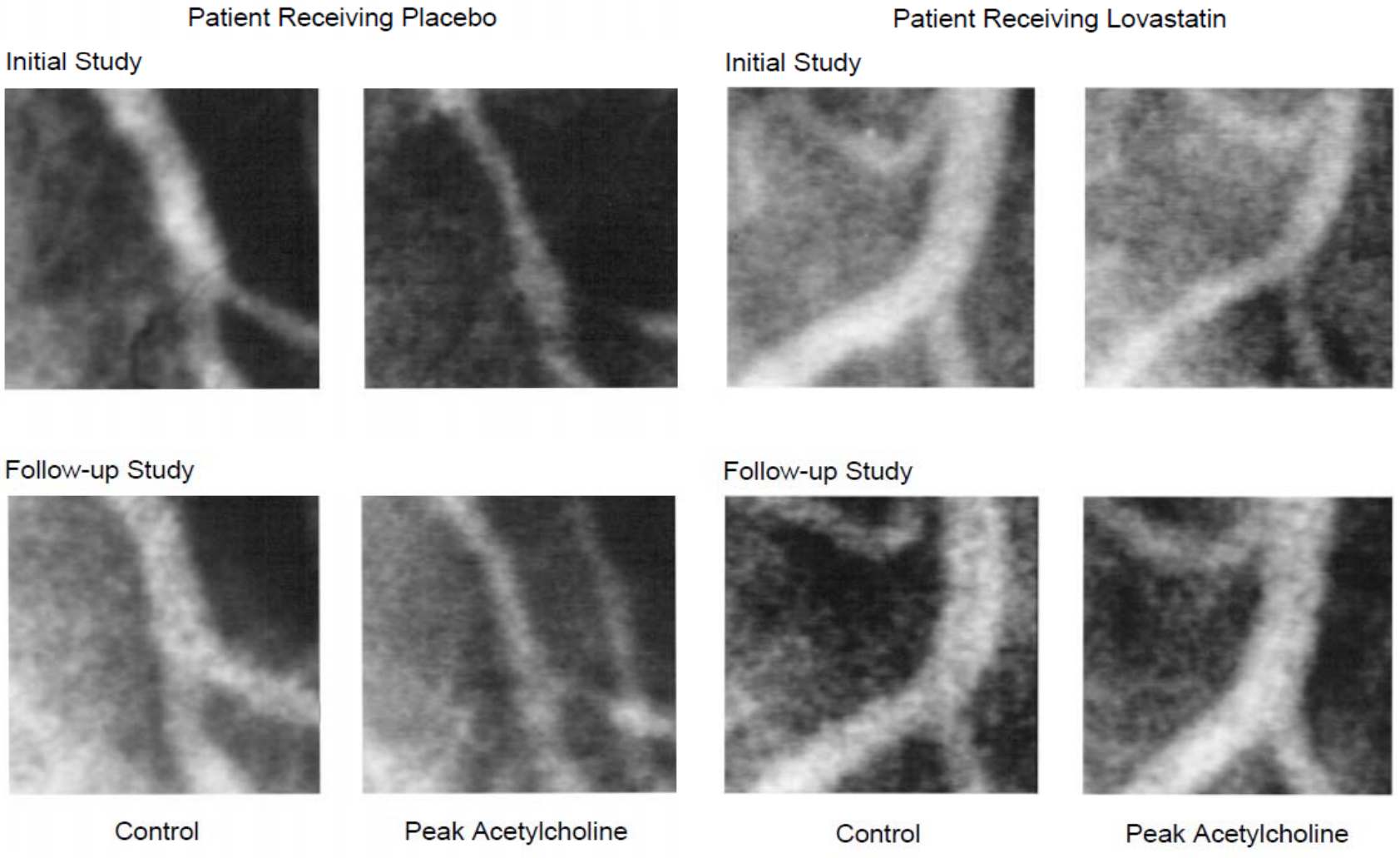
Circ J 2009; 73: 512 – 515

Korean VA, discharge medication

CCB	256 (100.0)
Diltiazem	251 (98.0)
Dihydropyridine-CCB	168 (65.6)
Verapamil	0 (0)
Nitrate	194 (75.8)
Molsidomine	13 (5.1)
Nicorandil	1 (0.4)
Statin	104 (40.6)
Aspirin	67 (26.7)
ARB/ACEI	75 (29.3)
Beta-blocker	1 (0.4)
Dosing interval	
QD	7 (2.8)
BID	248 (96.9)
TID	1 (0.4)
Stop all medications during follow-up	17 (6.6)

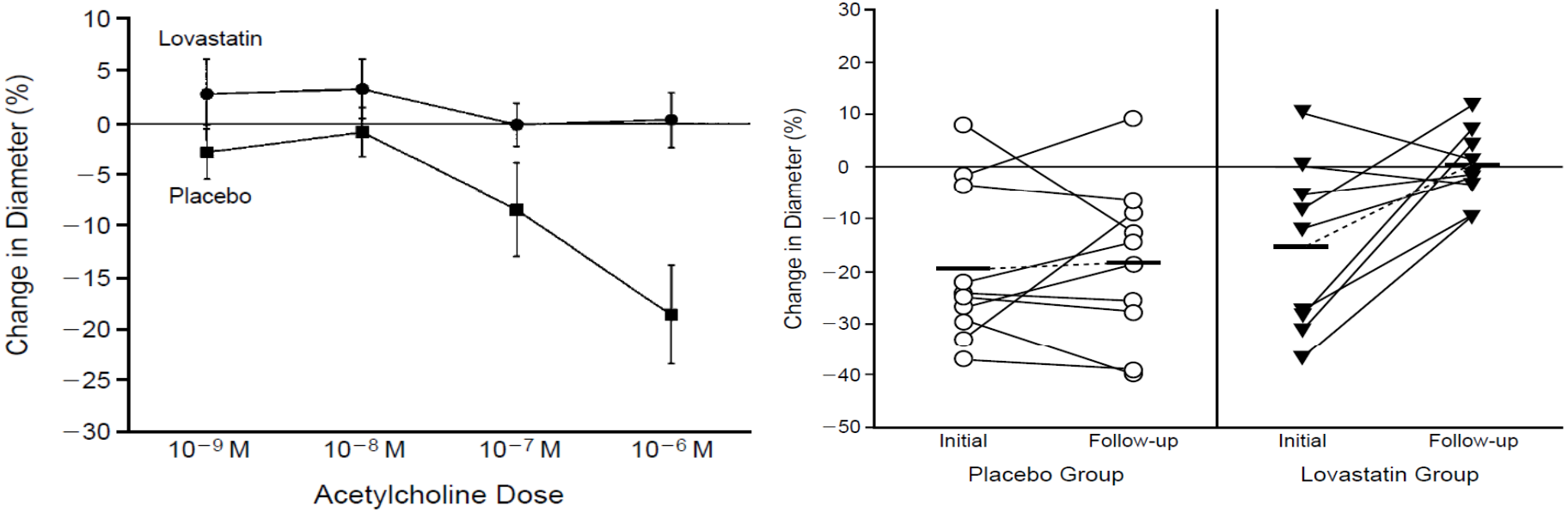
유상용등 Korean Circ J 2008;38:651-658

Statin as a vasodilator



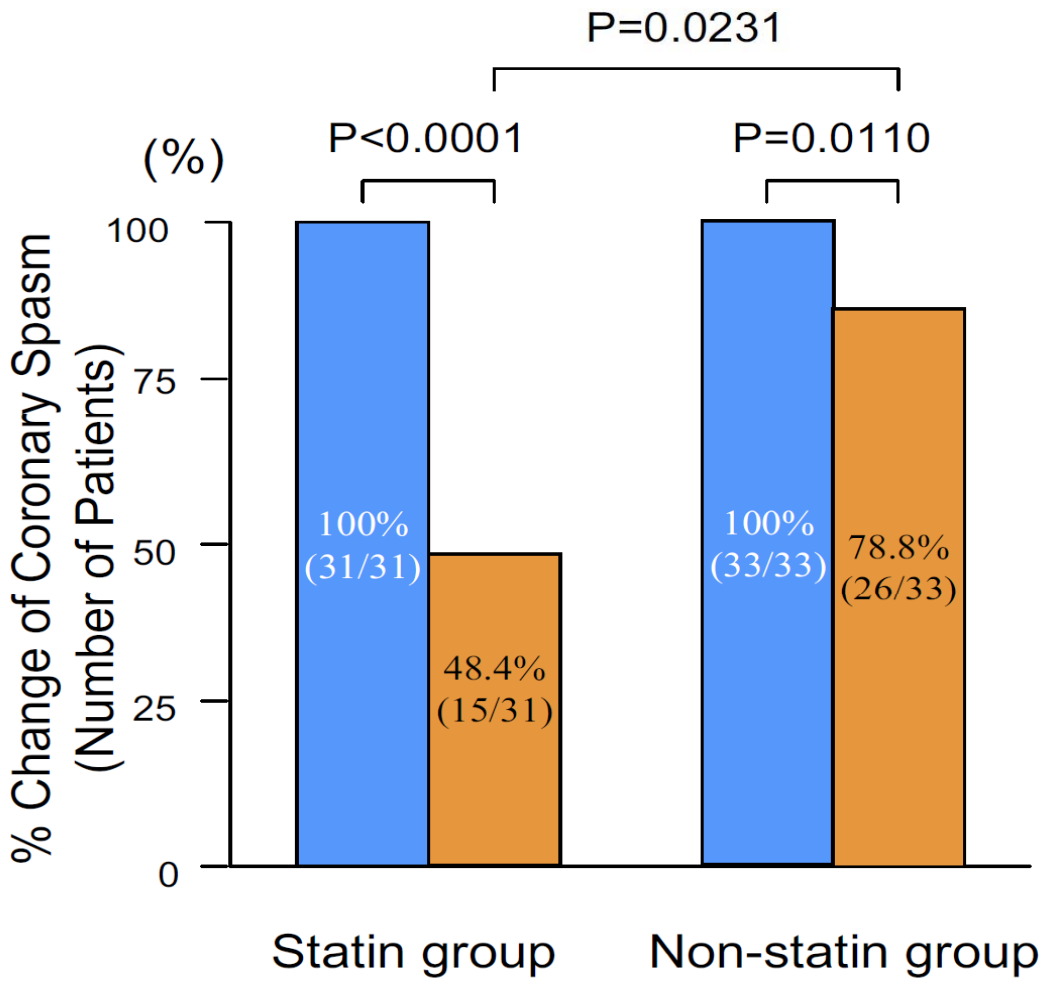
N Engl J Med 1995;332:481-7

Statin in Spasm



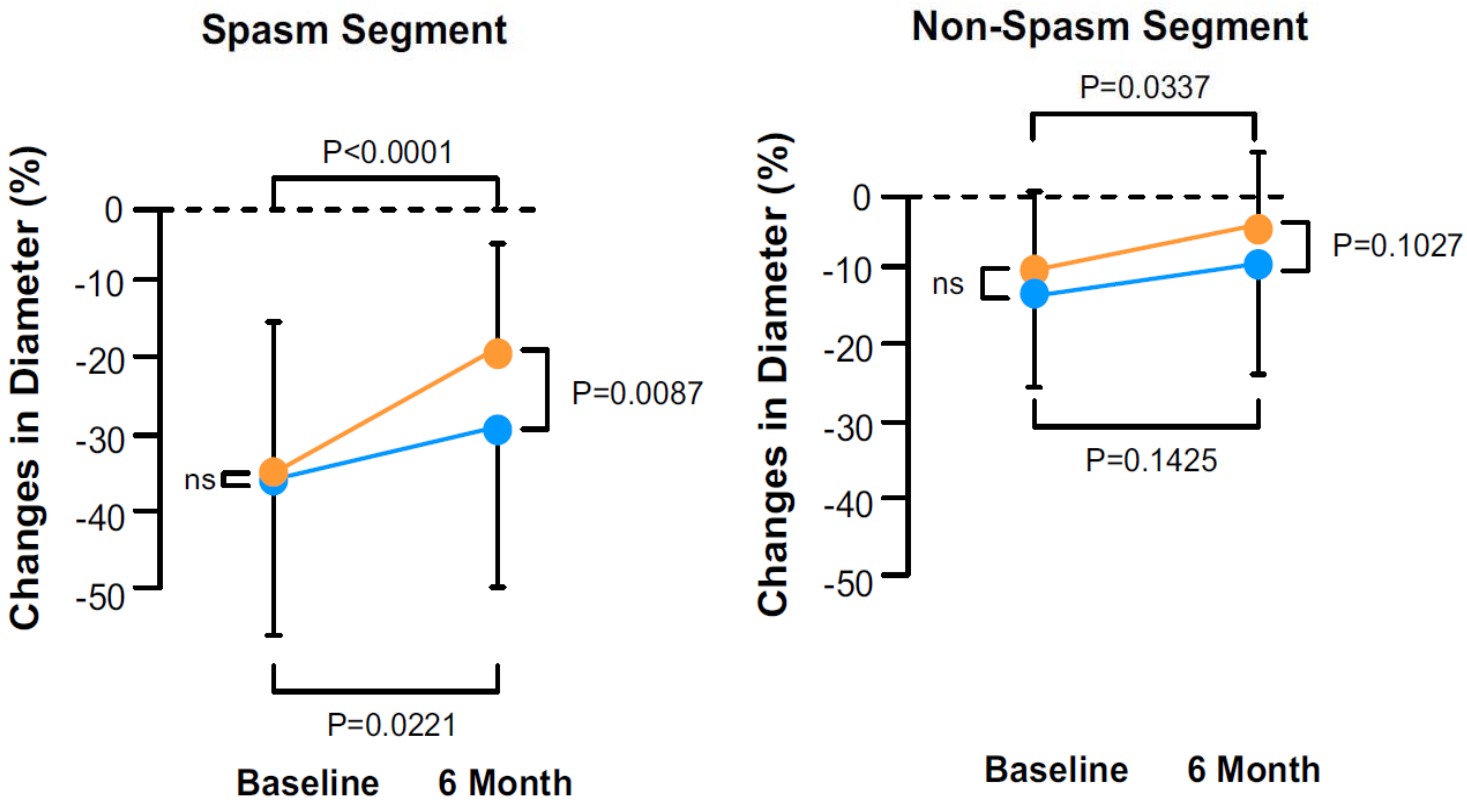
N Engl J Med 1995;332:481-7

Statin Reduce Ach-induced spasm



J Am Coll Cardiol 2008;51:1742–8

Coronary Artery Diameter Change to ACh Injection in Statin treatment



J Am Coll Cardiol 2008;51:1742–8

Successful Treatment of Refractory Vasospastic Angina With Corticosteroids

—— Coronary Arterial Hyperreactivity Caused by Local Inflammation? ——

Shuichi Takagi, MD; Yoichi Goto, MD; Eiki Hirose, MD; Masahiro Terashima, MD; Satoru Sakuragi, MD; Shoji Suzuki, MD; Yoshiaki Tsutsumi, MD; Shunichi Miyazaki, MD; Hiroshi Nonogi, MD

Background Although vasospastic angina usually responds well to treatment with calcium antagonists and/or nitrates, there have been anecdotal case reports of refractory vasospastic angina resistant to intensive treatment with high doses of calcium antagonists and nitrates.

Methods and Results Four patients with vasospastic angina, which was refractory to intensive treatment with high doses of calcium antagonists and nitrates, were completely controlled after administration of corticosteroids. Although none of the 4 patients showed eosinophilia, all had bronchial asthma or chronic thyroiditis, and in 2 cases, the activity of vasospastic angina corresponded with that of bronchial asthma.

Conclusions These findings suggest that in these patients, coronary spasm may have been induced by arterial hyperreactivity because of local inflammation in the coronary arterial wall and that the corticosteroids suppressed the arterial hyperreactivity by alleviating the inflammation. Corticosteroids may be considered as a treatment choice for patients with refractory vasospastic angina, particularly when the patient has an allergic tendency, such as bronchial asthma. (*Circ J* 2004; **68:** 17–22)

Circ J 2004; 68: 17–22

Prazosin therapy for refractory variant angina

The selective alpha$_1$ blocker prazosin was used to abolish Prinzmetal's variant angina in six patients. All had had an acute transmural myocardial infarction, after which the anginal attacks with transient ST segment elevation developed, and three of them had already suffered from variant angina prior to the infarction. Therapeutic trials with high doses of nifedipine, verapamil, nitrates, beta blockers, and (in one case) phenoxybenzamine were ineffective in all six patients. Prazosin, 8 to 30 mg/day, combined with low-dose nitrates or nifedipine completely abolished the attacks in four patients, markedly reduced their frequency and intensity in one patient, and had to be stopped in the sixth one because of hypotension and dizziness. Except for this last patient, the drug was well tolerated by all the others, and no changes in blood pressure were observed. In four patients discontinuation or reduction of prazosin resulted in exacerbation of symptoms, but its renewal was followed by disappearance of the attacks. Since the mean follow-up period in this study was 4 to 6 months, further evaluation appears necessary concerning the long-term effects of this drug in Prinzmetal's variant angina. (Am Heart J 105:262, 1983.)

Stenting and ICD in VA with aborted SCD

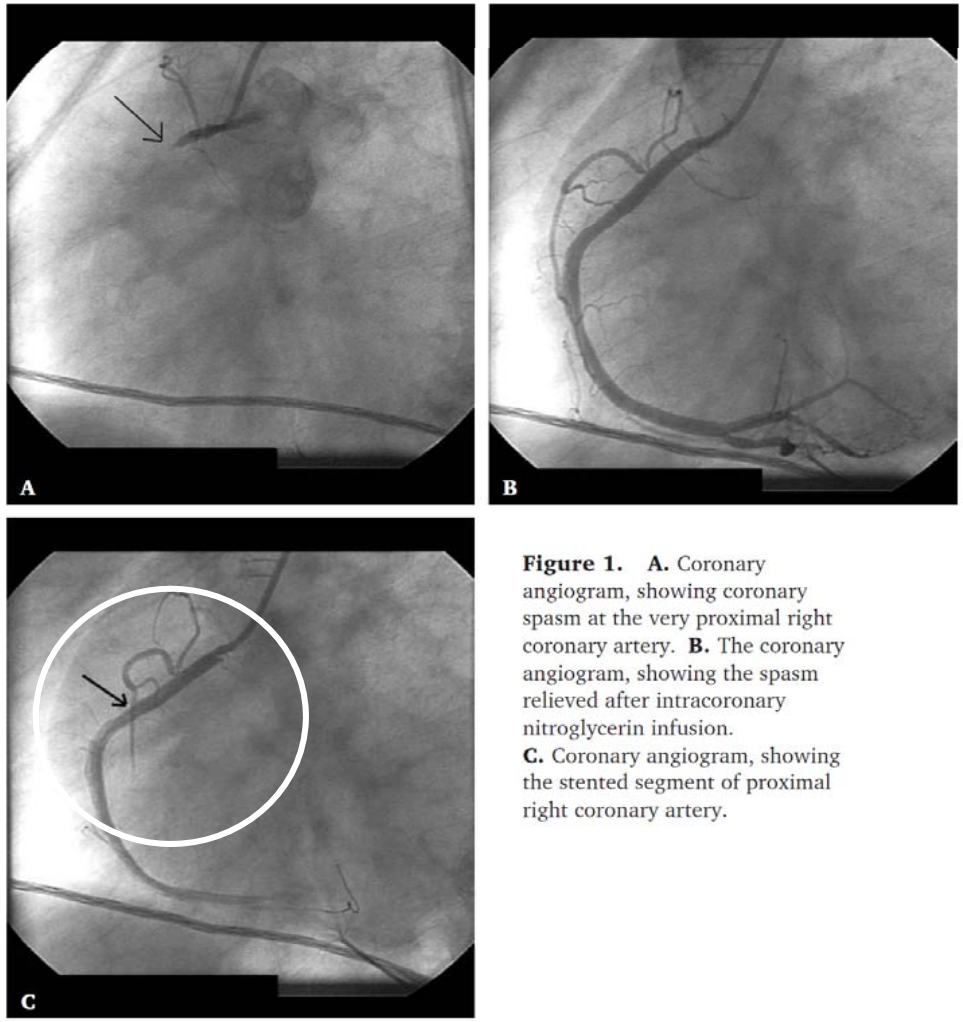


Figure 1. **A.** Coronary angiogram, showing coronary spasm at the very proximal right coronary artery. **B.** The coronary angiogram, showing the spasm relieved after intracoronary nitroglycerin infusion. **C.** Coronary angiogram, showing the stented segment of proximal right coronary artery.

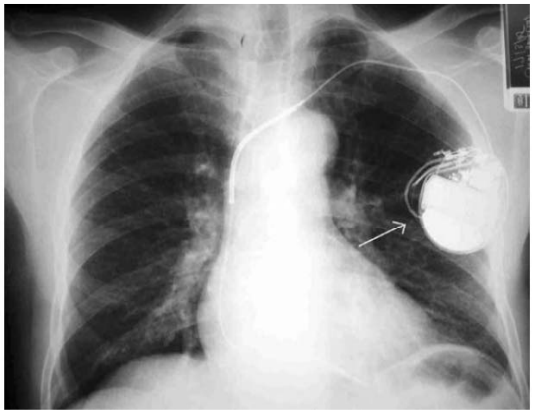
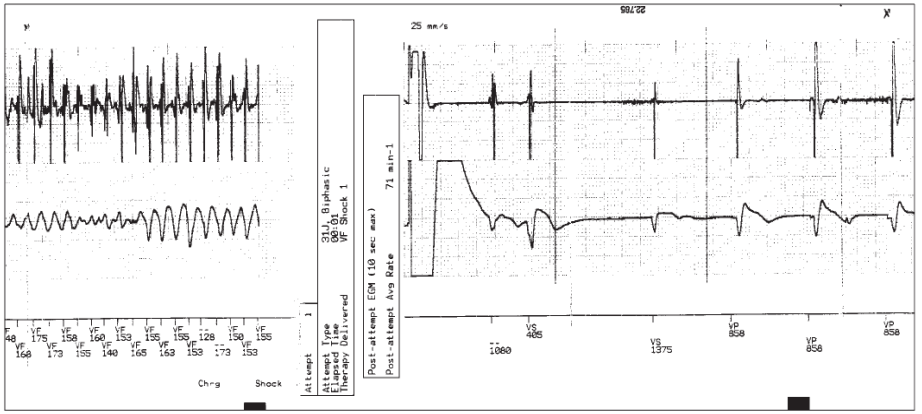


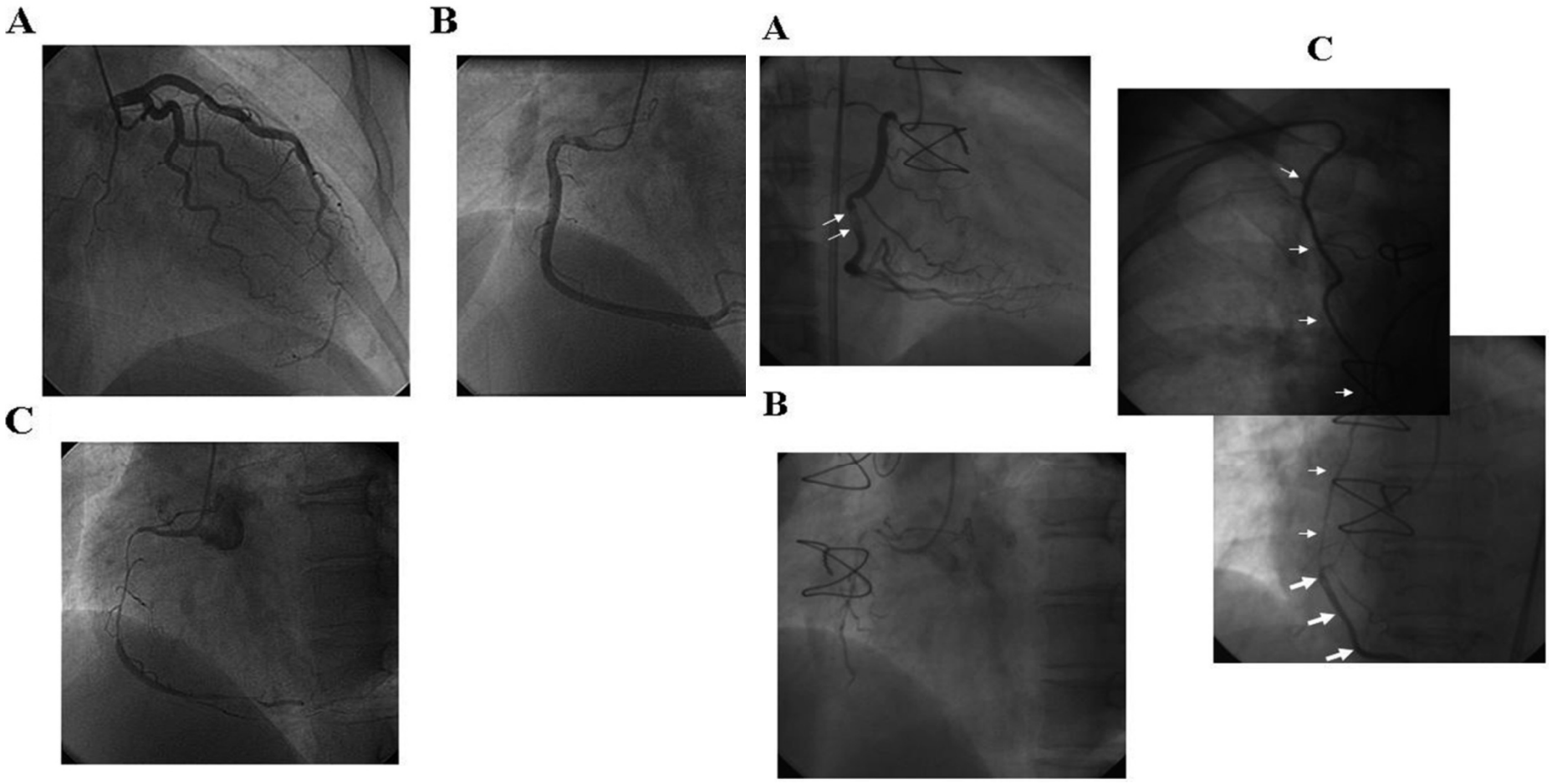
Figure 2. Chest radiograph showing cardioverter defibrillator implanted at the left pectoral region.

Figure 3. Stored electrocardiograph from the automatic implantable cardioverter defibrillator memory showing ventricular fibrillation detection and termination.



Angiology 2007; 58; 122

Bypass grafting in VA with normal coronary



Interact CardioVasc Thorac Surg. 2005;4:426-428

Cigarette smoking

- coronary endothelium becomes more sensitive to the deleterious effects of cigarette smoking
- Adversely affected nitric oxide mediated regulation of coronary artery tone
- Male > Female ?
- Decrease of incidence due to declining in smoking population ?

Conclusion

- Decreasing disease entity
- Suspicion
- Relation with ACS

- Stop smoking
- Calcium antagonist
- Nitrate
- Stenting, CABG, ICD

Provocation methods, diagnostic criteria in CAG,

➔ further study like Korean registry

Thank you