Published by Elsevier Science Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(02)02925-X

Assessment of Clinical Features in Transient Left Ventricular Apical Ballooning

Yoshiteru Abe, MD, Makoto Kondo, MD, Ryota Matsuoka, MD, Makoto Araki, MD, Kiyoshi Dohyama, MD, Hitoshi Tanio, MD

Shimada, Shizuoka, Japan

OBJECTIVES We sought to assess the clinical features of transient left ventricular (LV) apical ballooning.

BACKGROUND Although several cases regarding transient LV apical ballooning have been reported, the etiology remains unknown.

METHODS We investigated 17 patients (14 women, median age 74 years old with a range of 54 to 91 years old) who fulfilled the following criteria: 1) transient LV apical ballooning; 2) ST-T segment change in several leads in electrocardiogram; and 3) no history of old myocardial infarction, valvular heart disease, subarachnoid hemorrhage, or pheochromocytoma.

RESULTS Emotional and physical stress were observed in 16 patients (94%). Technetium-99m tetrofosmin tomographic imaging revealed decreased uptake at the apex of the left ventricle in 11 patients (85%) that later returned to uniform. No significant stenosis or angiographical slow flow in epicardial coronary arteries was observed (n = 9). Provocative focal vasospasm was induced in only one patient (14%) (n = 7). Moreover, no significant abnormality in the coronary microcirculation was detected by Doppler guidewire (n = 3) or contrast echocardiography (n = 1). No patients showed a rise in viral antibody titers. Biopsy specimens revealed interstitial fibrosis in six patients (100%) and slight cell infiltration in three others (50%) (n = 6).

CONCLUSIONS These findings suggested that neither abnormalities in the coronary circulation nor acute myocarditis was related to the etiology. Although neurogenic stunned myocardium induced by emotional or physical stress was suggested as the etiology, further investigations are necessary. (J Am Coll Cardiol 2003;41:737–42) © 2003 by the American College of Cardiology Foundation

Many previous studies reported several entities that had reversible left ventricular (LV) wall motion abnormalities including ischemic myocardial stunning, subarachnoid hemorrhage, pheochromocytoma crisis, acute myocarditis, and tachycardia-induced cardiomyopathy (1–5). Conversely, several cases with a unique morphologic LV feature distinct from the above entities were recently reported in Japan (6,7). These cases were as follows: 1) reversible balloon-like LV wall motion abnormality at the apex with hypercontraction of the basal segment (Fig. 1); 2) the ST-T segment abnormalities on electrocardiograms (ECG) were similar to acute myocardial infarction (MI) (Fig. 2); 3) minimal evidence of coronary circulation abnormality; 4) most cases were induced by physical and emotional stress; and 5) elderly women were common. However, the etiology remains unknown. In the present prospective study, we assessed the clinical features in transient LV apical ballooning.

METHODS

We evaluated 17 consecutive patients (14 women and 3 men) between April 1, 1996, and March 31, 2001, who met the following inclusion criteria: 1) reversible balloon-like LV wall motion abnormality at the apex with hypercontraction of the basal segment; 2) ST-segment elevation or T-wave inversion in several leads on the ECG, with these abnormalities returning to normal; 3) no history of old MI or valvular heart disease; and 4) no complication of subarachnoid hemorrhage or pheochromocytoma crisis.

Coronary risk factors and triggering factors were investigated from a chart review of medical records combined with the patient questionnaire. The ECG was recorded during the acute phase and was followed until the abnormality disappeared. Echocardiography was performed to clarify balloon-like LV wall motion abnormalities during the acute phase and its recovery. Rest technetium-99m tetrofosmin (TF) quantitative gated single-photon emission computed tomographic myocardial imaging was performed during the acute and chronic phases (8,9).

Multiple-plane coronary angiogram (CAG) was obtained in seven cases during the acute phase and in five cases during the chronic phase. In four patients, CAG was performed during the acute and chronic phase. Provocation of epicardial coronary vasospasm was also performed by an intracoronary infusion of acetylcholine in two cases during the acute phase and in five cases during the chronic phase (50 μg to the right coronary artery and 100 μg to the left coronary artery) to confirm coronary spasm (10).

During the acute phase, coronary blood flow velocity was

From the Division of Cardiology, Shimada Municipal Hospital, Shimada, Shizuoka, Japan.

Manuscript received January 20, 2002; revised manuscript received September 9, 2002, accepted September 20, 2002.

Abbreviations and Acronyms

CAG = coronary angiogram
CFR = coronary flow reserve
DDT = deceleration time of the diastolic flow velocity
DSVR = diastolic to systolic velocity ratio
ECG = electrocardiogram
ESRF = early systolic reverse flow
LV = left ventricular
MCE = myocardial contrast echocardiography
MI = myocardial infarction
TF = technetium-99m tetrofosmin

measured at the middle portion of the left anterior descending artery with a 0.014-in. Doppler guidewire to evaluate the following parameters: the diastolic to systolic velocity ratio (DSVR), the deceleration time of the diastolic flow velocity (DDT: ms), the early systolic reverse flow (ESRF), and the coronary flow reserve (CFR), which responded to an intracoronary injection of 0.5 mg nitroglycerin and 50 μg adenosine 5′-triphosphate in three patients on admission (11–13). Moreover, myocardial contrast echocardiography (MCE) was performed in one patient during the acute phase (14).

After left ventriculography, endomyocardial biopsy of the LV apex and posterior segment were performed during the acute phase in six patients to determine the underlying cardiac disease pathologically. Viral antibody titers were evaluated on admission and four weeks later in six patients, and a fourfold rise in viral antibody titers was considered significant.

RESULTS

Patients' characteristics and triggering factors. Patients' characteristics are shown in Table 1. The median age of the patients was 74 years, and 14 of 17 patients were female. There was no cocaine abuse or other drug abuse. Triggering factors were physical stress in 13 patients (77%) and emotional stress in 3 others (18%) (Table 2).

ECG. The ST-segment elevations were observed in several leads on the ECG during the acute phase in 14 patients (82%), which became negative T waves at a median of 4 days, with a range of 2 to 18 days after the onset (Fig. 2). The other three patients (18%) revealed inverted T waves in several leads during the acute phase. Deep negative T waves were characteristically seen during the course of recovery. Although there was one patient with transient small Q waves that developed in the II, III, and aVF leads, they disappeared at three months after the onset. A prolonged QTc interval was observed in all patients (median 500 ms, with a range of 436 to 581 ms) (15). The abnormality on the ECG returned to normal between 97 and 191 days after the onset.

Echocardiography. The echocardiography during the acute phase revealed balloon-like LV wall motion abnormalities at the apex with hypercontraction of the basal segment of the ventricle without pericardial effusion. These wall motion abnormalities disappeared at a median of 18 days (range 9 to 53 days) after the onset.

Rest TF tomographic myocardial imaging. Rest TF tomographic myocardial imaging was performed in 13 patients during the acute phase. There was a significantly decreased uptake at the apex of the left ventricle in 11 patients (85%). The apical abnormality returned to uniform between 25 and 90 days after the onset (Fig. 3). Moreover, the end-diastolic image revealed a decreased uptake at the apex of the left ventricle.

Angiographic findings. We performed CAGs in seven cases during the acute phase (Table 3). The CAG revealed no significant stenosis nor the slow flow phenomenon in the epicardial coronary artery with a pale myocardium (16), even in five cases that showed ST-segment elevation when CAG was performed during the acute phase. The coronary vasospasm provocation test was performed in two patients

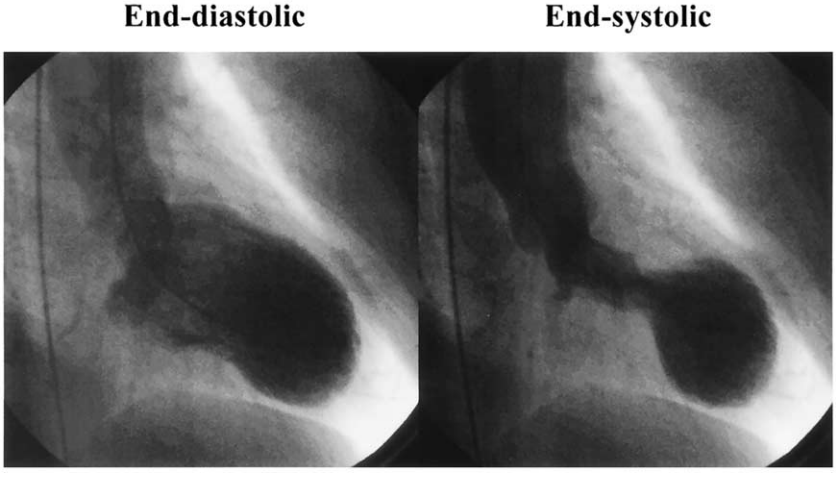

Figure 1. Left ventriculogram during the acute phase. Balloon-like asynergy at the apex with hypercontraction of the basal segment of the ventricle was observed.

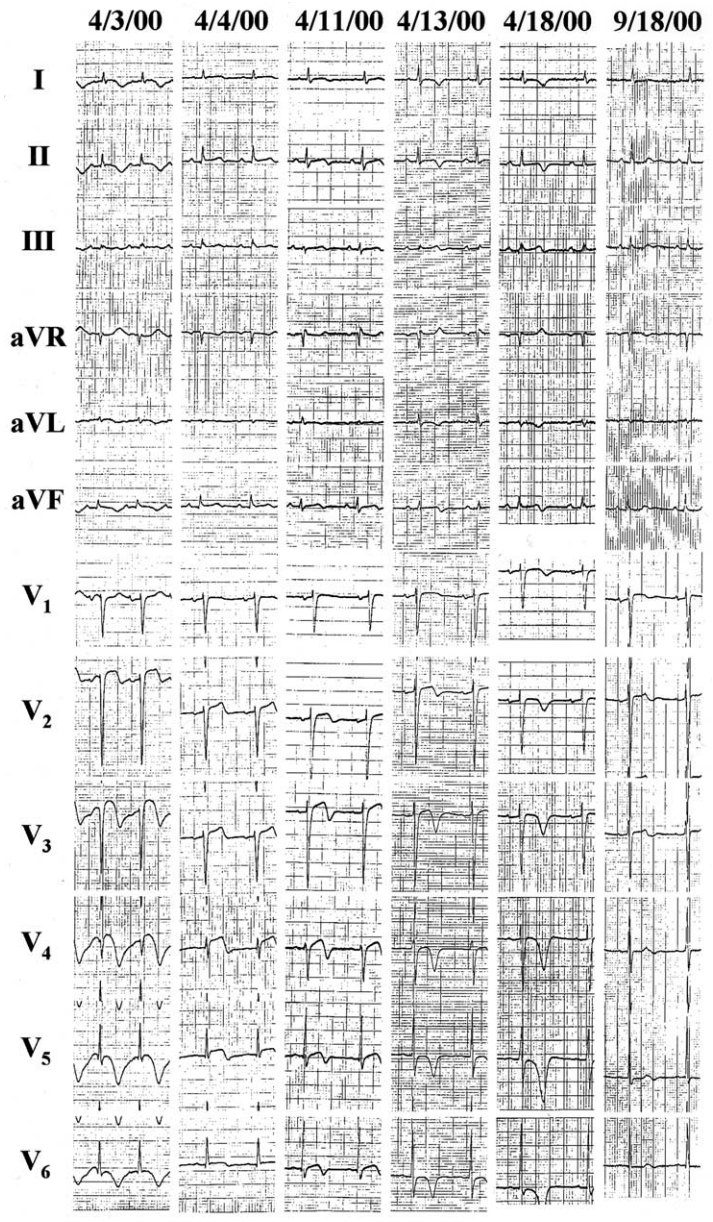

Figure 2. Serial electrocardiograms. Both the ST-segment elevation in leads I, aVF, and V_2 through V_6, and the loss of the R-wave voltage over the anterior precordial leads with the inverted T-wave in leads I, II, III, aVF, and V_2 through V_6 were observed on April 3, 2000. Note the rapid resolution of these changes.

Table 1. Patients' Characteristics

No. of patients	17
Age (yrs)	74 (54 to 91)*
Women	14 (82%)
Chest pain on admission	9 (53%)
Risk factors	
Hypertension	3 (18%)
Diabetes mellitus	0
Total cholesterol >250 mg/dl	3 (18%)
Active smoker	1 (6%)
Peak creatine kinase (IU/l)	275 (53 to 1,478)*
Rise in viral antibody titers	0

*Values are presented as medians and ranges.

Table 2. Triggering Factors

No. of patients	17
Physical stress	
External injury	3 (18%)
Heavy labor	1 (6%)
Travel	1 (6%)
Electrophysiologic study	1 (6%)
Dyspnea	5 (29%)
Angina-like chest pain	2 (11%)
Emotional stress	
Human relations	1 (6%)
Death of spouse	1 (6%)
Public performance	1 (6%)
Medical examination	1 (6%)

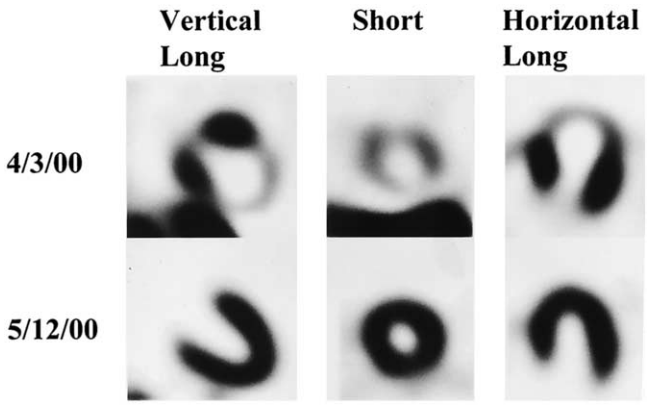

Figure 3. Resting technetium-99m tetrofosmin tomographic myocardial imaging. A decreased uptake at the apex of the ventricle that later returned to uniform was observed.

during the acute phase and in five patients during the chronic phase. During the acute phase, the results were negative in one patient, and diffuse vasoconstriction at segment 4AV of the right coronary artery without ST-segment elevation was seen in one patient (17,18). During the chronic phase, the results were negative in one patient, positive in only one patient at segment 1 of the right coronary artery with ST-segment elevation, and diffuse vasoconstriction was observed in three patients; the vasoconstrictions were at the middle portion of the left anterior descending artery in one patient, the distal portion of the left circumflex artery in one patient, and the distal portion of three coronary arteries in two patients without ST-segment elevation.

Coronary flow velocity spectrum and MCE. The DSVR, DDT, and CFR were median 2.0 (range 1.9 to 3.1), 640 ms (range 620 to 1560 ms), and 2.2 (range 1.3 to 3.6), respectively (Table 4). The ESRF was not observed in any patients. Moreover, MCE revealed a contrast-enhanced myocardium at the apex of the ventricle, which showed LV apical ballooning during the acute phase.

Virus antibody titers and cardiac biopsy. There was no patient with a fourfold rise in viral antibody titers. Interstitial fibrosis was a common finding in all patients (Table 5). Although small amounts of cell infiltration were recognized in three patients, no significant inflammatory infiltrate or necrosis of adjacent myocytes was seen in patients with acute viral myocarditis (Fig. 4).

Table 3. Angiographic Results

No. of patients	9
Significant stenosis in epicardial coronary artery	0
Provocation test	7
Positive	1 (14%)
Diffuse vasoconstriction	4 (57%)*
Negative	2 (29%)*

*The patients include one patient who underwent a provocation test during the acute phase (day 1).

Table 4. Indices of Doppler Guidewire

No. of patients	3
DSVR	2.0 (1.9 to 3.1)*
DDT (ms)	640 (620 to 1,560)*
CFR	2.2 (1.3 to 3.6)*
ESRF	0

*Values are presented as medians and ranges.

CFR = coronary flow reserve; DDT = deceleration time of the diastolic flow velocity; DSVR = diastolic to systolic velocity ratio; ESRF = early systolic reverse flow.

DISCUSSION

In this study, concerning patients with transient LV apical ballooning, the following were observed: 1) a reversible wall motion abnormality; 2) transient ST-T segment abnormalities on the ECG; 3) minimal evidence of epicardial coronary artery stenosis, vasospasm, and disturbance of microcirculation; 4) physical or emotional stress as a triggering factor; and 5) minimal pathologic evidence of acute myocarditis.

Clinical features and suggested etiology. Although the histologic findings of the present patients were consistent with those of a previous study, microvascular injury as the etiology of transient LV apical ballooning was not ruled out (7). Angina pectoris caused by coronary microvascular spasm has been reported (16). However, no present patients revealed angiographic slow flow with ST-segment elevation during the acute phase. The DDT was >600 ms and was considered within normal levels (11). The DSVR was distributed from 1.9 to 4.1 (median value 2.0) and no ESRF was observed (12). The CFR was distributed from 1.3 to 3.6; the CFR was considered to represent a relatively small value. Moreover, a contrast-enhanced myocardium at the apex of the ventricle was observed. Thus, the deleterious damage to the coronary microcirculation did not contribute to the etiology. It is suggested that this is the first study of findings of the coronary microcirculation in this entity.

A focal coronary vasospasm with ST-segment elevation

Table 5. Pathologic Findings

No. of patients	6
Myocardial disarray	0
Myocytes	
Myocyte hypertrophy (>20 μm)	3 (50%)
Cell diameter (μm)	18.7 (10.8 to 23.7)*
Nucleus	
Enlarged	0
Hyperchromatic	0
Irregular in shape	0
Nuclei	0
Cytoplasmic abnormality	0
Myocardial interstitium	
Interstitial fibrosis	6 (100%)
Fatty infiltration	0
Cell infiltration	3 (50%)
Endocardium	
Endocardial thickening	2 (33%)
Thrombus	0
Endocardial fibrosis	1 (17%)

*Values are presented as medians and ranges.

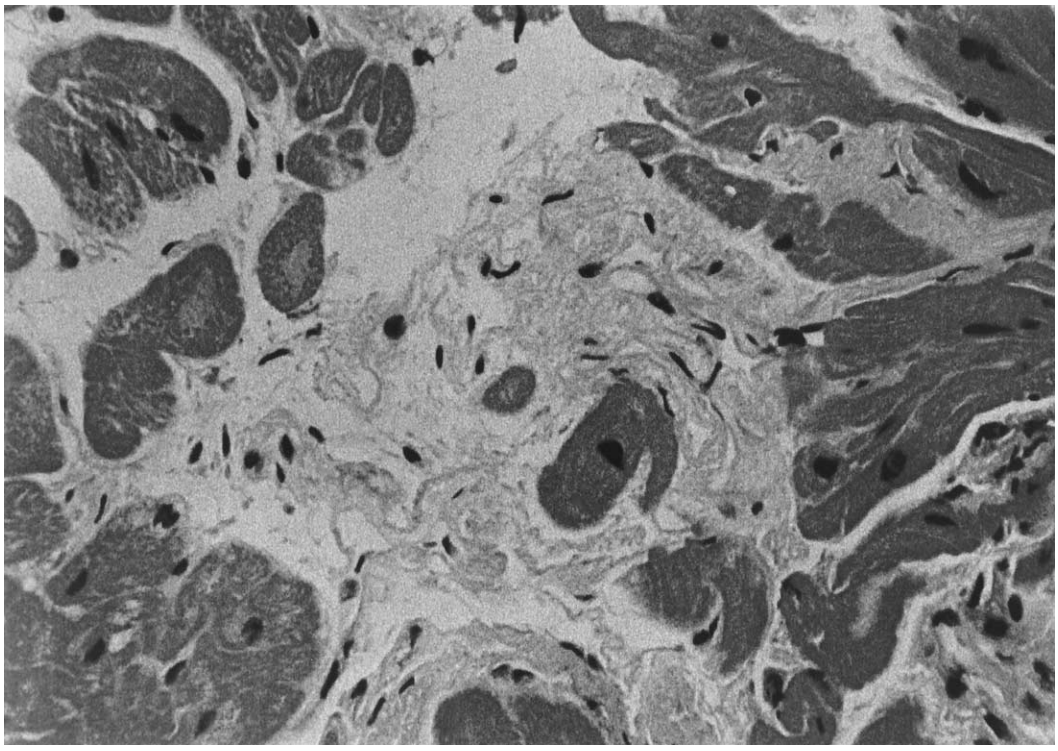

Figure 4. Endomyocardial biopsy specimen. Interstitial myocardial fibrosis and small amounts of cellular infiltrates were observed (hematoxylin and eosin stain, ×200).

was induced in only one patient, and diffuse vasoconstriction without ST-segment elevation was observed in four patients (18). Moreover, discrepancies between the hypokinetic area and coronary artery territories, which induced coronary vasospasm, were observed. Therefore, coronary vasospasm does not contribute to the etiology.

A rise in viral antibody titers was not observed. Additionally, significant inflammatory cell infiltration with myocyte damage was not observed in the specimens obtained from endocardial biopsy during the acute phase. Therefore, myocarditis was not suggested to be the etiology. The clinical significance of the interstitial fibrosis was not well defined.

From the above findings, the perfusion abnormality was not considered the cause of the scintigraphic abnormality. The mechanism of uptake of TF by myocytes was reported as via a metabolism-dependent process, and subcellular localization was in the mitochondria (19). Thus, it was suggested that the scintigraphic abnormality was caused by the abnormalities in the mitochondria. Two patients were without scintigraphic abnormality. Moreover, a scintigraphic abnormality was present in the end-diastolic image. Therefore, the scintigraphic abnormality was not considered as the partial volume effect (9).

Kono et al. (2) suggested that the cause of neurogenic stunned myocardium was an increased local norepinephrine release in the heart after subarachnoid hemorrhage, and was mediated by the direct toxic effect of norepinephrine. The significantly reduced myocardial iodine-123-metaiodobenzylguanidine uptake was observed in patients with pheochromocytoma (20). In the present study, 16 of 17 patients experienced physical or emotional stress before the onset. Thus, although the exact mechanism of this entity is still unclear, the participation by catecholamines is suggested.

Study limitations. Not all patients underwent all the mechanistic studies, and most of the tests were performed in a limited number of patients. However, we accrued novel findings including epicardial coronary artery, coronary vasospasm, coronary microcirculation, and pathologic findings. Although a neurogenic stunned myocardium was suggested as the etiology, further studies in a large group are needed before the present findings can be applied more generally to patients with this entity.

Acknowledgments

The investigators thank the nursing team of Shimada Municipal Hospital for contributing to clinical medicine. We also acknowledge Koji Nagayama and Sumie Tabata for collecting the clinical data, and Kiyozumi Akiyama and Yoshihisa Mori for technical assistance.

Reprint requests and correspondence: Dr. Makoto Kondo, Division of Cardiology, Shimada Municipal Hospital, 1200-5 Noda, Shimada City, Shizuoka, 427-8502 Japan. E-mail: kondo-m@gb3.so-net.ne.jp.

REFERENCES

1. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146–9.
2. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. J Am Coll Cardiol 1994;24:636–40.
3. Shaw TRD, Bafferty P, Tait GW. Transient shock and myocardial impairment caused by pheochromocytoma crisis. Br Heart J 1987;57:194–8.
4. Miklozek CL, Crumpacker CS, Royal HD, Come PC, Sullivan JL, Abelmann WH. Myocarditis presenting as acute myocardial infarction. Am Heart J 1988;115:768–76.
5. Shinbane JS, Wood MA, Jensen DM, Ellenbogen KA, Fitzpatrick AP, Scheirman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997;29:709–15.
6. Kawai S, Suzuki H, Yamaguchi H, et al. Ampulla cardiomyopathy ('Takotusbo' cardiomyopathy)—reversible left ventricular dysfunction with ST segment elevation. Jpn Circ J 2000;64:156–9.
7. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. J Am Coll Cardiol 2001;38:11–8.
8. Germano G, Kiat K, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 1995;36:2138–47.
9. Tawakol A, Skopicki HA, Abraham SA, et al. Evidence of reduced resting blood flow in viable myocardial regions with chronic asynergy. J Am Coll Cardiol 2000;36:2146–53.
10. Yasue H, Horio Y, Nakamura N, et al. 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. Circulation 1986;74:955–63.
11. Kawamoto T, Yoshida K, Akasaka T, et al. Can coronary blood flow velocity pattern after primary percutaneous transluminal coronary angiography predict recovery of regional left ventricular function in patients with acute myocardial infarction? Circulation 1999;100:339–45.
12. Wakatsuki T, Nakamura M, Tsunoda T, et al. Coronary flow velocity immediately after coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction. J Am Coll Cardiol 2000;35:1835–41.
13. Sonoda S, Takeuchi M, Nakashima Y, Kuroiwa A. Safety and optimal dose of intracoronary adenosine 5′-triphosphate for the measurement of coronary flow reserve. Am Heart J 1998;135:621–7.
14. Kaul S, Senior R, Dittrich H, Raval U, Khattar R, Lahiri A. Detection of coronary artery disease with myocardial contrast echocardiography. Circulation 1997;96:785–92.
15. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–70.
16. Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. Lancet 1998;351:1165–9.
17. Austen WG, Edwards JE, Frye RL, et al. AHA Committee Report: a reporting system on patients evaluated for coronary artery disease. Circulation 1975;51:1–38.
18. Uzui H, Kondo M, Murayama T, et al. Assessment of left ventricular myocardial perfusion and diastolic function during acetylcholine-induced diffuse coronary vasoconstriction by Doppler echocardiography and thallium-201 scintigraphy. Coron Artery Dis 1995;6:489–96.
19. Platts EA, North TL, Pickett RD, Kelly JD. Mechanism of uptake of technetium-tetrofosmin: I. J Nucl Cardiol 1995;2:317–26.
20. Suga K, Tsukamoto K, Nishigauchi K, et al. Iodine-123-MIBG imaging in pheochromocytoma with cardiomyopathy and pulmonary edema. J Nucl Med 1996;37:1361–4.