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Association between Ferrokinetic and its Prognostic Role in Coronary Artery Disease in a South American Hospital

Héctor Alonso Moreno-Parra[1] (iD), Luis Andrés Dulcey-Sarmiento[1,2] (iD),
Juan Sebastián Theran-León[3] (iD), Raimondo Caltagirone-Miceli[4] (iD)

Abstract

Introduction: Ferrokinetic alterations are associated with the worsening of cardiovascular diseases, their role being unknown in depth.

Objective: To determine the association between ferrokinetic with acute myocardial infarction with and without ST elevation in patients with coronary disease.

Methods: Analytical observational study in a sample of 72 patients who were admitted to a Coronary Care Unit of a fourth level Institution during the period from July 2017 to May 2018. The statistical association analysis was performed with the Chi-square test.

Results: The main gender affected was male, in ages over 56 years. The main comorbidity was arterial hypertension in 53.7% for ST-elevation infarction and in 74.2% for non-ST-elevation infarction. The prevalent ferrokinetic alteration was iron deficiency, in 36.6% of the patients with ST elevation and in 41.9% without ST elevation. Low hemoglobin levels were present on admission in 24.4% of patients with ST elevation and in 32.3% of those without ST elevation, associated with low hemoglobin values on day 7 of hospitalization. Deaths occurred in 2.77%, which presented low iron levels without anemia and infarction with ST elevation and shock. The gender variable presented a statistically significant association ($p = 0.034$) with the serum iron level.

Conclusions: Iron deficiency is a very common disorder with a higher mortality rate, so these parameters should be evaluated in cardiovascular diseases.

Keywords: infarction; ferritins; iron; hemoglobins.

[1] Universidad de Los Andes (Mérida, Venezuela).

[2] Universidad Autónoma de Bucaramanga (Santander, Colombia).

[3] Universidad de Santander (Bucaramanga, Colombia).

[4] Universidad de Los Andes (Mérida, Venezuela).

Corresponding author: Luis Andrés Dulcey-Sarmiento. Email: luismedintcol@gmail.com

Asociación entre la ferrocinética y su papel pronóstico en enfermedad coronaria en un hospital suramericano

Resumen

Introducción: Las alteraciones ferrocinéticas se asocian con un empeoramiento de las enfermedades cardiovasculares, pero se desconoce en profundidad su papel.

Objetivo: Determinar la asociación entre la ferrocinética con el infarto agudo al miocardio con y sin elevación del segmento ST en pacientes con enfermedad coronaria.

Métodos: Estudio observacional analítico en una muestra de 72 pacientes que ingresaron a una unidad de cuidados coronarios de una institución de cuarto nivel durante el lapso de julio de 2017 a mayo de 2018. El análisis de asociación estadística se realizó con la prueba de chi cuadrado.

Resultados: El principal género afectado fue el masculino, en edades superiores a 56 años. La principal comorbilidad fue hipertensión arterial, en un 53,7 % para infarto con elevación del segmento ST, y en un 74,2 % para infarto sin elevación de dicho segmento. La alteración ferrocinética prevalente fue el déficit de hierro, en un 36,6 % de los pacientes con elevación del intervalo ST y en un 41,9 % sin elevación del segmento ST. Las concentraciones bajas de hemoglobina estuvieron presentes al ingreso en el 24,4 % de los pacientes con elevación del ST y en el 32,3 % de aquellos sin elevación del ST, asociado con valores bajos de hemoglobina al séptimo día de hospitalización. Ocurrieron fallecimientos en el 2,77 %, con cantidades bajas de hierro sin anemia e infarto con elevación del segmento ST y choque. La variable g**é**nero presentó asociación estadísticamente significativa ($p = 0,034$) con el nivel de hierro sérico.

Conclusiones: La ferropenia es una alteración muy frecuente con una relación de mayor mortalidad, por lo que estos parámetros deberían evaluarse en enfermedades cardiovasculares.

Palabras clave: infarto; ferritina; hierro; hemoglobina.

Héctor Alonso Moreno-Parra, Luis Andrés Dulcey-Sarmiento, Juan Sebastián Theran-León, Raimondo Caltagirone-Miceli

Associação entre a ferrocinética e seu papel prognostico na doença cardíaca coronária em um hospital da América do Sul

Resumo

Introdução: Os distúrbios ferrocinéticos estão associados à piora da doença cardiovascular, mas seu papel é pouco conhecido.

Objetivo: Determinar a associação entre a ferrocinética e o infarto agudo do miocárdio com e sem elevação do segmento ST em pacientes com doença cardíaca coronária.

Métodos: Estudo observacional analítico em uma amostra de 72 pacientes admitidos em uma unidade de tratamento coronariano de uma instituição de quarto nível durante o período de julho de 2017 a maio de 2018. A análise de associação estatística foi realizada usando o teste do qui-quadrado.

Resultados: O principal gênero afetado foi o masculino, com idade superior a 56 anos. A principal comorbidade foi a hipertensão, em 53,7% para infarto do miocárdio com elevação do segmento ST e 74,2% para infarto do miocárdio sem elevação do segmento ST. O distúrbio ferrocinético prevalente foi a deficiência de ferro em 36,6% dos pacientes com elevação do segmento ST e 41,9% sem elevação do segmento ST. Concentrações baixas de hemoglobina estavam presentes na admissão em 24,4% dos pacientes com elevação do segmento ST e em 32,3% daqueles sem elevação do segmento ST, associadas a valores baixos de hemoglobina ao sétimo dia de hospitalização. Ocorreram mortes em 2,77%, com baixo teor de ferro sem anemia e infarto com elevação do segmento ST e choque. O gênero foi associado de forma estatisticamente significativa (p = 0,034) ao nível de ferro sérico.

Conclusões: A deficiência de ferro é um distúrbio muito comum com uma associação com o aumento da mortalidade, por tanto, esses parâmetros devem ser avaliados em doenças cardiovasculares.

Palavras-chaves: Infarto do miocárdio; ferritina; ferro; hemoglobina.

INTRODUCTION

Iron is an essential element for life since it participates in practically all oxidation-reduction processes. We can find it as a necessary part of the enzymes of the Krebs cycle, in cellular respiration, and as an electron transporter in cytochromes (1). Maintaining normal iron metabolism is vital for cells characterized by high mitogenic potential and high energy demand (2); thus, its deficiency can be a significant comorbidity in high-risk patients (3).

In angiographic studies, ferritin has been associated with coronary atherosclerosis in specific populations, such as the Iranian (4), while it has not done so in European or American women (5). Iron deficiency is the most common nutritional disorder and affects a third of the world's population (6). Anemia has been shown in other studies to be a significant independent determinant of adverse cardiovascular events and death (6). Over 17 million people die annually from cardiovascular diseases worldwide (7). In Latin America, few studies relate alterations in iron and hemoglobin values with cardiovascular diseases, such as acute coronary syndrome (ACS) and its prognostic implications (8).

ETHICAL ASPECTS

This article was adapted to the biomedical research recommendations of the World Medical Association's Declaration of Helsinki of the 64th General Assembly in Fortaleza (Brazil) in October 2013. We also followed the provisions in Title V, Chapter 4, of the Code of Medical Ethics of the Venezuelan Medical Federation dated March 20, 1985, referring to research on human beings. The Hospital Universitario de Los Andes's Ethics Committee and the Internal Medicine Specialization reviewed and approved the study.

MATERIALS AND METHODS

This analytical observational study aimed to determine the association between ferrokinetics and acute myocardial infarction with and without ST-segment elevation in patients with coronary artery disease. The sample comprised 72 patients admitted to the coronary care unit of a quaternary care center between July 1, 2017, and May 31, 2018, after retrospectively reviewing the medical records of patients with ACS diagnoses of both genders: ST-segment elevation and non-ST-segment elevation acute myocardial infarction with and without (NSTEMI and STEMI). The inclusion criteria were patients of both genders over 18 years of age with already established clinical and paraclinical criteria for ACS. The exclusion criteria were:

I. Ischemic heart disease

II. Chronic kidney disease stages IV and V

III. Body mass index > 39.9

IV. Congestive heart failure NYHA functional class IV

V. Patient on Killip IV risk scale

VI. Diagnosis of malignant neoplasm

VII. Having received a transfusion of blood products or supplements with iron salts in the last two months

VIII. Infectious processes in any form

IX. Hemorrhagic manifestations

Hemoglobin values were determined by the microhematocrit method, taking a blood sample from the fingertip with capillary on admission and seven days after hospitalization. The ferrokinetic profile was established on admission by the direct colorimetry method with Wiener Lab and Bioline reagents, processed in a STAT FAX reader, STAT FAX MILENIUM III with ELISA technique. The typical reference values of the ferrokinetic profile were taken as those established by the laboratory where the samples were processed (Table 1).

The data obtained through the collection form were processed in the SPSS program, version 21 (IBM Corporation, New York, United States) for Windows. Through this, the descriptive analysis of the data was performed using absolute frequencies, measures of central tendency, and measures of dispersion for categorical and continuous variables. The statistical association analysis was conducted with the chi-square test (χ^2). The analysis to estimate the strength of the association was by determining the relative risk.

Table 1. Reference values of ferrokinetic profile parameters

Ferrokinetic pattern	Normality value in adults
Serum iron	49-181 µ/dl
Ferritin	28-397 ng/dl
Transferrin	250-400 mg/dl
Transferrin saturation	20-55 %
TIBC	250-400 µg/dl

Source: Ferrokinetic profile determination test system insert; commercial brand Wiener lab® and Bioline®.

RESULTS

After meeting the inclusion and exclusion criteria, the sample comprised 72 patients with ST-segment elevation and non-ST segment elevation ACS, aged between 27 and 94 years, classified into two subsets according to clinical and paraclinical criteria (Figure 1).

Figure 1. Classification of patients with acute coronary syndrome admitted, June 2017–May 2018.

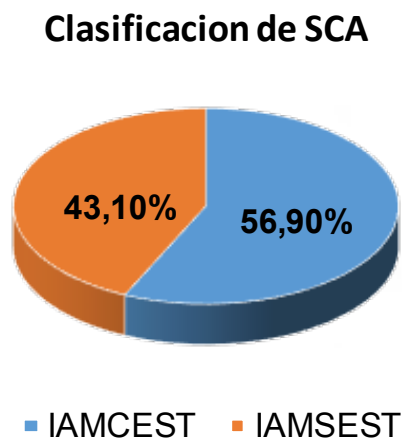## Clasificacion de SCA

43,10%   56,90%

■ IAMCEST   ■ IAMSEST

Table 2 presents the demographic characterization and comorbidities of the patients included in the study. The data show that the behavior is similar for the two groups with and without ST-segment elevation, where the male sex prevails, aged between 56 and 65 years with a comorbidity of high blood pressure.

The ferrokinetic profile parameters analyzed were serum iron, ferritin, transferrin, percentage of transferrin saturation, and total iron binding capacity, where typical values predominate for the two groups with and without ST-segment elevation. The behavior of these variables is reported in Table 3.

Table 2. Demographic characteristics and their comorbidities in patients with acute coronary syndrome admitted to the coronary unit of a quaternary care center, June 2017–May 2018

Variable	Acute myocardial infarction	
	ST elevation	No ST elevation
	$n = 41$ (56.9 %)	$n = 31$ (43.1 %)
Myocardial infarction ($\bar{X}$: SD)	63.1 ± 14.2	65.3 ± 11
Age [n (%)]		
≤ 55	11 (26.8)	7 (22.6)
56-65	13 (31.7)	9 (29)
66-75	10 (24.4)	8 (25.8)
>76	7 (17.1)	7 (22.6)
Gender [n (%)]		
Male	25 (61)	17 (54.8)
Female	16 (39)	14 (45.2)
COMORBIDITIES		
High blood pressure [n (%)]		
Yes	22 (53.7)	23 (74.2)
No	19 (46.3)	8 (25.8)
Diabetes [n (%)]		
Yes	9 (22)	9 (29)
No	32 (78)	22 (71)
Chronic obstructive pulmonary disease [n (%)]		
Yes	7 (17.1)	7 (22.6)
No	34 (82.9)	24 (77.4)

Table 3. Ferrokinetic profile of patients with acute coronary syndrome admitted to the coronary unit of a fourth-level hospital, June 2017-May 2018

Variable	Acute myocardial infarction	
	ST elevation $n = 41$ (56.9%)	No ST elevation $n = 31$ (43.1%)
Serum iron [n (%)]		
Normal	26 (63.4)	18 (58.1)
Low	15 (36.6)	13 (41.9)
Ferritin [*n* (%)]		
Normal	31 (75.6)	27 (87.1)
Low	7 (17.1)	2 (6.5)
High	3 (7.3)	2 (6.5)
Transferrin [*n* (%)]		
Normal	32 (78)	26 (83.9)
Low	9 (22)	4 (12.9)
High	0 (0)	1 (3.2)
Transferrin saturation percentage [*n* (%)]		
Normal	32 (78)	24 (77.4)
Low	9 (22)	7 (22.6)
Total iron fixing capacity [*n* (%)]		
Normal	30 (73.2)	22 (71)
Low	11 (26.8)	9 (29)

The behavior of hemoglobin and hematocrit values on admission and seven days later, classified by type of infarction, are reflected in Table 4.

Table 4. Hemoglobin and hematocrit values on admission and day 7 of patients with acute coronary syndrome admitted to a quaternary care center, June 2017-May 2018

Variable	Acute myocardial infarction	
	ST elevation $n = 41$ (56.9%)	No ST elevation $n = 31$ (43.1%)
Hemoglobin levels on admission ($\overline{X}$: SD)	13.3 ± 1.7	13 ± 1.8
Normal [*n* (%)]	30 (73.2)	21 (67.7)
Low [*n* (%)]	10 (24.4)	10 (32.3)
High [*n* (%)]	1 (2,4)	0 (0)
Hemoglobin levels at day 7 ($\overline{X}$: SD)	12.8 ± 1.8	12.9 ± 1.8
Normal [*n* (%)]	27 (65.8)	21 (67.7)
Low [*n* (%)]	13 (31.7)	10 (32.3)
High [*n* (%)]	1 (2.4)	0 (0)
Hematocrit levels on admission ($\overline{X}$: SD)	39.7 ± 5.4	39 ± 5.5
Normal [*n* (%)]	30 (73.2)	21 (67.7)
Low [*n* (%)]	10 (24.4)	10 (32.3)
High [*n* (%)]	1 (2.4)	0 (0)
Hematocrit levels at day 7 ($\overline{X}$: SD)	37.8 ± 5.9	38.8 ± 5.4
Normal [*n* (%)]	27 (65.8)	21 (67.7)
Low [*n* (%)]	13 (31.7)	10 (32.3)
High [*n* (%)]	1 (2.4)	0 (0)

Table 5 shows the association between serum iron concentrations, left ventricular ejection fraction (LVEF), and mortality found during follow-up. This indicates that gender statistically correlates with serum iron level ($p = 0.034$).

Table 5. Association of serum iron concentrations with the left ventricular ejection fraction and its mortality in patients with coronary syndrome

Variable	Serum iron concentrations [n (%)]		p-value
	Normal [n = 44 (%)]	Low [n = 28 (%)]	
Gender [n (%)]			
Male	25 (61)	17 (54.8)	*0.034
Female	16 (39)	14 (45.2)	
Age [n (%)]			
≤55	11 (26.8)	7 (22.6)	0.128
56-65	13 (31.7)	9 (29)	
66-75	10 (24.4)	8 (25.8)	
>76	7 (17.1)	7 (22.6)	
Left ventricular ejection fraction [n (%)]			
Preserved	29 (65.9)	14 (50)	0.263
Intermediate range	10 (22.7)	7 (25)	
Reduced	5 (11.4)	7 (25)	
Mortality [n (%)]			
No	44 (100)	26 (92.9)	0.072
Yes	0 (0)	2 (7.1)	
Myocardial infarction [n (%)]			
ST elevation	26 (59.1)	15 (53.6)	0.645
No ST elevation	18 (40.9)	13 (46.4)	

DISCUSSION

When representing the data of this study, we found that the primary gender with ACS was male, aged between 56 and 65 years, which agrees with Meroño et al.'s (9) study, where this clinical condition was present, especially in males. Among the comorbidities associated with ACS in the different subsets, the main one was high blood pressure, with 53.7 % for STEMI and 74.2 % for NSTEMI, which is similar to the findings by Ponikowska et al. (10).

Iron deficiency was the most frequent alteration of the ferrokinetic profile parameters studied, found in 36.6 % of patients with STEMI and 41.9 % of patients with NSTEMI. Thus, this clinical condition is prevalent in these patients, as was proven in the study by González et al. (11) in patients with ACS. Likewise, low ferritin concentrations were the second most frequent alteration in this study, as reported by Archbold et al. (12), since both serum ferritin and transferrin predicted an association of all-cause mortality.

Low amounts of hemoglobin were present on hospital admission in 24.42 % of the subgroup with STEMI and 32.30 % for NSTEMI. The percentage increased to 31.7 % in the first subgroup, with a relative risk (*RR*) of 2 (95 % *CI*: 0.131-30.63). The decrease in hemoglobin on day 7 of hospitalization was independently associated with a higher incidence of adverse events, as confirmed by Carberry et al. (13) and Colombo et al. (14).

The male gender had the highest frequency of low hemoglobin values on hospital admission, with 65 % and 35 % for the female gender. This finding

differs from what was found in the current literature, where the highest prevalence was attributed to the female gender, as reported in the study by Carberry et al. (13). Here, anemia is a powerful predictor of major adverse cardiovascular events in these patients, similar to what was observed in the Acharya's study (15).

In our study, no hemorrhagic complications justified attenuation upon admission or during the hospital stay, possibly associated with blood draws, inadvertent digestive bleeding, hematopoietic deficiency disorders, or other disorders that would undoubtedly contribute to the anemia (16).

In assessing low iron concentrations by gender and age group upon admission, we noted that women had the highest frequency of this condition, with 57% and a statistical significance of $p = 0.034$, as proven in other series of reviews, where it is described as a frequent comorbidity of cardiovascular diseases (17). Therefore, ages between 66 and 75 were the most prevalent, with 50% of the sample and a statistical significance of $p = 0.0001$, similar to the sociodemographic results in another study (18).

When associating comorbidities with iron deficiency in patients upon admission, this alteration was observed in 32.10% of patients with COPD, with a statistically significant value ($p = 0.030$). This finding in our study, when correlated with the results by Hsu et al. (18), was very similar since iron deficiency was statistically significant for the COPD variable ($p = 0.010$). However, in the case of this study (19), hypertension and its association with the iron deficiency variable showed a statistical value ($p < 0.001$).

LVEF correlated with serum iron amounts was preserved in 65.9% of patients with normal iron, intermediate-range LVEF in 22.7% in those with normal iron, and reduced LVEF in 11.4% in those with low iron without statistical significance. These results are not similar to those in the study by Huang et al. (19), where iron deficiency was associated with reduced functional capacity and a higher risk of adverse events in patients with heart failure.

Two deaths occurred in the first seven days of hospitalization, representing 2.77% of the total sample, with low iron levels without anemia and STEMI. The deceased had complications such as complete AV block and cardiogenic shock, which contrasts with what is described in the literature, where mortality in coronary heart disease was correlated with anemia (13). In our study, mortality occurred in 7.1% of patients with iron deficiency for the STEMI subgroup, this result being a critical determinant similar to what was reported in other studies (20), where alterations in iron concentrations strongly predicted cardiovascular disease and all-cause mortality independent of

other variables. We theorize that this may be associated with the elevation of these inflammatory markers, such as ferritin or other factors discussed above, in those patients with worse outcomes (21-24).

CONCLUSIONS

In patients with ACS, iron deficiency and decreased hemoglobin values are pervasive comorbidities with a relationship that has not been deeply analyzed in Latin American studies. Therefore, after being validated, both parameters can be considered in the future as determinants of prognostic stratification in the group of patients with acute or chronic cardiovascular disease. When evaluating the prognosis during the first seven days, associated with alterations in the ferrokinetic profile, the primary disorder found in this study was iron deficiency. Notably, two deaths occurred (2.77 %) with low iron concentrations without anemia and ST-segment elevation infarction complicated by cardiogenic shock. This suggests that, beyond hemoglobin levels, all ferrokinetic variables should be evaluated jointly in patients with an acute coronary event since current guidelines focus on hemoglobin targets higher than 8 g/dL and ignore iron levels, ferritin, and the percentage of transferrin saturation (8).

We are self-critical with the results reported herein. The biases mentioned in terms of the limited number of the sample, which reflects the broad values of the confidence intervals, the lack of a multicenter study, and the absence of statistical analysis to control confounding and interaction variables are necessary to generalize and validate our findings. With this study, a call is made to conduct this type of research in other latitudes, which contribute to understanding factors that have not been considered so far in the prognosis of cardiovascular diseases, both in their acute and chronic phases.

CONFLICT OF INTERESTS

The authors report no conflict of interest in the conduct of this study.

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