Original Article

Acute Coronary Syndromes in the Absence of Significant Coronary Artery Disease

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Objective

To assess the clinical characteristics, evolution, and in-hospital complications of patients with acute coronary syndromes (ACS) in the absence of significant obstructive coronary artery disease (CAD).

Methods

Cross-sectional study of patients hospitalized from August 1996 to March 2002 with acute coronary syndrome, with or without an elevation in the ST segment, and with (= 50%) or without (<50%) significant coronary stenosis. Their clinical and demographic characteristics and their in-hospital complications were analyzed.

Results

Of the 1351 patients admitted with acute coronary syndrome, 28% had an elevation in the ST segment and 72% had no elevation. The patients with acute coronary syndrome with no elevation in the ST segment and no significant coronary obstruction were younger, predominantly females, and had a lower frequency of dyslipidemia, previous coronary arterial disease, diabetes mellitus, smoking, and systemic arterial hypertension, when compared with those with significant obstructive lesion. Among the individuals with acute coronary syndrome and an elevation in the ST segment, smoking was the most prevalent risk factor in patients with nonsignificant obstructive lesion. In regard to complications, recurring ischemia, congestive heart failure, and arrhythmias were more frequent in patients with acute coronary syndrome with no elevation in the ST segment and no significant obstructive coronary lesion.

Conclusion

Patients with acute coronary syndrome with no elevation in the ST segment and with nonsignificant obstructive coronary lesions are younger, predominantly females, have a greater frequency of risk factors for coronary arterial disease, and a lower incidence of complications as compared with patients with significant obstructive coronary lesion.

Keywords

coronary arterial disease, clinical characteristics, coronary stenosis

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Acute coronary syndromes are usually caused by coronary obstruction due to an interaction of thrombotic and vasospastic phenomena and coronary atherosclerotic lesions, which can manifest as different clinical findings, such as unstable angina, acute myocardial infarction, or sudden death [1]. Initially, only the atheromatous plaques with significant obstruction, reducing the lumen of the vessel by more than 50%, were considered to have a potential for rupture, subsequent thrombosis, and vascular occlusion [2]. Recent studies, however, have challenged the old paradigm and shown that, even plaques with no significantly obstructive lesions, ie, with lumen reduction lower than 50%, also have a thrombogenic potential [3].

The association of acute coronary syndrome and nonsignificant coronary obstruction began to be reported in the 70s [4]. Since then, several studies have shown some differences in the prognosis and distribution of the risk factors in that group of patients, comparing those patients with others with acute coronary syndrome and significant obstructive lesions [5]. However, those studies had varied results and used different definitions and inclusion criteria. Therefore, a controversy persisted in regard to the aspects characterizing patients with acute coronary syndrome in the absence of significant obstructive coronary arterial disease.

This study aimed at defining the clinical characteristics and short-term evolution of patients with acute coronary syndrome with and without an elevation in the ST segment, comparing the individuals without significant obstructive lesion with those with significant coronary artery obstruction.

Methods

This was a retrospective cross-sectional study with patients admitted with acute coronary syndrome between August 1996 and March 2002. The acute coronary syndromes with an elevation in the ST segment were defined as follows: chest pain lasting more than 30 minutes; an elevation in the creatine phosphokinase isoenzyme (CK-total) and its myocardial fraction (CK-MB) of at least twice the basal value. The electrocardiographic alterations in this group included an elevation in the ST segment > 1 mm in 2 contiguous leads of the same ventricular wall in the peripheral leads, or an elevation in the ST segment > 2 mm in at least 2 contiguous leads in the horizontal plane, or both, associated or not with the recent appearance of left bundle-branch block [6]. Acute coronary syndromes with no elevation in the ST segment comprise acute myocardial infarction with no elevation in the ST segment and unstable angina. The individuals with unstable angina had precordial

pain at rest, depression in the ST segment > 1 mm in 2 contiguous leads of the same ventricular wall, and inversion of the T wave or spiked T wave, both symmetric. Infarction with no elevation in the ST segment affected individuals with chest pain and no elevation in the ST segment, but with an increase in the biochemical markers of myocardial necrosis (total CK and CK-MB) [7].

The following patients were excluded from the study: those who did not undergo coronary angiography during hospitalization; those who were transferred to another institution within less than 48 hours; and those who underwent previous coronary artery bypass grafting.

The patients were distributed into 2 groups according to the visual assessment of the severity of the coronary arterial lesions identified on coronary angiography in one or more of the 3 major coronary arteries, or their major branches, or both. The criterion of the BARI study [8] was used for defining the significant obstructive coronary lesion: the group with a significant obstructive coronary lesion had coronary stenosis = 50%, and the group without a significant obstructive coronary lesion had coronary stenosis < 50%, including normal coronary arteries. The coronary angiographies were performed during the patient's hospitalization and interpreted by more than 2 hemodynamicists.

The severity of the coronary lesion (lesion ≥ 50% and < 50%) found on coronary angiography was used for the comparative analysis of the clinical and demographic characteristics and complications of the individuals with acute coronary syndrome with and without an elevation in the ST segment.

The patients with acute coronary syndrome without an elevation in the ST segment received the conventional therapy, which consisted of rest, oxygen therapy, nitrate, antiplatelet agent, beta-blocker or calcium channel blocker, or both, in the case of vasospasm, and plain heparinization, if no contraindication existed. The patients with an elevation in the ST segment, who were admitted to the emergency unit within the first 12 hours of pain onset, underwent thrombolysis or were referred for primary angioplasty, depending on the availability of the service.

The clinical and demographic variables of the patients were stored in the Epidemiology of the Acute Coronary Syndromes (EPICOR) databank, which represents the recording of all admissions due to acute myocardial infarction or unstable angina at the Coronary Unit of the Cardiology and Cardiovascular Surgery Unit of the Fundação Bahiana de Cardiologia [9]. The follow-up of patients proceeded from admission until hospital discharge, and all therapeutic and diagnostic interventions adopted were recorded, as were the complications and outcomes of the patients with the syndromes studied during the in-hospital phase.

The definitions of risk factors for coronary arterial disease were those used by the II Brazilian Consensus on Dyslipidemia [10]. The following variables were analyzed: sex, age, systemic arterial hypertension, diabetes mellitus, sedentary lifestyle, dyslipidemia, obesity, familial history, previous coronary artery disease, and smoking. During hospitalization, the 5 major cardiovascular complications assessed were as follows: 1) recurring myocardial ischemia, translated by the reappearance of angina or acute myocardial infarction; 2) congestive heart failure defined by signs and symptoms of pulmonary congestion, requiring the use of specific therapy, such as diuretics, vasodilators, or digitalis, or both; 3) cardiogenic shock defined as systolic blood pressure < 90 mm Hg for more than 30 minutes, requiring the use of vasopressors; 4) arrhythmias requiring pharmacological treatment, electrical cardioversion or use of pacemaker; and 5) death.

The continuous variables were expressed as mean value ± standard deviation, and the categorical variables were expressed as proportions. The chi-square test or the Fisher exact test was used for testing the differences between the proportions after checking whether the data were in accordance with the premises for those tests. The continuous variables of the individuals with and without an elevation in the ST segment were compared by use of the Student *t* test for independent samples. The prevalence ratios were used with their respective 95% confidence intervals (95% CI), as an estimate of the measure of association between the coronary lesion and its possible or eventual predictors, in individuals with and without an elevation in the ST segment. Values lower than 5% ($P < 0.05$) were considered statistically significant.

Multiple logistic regression was used for identifying the possible independent predictors for the syndrome with and without an elevation in the ST segment in individuals with no significant coronary artery obstructions. The odds ratios (OR) and their respective 95% confidence intervals (95% CI) were used as estimates of the prevalence ratios of the risks of the association between the variables.

Results

From August 1996 to March 2002, 1866 patients were admitted with acute coronary syndrome. Of those, 515 patients were excluded from the study because they had not undergone coronary angiography, which resulted in a study with 1351 patients [722 (57.1%) men and 579 (42.9%) women]. Of the patients admitted with acute coronary syndrome, 374 (28%) had an elevation in the ST segment, and 977 (72%) had no elevation in that segment.

The analysis of the coronary angiographies showed that 182 (13.5%) patients had a 0 to 25% lesion, 39 (2.9%) patients had a 25% to 50% lesion, and 1130 (83.6%) had a lesion ≥ 50%. Of the individuals with no elevation in the ST segment, 21% had a lesion < 50% and 79% had a lesion ≥ 50%. Of the individuals with an elevation in the ST segment, 5% had a lesion < 50%, while 95% of the patients had a lesion ≥ 50% (fig. 1).

In regard to the age group of the patients with acute coronary syndrome with no elevation in the ST segment, we observed that those with nonsignificant obstructive coronary lesions were, on average, 4 years younger than those with significant obstructive lesions (57 ± 12 versus 61 ± 11; $P < 0.05$). These individuals also had a lower incidence of systemic arterial hypertension, diabetes mellitus, dyslipidemia, smoking, and previous coronary artery disease, as compared with those with significant obstructive lesion. In regard to the remaining risk factors, no statistically significant difference was observed between the groups.

The demographic characteristics of the individuals with acute coronary syndrome with an elevation in the ST segment obtained on admission showed that, although the patients with lesion <50% were younger than individuals with significant obstructive coronary lesions (45 versus 59 years; $P < 0.0001$), no difference in sex distribution was found, or in the prevalence of risk factors between the groups. Smoking, however, was the only risk factor with a greater prevalence in individuals with coronary obstruction < 50% (tab. I).

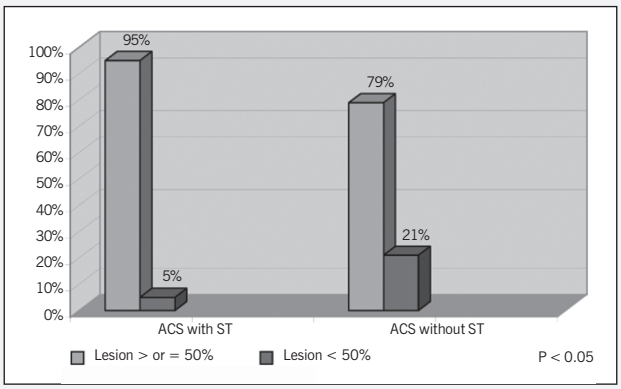

Fig. 1 – Distribution of acute coronary syndromes according to the severity of coronary lesion.

Of the clinical and demographic characteristics assessed in multivariate analysis, the most important predictive factors for acute coronary syndrome with an elevation in the ST segment in individuals with a nonsignificant obstructive coronary lesion were as follows: female sex, age < 60 years, and no previous coronary arterial disease. In individuals with acute coronary syndrome with an elevation in the ST segment, the most important predictive factor for a nonsignificant obstructive coronary lesion was age <60 years (tab. II).

In patients with acute coronary syndrome with an elevation in the ST segment, no difference was found in the incidence of complications, such as congestive heart failure, cardiogenic shock, arrhythmias, recurring ischemia, and sudden death between individuals with and without a significant obstructive lesion. Neither cardiogenic shock nor sudden death was reported in the group with a lesion < 50%.

In the group with acute coronary syndrome and no elevation in the ST segment, the patients with a nonsignificant obstructive coronary lesion had a lower incidence of recurring ischemia (22.9% versus 9.5%; P < 0.0001), cardiogenic shock (1.9% versus 0%; P = 0.04), and arrhythmias (3.3% versus 0%; P = 0.009), and no in-hospital mortality was observed (tab. III). They also had a shorter length of hospital stay when compared with the patients with significant obstructive coronary lesions (4.9 ± 3.08 versus 7.8 ± 4.3 days; P < 0.05). The individuals with acute coronary syndrome with an elevation in the ST segment had no statistically significant difference in regard to complications when individuals with and without a significant obstructive lesion were compared. However, those with lesions < 50% had a shorter length of hospital stay (6.0 ± 2.3 versus 8.8 ± 4.2; P < 0.05).

Discussion

The atherosclerotic lesion is usually responsible for acute coronary syndromes, whose clinical spectrum comprises unstable angina, acute myocardial infarction, and sudden death. In the last 40 years, studies with coronary angiography have identified patients without significant coronary obstruction in up to 20% of the patients admitted with acute coronary syndrome.

Recent studies have challenged the old paradigm based on the idea that the coronary syndromes resulted from the gradual and progressive luminal obstruction caused by the growth of the atherosclerotic plaque. In the new paradigm, the risk of rupture is directly related to the intrinsic characteristics of the plaque associated with local thrombogenesis and extrinsic triggers. These factors are more important than the degree of stenosis and size of the plaque, determining the most lethal clinical manifestations of coronary atherosclerosis [3].

In accordance with data in the literature [11,12], in our study,

Table I - Demographic and clinical characteristics of patients with acute coronary syndromes according to the degree of coronary stenosis

	ACS with ST elevation n=374			ACS without ST elevation n=977		
	Lesion < 50% n=20	Lesion ≥ 50% n=354	P	Lesion < 50% n=200	Lesion ≥ 50% n=777	P
Sex Male	14 (70%)	227 (64.3%)	0.6	82 (41.2%)	448 (57.6%)	<0.0001
Female	6 (30%)	125 (5.7%)		117 (58.8%)	330 (42.4%)	
Hypertension	254 (72.6)	257 (72.6%)	0.4	142 (71.4%)	642 (82.5%)	<0.0001
Diabetes	3 (15%)	96 (27.1%)	0.2	37 (18.6%)	227 (29.2%)	0.003
Dyslipidemia	7 (35%)	198 (56%)	0.07	101 (50.8%)	495 (63.6%)	0.001
Familial hist.	6 (30%)	86 (24.3%)	0.6	63 (31.7%)	247 (31.7%)	0.9
Smoking	14 (70%)	167 (47.1%)	0.04	44 (22.1%)	239 (30.7%)	0.02
Sedentary lifestyle	14 (70%)	260 (73.4%)	0.7	136 (68.3%)	569 (73.1%)	0.2
Mean age	45.3±11.5	59.4±11.8	0.03	57.7±12	61.8±11	0.05
Obesity	2 (10%)	67 (18.9%)	0.3	38 (19.1%)	111 (14.3%)	0.09
Previous coronary artery disease	19 (95%)	280 (79.1%)	0.09	146 (73.4%)	348 (44.7%)	<0.0001

Table II - Independent predictive factors for acute coronary syndromes in individuals with and without an elevation in the ST segment. Multivariate analysis

	Lesion < 50%			Lesion ≥ 50%		
	OR	95% IC	P	OR	95% IC	P
Male sex	0.4	0.28 - 0.58	<0.0001	0.9	0.33 - 2.71	0.92
Hypertension	1.9	1.30 - 2.96	0.001	0.8	0.29 - 2.36	0.74
Diabetes	1.8	1.19 - 2.75	0.005	1.5	0.41 - 5.68	0.52
Dyslipidemia	1.7	1.25 - 2.48	0.001	2.1	0.78 - 5.83	0.14
Smoking	2.2	1.45 - 3.35	0.001	0.6	0.21 - 1.71	0.35
Previous coronary artery disease	0.3	0.23 - 0.48	<0.0001	0.2	0.02 - 1.43	0.12
Age < 60 years	2.05	1.43 - 2.94	<0.0001	8.9	1.94 - 40.93	0.005

Table III - Evolution and complications in individuals with acute coronary syndromes with (≥ 50%) and without (< 50%) significant obstructive coronary lesion

	ACS with ST elevation n=374			ACS without ST elevation n=977		
	Lesion <50% n=20	Lesion ≥ 50% n=354	P	Lesion < 50% n=200	Lesion ≥ 50% n=777	P
CHF	2 (10%)	56 (15.7%)	0.1	12 (6%)	72 (9.3%)	0.2
Shock	0%	45 (12.6%)	0.2	0%	15 (1.9%)	0.04
Arrhythmia	1 (5%)	47 (13.1%)	0.3	0%	26 (3.3%)	0.009
Rec. Isch	3 (15%)	70 (19.7%)	0.6	19 (9.5%)	178 (22.9%)	<0.0001
Death	0%	29 (8.3%)	0.2	0%	43 (5.5%)	0.001
Lenth of hospital stay	6.0±2.3	8.8±4.2	0.05	4.9±3.08	7.8±4.3	0.05

CHF- congestive heart failure; Rec Isch- recurring ischemia.

16.3% of the patients admitted with acute coronary syndrome had nonsignificant obstructive coronary lesions. On admission, those individuals had predominantly the clinical manifestations of acute coronary syndrome without an elevation in the ST segment (72.3%), while only 27.7% had clinical findings of that syndrome with an elevation in the ST segment.

Some studies have shown contradictory results regarding the clinical and demographic characteristics in patients with acute coronary syndrome and coronary arteries without significant obstructive lesions. In regard to demographic characteristics in our case series, women predominated (58.8%) among the patients without an elevation in the ST segment, differing from individuals with an elevation in the ST segment, in whom no difference in sex distribution was observed in the groups with and without a significant obstructive lesion.

Unlike the report by Diver et al [12], Roe et al [13], and the present study, Costa et al [14] reported a greater frequency of men among the patients with acute coronary syndrome in the absence of significant coronary obstruction. On the other hand, Raymond et al [15] showed no difference in sex distribution between both groups. However, the latter 2 studies assessed only acute myocardial infarction, and analyzed patients with and without an elevation in the ST segment.

In regard to the mean age of patients with an elevation in the ST segment, our study, similarly to that of Roe et al [13], found that patients without a significant obstructive lesion belong to a younger age group than patients with significant obstructive lesions. However, in the TIMI IIIA study, Diver et al [12] reported a similar mean age in both groups.

In the group with an elevation in the ST segment, we also observed a lower mean age in individuals with a nonsignificant obstructive lesion when compared with that of patients with an obstructive lesion ≥ 50%.

In individuals with acute coronary syndrome with no elevation in the ST segment and with no significant obstructive coronary lesion, our study found a lower frequency of systemic arterial hypertension, diabetes mellitus, smoking, dyslipidemia, and coronary artery disease when compared with the findings in patients with significant coronary lesions. These results are in accordance with those reported by Roe et al [13] and Costa et al [14], who confirmed the low incidence of risk factors in that subgroup of individuals.

In patients with acute coronary syndrome with an elevation in the ST segment, this study found no difference in the distribution of risk factors in the groups with and without a significant obstructive coronary lesion, except for smoking, which was the most prevalent factor in individuals with a lesion < 50%. Zimmerman et al [16] and Fournier et al [17] reported an association between smoking, acute myocardial infarction, and coronary arteries without significant obstructions in younger individuals.

The most important independent predictors for acute coronary syndrome with no elevation in the ST segment in the absence of significant obstruction assessed in our study and in that of Roe et al [13] were as follows: female sex, age < 60 years, and absence of previous coronary artery disease.

The determining factors of worse prognosis during the in-hospital phase are related to recurring ischemia and left ventricular dysfunction [18]. Some researchers [11,12] , studying patients who evolve with acute coronary syndrome without an elevation in the ST segment, have reported a low incidence of complications in the acute phase of the ischemic event, such as arrhythmias, congestive heart failure, and hypotension, as compared with that of individuals with acute coronary syndrome and an elevation in the ST segment. In our case series, the patients with acute coronary syndrome and nonsignificant obstructive coronary lesion, with or without an elevation in the ST segment, had a shorter length of hospital stay as compared with that of patients with significant obstructive coronary lesions, probably due to the low incidence of complications.

The studies with patients with acute coronary syndrome and no significant obstructive coronary lesions are case series with a small number of individuals, in which most information is based on retrospective studies with varied results, and using different definitions and inclusion criteria. The lack of uniformity in defining significant obstructive coronary lesions leads to a variation in the prevalence of acute coronary syndrome in individuals with no significant obstructive coronary lesions, which in the literature corresponds to 1 to 20% of the individuals. Roe et al [13] and Raymond et al [15] have considered coronary stenosis < 50%, including normal coronary arteries, as nonsignificant obstructive coronary lesions. On the other hand, Zimmerman et al [16], considered only patients with completely normal coronary arteries.

The inclusion of patients with atypical chest pain, mainly women, whose cardiac catheterization showed the absence of coronary artery disease and no need for a routine coronary arteriography according to the recommendation of the attending physician, may have led to selection bias, therefore, hindering data analysis. Another limitation regards the limited angiographic information, which does not include the characteristics of the lesions. In this way, the method used for quantifying the severity of coronary lesions was visual assessment; however, quantitative angiography is known to be a more accurate method for assessing the degree of coronary stenosis [19].

Our results have shown that patients with acute coronary syndrome, an elevation in the ST segment, and nonsignificant obstructive coronary lesions were younger and had a greater prevalence of smoking when compared with individuals with significant obstructive coronary lesions. In regard to the individuals with acute coronary syndrome without an elevation in the ST segment, those with a nonsignificant obstructive coronary lesion were predominantly of the female sex, belonged to a younger age group, and had a lower frequency of risk factors when compared with individuals with a significant obstructive coronary lesion.

The individuals without a significant obstructive coronary lesion also had a lower rate of complications, which resulted in a shorter length of hospital stay in that group. In individuals with acute coronary syndrome and an elevation in the ST segment, no statistically significant difference was observed in the in-hospital evolution of those with or without a significant obstructive lesion.

References

1. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non q wave myocardial infarction. Circulation 1998; 97: 1195-206.
2. Falk E. Plaque Ruptures With Severe Pre-Existing Stenosis Precipitating Thrombosis: Characteristics Of Coronary Atherosclerotic Plaques Underlying Fatal Occlusive Thrombi. Br Heart J 1983; 50: 127-34.
3. Ambrose JA, Tannebaum MA, Alexopoulos D et al. Angiographic Progression of Coronary Artery Disease and the Development of Myocardial Infarction. J Am Coll Cardiol 1988; 12: 56-62.
4. Campeau L. Myocardial infarction with normal selective coronary arteriograms. Am Heart J 1970; 79: 139-41.
5. Alpert JS. Myocardial Infarction With Angiographically Normal Coronary Arteries. Arch Intern Med 1994; 154: 265-9.
6. II Diretriz Brasileira de Cardiologia para o tratamento de infarto agudo do miocárdio. Arq Bras Cardiol 2000; 74(suppl II):1-46.
7. Diretrizes da Sociedade Brasileira de Cardiologia sobre angina instável e infarto agudo do miocárdio sem supradesnivel do segmento ST. Arq Bras Cardiol 2001; 77 (suppl II): 1-38.
8. Rogers WJ, Alderman EL, Chaitman BR et al. Bypass Angioplasty Revascularization Investigation (BARI): Baseline Clinical and Angiographic Data. Am J Cardiol 1995; 75: 9-17C.
9. Passos LCP, Lopes AA, Costa U, Lobo N, Rabelo A. Differences in the hospital mortality of unstable angina pectoris between men and women. Arq Bras Cardiol 1999; 72: 673-9.
10. Consenso Brasileiro de Dislipidemia: detecção, avaliação e tratamento (II). Arq Bras Cardiol 1996; 67: 109-28.
11. Betriu A, Pare JC, Sanz GA et al. Myocardial Infarction With Normal Coronary Arteries: A Prospective Clinical Angiographic Study. Am J Cardiol 1981; 48: 28-32.
12. Diver DJ, Bier JD, Ferreira PE et al. Clinical and Arteriographic Characterization of Patients with Unstable Angina Without Critical Coronary Arterial Narrowing (from the TIMI IIIA trial). Am J Cardiol 1994; 74: 531-7.
13. Roe MT, Harrington RA, Prosper DM et al. Clinical And Therapeutic Profile Of Patients Presenting With Acute Coronary Syndromes Who Do Not Have Significant Coronary Artery Disease. Circulation 2000; 102: 1101-6.
14. Costa A, Isaaz K, Faure E, Mourot S, Cerisier A, Lamaud M. Clinical characteristics, etiological factors and long term prognosis of myocardial infarction with an absolutely normal coronary angiogram. Eur Heart J 2001; 22: 1459-65.
15. Raymond R, Lynch J, Underwood D, Leatherman J, Razavi M. Myocardial Infarction and Normal Coronary Arteriography: A 10 Year Clinical and Risk Analysis Of 74 Patients. J Am Coll Cardiol 1988; 11: 471-7.
16. Zimmerman FH, Cameron A, Fisher LD, Grace NG. Myocardial Infarction In Young Adults: Angiographic Characterization, Risk Factors and Prognosis (CASS). J Am Coll Cardiol 1995; 26: 654-61.
17. Fournier JA, Gonzalez AS, Quero J et al. Normal angiogram after myocardial infarction in young pacients. A prospective clinical angiographic and long term follow up study. Intl J Cardiol 1997; 60:281-7.
18. Henning H, Gilpin E, Covell JW, Swan EA, O'Rourke RA, Ross J. Prognosis After Acute Myocardial Infarction: A Multivariate Analyses Of Mortality And Survival. Circulation 1979; 59: 1124-27.
19. Kearney P, Erbel R. Imaging in the catheterization laboratory. Curr opin Cardiol 1993; 8: 988-99.