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ORIGINAL ARTICLE

Clinical and Prognostic Correlates of ST-Elevation Myocardial Infarction Patients with Normal Coronary Angiography

Pang-Yen Liu[1], Tsung-Neng Tsai[1], Chin-Sheng Lin[1], Wen-Yu Lin[1], Cheng-Chung Cheng[1], Wei-Shiang Lin[1], Chih-Hsueng Hsu[1], Jun-Ting Liou[1], Shu-Meng Cheng[1], Gen-Min Lin[2], Chun-Hsien Wu[1]

[1]Department of Internal Medicine, Division of Cardiology, National Defense Medical Center, Tri-Service General Hospital, Taipei, [2]Department of Medicine, Hualien-Armed Forces General Hospital, Hualien, Taiwan, ROC

Background: Revascularization within a 90-min door-to-balloon time is a strict policy enacted in Taiwan. Prompt diagnosis is critical to avoid an unnecessary procedure and catheterization laboratory activation. This study was aimed to investigate the clinical and prognostic characteristics of the patients with ST-elevation myocardial infarction (STEMI) referred for primary percutaneous coronary intervention (PCI) and normal coronary arteries found following coronary angiography (CAG). **Materials and Methods:** From October 2009 to December 2012, 216 consecutive patients with STEMI referred for primary PCI were enrolled. The data of clinical history, physical examination, laboratory results, electrocardiography, echocardiography, CAG findings, diagnosis, and outcomes were collected and analyzed. **Results:** A total of 17 patients were proved normal coronaries angiographically. The incidence of the conditions mimicking as STEMI is 7.9%. Alternative diagnosis was coronary spasm ($n = 7$), peri-myocarditis ($n = 6$), apical ballooning syndrome ($n = 3$), anaphylactic shock ($n = 1$). Compared with STEMI group, patients in normal coronaries group were younger, with a less premature family history of coronary artery disease (CAD), and reported angina. The 30-day mortality rate in the normal coronaries group was 5.9%. **Conclusions:** Cautiously evaluating CAD risk factors and symptoms of angina and awareness of alternative diagnosis are important to make a prompt diagnosis without compromising accuracy in the patients presenting as suspected STEMI.

Key words: ST-segment elevation myocardial infarction, differential diagnosis, normal coronary angiography

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a fatal disease, caused by the occluded coronary arteries following plaque rupture and aggregated platelet plug.[1] Rapid and accurate diagnosis of STEMI is urgent, owing to early revascularization improve the survival rate and life quality of affected patients.[2,3] Therefore, revascularization within 90-min of door-to-balloon time is a golden standard for treatment of STEMI today.[4,5] In Taiwan, we have strictly enacted this treatment principle since 2009. It makes most of the STEMI patients can receive recannularization in time. ST-segment elevations are easily to be recognized on electrocardiography (ECG). However, not all ST-segment elevations on ECG are contributed by acute myocardial infarction (AMI). Unnecessary coronary catheterization in non-AMI patients could lead to diagnosis delays of other masked fatal diseases. The importance of differential diagnosis in the patients presenting as suspected STEMI in the emergency room (ER) is crucial.

Various conditions may share identical ECG features as STEMI in clinical practice in the ER. Descriptions of these patients are limited to case reports and only a few systematic analyses.[6-9] In Taiwan, no systemic analysis has been published investigating this scenario. Thus, the current study aimed to investigate suspected STEMI patients referred for primary percutaneous coronary intervention (PCI) found with normal coronary arteries. We currently analyze the cases of suspected STEMI in the ER and confirmed with CAG. The overall incidence, clinical features, and the alternative diagnosis are currently described.

MATERIALS AND METHODS

Patient selection

The study was setting at Tri-Service General Hospital, a tertiary medical center north of Taiwan that provides 24-h primary PCI facilities. Between October 2009 and December

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Corresponding Author: Dr. Chun-Hsien Wu, Number 325, Section 2, Cheng-Kung Road, Neihu District, Taipei 114, Taiwan, ROC. Tel: 886-2-87927160; Fax: 886-2-87927161. E-mail: henrywudr@yahoo.com.tw

2012, patients referred from the ER for primary PCI with suspected STEMI were enrolled. A total of 216 consecutive patient's data were collected from the catheterization laboratory and applicable medical records. The initial diagnoses were made by an ER physician and a staff cardiologist following an ECG. All PCIs were performed in the activated catheterization laboratory with an agreement between the patients and cardiologist. The criteria for STEMI were met by all patients, including the onset of chest pain for at least 30 min and less 12 h before visiting, an ECG demonstrating ST-segment elevation ≥1 mV in two or more contiguous leads or newly developed left bundle branch block (LBBB). In the ER, aspirin, clopidogrel, morphine, intravenous nitrate, and heparin were administered if no contraindication were identified.

Data collection

Patient data including clinical features, laboratory examination results, and outcomes were obtained using medical records. Age, gender, comorbid conditions, vital signs (heart rate and blood pressure), serum biochemical test results, cardiac enzyme (creatine kinase and troponin I) were evaluated at admission. During hospitalization, peak values of cardiac enzymes and coronary angiography (CAG) results were recorded. The 30-day mortality rate was collected using admission charts and outpatient department medical records. Comorbid conditions included diabetes, hypertension, hyperlipidemia, coronary artery disease (CAD), stroke, smoking, and family history of cardiovascular disease. Any adverse events that occurred during the hospital stay were documented. Patients with identifiable culprit lesion in CAG were defined as STEMI group. In addition to normal coronary arteries, patients had either only minor diseases or pharmacologically reversible coronary spasms were defined as normal coronaries group for brevity at the rest of the analysis. All CAG results were confirmed by a total of three cardiologists. All final diagnoses were made by a treating cardiologist based on the described factors, following by a chart review performed by two additional cardiologists.

Definition

The ECG criteria of STEMI were defined as an ST-segment elevation ≥1 mm in two or more contiguous leads or newly developed LBBB. Peri-myocarditis was diagnosed based on the following clinical findings, including medical history, physical examination, laboratory test result, and ECG (ST-segment elevation and involvement of more than one coronary vascular territory). Apical ballooning syndrome was defined as having normal coronary arteries and characteristic left ventriculogram (LVG) (ballooning pattern: Apical akinesis with hyperkinesia over the basal region). Coronary spam was diagnosed based on the CAG findings, which were correlated to the ECG changes and recorded clinical features. Anaphylactic shock was indicated based on medical history, ECG, CAG, and laboratory data (elevated cardiac enzyme, white blood cell count and C-reactive protein).

Statistical analysis

Data are expressed as a percentage. The continuous variables were analyzed using a Student's *t*-test. The analyzed data are presented as mean and standard deviation. A $P < 0.05$ was considered significant.

RESULTS

Characteristics and incidence of suspected ST-elevation myocardial infarction

A total 216 patients presenting as suspected STEMI received an emergency CAG between October 2009 and December 2012. Among all patients, 182 received PCI for occluded coronary arteries, 13 were referred for coronary artery bypass graft and 4 patients received conservative treatment without revascularization [Figure 1]. No patient received thrombolytic therapy. 17 patients were suspected of STEMI, and the absence of occluded coronary artery lesions was confirmed using CAG, thus excluding myocardial infarction. The incidence of patients with ST-segment elevation mimicking STEMI was 7.9%. The majority of these patients were men, and the average age was 47 years. Most of them had abnormal body mass index (10/17; 58.8%).

Compared to STEMI group, patients in normal coronaries group were younger (47.94 ± 18.5 vs. 59.4 ± 13.2, $P < 0.001$), with less symptoms of angina pectoris (47.1% vs. 97.0%, $P < 0.001$), and with less hyperlipidemia (11.8% vs. 51.8%,

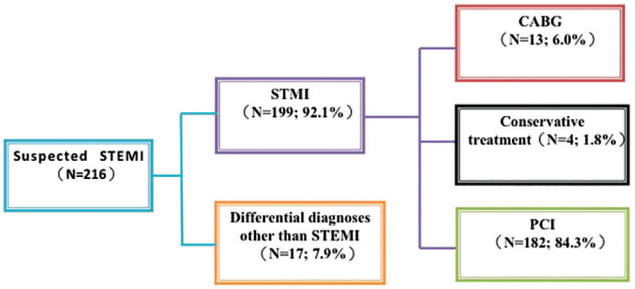

Figure 1. Collection of the study population. Total of 216 patients was enrolled in the study. 182 patients had PCI, 13 patients CABG and 4 patients conservative treatment for STEMI. Coronary angiography in 17 patients showed normal or insignificant stenosis with differential diagnoses other than STEMI. STEMI = ST-segment elevation myocardial infarction; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass grafting

P = 0.001). There was no significant difference in left ventricular (LV) ejection fraction (EF) between the two groups [Table 1].

Patients with an alternative diagnosis other than ST-elevation myocardial infarction

Among the 17 patients with an alternative diagnosis other than STEMI, seven of them were diagnosed with coronary spasm, six with peri-myocarditis, three with the apical ballooning syndrome and one with anaphylactic shock [Figure 2].

Table 1: Baseline characteristics of patients with normal coronaries group and STEMI group

Characteristics	Normal coronaries group (*n* = 17) (%)	STEMI group (*n* = 199) (%)	*P*
Sex (male/female)	15/2	176/23	NS
Age	47.94±18.5	59.4±13.2	<0.001
BMI ≤18 or ≥25	10/17 (58.8)	96/199 (48.2)	NS
Hypertension	8/17 (47.1)	119/199 (59.8)	NS
Previous history of CAD	1/17 (5.9)	6/199 (3.0)	NS
Stroke	0/17 (0)	10/199 (5.0)	NS
Diabetes	4/17 (23.5)	60/199 (30.2)	NS
Hyperlipidemia	2/17 (11.8)	103/199 (51.8)	0.001
Family history of CAD	2/17 (11.8)	15/199 (7.5)	NS
Symptom of angina	8/17 (47.1)	193/199 (97.0)	<0.001
Smoking	12/17 (70.6)	126/199 (63.3)	NS
Elevated troponin-I on admission	8/17 (47.1)	85/199 (42.7)	NS
EF	49.81±13.7	45.9±12.8	NS

BMI = Body mass index; CAD = Coronary artery disease; NS = Nonsignificant; STEMI = ST-segment elevation myocardial infarction; EF = Ejection fraction

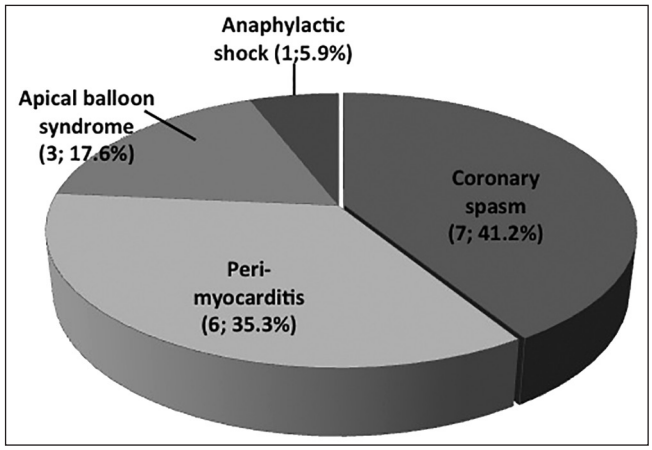

Figure 2. Differential diagnoses in 17 patients presenting as suspected ST-segment elevation myocardial infarction

Characteristics of coronary spasm in patients presented as suspected ST-elevation myocardial infarction

Coronary spasm was the major cause of suspected STEMI with normal coronaries when patients referred for primary PCI (7 out of 17 [41.2%]). Among those patients, 5 out of 7 (71.43%) of them coincided with the myocardial bridge. In the patients who presented with coronary spasms, involved vessels in 4 out of 7 (57.1%) were the right coronary artery, 2 out of 7 (28.6%) were the left anterior descending artery, and 1 out of 7 (14.3%) was the circumflex artery. All the patients survived after 30 days of follow-up.

Characteristics of peri-myocarditis in patients presented as suspected ST-elevation myocardial infarction

Totally, 6 out of 17 patients (35.3%) were diagnosed with peri-myocarditis. All the 6 patients had fever and elevated cardiac enzyme upon ER admission or during hospitalization. The identified ST-segment elevations were more common in the anterior and lateral leads. The echocardiography in the ER showed the majority of patients had normal (EF ≥55%) or preserved LV function (45% ≤ EF ≤54%) and only 1 patient had depressed LV function (EF <45%) [Table 2].1 patient died of refractory ventricular tachycardia; the remaining patients survived after 30 days of follow-up.

Characteristics of apical ballooning syndrome mimicking as ST-elevation myocardial infarction

Three patients (one male and two female; age range: 51-67 years of age) had been diagnosed with apical ballooning syndrome after CAG and LVG were performed. 1 patient had elevated troponin-I when she visited the ER, and all patients had elevated troponin-I during hospitalization. The ECG showed ST-segment elevations were localized at anterior precordial leads in all patients. The LV function of all the patients had been depressed initially in the ER and recovered in the outpatient department. 2 out of 3 patients had extended in-hospital days due to delayed recovery of LV function with persistent symptoms. However, all 3 patients survived after 30 days of follow-up [Table 3].

DISCUSSION

The present study demonstrated the alternative diagnoses in STEMI-mimicking patients referred for primary PCI. In previously reported literature, the incidence of chest pain coincided with ST-segment elevation with normal coronary artery is variable (range: 1.4-13%).[7-10] In the current study, the incidence was determined to be 7.9%, which is consistent with

Table 2: Data of 6 patients diagnosed with peri-myocarditis

Patient	1	2	3	4	5	6
Gender/age	Male/33	Male/79	Male/19	Male/19	Male/34	Male/29
CAD risk factor	Smoking	None	None	Smoking	None	Smoking
Laboratory data						
First CK (IU/L)	278	264	256	433	719	600
First troponin-I (μg/L)	3.15	15.41	2.76	5.03	9.82	13.68
Troponin-I peak (μg/L)	7.3	99	28.27	8.5	18.32	23.75
WBC (μl)	7300	15,600	8640	10,200	8230	9450
Hgb (mg/dl)	14.4	14.0	13.2	16.5	14.8	13.9
CRP (mg/dl)	NA	8.65	8.82	3.45	NA	6.29
Virology study	None	None	None	CMV	None	None
ECG leads with ST-segment elevation	V2-V5	I, II, aVF, V2-V3	V4-V6, lead I, II, aVL	V2-V6, I, aVL	V2-V6, I, II, aVL	V2-V6, I, II, aVL
EF (%)	30	55	50	48	50	55
Hospital stay (days)	3	1	3	4	6	7
30-day of follow-up	Survive	Expired	Survive	Survive	Survive	Survive

CAD = Coronary artery disease; CK = Creatine kinase; WBC = White blood cell; Hgb = Hemoglobin; CRP = C-reactive protein; ECG = Electrocardiography; EF = Ejection fraction; CMV = Cytomegalovirus; aVL = augmented vector left; aVF = augmented vector foot

Table 3: Data of 3 patients diagnosed with apical ballooning syndrome

Patient	1	2	3
Gender/age	Female/54	Male/67	Male/51
CAD risk factor	HT, DM, family history	HT, DM, smoking	HT, hyperlipidemia, smoking
Laboratory data			
First CK (IU/L)	117	54	90
First troponin-I (μg/L)	1.94	0.02	0.25
Troponin-I peak (μg/L)	1.94	3.09	0.64
WBC (/μl)	12,700	10,450	10,240
Hgb (mg/dl)	10.3	10.9	14.7
CRP (mg/dl)	0.82	9.64	1.82
ECG leads with ST-segment elevation	V2-V6	V2-V4	V2-V3
EF (%)	35	30	35
Hospital stay (days)	54	17	2
30-day of follow-up	Survive	Survive	Survive

CAD = Coronary artery disease; HT = Hypertension; DM = Diabetes mellitus; WBC = White blood cell; Hgb = Hemoglobin; CRP = C-reactive protein; ECG = Electrocardiography; EF = Ejection fraction; CK = Creatine kinase

previous reports. To the best of our knowledge, the current report is the first study in Taiwan and Asia to systemically analyze various diseases that mimicking STEMI with 30-day of follow-up.

In 2008, Ong *et al*. documented that the coronary spasm was the most common etiology of suspected myocardial infarction with normal coronary arteries.[11] Widimsky *et al*. have also demonstrated the coronary spasm (26.9%) are the major cause of STEMI.[9] However, instead of coronary spasm, Gu *et al*. reported pericarditis or peri-myocarditis remains one of the most frequently reported diseases in STEMI-mimicking entities.[12] In our study, we found coronary spasm (41.2%) was the most common alternative diagnosis of suspected STEMI. Compared with previous studies, the current study was collected in patients with suspected STEMI referred for primary PCI with a limited door-to-balloon time of 90-min. According to Gu *et al*., it may result in a high percentage of coronary spasm in this scenario due to time pressure.[12] Time pressure may lead to compromising diagnosis accuracy and postpone appropriate management.

Pericarditis and peri-myocarditis have been suggested to be the primary cause of suspected STEMI with the nonobstructive coronary artery. Ahmar *et al*. reported in a retrospective study that peri-myocarditis was the major cause of suspected STEMI.[8] Gu *et al*. reported 5 out of 19 of their patients had been diagnosed with pericarditis and myocarditis and were male.[12] We also found that most patients of peri-myocarditis were young male.

The manifestation of the apical ballooning syndrome is similar to acute coronary syndrome (ACS) and is related to the stress; hence, it is also termed stress-induced cardiomyopathy. In 2010, Hsu *et al*. reviewed 1338 cases of ACS and found 20 patients (11 female; 9 male) met the criteria of the apical ballooning syndrome (20/1338; 1.5%).[13] In our study, 3 out of 223 patients (1.3%) were diagnosed with the apical ballooning syndrome, consistent with previous reports; however, only 1

patient was female (1/3; 33%). This result might be due to the limited size of our study. Compared with the other studies carried out in the Netherlands (0%) and Czech Republic (0.1%),[9,12] our data showed a higher prevalence of patients that had been diagnosed with the apical ballooning syndrome. Although apical ballooning syndrome had been first reported in Japan in 1991, it has been increasingly described in Europe and North America in recent years.[14-17]

In the early 1960s, the Framingham Heart Study suggested the several risk factors for CAD, including age, diabetes, hypertension, dyslipidemia, smoking, and premature family history of CAD. These factors have been known to be critical in the development of cardiovascular events and related to morbidities and mortality of the patients.[18] Prasad *et al*. investigated 690 patients who were referred for PCI due to suspected STEMI. Their data demonstrate that patients with normal coronary arteries were younger and tended to have a lower prevalence of multiple conventional risk factors for CAD.[10] Gu *et al*. reported the normal coronaries group had fewer conventional risk factors, including smoking and premature family history of CAD.[12] Similarly, the current study also showed the normal coronaries group was younger and with less CAD risk factors, including hyperlipidemia ($P \leq 0.001$); [Table 1]. In addition, angina pectoris is less reported in the normal coronaries group, consistent with the reports by Prasad *et al*. and Gu *et al*.[10,12] In STEMI group, the prevalence of reported angina is up to 97%. In other words, a solid differentiation between alternative diagnosis and STEMI should be made in patients without angina pectoris.

In the standard treatment of STEMI, anti-platelet and anti-coagulation therapy are prescribed before performing CAG.[19] However, some conditions mimicking STEMI are contraindicated for their use or may result in catastrophic bleeding and deteriorate the clinical course.[20,21] Concomitant use of anti-platelet and anti-coagulation therapy may lead to hemorrhagic pericardial effusion, followed by complicated cardiac tamponade in acute pericarditis and aortic dissection patients.[22]

Limitations

Cardiac enzyme elevation patterns and ECG serial changes between two groups may be different. In practice, we did not follow up cardiac enzymes and serial ECG in normal coronaries group, especially after the procedure of CAG. This study was carried out as a retrospective review of patients' data from medical records, which may have led missing major information related to the diagnosis. In addition, investigation in a single tertiary medical center has a disadvantage of the limited size of the patient number. Furthermore, repeating this analysis in multiple medical centers and prospectively should be considered in order to verify the current results.

CONCLUSIONS

The incidence of alternative diagnosis in patients presenting as STEMI referred for primary PCI in our study is 7.9%. The alternative diagnoses were variable, including coronary spasm, peri-myocarditis, apical ballooning syndrome, and anaphylactic shock. The majority of these patients are male in middle age, less conventional CAD risk factors, and less reported angina. The 30-day mortality rate is 5.9%. Coronary spasm and peri-myocarditis were two frequent causes. A solid differentiation between various alternative diagnoses and STEMI, based on clinical characteristics and serial ECG, is crucial for making the accurate diagnosis and treatment in the ER.

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