18. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Sharp characteristic x-ray irradiation from weakly ionized linear plasma," *J. Electron Spectroscopy and Related Phenomena*, **137-140**, pp. 713-720, 2004.
19. E. Sato, R. Germer, Y. Hayasi, K. Murakami, Y. Koorikawa, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, F. Obata, K. Takahashi, S. Sato, K. Takayama and Ido, H.: Weakly ionized cerium plasma radiography, *SPIE*, **5210**, pp. 12-21, 2003.
20. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Demonstration of enhanced K-edge angiography using a cerium target x-ray generator," *Med. Phys.*, **31**, 2004. in press.
21. E. Sato, K. Sato and Y. Tamakawa, "Film-less computed radiography system for high-speed Imaging," *Ann. Rep. Iwate Med. Univ. Sch. Lib. Arts and Sci.*, **35**, pp. 13-23, 2000.
*dresato@iwate-med.ac.jp; phone +81-19-651-5111; fax +81-19-654-9282

Annual Report of Iwate Medical University
School of Liberal Arts and Sciences
No. 39(2004), 1 - 9.

Cerium X-ray Spectra without Filtering and their Application to High-contrast Angiography

Eiichi Sato[a], Akira Yamadera[b], Michiaki Sagae[a], Toshio Ichimaru[b], Norihiko Morino[b], Motoki Ikeda[b], Chie Sasaki[b], Etsuro Tanaka[c], Hidezo Mori[d], Toshiaki Kawai[e], Fumihito Ito[f], Shigehiro Sato[g], Kazuyoshi Takayama[h] and Hideaki Ido[i]

(Received November 5, 2004)

Abstract

The cerium-target x-ray tube is useful in order to perform cone-beam K-edge angiography because K-series characteristic x rays from the cerium target are absorbed effectively by iodine-based contrast media. The x-ray generator consists of a main controller, an x-ray tube unit with a high-voltage circuit and an insulation transformer, and a personal computer. The tube is a glass-enclosed diode with a cerium target and a 0.5-mm-thick beryllium window. The maximum tube voltage and current were 65 kV and 0.4 mA, respectively, and the focal-spot sizes were 1.2×0.8 mm. Sharp cerium K-series characteristic x rays were observed without using a filter, and the x-ray intensity was 209 μGy/s at 1.0 m from the source with a tube voltage of 60 kV and a current of 0.40 mA. Angiography was performed with a computed radiography system using iodine-based microspheres 15 μm in diameter. In angiography of non-living animals, we observed fine blood vessels of approximately 100 μm with high contrasts.

Keywords: x-ray tube, cerium target, x-ray spectra, characteristic x rays, K-edge angiography, energy-selective radiography

[a] Department of Physics, Iwate Medical University, 3-16-1 Honchodori, Morioka 020-0015, Japan
[b] Department of Radiological Technology, School of Health Sciences, Hirosaki University, 66-1 Honcho, Hirosaki 036-8564, Japan
[c] Department of Nutritional Science, Faculty of Applied Bio-science, Tokyo University of Agriculture, 1-1-1 Sakuragaoka, Setagaya-ku 156-8502, Japan
[d] Department of Cardiac Physiology, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan
[e] Electron Tube Division #2, Hamamatsu Photonics K. K., 314-5 Shimokanzo, Toyooka Village, Iwata-gun 438-0193, Japan
[f] Digital Culutre Technology Corp., Kanno The 2nd Bldg., 3-17-7 Chuodori, Morioka 020-0021, Japan
[g] Department of Microbiology, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan
[h] Shock Wave Research Center, Institute of Fluid Science, Tohoku University, 2-1-1 Katahira, Sendai 980-8577, Japan
[i] Department of Applied Physics and Informatics, Faculty of Engineering, Tohoku Gakuin University, 1-13-1 Chuo, Tagajo 985-8537, Japan

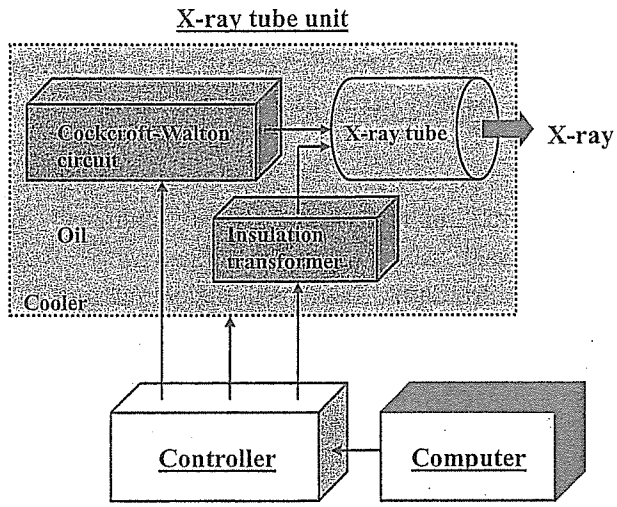

Fig. 1: Block diagram of compact x-ray generator with cerium-target radiation tube, which is used specially for K-edge angiography using iodine-based contrast media.

1. Introduction

The principle basis of quality assurance for enhanced K-edge angiography is the discontinuity of the absorption coefficient at the K-absorption edge of iodine-based contrast media, and angiography has been performed using monochromatic parallel x-ray beams with synchrotrons.[1-3] Subsequently, monochromatic x-ray computed tomography at two different energies has provided information on the electron density of human tissue.[4] In addition, a compact pulsed tunable monochromatic x-ray source has been designed, developed, and tested.[5] From the source, conical x-ray beams from 10 to 50 keV with pulse widths of 8 ps have been produced, and these beams are useful for biomedical imaging and protein crystallography.

In order to perform high-speed medical radiography, although several different flash x-ray generators[6-10] utilizing cold-cathode tubes have been developed, plasma flash x-ray generators[11-14] are useful to produce quasi-monochromatic x rays without using a K-edge filter. Therefore, we have performed a demonstration of cone-beam K-edge angiography[19] utilizing a cerium plasma generator, since K-series characteristic x rays from the cerium target are absorbed effectively by iodine.

Recently, we have developed a steady-state x-ray generator utilizing a cerium-target tube, and have demonstrated enhanced K-edge angiography utilizing a barium sulfate filter.[15] In this research, Kα lines (34.6 keV) were left by absorbing Kβ lines (39.2 keV), and bremsstrahlung x rays with photon energies of lower than the barium K-edge (37.4 keV) were also observed. However, because cerium Kβ lines are also absorbed effectively by iodine, both Kα and Kβ lines should be selected to perform angiography. In measurements of x-ray spectra, although we usually employed a cadmium tellurium detector with a photon energy resolution of 1.7 keV, the resolution should be improved as much as possible to measure the characteristic x-ray intensity.

In the present research, we measured the x-ray spectra from a cerium-target tube using a germanium detector, and performed a preliminary study on cone-beam K-edge angiography achieved with cerium characteristic x rays without using a filter.

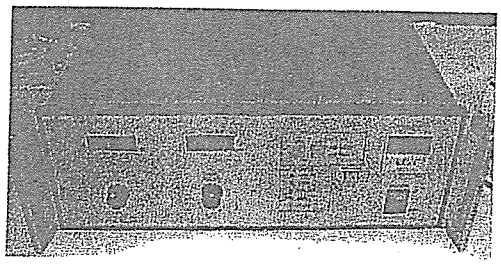

Fig. 2: Main controller.

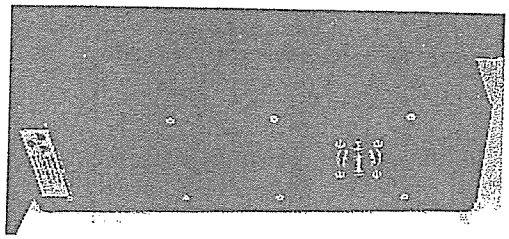

Fig. 3: X-ray tube unit.

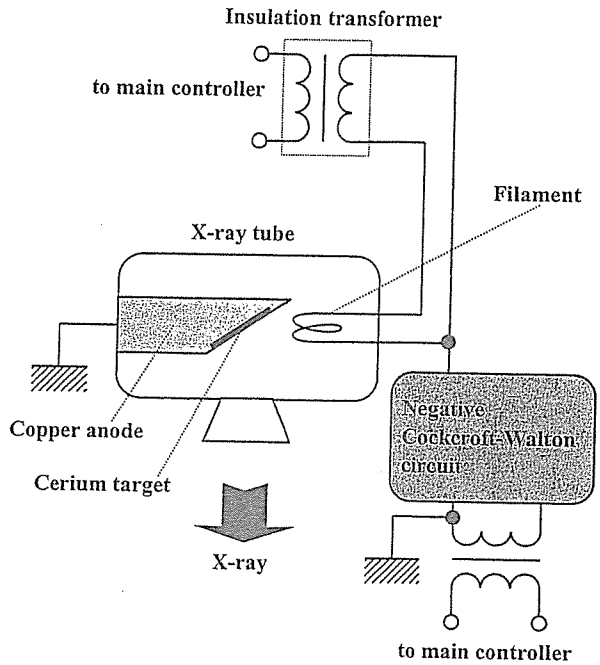

Fig. 4: Main circuit of x-ray generator.

2. Generator

Figure 1 shows the block diagram of the x-ray generator, which consists of a main controller (Fig. 2), a cerium-target x-ray tube unit (Fig. 3) with a Cockcroft-Walton circuit and an insulation transformer, and a personal computer. The tube voltage, the current, and the exposure time can be controlled by both the controller and the computer. The main circuit for producing x rays is illustrated in Fig. 4, and employs the Cockcroft-Walton circuit in order to decrease the dimensions of the tube unit. In the x-ray tube, the negative high-voltage is applied to the cathode electrode, and the anode (target) is connected to the tube unit case (ground potential) to cool the anode and the target effectively. The filament heating current is supplied by an AC power supply in the controller in conjunction with an insulation transformer. In this experiment, the tube voltage applied was from 45 to 65 kV, and the tube current was regulated to within 0.40 mA (maximum current) by the filament temperature. The exposure time is controlled in order to obtain optimum x-ray intensity.

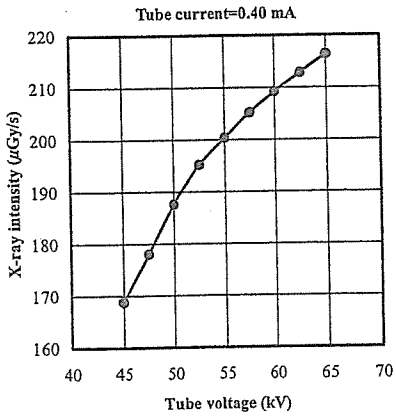

Fig. 5: X-ray intensity measured at 1.0 m from x-ray source according to changes in tube voltage.

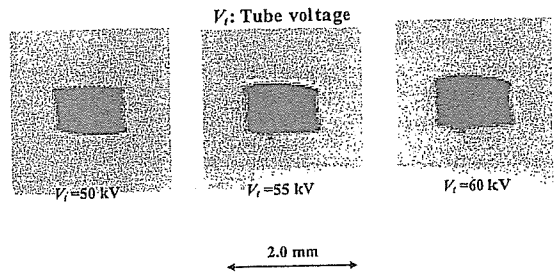

Fig. 6: Effective focal spots with changes in tube voltage.

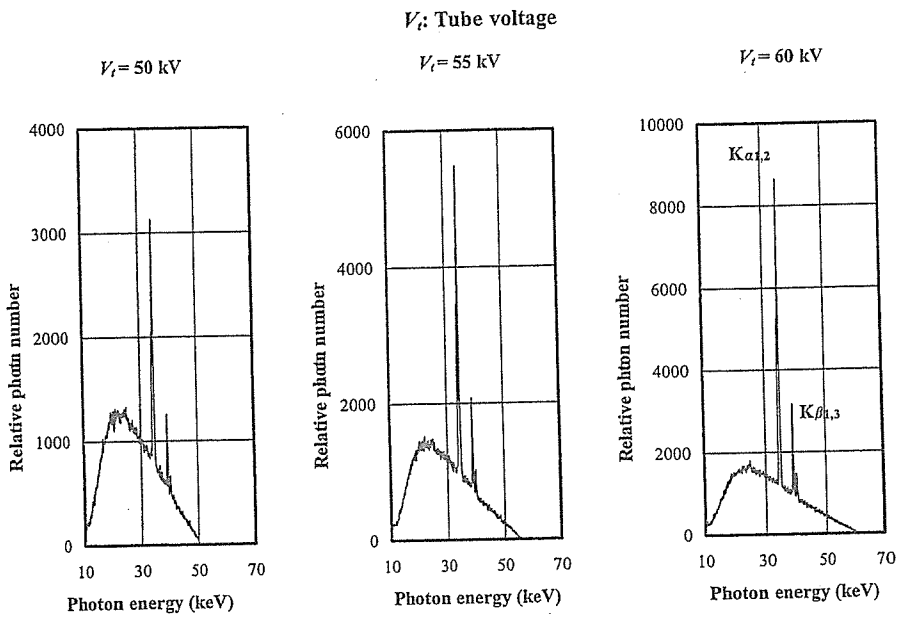

Fig. 7: X-ray spectra measured using germanium detector.

3. Characteristics

3.1 X-ray intensity

The x-ray intensity rate was measured by a Victoreen 660 ionization chamber at 1.0 m from the x-ray source (Fig. 5). At a constant tube current of 0.40 mA, the x-ray intensity increased when the tube voltage was increased. In this measurement, the intensity with a tube voltage of 60 kV and a current of 0.40 mA was 209 μGy/s with errors of less than 0.2%.

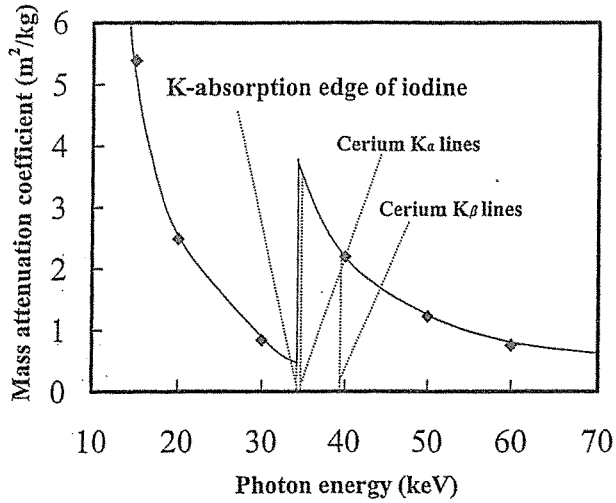

Fig. 8: Mass attenuation coefficients of iodine, and average photon energies of cerium $K\alpha$ and $K\beta$ lines.

3.2 Focal spot

In order to measure images of the x-ray source without filtration, we employed a pinhole camera with a hole diameter of 50 μm (magnification ratio of 1:2) in conjunction with a Computed Radiography (CR) system[16] with a sampling pitch of 87.5 μm. When the tube voltage was increased, spot dimensions increased slightly and had values of 1.2 × 0.8 mm (Fig. 6).

3.3 X-ray spectra

In order to measure x-ray spectra, we employed a germanium detector (GLP-10180/07-P, Ortec Inc.) (Fig. 7). When the tube voltage was increased, the characteristic x-ray intensities of $K\alpha$ and $K\beta$ lines substantially increased, and both the maximum photon energy and the intensities of bremsstrahlung x rays increased.

4. Angiography

Figure 8 shows the mass attenuation coefficients of iodine at the selected energies; the coefficient curve is discontinuous at the iodine K-edge. The average photon energy of the cerium $K\alpha$ and $K\beta$ lines are shown just above the iodine K-edge. Cerium is a rare earth element and has a high reactivity; however, the average photon energies of $K\alpha$ and $K\beta$ lines are 34.6 and 39.2 keV, respectively, and iodine contrast mediums with a K-absorption edge of 33.155 keV absorb the lines easily. Therefore, blood vessels were observed with high contrasts.

The angiography was performed by the CR system (Konica Regius 150) without using a filter, and the distance (between the x-ray source and the imaging plate) was 1.5 m. Firstly, rough measurements of spatial resolution were made using wires. Figure 9 shows radiograms of tungsten wires in a rod made of polymethyl methacrylate with a tube voltage of 55 kV. Although the image contrast decreased somewhat with decreases in the wire diameter, due to blurring of the image caused by the sampling

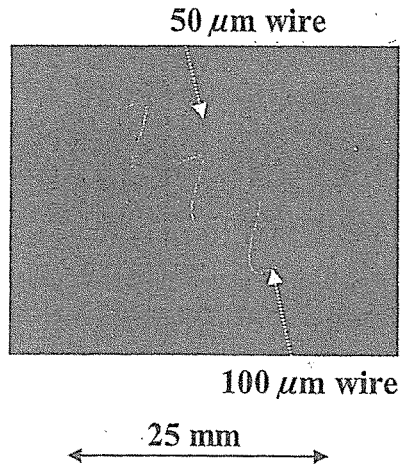

Fig. 9: Radiogram of tungsten wires in PMMA rod with tube voltage of 55 kV.

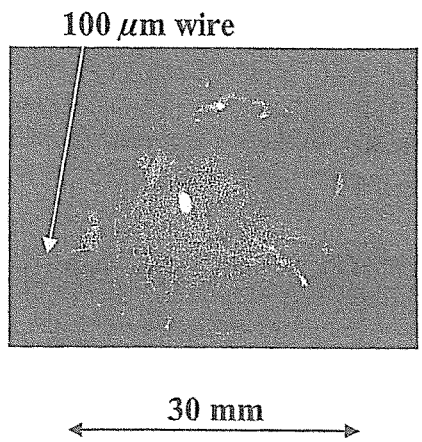

Fig. 11: Angiogram of extracted rabbit heart with tube voltage of 50 kV.

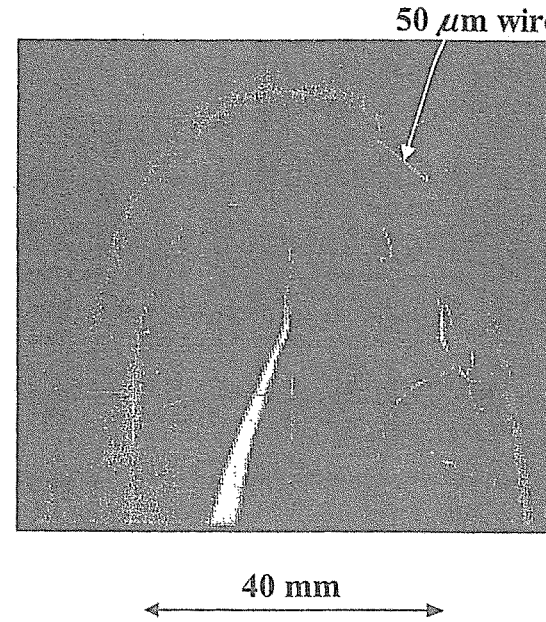

Fig. 10: Angiogram of rabbit ear with tube voltage of 50 kV.

pitch of 87.5 μm, a 50 μm-diameter wire could be observed.

Figures 10 and 11 show angiograms of a rabbit ear and heart, respectively. These images were obtained using iodine microspheres of 15 μm in diameter at a tube voltage of 50 kV. Fine blood vessels in the ear and the coronary arteries in the heart were visible. Figure 12 shows an angiogram of a larger dog heart at a tube voltage of 60 kV using iodine spheres. For comparison, we show 3-dimensional image of the coronary arteries constructed from x-ray CT images by Pascal (Digital Culture Tech. Corp.) with a tungsten x-ray tube (Fig. 13). Using this imaging technique, fine blood vessels were not observed at all.

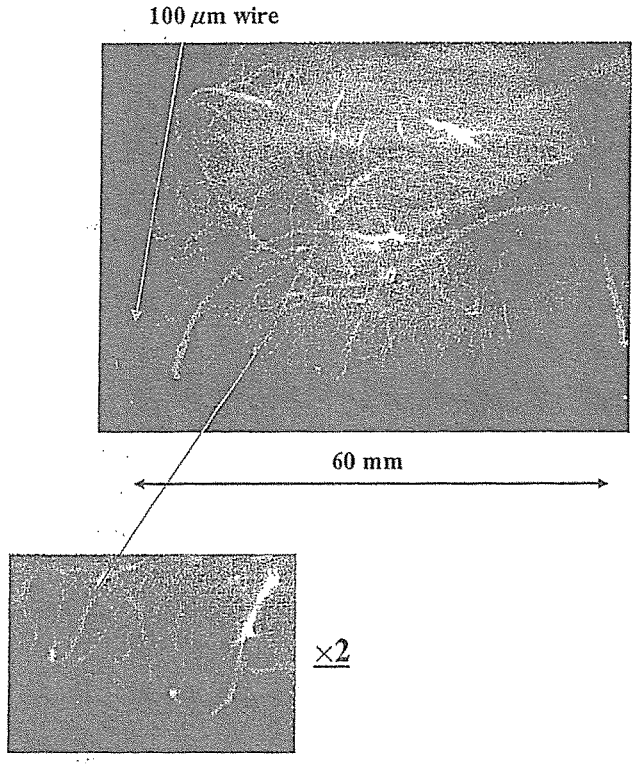

Fig. 12: Angiogram of extracted dog heart using iodine microspheres with tube voltage of 60 kV.

5. Discussion and results

In summary, we employed an x-ray generator with a cerium-target tube and succeeded in producing cerium characteristic x rays, which can be absorbed easily by iodine-based contrast media. Both the characteristic and the bremsstrahlung x-ray intensities increased with increases in the tube voltage, low-photon-energy bremsstrahlung x rays with energies of less than the iodine K edge should be absorbed by filtering to perform angiography. Without using the filter, bremsstrahlung intensity can be decreased effectively by considering the angle dependence, since bremsstrahlung rays are not emitted in the opposite direction to

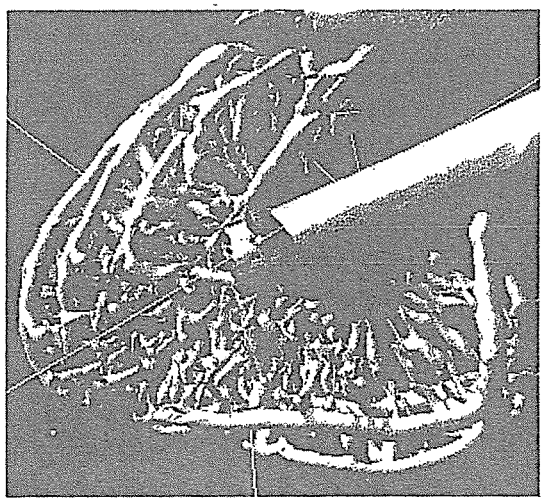

Fig. 13: 3-dimensional image of coronary arteries constructed from x-ray CT images by Pascal.

that of electron acceleration.

The x-ray intensity was limited because the thermal contact between the target and the anode was not good. However, the intensity can be increased by welding the target or using a cerium-alloy target. In addition, a rotation anode tube can be developed by sputtering of cerium.

As compared with 3-dimensional blood images constructed from x-ray CT images by Pascal, fine blood vessels were visible. Because the sampling pitch of the CR system is 87.5 μm, we obtained spatial resolutions of approximately 100 μm. In order to observe fine blood vessels of less than 100 μm, the spatial resolution of the CR system should be improved.

Acknowledgment

This work was supported by Grants-in-Aid for Scientific Research (13470154, 13877114, and 16591222) and Advanced Medical Scientific Research from MECSST, Health and Labor Sciences Research Grants (RAMT-nano-001, RHGTEFB-genome-005 and RHGTEFB-saisei-003), Grants from Keiryo Research Foundation, The Promotion and Mutual Aid Corporation for Private Schools of Japan, Japan Science and Technology Agency (JST), and New Energy and Industrial Technology Development Organization (NEDO, Industrial Technology Research Grant Program in '03).

References

1. A. C. Thompson, H. D. Zeman, G. S. Brown, J. Morrison, P. Reiser, V. Padmanabahn, L. Ong, S. Green, J. Giacomini, H. Gordon and E. Rubenstein, "First operation of the medical research facility at the NSLS for coronary angiography," *Rev. Sci. Instrum.*, **63**, 625-628, 1992.
2. H. Mori, K. Hyodo, E. Tanaka, M. U. Mohammed, A. Yamakawa, Y. Shinozaki, H. Nakazawa, Y. Tanaka, T. Sekka, Y. Iwata, S. Honda, K. Umetani, H. Ueki, T. Yokoyama, K. Tanioka, M. Kubota, H. Hosaka, N. Ishizawa and M. Ando, "Small-vessel radiography in situ with monochromatic synchrotoron radiation," *Radiology*, **201**, 173-177, 1996.
3. K. Hyodo, M. Ando, Y. Oku, S. Yamamoto, T. Takeda, Y. Itai, S. Ohtsuka, Y. Sugishita and J. Tada, "Development of a two-dimensional imaging system for clinical applications of intravenous coronary angiography using intense synchrotron radiation produced by a multipole wiggler," *J. Synchrotron Rad.*, **5**, 1123-1126, 1998.
4. M. Torikoshi, T. Tsunoo, M. Sasaki, M. Endo, Y. Noda, T. Kohno, K. Hyodo, K. Uesugi and N. Yagi: "Electron density measurement with dual-energy x-ray CT using synchrotron radiation," *Phys. Med. Biol.*, **48**, 673-685, 2003.
5. F. E. Carroll, M. H. Mendenhall, R. H. Traeger, C. Brau and J. W. Waters, "Pulsed tunable monochromatic x-ray beams from a compact source: New opportunities," *Am. J. Roentgenol.*, **181**, 1197-1202, 2003.
6. E. Sato, H. Isobe and F. Hoshino, "High intensity flash x-ray apparatus for biomedical radiography," *Rev. Sci. Instrum.*, **57**, 1399-1408, 1986.
7. E. Sato, S. Kimura, S. Kawasaki, H. Isobe, K. Takahashi, Y. Tamakawa and T. Yanagisawa, "Repetitive flash x-ray generator utilizing a simple diode with a new type of energy-selective function," *Rev. Sci. Instrum.*, **61**, 2343-2348, 1990.
8. A. Shikoda, E. Sato, M. Sagae, T. Oizumi, Y. Tamakawa and T. Yanagisawa, "Repetitive flash x-ray

generator having a high-durability diode driven by a two-cable-type line pulser," *Rev. Sci. Instrum.*, **65**, 850-856, 1994.

9. E. Sato, K. Takahashi, M. Sagae, S. Kimura, T. Oizumi, Y. Hayasi, Y. Tamakawa and T. Yanagisawa, "Sub-kilohertz flash x-ray generator utilizing a glass-enclosed cold-cathode triode," *Med. & Biol. Eng. & Comput.*, **32**, 289-294, 1994.
10. E. Sato, M. Sagae, E. Tanaka, Y. Hayasi, R. Germer, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Quasi-monochromatic flash x-ray generator utilizing a disk-cathode molybdenum tube," *Jpn. J. Appl. Phys.*, **43**, 7324-7328, 2004.
11. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, H. Obara, T. Ichimaru, K. Takayama and H. Ido, "Irradiation of intense characteristic x-rays from weakly ionized linear molybdenum plasma," *Jpn. J. Med. Phys.*, **23**, 123-131, 2003.
12. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, K. Takayama and H. Ido, "Quasi-monochromatic flash x-ray generator utilizing weakly ionized linear copper plasma," *Rev. Sci. Instrum.*, **74**, 5236-5240, 2003.
13. E. Sato, R. Germer, Y. Hayasi, Y. Koorikawa, K. Murakami, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, F. Obata, K. Takahashi, S. Sato, K. Takayama and H. Ido, "Weakly ionized plasma flash x-ray generator and its distinctive characteristics," *SPIE*, **5196**, 383-392, 2003.
14. E. Sato, Y. Hayasi, R. Germer, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Sharp characteristic x-ray irradiation from weakly ionized linear plasma," *J. Electron Spectrosc. Related Phenom.*, **137-140**, 713-720, 2004.
15. E. Sato, E. Tanaka, H. Mori, T. Kawai, T. Ichimaru, S. Sato, K. Takayama and H. Ido, "Demonstration of enhanced K-edge angiography using a cerium target x-ray generator," *Med. Phys*, **31**, 3017-3021, 2004.
16. E. Sato, K. Sato and Y. Tamakawa, "Film-less computed radiography system for high-speed imaging," *Ann. Rep. Iwate Med. Univ. Sch. Lib. Arts and Sci.*, **35**, 13-23, 2000.

Circ J 2004; **68:** 17–22

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)

Key Words: Coronary artery spasm; Corticosteroids; Inflammation; Vasospastic angina

Vasospastic angina (VSA) usually well responds to treatment with calcium antagonists and nitrates. We present 4 cases of VSA that was refractory to intensive anti-anginal treatment with high doses of calcium antagonists, nitrates and nicorandil.

Clinical Reports

Case 1

A 39-year-old woman was admitted to hospital because of frequent chest pain at rest (Table 1). She had chronic thyroiditis, which had been controlled with medications 11 years ago. Ten years ago, she suffered from anteroseptal myocardial infarction, and thereafter, had chest pain of short duration at rest 3–4 times per year for several years. Four years ago, she was admitted to hospital for work-up for worsening chest pain. A diagnosis of VSA was made because the 12-lead electrocardiogram (ECG) showed transient ST segment elevation in leads II, III and aVF during her chest pain attacks and coronary arteriography (CAG) showed normal coronary arteries without any atherosclerotic stenosis. Treatment with nifedipine 80 mg/day was begun, which effectively controlled her angina.

One month before the current admission, chest pain attacks at rest occurred 5–10 times per day despite intensive treatment with nifedipine (80 mg/day), isosorbide dinitrate (ISDN) (160 mg/day) and nicorandil (80 mg/day), and she was admitted with the diagnosis of unstable angina. The angina attacks were not related to her menstrual cycle. Analysis of her blood sample did not show any eosinophilia or elevation of serum inflammatory markers. Despite continuous intravenous infusion of both nitroglycerin ($2\mu g \cdot kg^{-1} \cdot min^{-1}$) and nicorandil (2 mg/h), the frequent chest pain attacks with ST segment elevation were not suppressed (Fig 1). CAG showed normal coronary arteries without any atherosclerotic stenosis and ultrasound cardiography (UCG) showed the anteroseptal old myocardial infarction without any new contraction abnormality. Oral administration of prednisolone 40 mg/day was begun, resulting in a complete relief of the chest pain attacks within 1 week, and the intravenous nitroglycerin and nicorandil were discontinued uneventfully. Because her angina recurred after a quick tapering of prednisolone to 5 mg/day, the dose was increased to 20 mg/day, resulting in amelioration of the angina again.

After her angina was satisfactorily controlled with prednisolone, we administered a placebo of prednisolone, while keeping other anti-anginal drugs unchanged, and her angina worsened again. Thereafter, prednisolone was slowly tapered off without a relapse of the angina. She remained well controlled with nifedipine, ISDN and nicorandil until 6 months after discontinuation of prednisolone, when she was re-admitted to hospital with a severe attack of VSA complicated with ventricular fibrillation. Despite intensive therapy, she died of multiple organ failure on the

(Received July 29, 2003; revised manuscript received September 26, 2003; accepted October 14, 2003)

Division of Cardiology, National Cardiovascular Center, Suita, Japan
Mailing address: Yoichi Goto, MD, PhD, Division of Cardiology, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. E-mail: ygoto@hsp.ncvc.go.jp

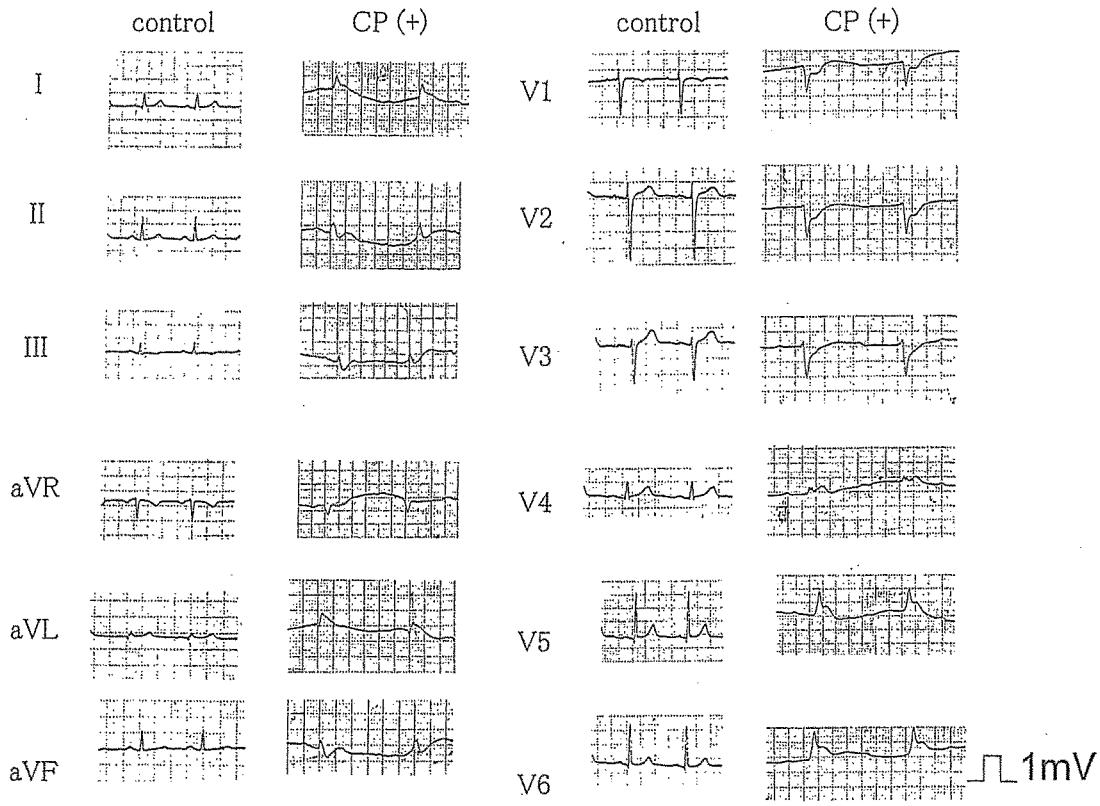

Fig 1. ECG of Case 1 showing bradycardia (heart rate: 50 beats/min), ST elevation in leads I, aVL and V4–6 and ST depression in leads V1–3 during chest pain (CP (+)) compared with control ECG.

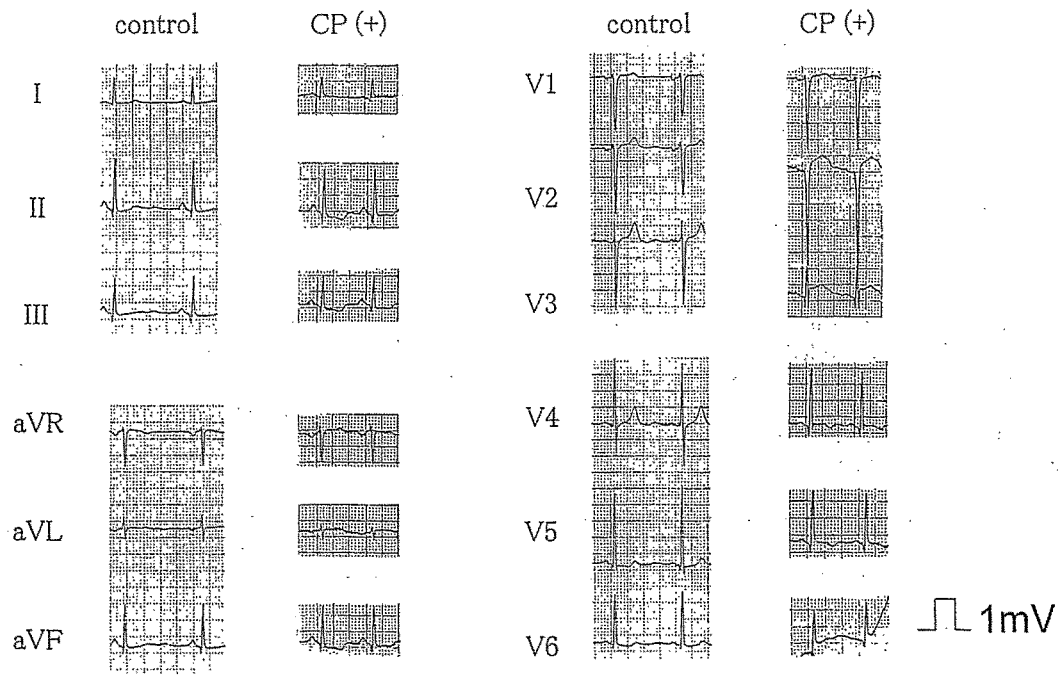

Fig 2. ECG of Case 2 showing ST elevation in leads V2–4 during chest pain (CP (+)) compared with control ECG.

82nd hospital day.

Case 2

A 43-year-old woman was admitted to hospital as an emergency because of frequent chest pain attacks at rest. She had bronchial asthma, which was controlled with medications 2 years ago. In the same year, she was admitted to hospital for work-up for episodes of chest pain at rest. CAG

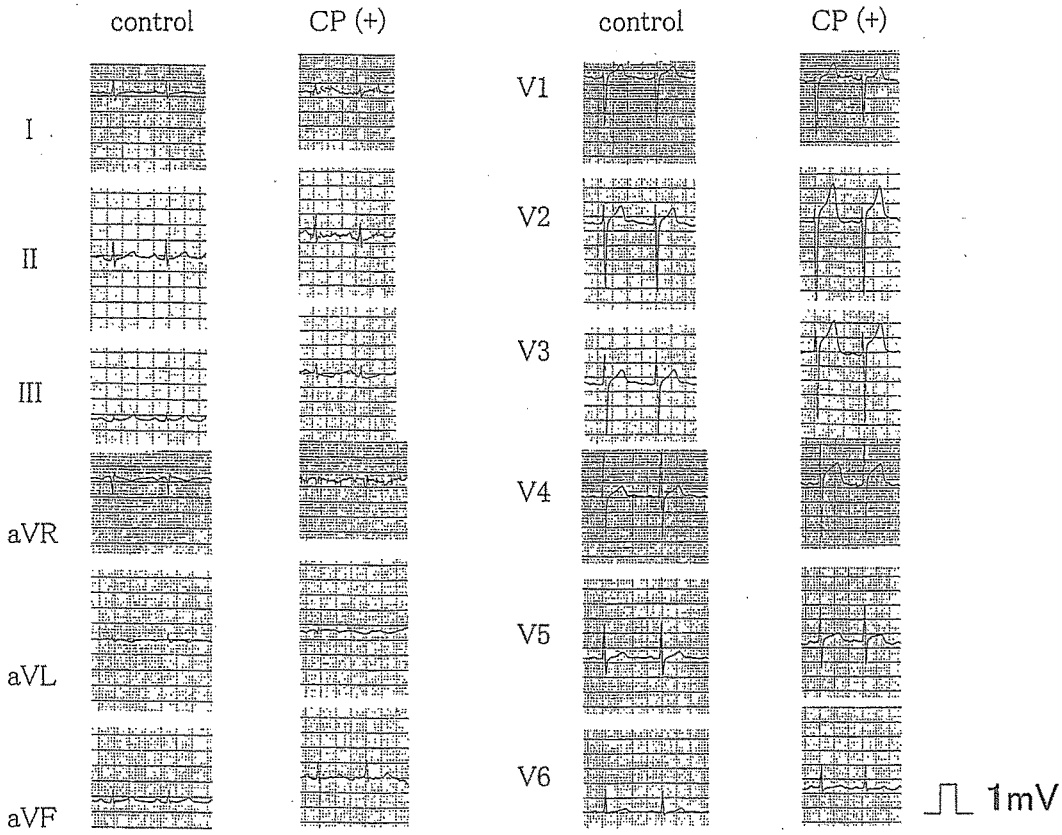

Fig 3. ECG of Case 3 showing ST elevation in leads I, aVL and V2-5 during chest pain (CP (+)) compared with control ECG.

Table 1 Characteristics of the 4 Cases

	Case no.			
	1	*2*	*3*	*4*
Gender	*Female*	*Female*	*Male*	*Female*
Onset age (year)	*29*	*41*	*45*	*43*
Smoking habit	*(–)*	*Past**	*(–)*	*(–)*
Diabetes mellitus	*(–)*	*(–)*	*(–)*	*(–)*
Hyperlipidemia	*(–)*	*(–)*	*(+)*	*(–)*
Hypertension	*(–)*	*(–)*	*(+)*	*(+)*
Complicating disease	*Chronic thyroiditis*	*Bronchial asthma*	*Bronchial asthma*	*Bronchial asthma*

Onset age, age at the onset of vasospastic angina; Past, history of smoking when 20–38 years old.*

showed no atherosclerotic stenosis in the coronary arteries and intracoronary administration of ergometrine maleate (40 μg) induced a transient occlusion of the left anterior descending coronary artery accompanied by ST segment elevation in leads V2-4 and chest pain, which were promptly relieved by intracoronary administration of 0.5 μg nitroglycerin (Fig 2). A diagnosis of VSA was made and treatment with nifedipine (40 mg/day), diltiazem (120 mg/day), nicorandil (20 mg/day) and ISDN (160 mg/day) effectively controlled her angina.

Ten days before the current admission, her bronchial asthma and chest pain attacks at rest recurred and worsened progressively. She was admitted as an emergency. There was no sign of heart failure and the chest pain attacks were not related to her menstrual cycle. Analysis of her blood sample showed a slight elevation of C-reactive protein (CRP: 0.5 mg/dl; normal <0.3 mg/dl), but did not show eosinophilia or an elevation of the erythrocyte sedimentation rate. Apart from the bronchial asthma, her chest pain at rest was diagnosed as VSA because it was accompanied by ST segment elevation in the anterior chest leads on ECG. Intravenous administration of corticosteroids (hydrocortisone sodium succinate 600 mg/day) and aminophylline (500 mg/day) was added to her regimen of oral anti-anginal drugs (nifedipine 40 mg/day, diltiazem 120 mg/day, nicorandil 20 mg/day and ISDN 160 mg/day) and a broncho-dilator (procaterol hydrochloride 100 μg/day), which successfully relieved both the bronchial asthma and angina attacks with ST segment elevation. Oral prednisolone (5 mg/day) was administered thereafter without any relapse of angina attacks. An uneventful course was confirmed at 5-year follow-up.

Case 3

A 55-year-old man was admitted to hospital as an emergency because of frequent chest pain attacks at rest. He had

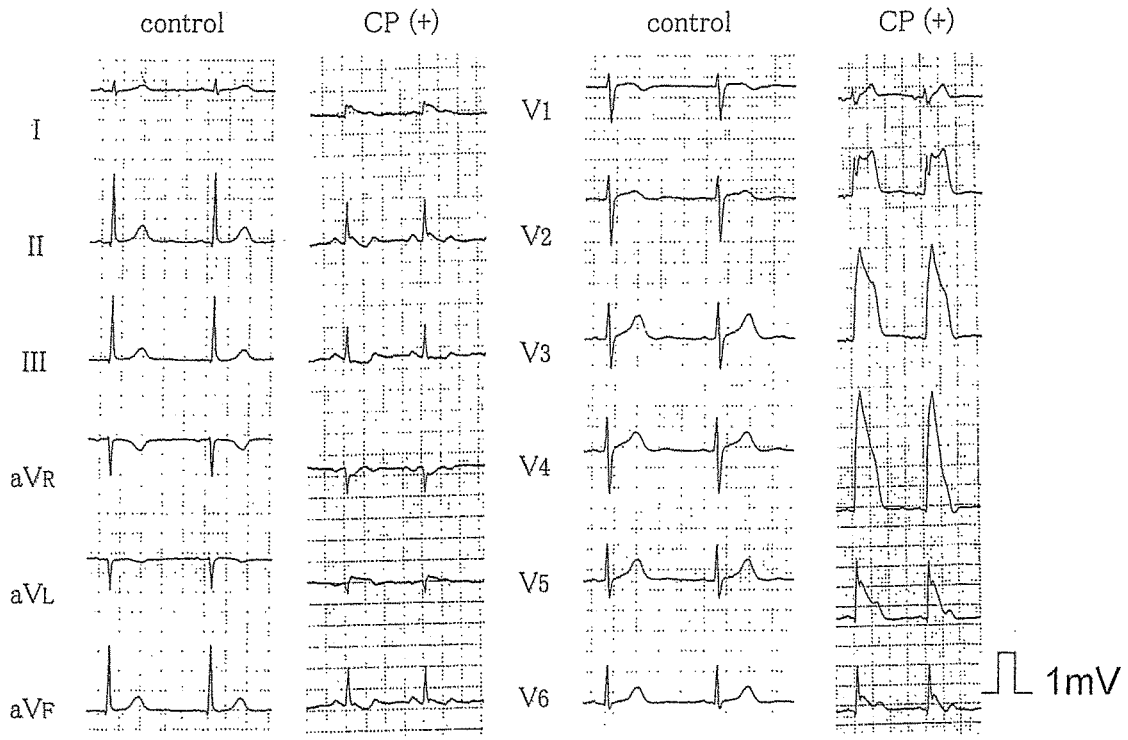

Fig 4. ECG of Case 4 showing ST elevation in leads I, aVL and V2–6 and ST depression in leads III and aVF during chest pain (CP (+)) compared with control ECG.

bronchial asthma, which was controlled with medications 27 years ago. Ten years ago, he was admitted to hospital because of episodes of chest pain at rest. CAG showed no atherosclerotic stenosis in the coronary arteries and intracoronary administration of ergometrine maleate (40 μg) induced a transient occlusion of the left anterior descending coronary artery with ST segment elevation in leads V1–6, which was relieved by intracoronary administration of nitroglycerin. A diagnosis of VSA was made and medications with diltiazem (200 mg/day) and ISDN (40 mg/day) effectively controlled his angina.

One month before the current admission, his bronchial asthma and chest pain attacks at rest recurred despite the unchanged medications. At 06.00 h on the day of admission, severe chest pain occurred and did not respond to sublingual nitroglycerin. He was admitted as an emergency. Analysis of his blood sample did not show any elevation of serum inflammation markers or eosinophilia. CAG showed no atherosclerotic stenosis in the coronary arteries and the UCG findings were within normal limits. Because transient ST segment elevation in leads V1–6 was documented during his chest pain attack at rest (Fig 3), the chest pain attack was diagnosed as VSA and nifedipine (80 mg/day) was added to the treatment regimen. Because the attacks of both bronchial asthma and VSA did not improve, oral corticosteroid therapy (prednisolone 30 mg/day) was started, which successfully relieved both conditions. At 5-year follow-up, he has been taking oral prednisolone 5 mg/day with occasional asthma attacks, but without any angina.

Case 4

A 46-year-old woman was admitted to hospital because of chest pain at rest. Although she was diagnosed as having bronchial asthma in childhood, she has not had symptoms in the past 5 years and was not taking any anti-asthmatic medication. Ten years ago, she started to have episodes of chest pain at rest 2–3 times a day, and 3 years ago, she was admitted to another hospital because she had severe chest pain accompanied by syncope. CAG showed no atherosclerotic stenosis in the coronary arteries and intracoronary administration of ergometrine maleate induced transient stenoses (vasospasm) in the left anterior descending and circumflex coronary arteries with ST segment elevation in leads V3–6. A diagnosis of VSA was made and medication with nifedipine 20 mg/day, diltiazem 120 mg/day, amlodipine 10 mg/day, nicorandil 20 mg/day, ISDN 80 mg/day, and isosorbide mononitrate 80 mg/day significantly, but not completely, decreased her angina attacks.

At 04.30 h on the day of the current admission, she had severe chest pain at rest accompanied by syncope and urinary incontinence, and was admitted as an emergency. The angina attacks were not related to her menstrual cycle. Neurological examinations revealed no abnormality and the chemical analysis of her blood samples and the UCG findings were within normal limits. Although her angina attacks with ST segment elevation in leads V3–6 were effectively controlled with intravenous infusion of nitroglycerin, they relapsed when the infusion was tapered (Fig 4). Increasing doses of the oral anti-anginal medications (nifedipine 80 mg/day, diltiazem 240 mg/day, nicorandil 40 mg/day, ISDN 120 mg/day) controlled the spontaneous angina attacks, but did not suppress the attacks with ST depression in leads V3–6 provoked by a hyperventilation test performed 10 days after increasing the dosages of the anti-anginal medications. Oral corticosteroid (prednisolone 30 mg/day) was started, which completely suppressed the spontaneous angina attacks, and neither chest pain nor ST segment change was provoked in a hyperventilation test

performed 10 days after starting the corticosteroid.

One year after hospital discharge when the dose of prednisolone was gradually decreased and reached 10 mg/day, her angina attacks at rest relapsed and the dosage had to be increased again to 15 mg/day, resulting in symptomatic improvement.

Discussion

This is the first report demonstrating that there is a group of patients with severe VSA refractory to intensive antianginal treatment who benefit from corticosteroid therapy. The allergic component and the effectiveness of corticosteroids suggest that coronary vascular hyperreactivity because of local inflammation of the vessel wall may be responsible for coronary artery spasm in these patients.

Refractory VSA

Vasospastic angina usually responds well to treatment with calcium antagonists and/or nitrates, but there have been case reports of refractory VSA resistant to intensive treatment with high doses of these drugs[1,2] and all of the 4 cases presented here were highly resistant to intensive treatment with high doses of calcium antagonists, nitrates and nicorandil. Although percutaneous coronary intervention with stenting has been reported to be effective in such cases[1,2] it may not work in cases of multivessel coronary spasm or diffuse spasm in the entire coronary artery tree, and the problem of restenosis affecting the long-term prognosis has not been solved[3]

Mechanism of Efficacy of Corticosteroids

Several reports have suggested a possible link between allergic diseases and coronary spasm[4–8] Okada et al reported a case of VSA accompanied by chronic thyroiditis and eosinophilia in which corticosteroid therapy effectively alleviated the VSA, suggesting that the corticosteroids suppressed some allergic response of the coronary artery associated with eosinophilia[4] Although none of the present cases showed eosinophilia, all 4 had either bronchial asthma or chronic thyroiditis, and in 2 cases, the occurrence of the VSA coincided with that of bronchial asthma.

The pathogenesis of bronchial asthma has been recently attributed to hyperreactivity of the airway caused by inflammation and corticosteroids are considered to work by alleviating that inflammation[9,10] There is an analogy with the pathophysiology of VSA; that is, coronary spasm may be induced by arterial hyperreactivity caused by local inflammation in the coronary arterial wall and corticosteroids suppress the hyperreactivity by alleviating the inflammation in the vessel wall. In fact, Forman et al reported a patient with VSA complicated by sudden death in whom mast cell infiltration was found at the site of angiographic documentation of coronary spasm[11] Also, Kohchi et al reported that focal infiltration of inflammatory cells was seen in the adventitia of the coronary artery in patients with VSA[12,13] Thus, local inflammation of the coronary arterial wall is likely to play an important role in the pathogenesis of coronary spasm.

Another potential mechanism of the efficacy of corticosteroids in VSA is a direct action on coronary arterial vascular smooth muscle cells. Miyagawa et al suggested that vascular hyperreactivity in postmenopausal women can be normalized by ovarian steroid hormone through its direct action on the intracellular Ca^{2+} signals and protein kinase C of coronary arterial vascular smooth muscle cells[14–16]

Clinical Implications

The result of the present study indicates that corticosteroids should be considered in the choice of treatment for patients with refractory VSA. Because the exact underlying mechanisms of vasospastic angina remain unknown, corticosteroid therapy deserves further investigation in a larger number of patients with VSA.

Whether this treatment strategy can be applied to patients with the usual (non-vasospastic) type of unstable angina is unknown. Intriguingly, there is an emerging view that inflammation in the coronary arterial wall may play a significant role in the pathogenesis of unstable angina[17,18] However, Azar et al reported that anti-inflammatory therapy with methylprednisolone was not effective in the treatment of patients with unstable angina[19] and therefore, the present result can not be generalized.

On the basis of the present findings, the therapeutic options for refractory VSA not responding to intensive treatment with high doses of 2 kinds of calcium antagonists and a sufficient dose of nitrate can be discussed. When localized coronary spasm at the site of a segmental arteriosclerotic stenosis is responsible for the symptoms, percutaneous coronary intervention may be the choice. When a patient with refractory VSA has an allergic tendency, such as bronchial asthma, corticosteroids may be the choice. Alternatively, there are case reports showing that β-stimulants were effective[20,21] Of course, further studies are necessary to determine the long term efficacy of each treatment option and thereby establish the definitive treatment strategy for refractory VSA.

Conclusion

We report 4 cases of VSA that were refractory to the usual intensive treatment, but were successfully treated with corticosteroids. Therefore, corticosteroids should be considered in the treatment of patients with refractory VSA.

Acknowledgments

We thank Eriko Ikada and Emiko Terasaka for their assistance with the manuscript.

References

1. Serrador A, Roman JA, Duran JM, Gimeno F, Vega JL, Fernandez-Aviles F. Successful treatment of vasospastic angina with a coronary stent. *J Invasive Cardiol* 2000; **12:** 586–588.
2. Rabinowitz A, Dodek A, Carere RG, Webb JG. Stenting for treatment of coronary vasospasm. *Cathet Cardiovasc Diagn* 1996; **39:** 372–375.
3. Tanabe Y, Itoh E, Suzuki K, Ito M, Hosaka Y, Nakagawa I, et al. Limited role of coronary angioplasty and stenting in coronary spastic angina with organic stenosis. *J Am Coll Cardiol* 2002; **39:** 1120–1126.
4. Okada H, Koganei H, Yoshioka S, Enta K, Suzuki K, Kato J, et al. Multi-vasospastic angina refractory to medical therapy caused by hyperthyroid stage of chronic thyroiditis and hypereosinophilia: A case report. *J Cardiol* 2000; **35**(Suppl): 189–196 (in Japanese).
5. Iwata K, Yamaguchi K, Amagasa S, Horikawa H. Coronary artery spasm during anesthetic induction in a patient with bronchial asthma. *Masui (Jpn J Anesth)* 1997; **46:** 1499–1502 (in Japanese).
6. Habbab MA, Szwed SA, Haft JI. Is coronary arterial spasm part of the aspirin-induced asthma syndrome? *Chest* 1986; **90:** 141–143.

7. Jazayeri MR, Reen BM, Edwards JA. Asthma induced myocardial infarction in a patient with normal coronary arteries: A case report and a pathogenetic hypothesis. *J Med* 1983; **14:** 351–361.
8. Gersh BJ, Bassendine MF, Forman R, Walls RS, Beck W. Coronary artery spasm and myocardial infarction in the absence of angiographically demonstrable obstructive coronary disease. *Mayo Clin Proc* 1981; **56:** 700–708.
9. Creticos PS. Managing asthma in adults. *Am J Manag Care* 2000; **6**(Suppl): S940–S963.
10. Busse WW, Lemanske RF Jr. Asthma. *N Engl J Med* 2001; **344:** 350–362.
11. Forman MB, Oates JA, Robertson D, Robertson RM, Roberts LJ 2nd, Virmani R. Increased adventitial mast cells in a patient with coronary spasm. *N Engl J Med* 1985; **313:** 1138–1141.
12. Kohchi K, Takebayashi S, Miyamoto AT, Nobuyoshi M. Coronary artery spasm and vascular nerve lesion. *Am Heart J* 1985; **110:** 1071–1074.
13. Kohchi K, Takebayashi S, Hiroki T, Nobuyoshi M. Significance of adventitial inflammation of the coronary artery in patients with unstable angina: Results at autopsy. *Circulation* 1985; **71:** 709–716.
14. Minshall RD, Miyagawa K, Chadwick CC, Novy MJ, Hermsmeyer K. In vitro modulation of primate coronary vascular muscle cell reactivity by ovarian steroid hormones. *FASEB J* 1998; **12:** 1419–1429.
15. Miyagawa K, Vidgoff J, Hermsmeyer K. Ca^{2+} release mechanism of primate drug-induced coronary vasospasm. *Am J Physiol* 1997; **272:** H2645–H2654.
16. Miyagawa K, Rosch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nat Med* 1997; **3:** 324–327.
17. Biasucci LM, Liuzzo G, Angiolillo DJ, Maseri SG. Inflammation and acute coronary syndrome. *Herz* 2000; **25:** 108–112.
18. Koenig W. Inflammation and coronary heart disease: An overview. *Cardiol Rev* 2001; **9:** 31–35.
19. Azar RR, Rinfret S, Theroux P, Stone PH, Dakshinamurthy R, Feng YJ, et al. A randomized placebo-controlled trial to assess the efficacy of anti-inflammatory therapy with methylprednisolone in unstable angina (MUNA trial). *Eur Heart J* 2000; **21:** 2026–2032.
20. Shimizu H, Lee JD, Ogawa KB, Shimizu K, Yamamoto M, Hara A, et al. Efficacy of denopamine, a beta 1 adrenoceptor agonist, in preventing coronary artery spasm. *Jpn Circ J* 1993; **57:** 175–182.
21. Shimizu H, Lee JD, Ogawa KB, Sugiyama T, Yamamoto M, Hara A, et al. Refractory variant angina relieved by denopamine: A case report. *Jpn Circ J* 1991; **55:** 692–694.

Predictors of Left Ventricular Remodeling in Patients With Acute Myocardial Infarction Participating in Cardiac Rehabilitation

—— Brain Natriuretic Peptide and Anterior Infarction ——

Shuichi Takagi, MD; Satoru Sakuragi, MD; Takeshi Baba, MD; Hiroshi Takaki, MD; Naohiko Aihara, MD; Yoshio Yasumura, MD; Hitoshi Sumida, MD; Hiroshi Nonogi, MD; Yoichi Goto, MD

Background This study was designed to determine the factors influencing the development of left ventricular (LV) remodeling in patients participating in a comprehensive cardiac rehabilitation (CR) program after acute myocardial infarction (AMI), with special reference to exercise intensity and frequency.

Methods and Results A total of 72 patients with AMI participated in CR consisting of exercise training of moderate intensity (heart rate reserve 40–60%) and education for 12 weeks. Plasma concentration of brain natriuretic peptide (BNP) was measured at the beginning and the end of CR. Echocardiography was performed before and 1 year after CR. An increase in LV end-diastolic dimension (delta-LVDd) from baseline was used as an index of remodeling. Delta-LVDd was significantly greater in patients with an anterior AMI than with other infarct locations ($p<0.05$) and correlated significantly with baseline BNP concentration ($p<0.05$). Delta-LVDd >5 mm occurred exclusively in patients with baseline BNP >150 pg/ml. Variables representing the intensity and frequency of exercise training did not correlate with delta-LVDd.

Conclusion In patients with AMI participating in CR, those having both anterior infarction and baseline BNP concentration >150 pg/ml are at high risk for subsequent LV remodeling, whereas neither exercise intensity nor participation frequency in CR appears to be associated with LV remodeling. (*Circ J* 2004; **68:** 214–219)

Key Words: Acute myocardial infarction; Brain natriuretic peptide; Cardiopulmonary exercise test; Exercise training; Ventricular remodeling

Comprehensive cardiac rehabilitation (CR) has been shown to improve exercise capacity in patients with acute myocardial infarction (AMI), even in patients with moderate or severe left ventricular (LV) dysfunction[1–7] However, Jugdutt et al reported possible detrimental effects of exercise training on LV function and remodeling among patients with anterior Q-wave infarction[8] In contrast, the EAMI trial reported that patients with a baseline left ventricular ejection fraction (LVEF) <40% were prone to LV dilatation, and that physical training did not appear to worsen this anticipated effect[9] Moreover, the ELVD study reported attenuation of unfavorable remodeling by exercise training in postinfarction patients with LV dysfunction[10] In all those studies, however, exercise training was started late (3–8 weeks) after the onset of AMI, which may differ from the current clinical practice of early (2 weeks after onset) start of exercise training. In addition, those studies did not comprehensively analyze the predictive factors of LV remodeling in their study patients.

LV remodeling is a complex pathologic process of progressive dilatation, leading to dysfunction and heart failure in patients after myocardial infarction[11–16] Many factors have been reported to be related to LV remodeling in patients with AMI[17] and we have previously reported that the plasma brain natriuretic peptide (BNP) concentration is a predictor of progressive ventricular remodeling after AMI[13] However, the predictive factors of LV remodeling in patients participating in exercise CR have not been fully studied and this issue is important because exercise prescription with an appropriate exercise intensity should be given to all patients after AMI. Accordingly, the purpose of the present study was to clarify the predictive factors of LV remodeling in patients after AMI participating in CR with exercise training starting early (10–20 days) after onset. Our hypotheses were that the baseline plasma BNP concentration would be a predictive factor of LV remodeling in postinfarction patients participating in exercise CR and that variables representing exercise intensity or frequency may not unfavorably affect LV remodeling in these patients.

(Received July 29, 2003; revised manuscript received December 12, 2003; accepted December 22, 2003)

Division of Cardiology, National Cardiovascular Center, Suita, Japan
Mailing address: Yoichi Goto, MD, PhD, Division of Cardiology, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: ygoto@hsp.ncvc.go.jp

Methods

Patients

The study group included 72 patients with an AMI who completed the recovery phase CR program with exercise training. The diagnosis of AMI was confirmed by typical chest pain, electrocardiographic (ECG) findings and subsequent elevation of cardiac enzymes. Patients with the usual contraindications for exercise training were excluded. Written informed consent was obtained from all enrolled

patients. Baseline clinical characteristics and medications are shown in Table 1. All patients underwent coronary arteriography and left ventriculography 3–4 weeks after the onset of infarction. The LVEF averaged 44±10% (range, 19–67%).

Exercise Training

The CR program consisted of exercise training of moderate intensity and education for 12 weeks[18,19] Patients who did not have angina or ischemic changes on the ECG at a low level of exercise intensity (500 m walking) were enrolled in the exercise training approximately 10–20 days (median 15 days) after AMI.[20] The exercise program consisted of walking, bicycling on ergometer, and aerobic dance with a duration of 50–90 min per session and a frequency of 3–5 sessions per week for 3 months. Exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen's equation, k=0.5–0.6)[21] obtained in maximal symptom-limited cardiopulmonary exercise testing (CPX) or at level 13 ('a little hard') of the 6–20 scale perceived rating of exercise (original Borg's score).[22] Care was taken to prescribe a slightly lower level of exercise intensity (40–50% of heart rate reserve) to patients with low LVEF (<40%). The exercise program was started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice-a-week supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30–60 min 3–5 times a week. At the end of the 3-month program, patients were encouraged to continue exercise training at home by giving them an individual exercise prescription.[19] Although exercise intensity during home exercise was not investigated in the present study, the average adherence rate to home exercise was 84% at 6 months and 64% at 1 year after the completion of the 3-month CR in our program.

Cardiopulmonary Exercise Testing (CPX)

A maximal symptom-limited cardiopulmonary exercise test (CPX) was performed at the beginning and the end of the 12-week CR program. In the CPX, after a 2-min rest on the bicycle ergometer (Examiner, Lode B.V. Groningen-Holland), patients started pedaling at an intensity of 0 W for 1 min (warm-up), then performed an incremental (15 W/min) exercise test until exhaustion. During exercise testing, breathed gas was continuously collected, and the respiration rate, tidal volume, oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation (VE) were measured breath by breath. A face mask was used to collect gas samples, which were analyzed using a gas analyzer AE280 (Minato Medical Electronics, Osaka, Japan) connected to a personal computer equipped with analyzing software. Blood pressure was measured every minute by a manual method. A 12-lead ECG was also continuously monitored during exercise. Only 2 patients showed definite ischemic ECG changes in the initial exercise test; one underwent percutaneous coronary intervention therapy 2 days after the CPX, and the other patient refused coronary intervention therapy, although no ischemic change on the ECG was noted during subsequent exercise training.

Plasma BNP Concentration

Plasma BNP concentration was measured at the beginning and the end of the 12-week CR program, using a specific immunoradiometric assay kit from Shionoria BNP (Shionogi Co, Ltd, Japan) for human BNP in the SRL Inc (Tokyo, Japan).

Table 1 Patient Characteristics and Medications (n=72)

Age (years)	*62±10*
M/F	*58/14*
Hypertension	*36 (50)*
Diabates mellitus	*25 (35)*
Hyperlipidemia	*37 (51)*
Smoking	*44 (61)*
Family history	*16 (22)*
Prior MI	*9 (13)*
≥killip II	*9 (13)*
Anteroseptal AMI	*36 (50)*
Successful reperfusion therapy	*47 (65)*
Restenosis of culprit lesion#	*0 (0)*
Peak CK (U/L)	*3,529±2,453*
Ejection fraction (%)	*44±10*
No. of diseased arteries	*0.8±0.8*
Medication	
ACEI	*46 (64)*
β-blocker	*15 (21)*
Ca antagonist	*32 (44)*
Digitalis	*5 (7)*
Nitrates	*32 (44)*
Diuretics	*5 (7)*

Data are presented as the mean value±SD or number (%) of patients. AMI, acute myocardial infarction; CK, serum creatine kinase; ACEI, angiotensin-converting enzyme inhibitor; #no. of restenoses of culprit lesion during the cardiac rehabilitation program.

Echocardiography

All patients underwent a complete Doppler echocardiographic study at the beginning and 1 year after the end of the CR program. Standard views, including the parasternal long-axis, short-axis at the papillary muscle level, and apical 4- and 2-chamber views were recorded. An increase in LV end-diastolic dimension (delta-LVDd) from the baseline to follow-up was used as an index of LV remodeling.

Statistical Analysis

Values are expressed as mean±SD. Univariate analysis was performed using paired or unpaired Student's t-tests. Categorical data were compared against a chi-square distribution. Linear regression analysis was used to determine the correlation between continuous variables. Multivariate analyses were performed using the StatView statistical software packages (SAS Institute Inc, Cary, NC, USA). A p-value less than 0.05 was considered statistically significant.

Results

Changes in Clinical Variables After Cardiac Rehabilitation

All patients safely completed the 12-week CR program. Peak $\dot{V}O_2$ increased significantly from 1,283±409 ml/min to 1,457±470 ml/min ($p<0.05$) at the end of the 12-week program. Plasma BNP concentrations decreased significantly from 232±211 pg/ml to 146±239 pg/ml ($p<0.05$). However, LVDd did not significantly change from baseline to follow-up (52.0±5.7 mm to 51.5±6.5 mm, NS).

Relation Between Clinical Characteristics and Delta-LVDd

To assess determinants of LV remodeling, delta-LVDd was compared between subgroups of patients according to clinical characteristics and medications. There were no significant differences in delta-LVDd between subgroups

Table 2 Comparison of Delta-LVDd According to the Clinical Characteristics

	Delta-LVDd (mm)	p value
M/F	−0.8±4.2 / 1.1±4.6	NS
Age (≥70/<70 years)	−0.7±4.6 / −0.3±4.6	NS
Hypertension (with/none)	−0.1±5.0 / −0.8±4.3	NS
Diabates mellitus (with/none)	−0.4±4.3 / −0.5±4.8	NS
Hyperlipidemia (with/none)	−0.7±5.0 / −0.1±5.0	NS
Smoking (with/none)	−0.6±4.6 / 0.9±4.2	NS
Family history (with/none)	−0.1±4.0 / −0.7±4.9	NS
Prior MI (with/none)	1.2±4.1 / −0.9±4.5	NS
≥Killip II (with/none)	1.4±4.7 / −0.8±4.6	NS
Anteroseptal MI (with/none)	0.7±4.6 / −1.6±4.2	<0.05
Successful coronary artery reperfusion (with/none)	−0.6±4.3 / −0.2±5.1	NS
ACEI (with/none)	−0.3±4.2 / −1.0±5.1	NS
β-blocker (with/none)	−0.9±4.3 / −0.4±4.7	NS
Ca antagonist (with/none)	−1.1±4.6 / 0.01±4.5	NS
Digitalis (with/none)	2.1±4.9 / −0.7±4.5	NS
Nitrates (with/none)	−0.2±4.7 / −0.2±4.4	NS
Diuretics (with/none)	2.3±3.0 / −0.7±4.6	NS

Data are presented as mean value±SD. MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; Successful reperfusion, successful reperfusion of an infarct-related artery within 24 h of onset.

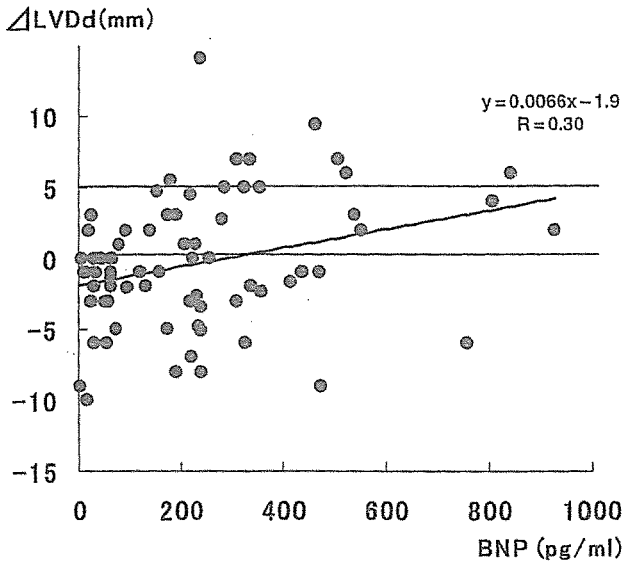

Fig 1. Correlation between plasma BNP concentrations and delta-LVDd (ΔLVDd). Increases in the left ventricular end-diastolic dimension (delta-LVDd) from baseline to follow-up were plotted against plasma BNP concentrations measured at the beginning of the cardiac rehabilitation program. Plasma BNP concentration significantly correlated with delta-LVDd (Y=0.0066X−1.9, r=0.30, p<0.05).

of patients divided by sex, age (≥70/<70 years), presence or absence of coronary risk factors, prior myocardial infarction (MI), Killip's classification≥II, successful/unsuccessful coronary reperfusion, or medications (Table 2).

Of note, delta-LVDd was significantly greater in patients with an anterior MI than in patients with other infarct locations (0.7±5.1 vs −1.60±3.7 mm, p<0.05, unpaired t-test). There was a weak trend that delta-LVDd in the subgroups with prior MI, Killip's classification≥II, with nitrates, and with diuretics was greater than the delta-LVDd in the subgroups without these factors, although none of these differences reached statistical significance (0.1<p<0.2).

Table 3 Effect of the Factors of Cardiac Function on Delta-LVDd

	r	p value
LVDd	−0.21	NS
LVDs	0.08	NS
FS	−0.19	NS
EF (left ventriculography)	−0.17	NS
No. of diseased arteries	−0.07	NS
LVEDVI	0.11	NS
LVESVI	0.18	NS
BNP (pre)	0.30	<0.05
BNP (post)	0.25	NS
Delta-BNP	−0.06	NS
Peak $\dot{V}O_2$	0.11	NS
VE/VCO_2 slope (pre)	−0.07	NS
VE/VCO_2 slope (post)	−0.04	NS
VE/VCO_2 slope (delta)	0.003	NS

LVDd, end-diastolic left ventricular dimension; LVDs, end-systolic left ventricular dimension; FS, fractional shortening; EF, ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; BNP (pre), BNP measured at the beginning of cardiac rehabilitation; BNP (post), BNP measured at the end of 12-week cardiac rehabilitation; Delta-BNP, decrease in BNP from the beginning to the end of cardiac rehabilitation; Peak $\dot{V}O_2$, peak oxygen uptake at the beginning of cardiac rehabilitation; VE/VCO_2 slope, the slope of the relation between minute ventilation and carbon dioxide production during initial exercise testing.

Relation Between Angiographic, Neurohumoral, and Exercise Variables and Delta-LVDd

Correlations between angiographic, neurohumoral, and exercise variables and delta-LVDd are summarized in Table 3. There was no significant correlation, except for baseline plasma BNP concentrations (r=0.30, p<0.05, Fig 1). In addition, none of the 29 patients with baseline plasma BNP concentration≤ 150 pg/ml had an increase in delta-LVDd >5 mm, whereas 8 of 43 patients (18.6%) with plasma BNP concentration >150 pg/ml had increases in delta-LVDd >5 mm (p<0.05) (Fig 2).

With regard to infarct location, there was a tendency that patients with an anterior infarction had a higher incidence of delta-LVDd >5 mm than patients with other infarct locations (16.7% vs 5.6%, p=0.14), although the difference did not reach statistical significance. Of note, 3 of 8 patients (37.5%) with both an anterior MI and a baseline BNP con-

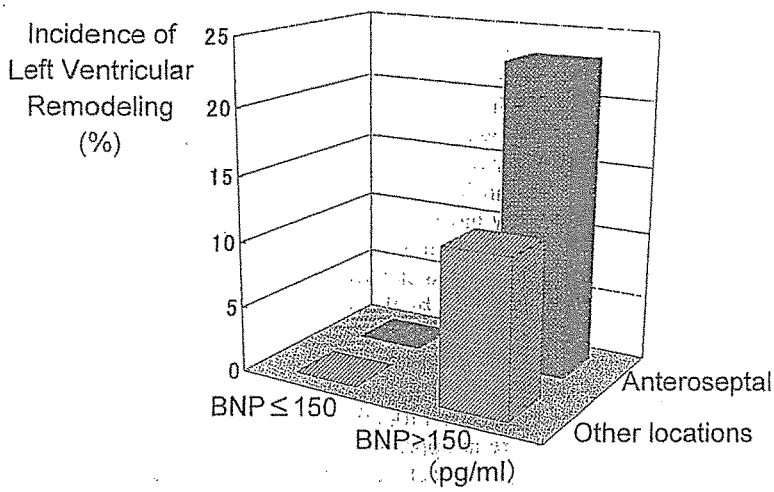

Fig 2. Incidence of left ventricular remodeling according to plasma BNP concentrations and infarct location. The bars indicate the percentage of patients who showed left ventricular remodeling (delta-LVDd >5 mm) in each category. The incidence of left ventricular remodeling was 23.1% in the category of anteroseptal infarction and BNP >150 pg/ml, 11.8% in the category of other locations and BNP >150 pg/ml, and 0% in the two categories with BNP ≤150 pg/ml regardless of infarct location.

centration >500 pg/ml had delta-LVDd >5 mm at follow-up, suggesting that patients with both of these factors may be at high risk of LV remodeling.

The 2 patients who showed definite ischemic ECG changes in the initial exercise test had delta-LVDd <5 mm.

Relation Between Exercise Variables and Delta-LVDd

To examine a possibility that excessive exercise intensity or frequency might be associated with LV remodeling, correlations between exercise variables (ie, prescribed training heart rate, frequency of participation in exercise training sessions, and the increase and percentage increase in peak $\dot{V}O_2$ at the end of the 12-week program) and delta-LVDd were assessed (Table 4). The ranges of distribution of these variables were 75–140 beats/min for prescribed training heart rate, 2–76 attendances at exercise sessions, −348–692 ml/min for the increase in peak $\dot{V}O_2$, and −32–64% for percentage increase in peak $\dot{V}O_2$ for all patients. These variables were considered to reflect the intensity, frequency and overall amount of exercise training that could potentially affect the development of LV remodeling. However, none of these variables significantly correlated with delta-LVDd (Table 4), suggesting that exercise training with appropriate intensity and frequency is not associated with LV remodeling.

Table 4 Effect of Exercise Intensity and Frequency on Delta-LVDd

	r	*p value*
Training heart rate	*0.07*	*NS*
Frequency of participation in the rehabilitation program	*−0.19*	*NS*
Delta peak $\dot{V}O_2$	*−0.01*	*NS*
% Delta peak $\dot{V}O_2$	*0.11*	*NS*

Multivariate Analysis

Multiple linear regression analysis using 2 variables (the baseline plasma BNP concentration and infarct location, which affected the development of LV remodeling in the univariate analysis) indicated that only the baseline plasma BNP concentration significantly affected the development of LV remodeling ($p=0.046$), whereas the infarct location (anterior) had a tendency to affect the development of LV remodeling ($p=0.18$).

The combination of the baseline plasma BNP concentration and infarct location (anterior) improved the specificity and positive predictive value for delta-LVDd >5 mm better than the individual variables (Table 5).

Discussion

The major findings of the present study of patients with AMI participating in a 12-week exercise CR program are that (1) delta-LVDd at 1 year after the end of the program was significantly greater in patients with an anterior MI than with other infarct locations ($p<0.05$), (2) delta-LVDd correlated significantly with the baseline BNP concentration ($p<0.05$) and delta-LVDd >5 mm occurred exclusively in patients with a baseline BNP concentration higher than 150 pg/ml, and (3) variables representing the intensity and frequency of exercise training did not significantly correlate with delta-LVDd. These findings suggest that in patients with AMI participating in exercise CR, the baseline plasma BNP concentration and infarct location, but not exercise intensity or frequency, are factors influencing the development of LV remodeling.

Previous Studies

The EAMI study[9] and Dubach et al[23] have demonstrated that exercise training does not aggravate LV remodeling, and the ELVD study[10] has shown that exercise training instead attenuates LV remodeling. However, these studies did not analyze the predictive factors of LV remodeling in

Table 5 Sensitivity, Specificity and Positive (PPV) and Negative (NPV) Predictive Values of Baseline Plasma BNP Concentration and the Infarct Location (anterior) Against Delta-LVDd >5 mm

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Anterior infarction and BNP >150 pg/ml	*75.0*	*68.8*	*23.1*	*95.6*
Anterior infarction	*75.0*	*53.1*	*16.7*	*94.4*
BNP >150 pg/ml	*100*	*45.3*	*18.6*	*100*