Prevalence of normal coronary angiography in the acute phase of suspected ST-elevation myocardial infarction: Experience from the PRAGUE studies

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P Widimsky, B Stellova, L Groch, et al; on behalf of the PRAGUE Study Group Investigators. Prevalence of normal coronary angiography in the acute phase of suspected ST-elevation myocardial infarction: Experience from the PRAGUE studies. Can J Cardiol 2006;22(13):1147-1152.

BACKGROUND: Acute ST-elevation myocardial infarction in patients with normal coronary arteries has previously been described, but coronary angiography in these patients was performed after the acute phase of the infarction. It is possible that these patients did not have normal angiograms during the acute phase (transient coronary thrombosis or spasm were usually suspected to be the cause). Information on the prevalence of truly normal coronary angiograms during the acute phase of a suspected ST-elevation myocardial infarction is lacking.

PATIENTS AND METHODS: The PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-1 (PRAGUE-1) and PRAGUE-2 studies enrolled 1150 patients with ST-elevation acute myocardial infarction, in whom 625 coronary angiograms were performed within 2 h of the initial electrocardiogram. A simultaneous registry included an additional 379 coronary angiograms performed during the ST-elevation phase of a suspected myocardial infarction. Thus, a total of 1004 angiograms were retrospectively analyzed. A normal coronary angiogram was defined as one with the absence of any visible angiographic signs of atherosclerosis, thrombosis or spontaneous spasm.

RESULTS: Normal coronary angiograms were obtained for 26 patients (2.6%). Among these, the diagnosis at discharge was a small myocardial infarction in seven patients (0.7%), acute (peri)myocarditis in five patients, dilated cardiomyopathy in four patients, hypertension with left ventricular hypertrophy in three patients, pulmonary embolism in two patients and misinterpretation of the electrocardiogram (ie, no cardiac disease) in five patients. Seven patients with small infarctions underwent angiography within 30 min to 90 min of complete relief of the signs of acute ischemia, and thus, angiograms during pain were not taken. None of the 898 patients catheterized during ongoing symptoms of ischemia had a normal coronary angiogram. Spontaneous coronary spasm as the only cause (without underlying coronary atherosclerosis) for the evolving infarction was not seen among these 898 patients. Thus, the causes of the seven small infarcts in patients with normal angiograms remain uncertain.

CONCLUSIONS: The observed prevalence of normal coronary angiography in patients presenting with acute chest pain and ST elevations was 2.6%. Most of these cases were misdiagnoses, not infarctions. A normal angiogram during a biochemically confirmed infarction is extremely rare (0.7%) and was not seen during the ongoing symptoms of ischemia.

Key Words: *Acute myocardial infarction; Coronary spasm; Normal coronary angiography; ST elevation*

La prévalence de coronarographies normales pendant la phase aiguë d'une présomption d'infarctus du myocarde avec surélévation du segment ST : L'expérience des études PRAGUE

HISTORIQUE : On a déjà décrit des infarctus du myocarde avec surélévation du segment ST chez des patients aux artères coronaires saines, mais la coronarographie avait été effectuée après la phase aiguë de l'infarctus. Est-il possible que la coronarographie n'ait pas été normale pendant la phase aiguë (on présumait généralement une thrombose coronaire transitoire ou des spasmes). On ne possède pas d'information sur la prévalence d'une coronarographie vraiment normale pendant la phase aiguë d'une présomption d'infarctus du myocarde avec surélévation du segment ST.

PATIENTS ET MÉTHODOLOGIE : Dans le cadre des études PRAGUE-1 et PRAGUE-2 sur l'angioplastie primaire de patients transférés d'un hôpital général à une unité spécialisée de coronaropathie percutanée transluminale, on a enrôlé 1 150 patients ayant un infarctus aigu du myocarde avec surélévation du segment ST, chez qui 625 coronarographies ont été effectuées dans les deux heures suivant le premier électrocardiogramme. Un registre simultané contenait 379 autres coronarographies exécutées pendant la phase de surélévation du segment ST d'une présomption d'infarctus du myocarde. Ainsi, au total, 1 004 coronarographies ont fait l'objet d'une analyse rétrospective. Une coronarographie normale était définie comme un examen ne comportant aucun signe angiographique visible d'artériosclérose, de thrombose ou de spasme spontané.

RÉSULTATS : On a obtenu des coronarographies normales auprès de 26 patients (2,6 %). De ce nombre, à leur congé, sept patients avaient un diagnostic de petit infarctus du myocarde (0,7 %) au congé, cinq patients, une (péri)myocardite, quatre patients, une myocardiopathie dilatée, trois patients, une hypertension accompagnée d'une hypertrophie ventriculaire gauche, deux patients, une embolie pulmonaire et cinq patients, une mauvaise interprétation de l'électrocardiogramme (c'est-à-dire, pas de maladie cardiaque). Les sept patients ayant un petit infarctus ont subi une angiographie de 30 à 90 minutes après le soulagement complet des signes d'ischémie aiguë, et non pendant la douleur. Aucun des 898 patients ayant subi un cathétérisme pendant des symptômes d'ischémie ne présentait de coronarographie normale. Chez ces 898 patients, on n'a observé aucun cas de spasme coronaire spontané (sans artériosclérose coronarienne sous-jacente) expliquant l'infarctus en évolution. Ainsi, les causes des petits infarctus chez les sept patients ayant une angiographie normale ne sont pas claires.

CONCLUSIONS : On a observé une prévalence de 2,6 % de coronarographies normales chez les patients ayant des douleurs thoraciques aiguës et une surélévation du segment ST. La plupart de ces cas étaient des mauvais diagnostics et non des infarctus. Il est extrêmement rare de constater une coronarographie normale pendant un infarctus confirmé biologiquement (0,7 %), et on n'en a pas observé pendant les symptômes continus d'ischémie.

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Received for publication November 8, 2005. Accepted March 22, 2006

Acute myocardial infarction is generally caused by arterial thrombosis superimposed on an atherosclerotic plaque in an epicardial coronary artery. The underlying pathophysiological mechanism is a complex interaction among the atherosclerotic plaque, platelet activation, thrombus formation and coronary vasospasm. However, numerous authors (1-10) have reported many patients with myocardial infarction and normal coronary angiograms. The exact explanation for angiographically normal coronary arteries in these patients is not known. Various mechanisms, including coronary spasm (5), coagulation disorders (5-9), embolism (5) and hypertension (4), have been hypothesized. Despite the extensive available literature on patients with acute myocardial infarctions and normal coronary arteries, our own experience involving more than 3500 acute phase coronary angiograms before primary percutaneous coronary intervention (PCI) since 1993 has been different – we believe this entity is almost nonexistent. Thus, we decided to analyze the frequency of normal coronary angiograms in patients referred for primary PCI due to acute chest pain with ST elevations on an electrocardiogram (ECG). Special emphasis was placed on timing of coronary angiography in these patients – whether it was performed during the ongoing symptoms of ischemia or after the resolution of such symptoms.

PATIENTS AND METHODS

Patients

All coronary angiograms from the PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-1 (PRAGUE-1) study (11) and the PRAGUE-2 study (12) (PRAGUE study angiograms, n=625) were retrospectively analyzed, along with coronary angiograms obtained during the last year of the PRAGUE-2 study (2002) at the Kralovske Vinohrady University Hospital, Prague, Czech Republic ('the hospital'), for this indication (PRAGUE ST-Elevation Myocardial Infarction [STEMI] registry angiograms, n=379). The inclusion criteria were acute myocardial infarction (ST elevations greater than 1 mm in at least two leads or a new bundle branch block on initial ECG), less than 12 h of symptoms and signed, informed consent. The exclusion criteria for the PRAGUE studies were contraindication to thrombolysis and the absence of bilateral femoral artery pulsations. There were no exclusion criteria for the registry patients (since 1995, all patients presenting at the hospital with STEMI were sent for primary PCI, irrespective of age or clinical condition). The baseline patient characteristics are shown in Table 1.

TABLE 1
Baseline patient characteristics

	PRAGUE studies (n=625)	STEMI registry (n=379)
Normal CAG, n (%)	13 (2.1)	13 (3.4)
Mean age, years	63.5	65.0*
Time from symptom onset to CAG, min	232	246
Killip class >I, %	16	34**
Diabetes mellitus, %	23	24
Mean time from diagnostic ECG, min	78 (transported patients only)	53 (transported and directly admitted patients)
PCI performed, %	89	85
PCI success rate, %	94 (TIMI 2–3) 87 (TIMI 3)	93 (TIMI 2–3) 88 (TIMI 3)

**P<0.01; **P<0.005. CAG Coronary angiogram; ECG Electrocardiogram; PCI Percutaneous coronary intervention; PRAGUE PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis; STEMI ST-elevation myocardial infarction; TIMI Thrombolysis In Myocardial Infarction*

TABLE 2
Data on patients with coronary atherosclerosis, but less than 50% diameter stenosis lesions on coronary angiography (n=9)

Women, n	4
Mean age, years (range)	54 (47–79)
Mean number of diseased coronary arteries (<50% diameter stenosis)	2.2
Peak CK-MB, µkat/L (CK-MB/CK ratio)	3.15 (0.12)
Mean ejection fraction by echocardiography	55%
Regional wall motion (echocardiography)	Hypokinesis (7 patients), akinesis (1 patient), normal (1 patient)
Location of ECG (± echocardiography) abnormalities	Inferior (4 patients), anterior (4), lateral (1 patient)
Killip class	I (all patients)
Smokers, n	4
Diabetes mellitus, n	4
Hypertension, n	5

CK-MB Creatine kinase (muscle-brain); ECG Electrocardiogram

Coronary angiography

Most angiograms were performed within 90 min of the initial ECG, and all were performed within 2 h. All angiograms were analyzed independently by at least two experienced angiographers. A normal coronary angiogram was defined as one with the absence of any visible angiographic pathology (including any signs of atherosclerosis, thrombosis or spontaneous spasm). Specifically, nine patients (0.9% of all acute phase angiograms) with mild coronary atherosclerosis (lesions of less than 50% diameter stenosis) were diagnosed as having a pathological coronary angiogram (Table 2). A typical example is shown in Figure 1.

Echocardiography

Echocardiographic examination was performed within 24 h of admission in 81% of patients and within 72 h in the remaining 19%. Left ventricular (LV) ejection fraction and wall thickness, regional and global wall motion abnormalities, presence or absence of pericardial effusion, and right ventricular (RV) diameter (including RV/LV ratio) were routinely described in all.

Biomarkers

Creatine kinase (CK) and CK (muscle-brain) values were available for all 1004 patients. A troponin assessment was only performed in 44% of the study population. Thus, the diagnosis of acute myocardial infarction was based on the serial rise (more than two times the upper limit of normal) and subsequent fall of CK (muscle-brain), along with the symptoms and ECG changes described above (as the inclusion criteria).

Diagnosis at discharge

The diagnosis at discharge was based on agreement of at least three experienced cardiologists. In the case of an acute myocardial infarction, diagnosis was based on the above-mentioned criteria. Pulmonary embolism was diagnosed using computer tomography

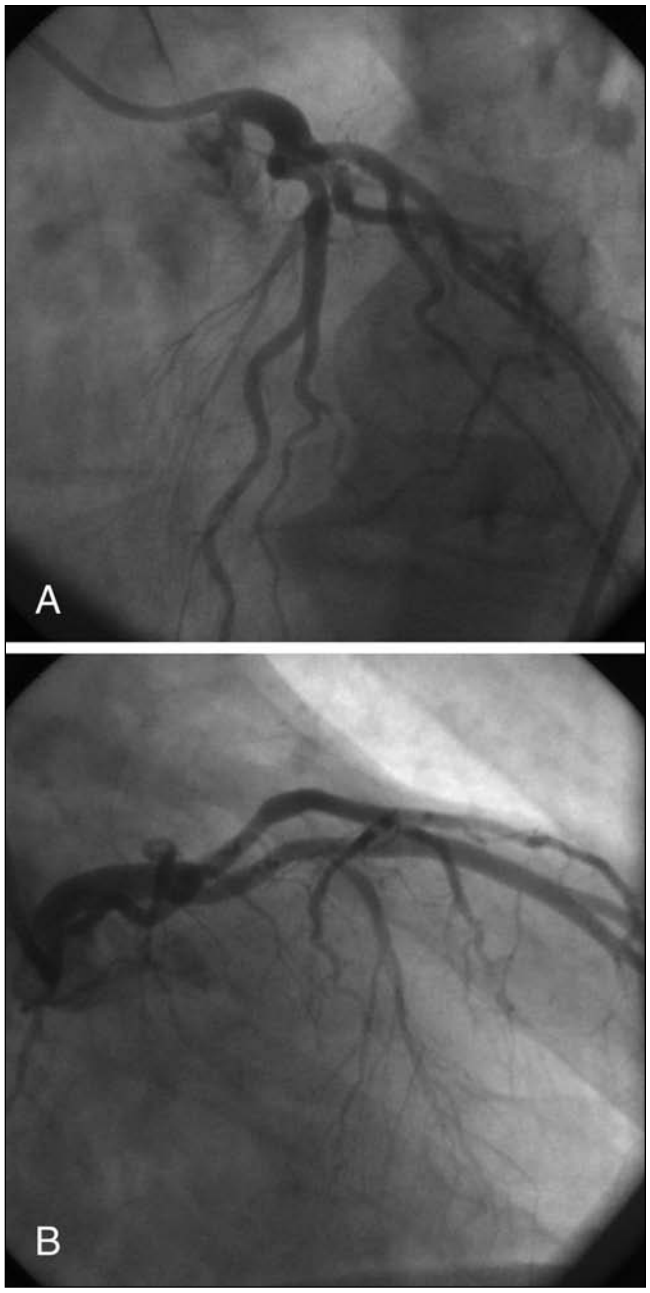

Figure 1) *A mild (measured 29% diameter stenosis), but long (22 mm) atherosclerotic lesion in the tortuous proximal segment of the left anterior descending coronary artery. This patient had chest pain and ST elevations in the prehospital phase, and was treated in the emergency ambulance by acetylsalicylic acid, clopidogrel and heparin. The patient arrived at the catheterization laboratory already without symptoms, but with echocardiographic (anteroapical akinesis) and electrocardiographic (deep negative T waves in lead positions V1 to V6) signs of myocardial stunning.* **A** *Left superior oblique projection.* **B** *Right superior oblique projection*

and one additional method (perfusion scan, echocardiography or pulmonary angiography). Dilated cardiomyopathy was diagnosed when diffuse LV hypokinesis with dilation was accompanied by negative biomarkers of myocardial damage and normal coronary angiography. Acute (peri)myocarditis was diagnosed when a normal coronary angiogram, positive biomarkers, echocardiographic LV dysfunction and/or pericardial effusion were found in a patient with fever or other signs of an acute infectious disease. A diagnosis of hypertension was based on the history and current blood pressure greater than 140/90 mmHg and concentric LV hypertrophy on echocardiography in patients with negative biomarkers, no LV dysfunction and normal coronary angiography. The clinical conclusion was no cardiac disease when results of the following examinations were normal: echocardiography, coronary angiography, biomarkers, chest x-ray and computed tomography (or perfusion scan).

TABLE 3
Comparison of patients with normal coronary angiograms (CAG) (n=26) with those with pathological CAG (n=978)

	Normal	Pathological
Mean age, years (range)	51 (39–83)	64 (22–92)
Women, %	15	30
Diabetes mellitus, %	8	23
Hypertension, %	23	49
Smokers, %	8	44
Previous myocardial infarction, %	0	16
Ongoing pain and/or ST elevation at the time of CAG, %	4	86
Highest ST elevation amplitude >2 mm, %	12	83
Bundle branch block, %	12	3
Killip class >I, %	0	23
Acetylsalicylic acid before entering cath lab, %	69	80
Heparin before entering cath lab, %	73	88
Cardiopulmonary resuscitation before CAG, %	4	8
Mean admission blood pressure, mmHg	131/74	133/75
Mean admission heart rate, beats/min	74	75
Mean body weight, kg	81	82
Mean height, cm	177	176
Mean cholesterol, mmol/L	4.1	5.2
Direct admission to PCI centre, %	19	22
Transfer from another hospital, %	81	78
Positive biomarkers for acute MI, %	31	96
Regional wall motion abnormality, %	31	91
Diffuse left ventricular hypokinesis, %	15	8
Mean ejection fraction, %	57	49

Cath lab Catheterization laboratory; MI Myocardial infarction; PCI Percutaneous coronary intervention

RESULTS

Coronary angiograms were normal in 26 patients (ie, 26% of all angiograms performed during the acute phase of suspected STEMI). The characteristics of these patients, compared with those of the 978 patients with pathological angiograms, are shown in Table 3.

Coronary angiography

Chest pain persisted during catheterization in only one of 26 patients with normal coronary angiograms; the final diagnosis at discharge in this patient was pulmonary embolism. The remaining 25 patients with normal angiograms had complete pain relief between the initial diagnostic ECG and catheterization procedure (ie, these patients had no symptoms during angiography). None of the 898 patients catheterized during ongoing symptoms of ischemia had normal coronary angiograms.

TABLE 4
Data of seven patients with confirmed myocardial infarctions but normal coronary angiograms

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex, age (years)	M, 48	F, 78	M, 54	M, 54	M, 64	F, 62	F, 57
Coronary angiography status	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Peak CK-MB, µkat/L (CK-MB/CK ratio)*	3.30 (0.13)	2.57 (0.18)	1.11 (0.12)	1.11 (0.11)	2.15 (0.12)	1.85 (0.11)	1.99 (0.13)
Ejection fraction (on echocardiography), %	53	65	52	60	54	52	45
Regional wall motion (on echocardiography)	Hypokinesis	Normal	Hypokinesis	Normal	Normal	Normal	Akinesis
Location of ECG (± echocardiographic) abnormalities	Inferior	Anterior	Inferior	Inferior	Anterior	Inferior	Lateral
Killip class	I	I	I	I	I	I	I
Cigarettes smoked per day	0	20	40	0	60	0	10
Diabetes mellitus	No	No	No	No	No	No	No
Hypertension	No	No	Yes	No	Yes	Yes	Yes

**Normal values: creatine kinase (muscle-brain) (CK-MB) <0.35 µkat/L, CK <4.00 µkat/L, CK-MB/CK ratio of <0.10; mean CK values in patients with infarctions and significant coronary artery disease on angiograms: CK-MB 4.75 µkat/L, CK 33.50 µkat/L, CK-MB/CK ratio of 0.14. ECG Electrocardiogram; F Female; M Male*

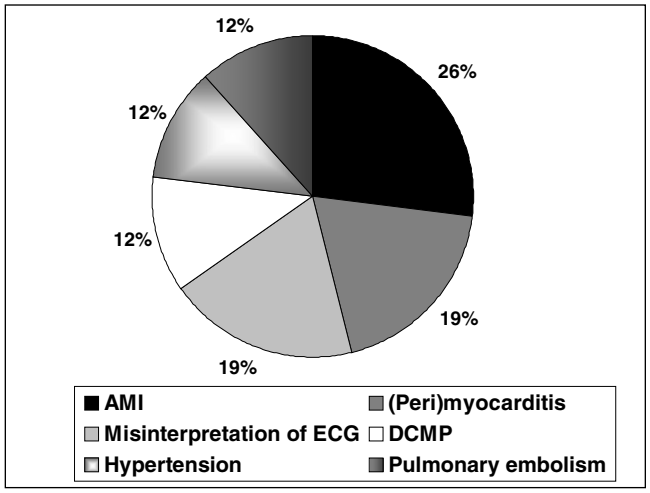

Figure 2) *Diagnosis at discharge of 26 patients with normal coronary angiograms. AMI Acute myocardial infarction; ECG Electrocardiogram; DCMP Dilated cardiomyopathy*

Echocardiography

Normal LV function was found in 54% of patients who had normal angiograms. Diffuse LV hypokinesis was seen in 15% of patients and regional wall motion abnormality was seen in 31%. The mean ejection fraction was 57%. A dilated RV and/or an RV/LV ratio greater than 0.8 were observed in 12% of patients (with pulmonary embolism as the final diagnosis). A small pericardial effusion was found in only one patient.

Diagnosis at discharge

Patient diagnoses at discharge are shown in Figure 2. All seven patients with small myocardial infarctions underwent coronary angiography within 30 min to 90 min of complete relief of symptoms. Transient coronary spasm and/or the resolution of transient coronary thrombosis before angiography was assumed to be the cause of these small infarcts. The data of these seven patients are shown in Table 4. Other cardiac causes of this clinically important discrepancy (ie, suspected STEMI with normal acute phase angiography) include acute (peri)myocarditis (n=5), dilated cardiomyopathy (n=3), pulmonary embolism (n=3) and hypertension (n=3). No cardiac disease (ie, ECG misinterpretation) was present in five patients (0.5% of the entire study population).

DISCUSSION

Many previously published studies (1-10) reported on patients after an acute myocardial infarction with normal coronary arteries. However, none of these patients' angiograms were performed at the time of ongoing symptoms of ischemia. All angiograms in our study were performed during the acute phase of a suspected acute STEMI, within 2 h of the initial ECG. Patients were selected as candidates for primary angioplasty on the basis of acute symptom onset and ST elevations on ECG. In fact, they represented suspected rather than confirmed cases of acute myocardial infarction. Chest pain lasted during the acute phase myocardial infarction in only one of the 26 patients with normal coronary angiograms. The final diagnosis in that case was pulmonary embolism.

A small myocardial infarction was documented biochemically in seven patients. Transient coronary spasm and/or thrombosis resolving before angiography were assumed to be the causes for these small infarcts. The development of an acute myocardial infarction in association with a normal coronary angiogram has never been convincingly explained. Data from angiographic and pathological studies (13) have established a clear association between plaque fissure or rupture and the development of the acute coronary syndrome.

The pioneering angiographic work of DeWood et al (14), published in 1980, first described an acute thrombotic coronary occlusion during the initial hours of myocardial infarction and thus triggered the interest in reperfusion therapy.

Schwartz and Bourasa (15) summarized the pathophysiological features, investigation and treatment of chest pain in patients with myocardial infarction and angiographically normal coronary arteries. Coronary vasospasm, congenital coronary anomaly, other cardiac conditions (aortic stenosis, cardiomyopathy, hypertension), extracardiac diseases (diseases of distal esophagus and musculoskeletal system) and psychological disorders were suggested as possible explanations. Mohri et al (16) applied acetylcholine to the coronary arteries in 117 patients with angina pectoris. They induced chest pain with ischemic ECG changes in 25% of their patients, but no spasm of the large epicardial coronary arteries occurred.

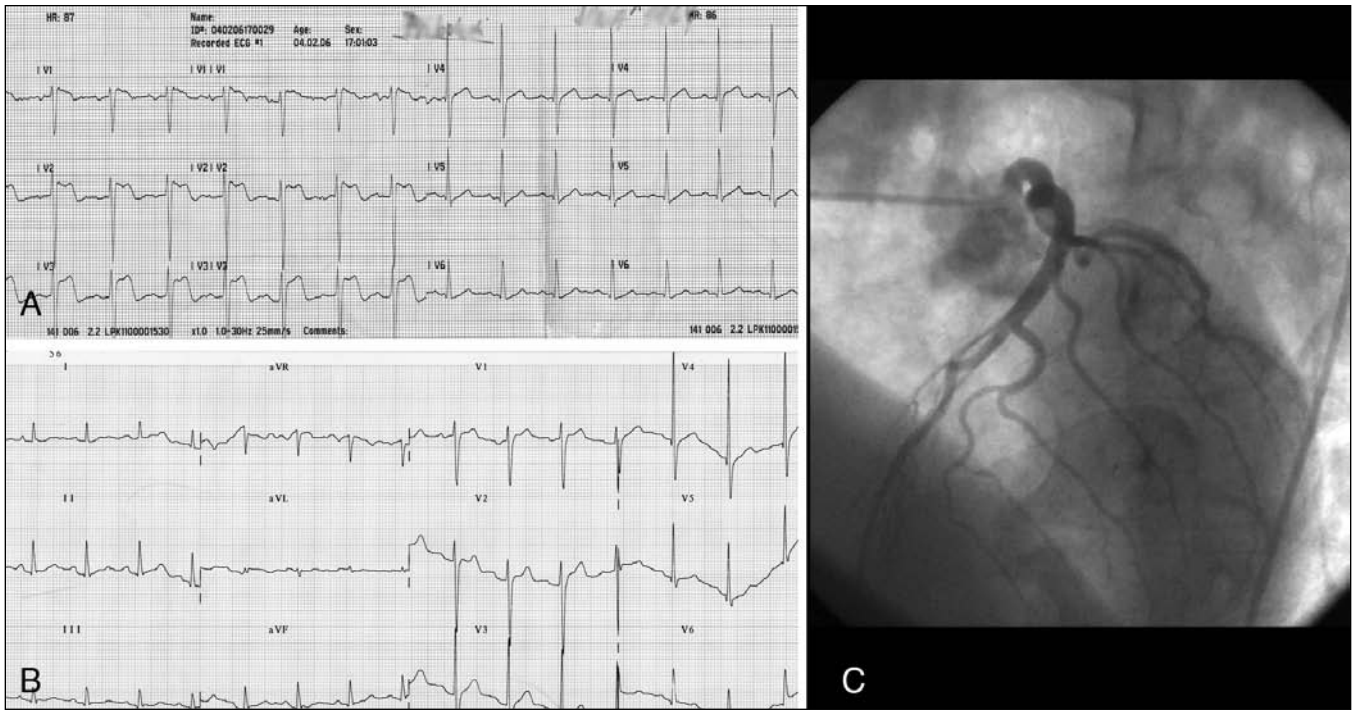

Figure 3) A *Prehospital electrocardiogram (ECG) (chest lead positions V1 to V6) of a 48-year-old male patient (heavy smoker with hypertension and a positive family history) with a sudden onset of chest pain. On the basis of this ECG, the patient was treated in the prehospital phase with heparin, acetylsalicylic acid and clopidogrel; subsequently, he was admitted to the catheterization laboratory.* **B** *ECG of the same patient recorded in the catheterization laboratory immediately on arrival. Despite the results of this ECG, the interventional cardiologist decided to proceed with immediate coronary angiography due to typical symptoms, multiple risk factors and results of prehospital ECG.* **C** *Normal coronary angiogram of the same patient*

Many studies have described acute myocardial infarction with normal coronary angiograms in the patients with hypercoagulable states (6-9). Mansourati et al (6) evaluated the prevalence of factor V Leiden in patients with acute myocardial infarctions and normal coronary angiograms, in patients with acute myocardial infarctions and significant coronary artery stenosis, and in healthy patients. The study showed the prevalence of factor V Leiden in patients with acute myocardial infarction, and that normal coronary angiography was higher in these patients than in both comparative groups.

The relatively high prevalence of acute myocardial infarction associated with normal coronary angiography was described in young patients (younger than 40 years of age) (17,18). Zimmerman et al (18) studied the angiographic characteristics, coronary risk factors and prognoses in young women and men with a history of myocardial infarction. These authors reported normal coronary angiography, or nonobstructive disease, in 34% of young women and 22% of young men. However, nonobstructive disease was defined as 50% to 69% diameter stenosis in major coronary artery segments, 70% to 100% in minor segments or 30% to 49% in the left main coronary artery. In our institution, a normal coronary angiogram is defined differently: there must be absence of any visible coronary pathology; even mild atherosclerotic plaques of less than 50% diameter stenosis cannot be present. This explains the much lower frequency of normal coronary angiographic results in our group. A normal coronary angiogram does not necessarily mean the absence of any atherosclerosis. Our results indicate that the so-called 'myocardial infarction with normal coronary arteries' includes a heterogeneous group, including cases of misdiagnosis (eg, pulmonary embolism, acute pericarditis, etc), as well as true infarctions most likely caused by transient coronary spasm and/or thrombus. The role of stress-induced myocardial stunning (described below) needs to be further established in this context.

Indeed, ECG misinterpretation was the cause for most of these diagnostic errors. ECG-documented ST elevations are known to occur in several other conditions (eg, acute myocarditis or pericarditis, dilated or hypertrophic cardiomyopathy, Brugada syndrome and others). If we reverse our observations, we can conclude that ST elevations resulted in the proper diagnosis of acute coronary occlusion (or significant unstable stenosis) in 969 patients, or in 96.5% of cases (all 1004 minus the 26 with normal angiograms, minus the nine with less than 50% diameter stenosis). An example of a false-positive ECG is shown in Figures 3A to 3C.

Da Costa et al (5) summarized the etiological factors of myocardial infarction with normal coronary arteries. Coronary spasm was documented in 15.5% of cases, congenital coagulation disorders in 13.3%, collagen tissue disorders in 2.2%, embolism in 2.2% and oral contraceptive use in 1.1%. Etiological factors were identified in only one of three patients. Coronary angiography was performed 6.2±4 days (range one to 15 days) after the onset of myocardial infarction. By then, coronary thrombus or spasm may have resolved in these patients.

Wittstein et al (19) recently proposed the concept of "stress-induced myocardial stunning", a neurohumoral reaction to a sudden emotional stress (a syndrome also called apical LV ballooning, or tako-tsubo cardiomyopathy). Ninety-five per cent of patients in the study were female, with a mean age of 63 years, which is remarkably different from our

series, in which 85% of patients were male, with a mean age of 12 years younger. In fact, stress-induced myocardial stunning could be a hypothetical explanation for only one of our patients. The generally good prognosis of most of these patients is a feature shared by most studies that report suspected myocardial infarctions with normal coronary angiograms.

Diagnostic errors occurred in 19 patients (1.9%), with other cardiac pathologies present in 14 patients (1.4%). We find this acceptable when it is compared with the 10% to 15% prevalence of normal coronary angiograms in the nonacute (elective) situation. It would hardly be feasible to bring this figure to 0%. Elimination of diagnostic mistakes would require at least repeated ECGs and echocardiography performed in the catheterization laboratory (almost all our patients arrive directly to the catheterization laboratory) before pulmonary angiography. In our view, awareness of a normal coronary angiogram helped the management of at least some of these 19 patients, in terms of, for example, shortening their hospital stay, stopping antithrombotic medications or focusing on other diagnostic possibilities.

The present study revealed a 2.6% prevalence of normal coronary angiography among patients who presented with suspected STEMI. Most of these patients had other cardiac pathologies. Because all our patients with confirmed infarction underwent angiography only after symptom resolution, we conclude that a normal coronary angiogram during ongoing symptoms of ischemia was not detected.

ACKNOWLEDGEMENTS: This study was partially supported by the research project number MSM0021620817 of Charles University in Prague, Czech Republic.

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