




Risk factors for sudden death in patients with acute myocardial infarction

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: January 31, 2020

Accepted: March 5, 2020

Competing interests

The authors declare no competing interests.

Abbreviations

AMI: Acute myocardial infarction

LVEF: Left ventricular ejection fraction

SCD: Sudden cardiac death

ABSTRACT

Introduction: Several investigations have addressed the identification of clinical markers for the risk of sudden cardiac death in acute myocardial infarction.

Objectives: To determine the risk factors for this type of death in patients with acute myocardial infarction.

Methods: A case-control analytical study was conducted at the Department of Cardiology in Las Tunas from 2011 to 2017. The study population consisted of 1150 patients admitted for myocardial infarction previously registered in the department's database. The 45 patients who died from sudden death made up the "case group" and for each of them, 2 patients—who did not die suddenly—were randomly assigned to the "control group". Descriptive statistics were used for descriptive variables. To assess risk factors, multivariate analyses were performed and the odds ratio (OR) was evaluated with 99% reliability.

Results: Male sex predominated in both groups and high blood pressure was the most frequent associated factor. Mean age and Killip-Kimball class III-IV percentage were similar. A 43% of patients with sudden death were diabetic and presented a higher percentage of biventricular infarctions (22.7%), ineffective thrombolysis (41.8%), and cardiac rupture (13.6%). Glycemia >15.0 mmol/L on admission (OR 2.57; p=0.027) and ineffective thrombolysis (OR 2.19; p=0.024) were associated with the occurrence of sudden death.

Conclusions: Both, Glycemia >15.0 mmol/L on admission and ineffective thrombolysis, behaved as risk factors for sudden death.

Keywords: Acute myocardial infarction, Sudden cardiac death, Risk factors

Factores de riesgo de muerte súbita en pacientes con infarto agudo de miocardio

RESUMEN

Introducción: La identificación de marcadores clínicos del riesgo de muerte súbita cardíaca en el infarto agudo de miocardio ha sido objeto de múltiples investigaciones.

Objetivos: Determinar los factores de riesgo de este tipo de muerte en pacientes con infarto agudo de miocardio.

Método: Se realizó un estudio analítico caso-control en el Servicio de Cardiología de Las Tunas (Cuba) entre 2011 y 2017. El universo estuvo constituido por 1150 pacientes ingresados por infarto, registrados en la base de datos del servicio. Los 45 pacientes fallecidos con muerte súbita representaron el «grupo casos» y por cada uno de ellos se seleccionaron aleatoriamente a 2 pacientes fallecidos de for-

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MSM: Conception and design of the research; collection, analysis and interpretation of data; and drafting of the manuscript.

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All authors read and unanimously approved the final manuscript.

ma no súbita, quienes conformaron el «grupo control». Se utilizó la estadística descriptiva para las variables descriptivas. Para el estudio de los factores de riesgo se realizaron análisis multivariados y se evaluó la razón de productos cruzados de probabilidad (odds ratio [OR]) con un 99% de confiabilidad.

Resultados: En ambos grupos predominó el sexo masculino y la hipertensión arterial fue el factor asociado más frecuente. La edad media y el porcentaje de la clase de Killip y Kimball III-IV fueron similares. Un 43% de los pacientes con muerte súbita eran diabéticos y presentaron mayor porcentaje de infartos biventriculares (22,7%), de trombósis no efectiva (41,8%) y de rotura cardíaca (13,6%). La glucemia >15,0 mmol/L al ingreso (OR 2,57; p=0,027) y la trombósis no efectiva (OR 2,19; p=0,024) se asociaron a la aparición de muerte súbita.

Conclusiones: La glucemia al ingreso >15,0 mmol/L y la presencia de trombósis no efectiva se comportaron como factores de riesgo de muerte súbita.

Palabras clave: Infarto agudo de miocardio, Muerte súbita cardíaca, Factores de riesgo

INTRODUCTION

At present, acute myocardial infarction (AMI) is a serious health problem and a major socioeconomic burden, with high morbidity and mortality rates; furthermore, AMI is challenging for both healthcare professionals involved and decision-making processes^{1,2}.

According to the World Health Organization (WHO), AMI accounts for 8 million deaths annually. This scenario becomes even more complex in Latin America, as nearly 40% of deaths are premature, occurring at the most productive age, when the economic and social impact is at its worst. In addition, the resulting disability rates are virtually unbearable for individuals, families and health systems^{3,4}.

Prospective studies have shown that about 50% of all deaths from coronary artery disease are sudden and unexpected. Mortality due to coronary artery disease has declined over the last 30 years; conversely, sudden cardiac death (SCD) has not decreased as sudden cardiac arrests have remained steady or have increased in relation to total mortality⁵. Since figures vary according to the prevalence of coronary artery disease in different countries, it is rather difficult to estimate the annual incidence of SCD. In the United States, the annual number of SCD comes from a number of sources; according to the American Heart Association (AHA), between 300-350 thousand people die from SCD every year, which represents 1-2 deaths for every 1000 people².

Sudden cardiac death is a medical and public health issue given its high incidence, unexpected onset, poor resuscitation rates, and epidemiological study limitations resulting from the reference sources

and the myriad definitions that have been proposed. The current concept for sudden cardiac death describes the unexpected natural death from a cardiac cause within a short time period, generally less than one hour from the onset of symptoms. A pre-existing heart condition may or may not have been known, although the time and way of death are unexpected^{6,7}.

The identification of specific clinical risk markers for SCD as an expression of coronary artery disease, especially in patients with AMI, has been subject of research for years in the search for alternatives to reduce its incidence^{8,9}. Reduced left ventricular ejection fraction (LVEF) is the best known predictor of sudden death; hence its use in selecting patients in primary prevention studies for implantable cardioverter-defibrillator (ICD) implantation. However, most studies agree that LVEF is limited by its low sensitivity to prevent SCD, especially during hospitalization due to acute coronary events, since less than 50% of patients with prior AMI, who suffer sudden cardiac arrest or SCD have a LVEF below 30%^{9,10}.

There is no specific risk factor for the appearance of SCD, therefore, it is difficult to determine a profile based on coronary risk factors for its prediction. Ischemic heart disease facilitates the creation of an arrhythmogenic substrate that must be activated by triggers such as: acute ischemia, hemodynamic and electrolyte disorders, toxic effect of some drugs, plaque instability, activation of the autonomic nervous system and psychosocial factors. Apparently, a vulnerable heart –with ischemic heart disease and predisposing factors to SCD (LVEF <35%, cardiovascular risk factors, prior infarction, family history of sudden death, among others)– is affected by trigger-

ing factors that precipitate lethal arrhythmia and SCD. It is extremely important to be aware of these factors since many of them can be modified¹¹.

The aim of the present study was to determine the risk factors for sudden death in patients with AMI cared for in 2011-2017.

METHOD

A case-control analytical study was conducted at the Department of Cardiology in the *Hospital General Docente Dr. Ernesto Guevara de la Serna* (Las Tunas, Cuba), between January 2011 and December 2017. The study population consisted of 1150 patients admitted for AMI, recorded in the department's database. The 45 patients who died of sudden death made up the "case group" and for each of them 2 patients who did not die suddenly (control group) were randomly selected.

The following variables were analyzed: sex, age, history of high blood pressure, diabetes mellitus, dyslipidemia and ischemic heart disease, smoking, type and topography of infarction, number of leads involved, LVEF, first medical care (drugs used, delay time), effectiveness of thrombolytic therapy, time between the onset of symptoms and administration, blood tests on admission (creatinine kinase [CK], creatinine and glycemia), heart rate/blood pressure on admission and complications during hospitalization.

Data were entered into an Excel database and were further processed in the Epiinfo version 6 statistical software package. Descriptive statistics through percentage analysis and arithmetic mean were also used. Multivariate analysis and calculation of odds ratios (OR) and confidence intervals were performed to assess risk factors related to sudden death, with 99% reliability.

RESULTS

The mean age of the two groups was the same. Male sex predominated (52.0% in patients who died suddenly and 54.3% in the rest of the deceased). The

Table 1. Baseline characteristics of patients with acute myocardial infarction, with presence of sudden death and control group. Department of Cardiology, *Hospital General Docente Dr. Ernesto Guevara de la Serna*, Las Tunas, Cuba (2011-2017).

Aspects	Case group (n=44)	Control group (n=88)
Male Sex	52.0	54.3
Age (years)	74 ± 18	74 ± 21
Associated factors		
High blood pressure	81.8	81.0
Diabetes mellitus	43.1	30.7
Smoking	27.2	25.0
Dyslipidemias	9.0	15.2
PH of ischemic heart disease	34.1	29.5
Late arrival at FMC	52.3	73.8
Medication during FMC		
Antiplatelet agents	65.9	77.2
Beta-blockers	17.8	25.0
Clinical and laboratory variables at admission		
Glycemia (mmol/L)	11.7 ± 6	15.6 ± 4
Creatinine (µmol/L)	111 ± 20	131 ± 28
Total creatine kinase (UI)	1126 ± 22	1171 ± 32
SBP (mmHg)	102 ± 8	117 ± 10
Heart rate (bpm)	77 ± 10	86 ± 12

Values express percentage and mean±standard deviation. FMC, first medical care; PH, personal history; SBP, systolic blood pressure.

most frequent associated factor was high blood pressure, behaving similarly in both groups (**Table 1**). A 43.1% of patients with SCD were found to be diabetic, while the disease was present in 30.7% individuals of the control group. Those who did not die suddenly arrived later at first medical care (73.8% vs 52.3%). Both groups exhibited low beta-blocker administration rates at the first health care site (17.8% vs 25.0%) and SCD patients had a lower percentage of antiplatelet agents administration (65.9%).

Table 1 also shows that patients who died of AMI with SCD had lower mean glycemia, creatinine and total CK levels than patients in the control group.

A total of 56.8% of patients with SCD on admission had more than 7 electrocardiographic leads involved with ischemia (**Table 2**), slightly lower than in the control group (61.3%). Inferior ST-segment elevation AMI predominated in both groups, although most were not strictly inferior. A higher per-

Table 2. Electrocardiographic disorders, type of infarction on admission and left ventricular ejection fraction.

Variables	Case group (n=44)	Control group (n=88)
Alteraciones en el ECG		
> 7 leads involved	56.8	61.3
Type of infarction		
Non ST elevation	9.1	-
ST elevation	90.9	100.0
- Anterior	30.0	38.6
- Inferior	38.4	43.3
- Biventricular	22.5	18.1
LVEF		
> 35%	30.5	53.5
< 35%	18.6	27.0
Not calculated	50.9	19.5

Values express percentages.

LVEF, left ventricular ejection fraction.

Table 3. Patients with or without sudden death according to implementation, time of onset and thrombolysis effectiveness.

Variables	Case group (n=44)	Control group (n=88)
Thrombolysis		
Effective	12.7	21.7
Ineffective	41.8	23.9
No thrombolysis		
< 3 hours between the onset of symptom and thrombolysis	25.0	34.4

Values express percentages.

Table 4. Complications in patients with myocardial infarction, with or without sudden death.

Complications	Case group (n=44)	Control group (n=88)
Killip y Kimball III-IV	65.9	67.0
VT-VF	30.9	29.5
Myocardial reinfarction	4.5	16.4
High-degree AVB	29.5	27.8
Atrial fibrillation	13.6	13.9
Cardiac rupture	13.6	7.6

Values express percentages.

AVB, atrioventricular block; VF, ventricular fibrillation;

VT, ventricular tachycardia.

centage of biventricular AMI was evident in the group of patients with SCD (22.5% vs 18.1%).

Both groups showed a non-negligible percentage of cases where LVEF measurement on admission was impossible. Some 53.5% of the individuals in the control group and 30.5% of those in the study group presented LVEF values greater than 35%.

The 54.5% of patients who died of SCD underwent thrombolysis (**Table 3**), far more than the 45.6% of the control group; however, it is noteworthy that thrombolysis was ineffective in 41.8%, as compared to 23.9% in the control group. Applying this therapeutic strategy before 3 hours after the onset of symptoms achieved success in only 1 out of 4 patients (25%) who died of SCD.

A similar frequency of pump failure (Killip classes III-IV) and electrical complications was observed in both groups (**Table 4**). Main differences were incidence of reinfarction (4.5% vs 16.4%) and cardiac rupture (13.6% vs 7.6%).

Table 5 highlights that glycemic index greater than 15.5 mmol/L on admission (OR 2.57; p=0.027) and ineffective thrombolysis (OR 2.19; p=0.024) were risk factors for SCD in patients admitted with AMI. History of diabetes mellitus (OR 1.71; p=0.082), presence of cardiac rupture (OR 2.14; p=0.112) and no administration of antiplatelet agents at first medical care (OR 1.75; p=0.087), although exhibiting OR>1, did not reach statistically significant values.

DISCUSSION

Ethnic and demographic differences, dissimilar prevalence profiles of coronary risk factors in each country, and disparities between health care systems with the influence that certain treatments have had, say, primary percutaneous coronary intervention in patients with AMI, among others-make it rather difficult to determine constant predictors of SCD in the various populations; hence the differences found in the literature reviewed.

The VALIANT study (Valsartan in Acute Myocardial Infarction trial)¹² evaluated several factors: abnormal creatinine clearance and elevated heart rate on admission were the variables most associated with SCD. During the 3-year follow-up, the greatest predictors were history of AMI, initial LVEF below 40%, and recurrence of cardiovascular events. In another clinical trial during hospitalization of infarct-

Table 5. Risk factors for sudden death in patients with acute myocardial infarction.

Risk factors	Case group (n=44)		Control group (n=88)		OR	p
	Nº	%	Nº	%		
History of diabetes mellitus	19	43.1	27	30.7	1.71	0.082
History of ischemic heart disease	15	34.1	26	29.5	1.23	0.299
Smoking	12	27.2	22	25.0	1.12	0.387
Creatinine >200 µmol/L	4	9.1	8	8.1	1.00	0.489
Glycemia >15 mmol/L	11	25.0	10	11.3	2.57	0.027
Anterior wall AMI	12	30.0	34	38.6	0.53	0.055
Biventricular AMI	9	22.5	16	18.1	0.89	0.411
More than 7 leads involved in the ECG	25	56.8	54	61.3	0.82	0.309
Ineffective thrombolysis	18	41.8	21	23.9	2.19	0.024
No thrombolysis	20	45.5	48	54.4	0.69	0.166
Cardiac rupture	6	13.6	6	6.8	2.14	0.112
Killip-Kimball III-IV	29	65.9	59	67.0	0.95	0.446
Non-use of antiplatelet agents in FMC	15	34.1	20	22.8	1.75	0.087
Non-use of beta-blockers in FMC	36	82.2	66	75.0	1.00	0.496

AMI, acute myocardial infarction; ECG, electrocardiogram; FMC, first medical care.

ed patients, the sole factor associated with SCD was the lack of adequate treatments such as beta-blockers or antiplatelet agents^{10,12}.

Knowledge of the different predictive factors for sudden cardiac arrest and sudden death has enabled the creation of risk scores. In data from the DUKE registry (Data bank for Cardiovascular disease, DUKE University Medical Center), which includes patients with coronary angiography and presence of at least one lesion greater than 75%, several factors related to the patient's history that may increase the risk of SCD were identified: history of diabetes mellitus, high blood pressure, stroke/heart failure, LVEF and arteries involved. These factors were used to develop the DUKE sudden cardiac death risk score. In this study, low LVEF was the factor with the strongest statistical association when compared with the other variables¹³.

In 2011 the number of deaths from AMI in Cuba was 6.128 patients but by the end of 2017 this number had increased to 7.982¹⁴. The overall aging of the Cuban population and high prevalence of coronary risk factors suggest that mortality from this type of condition –with a high percentage of sudden death– will probably continue to increase in the coming years. Thus, it is of utmost importance to determine the factors contributing to overall mortality due to AMI and, particularly, to the occurrence of sudden death in order to improve the care of these patients

by targeting the factors that can be leveraged.

Coronary artery disease is the most frequent cause of SCD with acute coronary injuries (plaque rupture, thrombosis) detected in autopsies in 20-80% of cases and sudden cardiac arrest in primary ventricular fibrillation is directly responsible in more than 60% of patients⁵. In those with previous AMI, the risk of SCD is mainly due to the presence of electrical instability and its interaction with left ventricular dysfunction and ischemia. These three factors shape the imaginary risk of post-infarction complications triangle. A number of studies have been carried out in this field and a large group of predictors (clinical, electrocardiographic, and echocardiographic) for SCD in patients with AMI have been identified. These studies have contributed to the creation of a series of risk scores to improve prevention of SCD and to identify patients at higher risk in order to carry out treatment actions aimed at reducing the incidence of SCD¹⁵⁻¹⁷.

The risk of SCD is higher in men before reaching 65 years, but an increase in the number of sudden deaths in women has been reported after this age. It is currently estimated that 40% of all sudden deaths occurring in the United States concern the female sex⁸.

Many electrocardiographic markers have been associated with increased SCD. Heart rate variability, QRS duration, QT dispersion and prolonged QT are

among the most studied^{18,19}. Other markers such as microvolt T-wave alternans –related to the occurrence of ventricular arrhythmias and sudden death in post-AMI follow-up– are currently being identified. The REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) study, cited by Yodogawa and Shimizu²⁰, showed that the combination of heart rate assessment, T-wave microvoltage alternans and LVEF less than 50%, assessed 8 weeks after AMI, identified patients at risk of SCD or resuscitated sudden death due to malignant ventricular arrhythmias; ST segment disorders (elevation, depression or both) in 7 or more involved leads, condition a larger ischemic substrate, where more myocardium is at risk, which is related to an important sub-occlusion of the common trunk or when there is proximal involvement of the three vessels (left anterior descending, circumflex and right coronary arteries), which has been associated with a higher risk of cardiac rupture, malignant ventricular arrhythmias and, therefore, SCD^{2,20}.

The main limitation of our paper is that LVEF could not be calculated in most patients with sudden death since this variable is in fact the main high-risk element for presenting SCD regardless of the patient's heart disease. However, its sensitivity is low, considering that most cases with SCD have preserved LVEF.

Less than 50% of patients with prior AMI who die suddenly present with LVEF below 30%^{2,9}. What has indeed been demonstrated is that patients with LVEF less than 35% are at increased risk of suffering SCD as compared to those with higher values. The REFINE study showed, in 322 patients with AMI, that those with LVEF <30% had a higher risk of fatal or non-fatal SCD (OR 3.30; p=0.005) compared to those with LVEF >30%^{2,20}.

Several studies suggest that severely decreased LVEF in conjunction with other factors constitutes a risk factor; hence, a number of researchers have devoted efforts to demonstrate the association of other variables, mostly clinical ones, which, associated with or without decreased LVEF, improve prediction of SCD^{2,9}. It is worth recalling the results of the VALIANT study¹² and the DUKE registry¹³ mentioned above; while a study by Chitnis *et al*¹⁰ found that the only factor associated with SCD during hospitalization was the lack of adequate treatments, namely, (beta-blockers and antiplatelet agents treatments).

In our report, the presence of glycemia above 15.0 mmol/L on admission and ineffective thrombo-

lysis were the two risk factors found to contribute to the occurrence of SCD. The benefits of fibrinolytic therapy are well demonstrated, but we must emphasize that it is not only about performing it but also about being effective, as with any other reperfusion procedure. The results of the INJECT study, cited by Mann *et al*² and Ruesga *et al*²¹ demonstrated the relationship between ST-segment resolution after thrombolysis and mortality. Three types of resolution were considered: complete (> 70%), partial (30-70%) and no resolution (< 30%). The documented mortality in each situation was 2.5%, 4.3% and 17.5%, respectively (p<0.0001).

When considering all baseline characteristics, ST-segment resolution was the main independent predictor at 35 days; therefore, the absence of ST-segment resolution, which occurs in up to 25% to 50% of patients, indicates reperfusion failure and predicts high mortality^{2,21}.

Another aspect that has been related to potential risk of death in patients with AMI who underwent thrombolytic treatment has been the presence of myocardial reperfusion injury, which paradoxically reduces the benefits of this therapy and may lead to cardiomyocyte death which were viable before reperfusion and to an increase in the size of the infarct. This form of myocardial injury may, in part, explain why despite an optimal strategy of chemical myocardial reperfusion, the frequency of death after AMI reaches 10% and the incidence of severe heart failure is almost 25%^{2,22}. Diabetes mellitus, on the other hand, has been identified as a potent –in-hospital/out-of-hospital– independent predictor of SCD as it accelerates the process of atherosclerosis with changes in thrombogenicity, and a high prevalence of prolonged QT has been observed⁸. Furthermore, several studies^{2,23} have found hyperglycemia in more than 30% of patients with SCD due to AMI and it is considered an excellent short-term prognostic predictor in cases of large, acute myocardial infarction. Glucose levels of 140 mg/dL or more in non-diabetic patients, and greater than or equal to 180 mg/dL in diabetics, are associated with a relative risk of death 3.9 times higher than those with lower levels.

In our study, the association of SCD with diabetes mellitus (OR 1.71, p=0.082), cardiac rupture (OR 2.14, p=0.112) and non-use of antiplatelet agents at first medical care (OR 1.75, p=0.087) did not reach statistical significance, probably due to the small sample size –since it is evident that cardiac rupture causes MSC– but they had an OR > 1, so they should also be

taken into account.

CONCLUSIONS

Glycemia on admission >15.0 mmol/L and ineffective thrombolysis were risk factors for sudden death. A history of diabetes mellitus and no indication for antiplatelet agents at first medical care are factors that should also be taken into account.

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