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ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 92 N° 2 APRIL 2024
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VOL 92 Nº 2
APRIL 2024

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EDITORIAL

MINOCA (Myocardial Infarction with non-Obstructive Coronary Arteries). Importance of Multicenter Registries

MINOCA (infarto de miocardio en ausencia de obstrucciones coronarias). Importancia de los registros multicéntricos

AGUSTINA SCIANCALEPORE[1, 2], JUAN CARLOS KASKI[3, DSC, MD, FRCP, FRSM, FESC, FHFA, FACC, FAHA]

Myocardial infarction with non-obstructive obstructive coronary arteries (MINOCA) defines a syndrome characterized by the presence of myocardial infarction criteria and the absence of significant epicardial coronary obstructions (<50% reduction in coronary diameter). (1) MINOCA includes different pathophysiological processes such as plaque disruption, microvascular dysfunction, coronary embolism, coronary spasm and coronary dissection. The objective diagnosis of the causal mechanisms is one of the main challenges that this syndrome presents in clinical practice. (2) Today, due to diagnostic advances, mainly imaging methods, it has been possible to characterize and define more accurately this currently relevant acute syndrome with a prevalence described in the literature of 5-10% according to different reports. (3)

For many years MINOCA was considered a relatively benign disease whose pathophysiology remained poorly defined until very recently. Today, we know that patients with MINOCA have a higher rate of reinfarction, compared to the general population. (4)

The entwined pathophysiology of this entity makes its management and accurate diagnosis of the underlying cause, or causes, difficult. There are numerous questions about the diagnosis and treatment of these patients, which might only be answered by systematic records and scientific studies that shed light on the different forms of clinical presentation, the mechanisms responsible for MINOCA and its treatment.

In this issue of the Argentine Journal of Cardiology, a relevant article by Dr. Rivero et al. is published, in which the authors analyze the results of the ReSCAR registry, which provides data of great value regarding the clinical characteristics of patients with MINOCA in the hospital environment. (5) Rivero et al. describe a prevalence of 8.6%, similar to that published in former international studies, (3) with a slight predominance of women (51.8%) and an average age of 65 years (53-63). The main cardiovascular risk factors were hypertension, dyslipidemia, diabetes and smoking. The rate of in-hospital complications, including mortality, was low.

Compared to patients with myocardial infarction caused by obstructive coronary lesions, type I of the Universal Definition (6), the ReSCAR registry in patients with MINOCA, shows a greater proportion of women (51.8% vs. 20.4%, p<0.001), a lower prevalence of diabetes (10.6% vs. 26.8%, p<0.001), smoking (27.1% vs. 47.3%, p=0.012) and previous infarction (11 .8% vs. 24.7%, p=0.006) and a higher prevalence of chronic angina (8.2% vs. 3.8%, p=0.084). Microvascular dysfunction was the most common causal mechanism found in the registry, although in many cases complementary diagnostic methods, either invasive (coronary physiology studies, optical coherence tomography, etc.) or non-invasive (imaging studies), which allow to establish the underlying mechanism were not used. MINOCA is a descriptive diagnosis that requires continuing with complementary diagnostic studies upon discharge, mainly cardiac magnetic resonance, in order to establish the causal mechanisms and determine what the most appropriate therapeutic and secondary prevention strategies will be. In a high percentage of patients, the cause of MINOCA is diagnosed after hospital discharge once complementary studies have been carried out on an outpatient basis.

Because the figures reported in the study by Rivero et al. regarding the etiology and pathophysiological mechanisms of MINOCA reflect the usual limitations of the in-hospital diagnostic approach, they mostly represent presumptive diagnoses, whose confirmation will depend on the possibility of continuing studies af-

Rev Argent Cardiol 2024;92:97-98. http://dx.doi.org/10.7775/rac.v92.i2.20750

SEE RELATED ARTICLE: Rev Argent Cardiol 2024;92:110-118. http://dx.doi.org/10.7775/rac.v92.i2.20746

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ter discharge. We must emphasize that the scarcity of medium and high complexity diagnostic resources in many centers in our country limits the possibilities of reaching a certain pathophysiological diagnosis in a high percentage of MINOCA cases.

ReSCAR is the first systematic registry involving patients diagnosed with MINOCA in Argentina. Multiple centers throughout the country participate in this registry, and its design reflects the joint effort of the researchers to define, in a coordinated and meticulous manner, variables of clinical importance and unified criteria for data collection. This is a considerable effort, especially when addressing a complex issue such as MINOCA, with great variability in its expression and pathophysiology, added to the complexity of the methods generally required for its diagnosis.

Knowing the real situation of this population in our setting with respect to incidence, clinical characteristics, gender differences, and pathophysiological mechanisms, is of great importance to guide the implementation of key diagnostic and therapeutic strategies to improve care, survival, and quality of life in this group of patients.

Certainly, this registry represents a solid basis to progress in our knowledge of this entity, promote its diffusion and take a step forward in relation to its diagnosis and treatment. An important aspect of the ReSCAR registry is that this project includes long-term follow-up of patients diagnosed with MINOCA which will allow us to know both the impact of therapeutic actions and its prognosis. Comparing these data with those of other international studies and registries and establishing cooperative studies with top-level centers on both sides of the Atlantic appears to be an attractive opportunity that will give added value to the ReSCAR registry.

Conflicts of interest

None declared.

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EDITORIAL

Pulmonary Embolism and Cancer: Challenging Data from a Feared Combination

Tromboembolismo pulmonar y cáncer, datos desafiantes de una combinación temida

FLORENCIA PERAZZO[1, 2, 3,]

Venous thromboembolism (VTE), which includes deep venous thrombosis and pulmonary embolism (PE), is the main cause of morbidity and mortality among patients with cancer. The risk is 4 to 7 times higher when there is underlying malignancy. (1) VTE has been reported as the second cause of death in cancer patients, (2) with different risk variables depending on the age of the patient and the type of cancer; (3,4) it is more common in pancreas cancer, stomach cancer, central nervous system primary tumors, ovarian cancer, and lung cancer, followed by genitourinary tumors. (5-7)

The mortality rate due to acute PE is significantly higher in patients with cancer versus those with no cancer (19.6% vs 3.2%, $p<0.001$). (2)

Patients with cancer who have developed VTE have a high risk of recurrence, which is even higher when the first event has been PE (OR 10.5, 95% CI 9.3-11.7). (3)

Malignant disease per se favors hypercoagulability via different mechanisms. The host shows an immune response promoting chronic inflammation, with metabolic and neuroendocrine changes leading to procoagulant reactions that alter vascular homeostasis. (8)

The pathogenesis of cancer-related coagulopathy is complex and multifactorial. Several clinical factors affect the increased risk of thrombosis in patients with cancer, making them high risk patients.

The most significant clinical factors are cancer-specific factors, the patient's characteristics, and cancer therapies.

Cancer-related factors depend on location (pancreas, stomach, central nervous system, lung, ovary), the stage of disease, the histologic grade, and the time to diagnosis. The risk is higher when closer to diagnosis and decreases with response to treatment.

Patient-related factors are age over 65, obesity, smoking, a family history of VTE, the performance status, and a reduced renal function.

Treatment-related factors play a role as well, with cisplatin, asparaginase, tamoxifen, bevacizumab (angiogenesis inhibitors), thalidomide and lenalidomide, immunotherapy, and erythropoiesis-stimulating agents involving a higher risk. (9)

Models have been developed to evaluate the risk of thrombosis in cancer patients, which makes it possible to identify patients with a high risk of developing thrombosis during chemotherapy. The Khorana model is based on 5 predictors: tumor location, platelet count, hemoglobin levels or the use of erythropoiesis-stimulating agents, leukocyte count, and body mass index. High risk is defined as a score ≥3. (10,11)

By contrast, the Pulmonary Embolism Severity Index (PESI) (12) is a prognostic model used to estimate intrahospital and 30-day mortality when the patient has already developed PE and is very useful to identify high-risk patients (score ≥86). A simplified PESI (sPESI) score of >1 has a similar use. (13) By definition, cancer patients are always part of the sPESI high-risk group, as a history of cancer adds one point to the score.

The paper by J. Bonorino et al., published in this issue of the Argentine Journal of Cardiology, (14) is very interesting, as there is limited information on whether cancer patients with PE and an intermediate or high PESI score (≥86 points) have a higher risk of unfavorable progression versus non-cancer patients. The group of patients in this paper is similar to global numbers, with gastrointestinal tumors being the most common.

From a cancer perspective, please note that the above-cited paper defines active cancer as solid or hematologic malignancy under chemotherapy and/or radiotherapy in the last year, or under no active treatment but with palliative care. We need to consider that this last group of patients have advanced disease with no chance of therapy, a poor general condition,

Rev Argent Cardiol 2024;92:99-100. http://dx.doi.org/10.7775/rac.v92.i2.20755

SEE RELATED ARTICLE: Rev Argent Cardiol 2024;92:101-107. http://dx.doi.org/10.7775/rac.v92.i2.20744

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and a longer time confined to bed, which increases the risk of developing PE.

In this study, cancer did not involve an adverse prognosis for patients with an intermediate to high PESI. While the reasons put forward by the authors may be considered (younger cancer patients with lower hypertension prevalence and right ventricular involvement), it is also important to consider the number of patients included, as power is low for finding a significant difference.

The study by Bonorino et al. should be continued to be able to figure out the close relationship among cancer, EP, and vital prognosis.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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ORIGINAL ARTICLE

Do Patients with Acute Pulmonary Embolism and an Intermediate or High PESI (Pulmonary Embolism Severity Index) Score Associated with Active Cancer Higher Risk of an Unfavorable Progression Versus Those Without Cancer?

¿Tienen los pacientes con tromboembolismo pulmonar agudo y un puntaje PESI (Índice de Severidad del Embolismo Pulmonar) intermedio o alto, asociado a cáncer activo, un mayor riesgo de presentar una evolución desfavorable respecto de aquellos sin cáncer?

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ABSTRACT

Background: The Pulmonary Embolism Severity Index (PESI) is used to categorize the risk of death in acute pulmonary embolism (PE). By definition, cancer patients will always have a high simplified PESI score and will be considered at high risk. There is limited information regarding whether patients with an intermediate or high PESI score (≥86 points) associated with active cancer are at greater risk of an unfavorable progression versus those without cancer.
Objectives: To determine whether the presence of active cancer in patients with a PESI score ≥86 points is associated with an unfavorable progression versus those without cancer.
Methods: A retrospective analysis in patients with PE and a PESI score ≥86, between 2008 and 2022. The occurrence of in-hospital mortality (IHM), the use of vasopressor drugs (VDs), and the need for mechanical ventilatory support (MVS) were evaluated in patients with vs. without cancer.
Results: 209 patients were analyzed. The population with cancer was younger than patients without cancer (65 vs 70 years; p=0.006), showed high simplified PESI values more frequently (100% vs 84%; p<0.001), had lower MVS requirement (9% vs 34%; p=0.005), and used fewer VDs (11% vs 23%; p=0.019). However, no difference was observed in IHM rates (12.7% vs 8%; p=NS), respectively.
Conclusions: Patients with PE and a PESI score ≥86 who have cancer did not show higher IHM and also had lower MVS and VDs requirement. Therefore, in the studied population, patients with PE and cancer had no greater risk of having an unfavorable progression.

Key words: Pulmonary Embolism – Cancer - Hospital Mortality - Risk Factors - PESI - Pulmonary Embolism Severity Index - Simplified PESI.

RESUMEN

Introducción: El Índice de Severidad del Embolismo Pulmonar (PESI) se utiliza para categorizar el riesgo de mortalidad en el tromboembolismo pulmonar agudo (TEP). Por definición, los pacientes con cáncer siempre presentarán un puntaje PESI simplificado alto y serán considerados de mayor riesgo. Existe información limitada respecto de si los pacientes con PESI intermedio o alto (≥86 puntos) y cáncer activo tienen mayor riesgo de presentar una evolución desfavorable respecto de aquellos sin cáncer.
Objetivos: Determinar si en pacientes con TEP y un puntaje PESI ≥86 puntos, la presencia de cáncer activo se asocia a una evolución desfavorable respecto de aquellos sin cáncer.
Material y métodos: Análisis retrospectivo en pacientes con TEP y un puntaje PESI ≥86, entre los años 2008 y 2022. Se evaluó la ocurrencia de muerte intrahospitalaria (MIH), uso de drogas vasopresoras (DV) y necesidad de asistencia respiratoria mecánica (ARM) en los pacientes con vs. sin cáncer.
Resultados: Se analizaron 209 pacientes. La población con cáncer, respecto de aquella sin cáncer, resultó ser más joven (65 vs. 70 años; p=0,006), presentó valores de PESI simplificado altos con mayor frecuencia (100 % vs. 84 %; p<0,001), tuvo menor requerimiento de ARM (9 % vs. 34 %; p=0,005) y menor uso de DV (11 % vs. 23 %; p=0,019), aunque no se observaron diferencias en las tasas de MIH (12,7 % vs. 8 %; p=NS).

Rev Argent Cardiol 2024;92:101-107. http://dx.doi.org/10.7775/rac.v92.i2.20744

SEE RELATED ARTICLE: Rev Argent Cardiol 2024;92:99-100. http://dx.doi.org/10.7775/rac.v92.i2.20755

Received: 30/09/2024 – *Accepted:* 05/03/2024

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Conclusiones: Los pacientes con TEP y un puntaje PESI ≥86 con cáncer no presentaron mayor MIH e incluso tuvieron menor requerimiento de ARM y DV. En la población estudiada, los pacientes con TEP y cáncer no tuvieron mayor riesgo de presentar una evolución desfavorable.

Palabras clave: Embolia pulmonar - Cáncer - Mortalidad hospitalaria - Puntuaciones de riesgo - PESI - Pulmonary Embolism Severity Index - PESI simplificado

INTRODUCTION

Acute pulmonary embolism (PE) is the second cause of death in cancer patients, only preceded by deaths resulting from cancer itself, (1) and it is estimated that up to 20% of patients with cancer will experience PE. (2,3)

Argentina has an intermediate to high cancer incidence, which, in addition to cardiovascular diseases, account for more than 40% of deaths based on the latest epidemiology registries. (4)

Cancer-associated PE (CA-PE) shows higher mortality in several registries, regardless of the characteristics of cancer (5-7) and any related symptoms. (8,9)

The Pulmonary Embolism Severity Index (PESI) is a useful prognostic method to estimate in-hospital death and 30-day mortality. Complications or fatal events in low or very low risk patients (<86 points) are lower than 1.9% and 1.1%, respectively. (10)

Based on the simplified version of PESI (sPESI), for individuals with a sPESI score <1, 30-day mortality was 1.1% (low risk), while for those with a score ≥1, it was 8.9% (high risk). (11) Both scores have been validated in Argentina and have shown good mortality correlation. (12)

Current guidelines recommend the use of any of these two scores (PESI or sPESI) for risk stratification. (13-15) Those with low PESI or sPESI scores may receive anticoagulants alone and, eventually, early hospital discharge. (16)

Patients with CA-PE will inevitably have a high sPESI score, as cancer history is considered a risk variable by definition and, therefore, will be considered at high risk when using this classification.

There is limited information on whether patients with CA-PE and an intermediate or high PESI (≥86 points) have a higher risk of an unfavorable progression versus those without cancer. It is also unknown if patients with CA-PE might have a better prognosis with a PESI <86 points.

METHODS

A retrospective analysis of a prospective single-center cohort from an Argentine University Hospital in patients hospitalized with PE between 2008 and 2022 and with a PESI score ≥86 points. The objective of this study is to determine whether in patients with PE and a PESI score ≥86 points the presence of active cancer is associated with an unfavorable progression versus those without cancer.

The incidence of in-hospital mortality (IHM), the use of vasopressor drugs (VDs), and the need for mechanical ventilatory support (MVS) were evaluated in patients with and without CA-PE. In addition, IHM and the incidence of BARC bleeding (17) were evaluated in patients with CA-PE and a PESI score <86 points.

Active cancer was defined as solid or hematologic malignancy treated with chemotherapy and/or radiotherapy within the past year, or with no active treatment but under palliative care. Patients with advanced cancer and brain neoplasms were included, whether anticoagulants or reperfusion therapy were contraindicated or not. Skin neoplasms, except for melanoma, were not considered active cancer. Right ventricular (RV) dilatation was defined as a RV/left ventricular diameter ratio >0.9 upon four-chamber view, and RV failure was defined as RV dilatation with at least one of the following: free wall hypokinesia, tricuspid annular plane systolic excursion (TAPSE) lower than 16 mm, and/or interventricular septal bulge.

Data were collected from the medical record and stored in an encrypted database approved by the Institutional Research Ethics Committee. All informed consents for the anonymous use of data were obtained, and the protocol was approved by our Institutional Bioethics Committee under regulation number 19-041.

Mean and standard deviation, or median and interquartile range (IQR) 25-75 were used to describe quantitative variables based on whether distribution was normal or not. Qualitative variables were displayed as frequency and percentage tables. For quantitative variables comparison, the t test or Wilcoxon test were used for single or paired samples, according to each case. For dichotomous variables comparison, the $\chi 2$ or McNemar tests were used. A multivariate logistic regression analysis was conducted to evaluate the stability of results on IHM, MVS, and use of VDs, adjusted by age, sex, hypertension (HT), diabetes, and active cancer. A two-tailed p value <0.05 was considered significant. The analysis was performed with Stata/SE v13.0 (StataCorp, United States).

RESULTS

Out of 456 patients hospitalized due to PE diagnosis and included in our registry, 209 patients with a PESI score ≥86 were evaluated. From this population, 126 (60.3%) patients had active cancer and 83 (39.7%) patients had no cancer (Figure 1). For the cancer population, 23% were incidental PE and 12.6% had limited therapeutic effort. An elevated prevalence of solid tumors was recorded: lung (17.4%), gastrointestinal (17.4%), breast (11.1%), biliopancreatic (10.3%), gynecological (9.5%), renal vesical (8.7%), prostatic (7.1%), central nervous system (4.7%), and other malignancies (6.3%), with a lower prevalence of hematologic malignancies (7.1%). (Figure 2). Baseline characteristics, prognostic markers, and reperfusion therapy prescribed for each population, with and without cancer, are shown in Table 1. The population with CA-PE was younger than the popula-

tion without (65 vs 70 years; p=0.006), respectively. Patients with CA-PE had a lower prevalence of HT (48% vs 72%; p<0.001) but a higher prevalence of diabetes (19% vs 8%; p= 0.045). By definition, all patients with CA-PE had a high sPESI score, with higher prevalence versus patients without cancer (100% vs 84%; p<0.001). There was an elevated rate of anticoagulant use in patients with CA-PE and in those without (97.6% vs 97.5%; p=NS). The population with CA-PE had lower RV dilatation versus the population without cancer (16.6% vs 50.1%; p<0.001) and lower RV dysfunction (13.4% vs 37.3%; p<0.001). CA-PE patients were prescribed some kind of reperfusion therapy less frequently (9.6% vs. 32.6%; p<0.001), with less fibrinolytic drugs indication. (Table 1). No differences were observed in terms of major bleeding rates (BARC ≥3) among patients with CA-PE versus patients without cancer (2.3% vs 4.8%; p=NS). There was no fatal bleeding (type 5 BARC), and a case of surgical bleeding was recorded (type 4 BARC) in each group.

Patients with CA-PE did not show any differences in IHM rates versus patients without cancer (12.7% vs 8.4%; p=NS), even though they had a lower requirement of MVS (9.5% vs 24%; p=0.005) and use of VDs (11% vs 23%; p=0.019 (Table 2). Absence of active cancer was correlated with a higher risk of MVS, but not higher IHM, in multivariable analysis adjusting for age, sex, HT and diabetes (Table 3). The statistical model had good graphic and statistical calibration, with a ROC area under the curve of 0.70 (95% CI 0.65-0.73) and a Hosmer-Lemeshow test p value = 0.521.

None of the patients with a PESI score <86 points, either with cancer (n=24) or without cancer (n=151), died during hospitalization. In cancer patients, a PESI score <86 vs ≥86 points was not useful to predict IHD

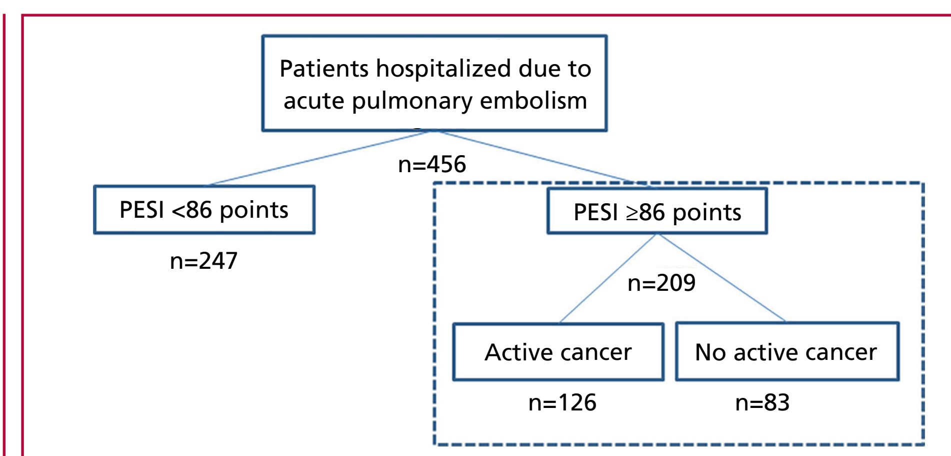
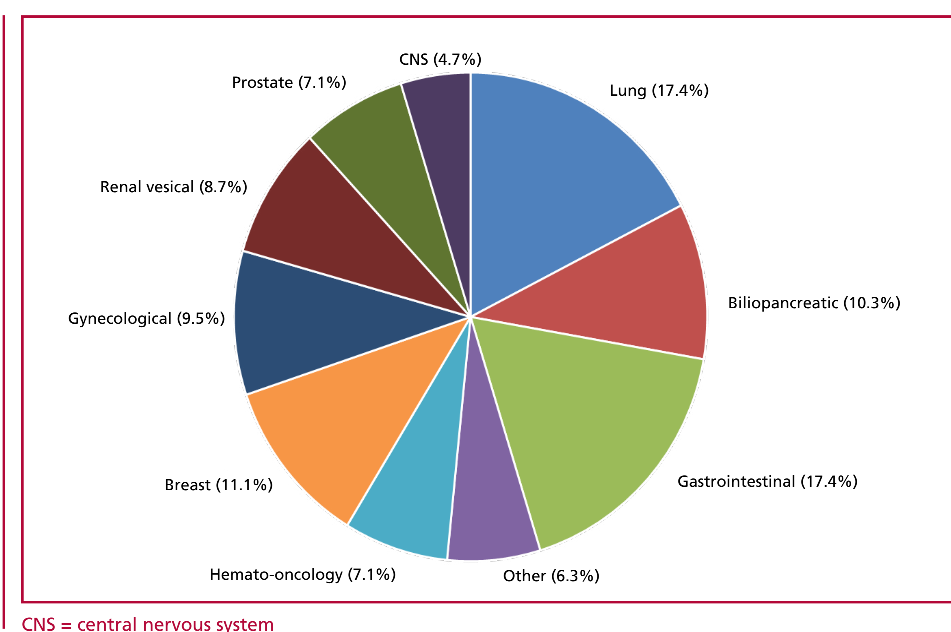


Fig. 1. Flow diagram. Patients hospitalized due to acute pulmonary embolism with a PESI score ≥86 points, with active cancer vs with no active cancer.



CNS = central nervous system

Fig. 2. Patients with acute pulmonary embolism and active cancer (n=126). Types of malignancy.

Table 1. Clinical characteristics, prognostic markers, and reperfusion therapy prescribed for patients with pulmonary embolism (PE) and PESI ≥86 points.

Clinical characteristics, prognostic markers and prescribed reperfusion therapies	With cancer n:126 (60.2%)	Without cancer n:83 (39.7%)	p value
Age (years, mean)	65	70	0.006
Female	62 (49%)	38 (45%)	0.672
Hypertension	61 (48%)	60 (72%)	<0.001
Diabetes	24 (19%)	7 (8%)	0.045
COPD	6 (5%)	7 (8%)	0.381
Smoking	54 (43%)	31 (37%)	0.473
Dyslipidemia	46 (36%)	27 (32%)	0.656
Anticoagulant therapy	123 (97.6%)	81 (97.5%)	1
PESI score			
PESI ≥86 points	126 (100%)	83 (100%)	1
sPESI ≥1 point	126 (100%)	70 (84%)	<0.001
Right ventricular involvement			
Right ventricular dilatation	21 (16.6%)	42 (50.1%)	<0.001
Right ventricular failure	17 (13.4%)	31 (37.3%)	<0.001
Myocardial injury biomarkers			
Troponin T > 14 pg/ml	63 (50%)	53 (63%)	0.064
Hospitalization reperfusion strategy			
Anticoagulation alone	114 (90.4%)	56 (67.4%)	<0.001
Catheter-directed reperfusion therapy	8 (6.3%)	11 (13.2%)	0.138
Surgical thrombectomy	1 (0.7%)	3 (3.6%)	0.303
Fibrinolytics	3 (2.3%)	14 (16.8%)	<0.001

COPD: chronic obstructive pulmonary disease; sPESI: simplified PE Severity Index. Right ventricular (RV) failure: RV dilatation with at least one of the following: free wall hypokinesia, TAPSE <16 mm, interventricular septal bulge.

(0% vs 12%; p=NS). No patient with CA-PE and PESI <86 had bleeding or right ventricular dysfunction, and only 8.3% had mild RV dilatation.

DISCUSSION

PESI score assessment is part of the initial stratification of EP patients, whether they have active cancer or not. In this sense, it is assumed that patients with CA-PE have a higher risk than those with no active cancer. Patients with a high PESI score, RV dilatation, and elevated troponin are considered intermediate to high risk patients in terms of an unfavorable progression. Use of some kind of reperfusion therapy is considered for these patients, as well as patients with hemodynamic instability. Thus, the importance of establishing whether the sole presence of active cancer might have an impact on prognosis for PE patients. Several models attempt to identify patients with CA-PE and a low risk of complications who might be offered a therapeutic alternative that may avoid or reduce hospitalization. (18)

As observed in other registries, (19,20) IHM in patients with PE and a PESI score ≥86 points was high, even though no differences were observed in the population without cancer vs patients with CA-PE (8% vs 12.7%, p=NS). Unlike other studies, (21,22) where CA-PE patients are older than those without cancer, the CA-PE population was younger in our study. The multivariate analysis for IHM, adjusted for age, sex, HT, and diabetes, failed to show that cancer is an independent adverse prognostic marker. However, note that patients with cancer had lower HT prevalence, which may have affected the result. It is also likely that a higher risk of MVS and VDs requirement in patients without cancer is related to a higher prevalence in this population with adverse prognostic predictors, with greater dilatation and RV dysfunction. Also, reperfusion therapies were more commonly prescribed in the population without cancer, suggesting a more severe condition for these patients. These findings suggest that the PESI has mainly a negative predictive value for adverse prognosis; a high PESI score requires concomitant RV dilatation and/or dysfunction, and elevated troponin to predict IHM.

While this study did not evaluate other predictive models useful for CA-PE, there are various potentially helpful prognostic scores. The POMPE-C predictive model has adequate prognostic accuracy for 30-day

Table 2. Incidence of in-hospital adverse events in patients with PESI score ≥ 86, with vs. without cancer

Hospital Adverse Events	With Cancer n=126 (60.3%)	Without Cancer n=83 (39.7%)	p value
Mechanical Ventilatory Support	12 (9.5%)	20 (24%)	0.005
Use of Vasopressor Drugs	14 (11%)	19 (23%)	0.019
In-hospital Death	16 (12.7%)	7 (8%)	0.232

Table 3. Multivariate analysis for the prediction of hospital adverse events.

Hospital Adverse Events	Odds Ratio (95% CI)	Std. Error	p value
Mechanical Ventilatory Support			
Age (years)	0.99 (0.96-1.02)	0.01	0.759
Hypertension	0.99 (0.38-2.53)	0.47	0.986
Diabetes	1.34 (0.43-4.18)	0.77	0.605
Male Sex	1.98 (0.88-4.49)	0.82	0.098
Active Cancer	0.30 (0.14-0.65)	0.11	0.002
Use of Vasopressor Drugs			
Age (years)	0.99 (0.96-1.02)	0.01	0.721
Male Sex	1.11 (0.51-2.37)	0.43	0.786
Diabetes	2.13 (0.79-5.74)	1.07	0.132
Active Cancer	0.39 (0.19-0.80)	0.14	0.010
In-hospital Death			
Age (years)	1.01 (0.97-1.05)	0.01	0.405
Hypertension	0.35 (0.13-0.95)	0.17	0.040
Diabetes	1.99 (0.63-6.30)	1.17	0.237
Male Sex	1.46 (0.60-3.54)	0.65	0.402
Active Cancer	0.90 (0.42-1.93)	0.35	0.800

mortality and a better performance than PESI. According to Kline et al., the ROC area under the curve for POMPE-C was 0.84 (95% CI 0.82-0.88). No patient with POMPE-C ≤5% died within 30 days, while 77% of patients with POMPE-C >50% died during 30-day follow-up. (23) RIETE-VTE and the modified Ottawa score are risk models that might be useful to identify patients with CA-PE and a low risk of IHD. In a study by Pfaundler et al., no patient classified as low risk according to RIETE-VTE models or the modified Ottawa score died within 30 days. (24) The HESTIA model showed that a total zero score was consistent with a very low rate of adverse events, even though it has not been sufficiently validated in patients with active cancer. (25) Roy et al. compared the HESTIA model and sPESI to determine which of them might be more accurate to identify patients adequate for outpatient treatment. In the HESTIA model arm, the primary endpoint at 90 days occurred in 2.96% vs 1.40%; p=NS. Both scores showed similar efficacy and safety. (26)

Prognosis for CA-PE patients might be more affected by advanced cancer and overall patient condition than by risk scores such as PESI. Li et al. showed that, in a CA-PE population, patients who died within 30 days had a higher rate of metastatic cancer and an Eastern Cooperative Oncology Group performance status ≥2. This study showed that the incidence of death and adverse events was associated with more specific models for CA-PE patients (RIETE and POMPE-C), rather than with more general models (PESI and HESTIA) or the modified Ottawa score. Except for the HESTIA score, with a 73.5% sensitivity, the other four scores were highly sensitive (>94%) for mortality at 30 days. All these models showed an excellent negative predictive value (>92%) for mortality at 30 days, especially, for RIETE and POMPE-C scores (98.6% and 96.5%, respectively). (18) Other models such as EPIPHANY and COMMAND VTE are also useful for patients with CA-PE, even though they have not been sufficiently validated. (27,28)

Among the multiple limitations of this study, the single-center nature must be noted. Therefore, prevalence of certain types of tumors could differ from other sites. There was no 30-day follow-up, incidental PE

occurrences were included, no outpatients were enrolled, and neither RV dilatation nor RV dysfunction were considered for the multivariate analysis.

The present study shows that, in our setting, patients with CA-PE and PESI ≥86 points have high IHM, even though not higher than in patients without cancer. In addition, it is suggested that the sPESI might overestimate the risk in patients with CA-PE, as no patient with PESI <86 points either with or without cancer died during hospitalization. No further studies are needed to check these findings and evaluate the use of PESI and other prognostic models for patients with CA-PE.

CONCLUSIONS

In the studied population, patients with CA-PE and an intermediate or high PESI score did not have greater risk of an unfavorable progression. In this cancer population, mortality was not higher and there was lower MVS and VDs requirement.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Funding

Support Sources: CEDECAFO, Hospital Universitario Austral Institute of Cardiology.

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ORIGINAL ARTICLE

Argentine MINOCA Registry. Description of the Population

Registro argentino de MINOCA. Descripción de la población

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(ON BEHALF OF THE INVESTIGATORS OF THE RESCAR REGISTRY)

ABSTRACT

Background: Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a well-known condition that has been recently redefined after excluding non-ischemic myocardial injury. ReSCAR was a prospective, multicenter registry of patients hospitalized for acute coronary syndrome (ACS) from January to August 2022.
Objective: One of the main objectives of the registry was to define the prevalence of patients with MINOCA, their baseline clinical and paraclinical characteristics, and in-hospital outcome. This publication focuses on the results of the respective analysis.
Methods: We conducted a nationwide, multicenter, prospective study of patients with ACS. The diagnosis of MINOCA was made following the Fourth Universal Definition of Myocardial Infarction. The baseline characteristics of the patients were analyzed, as well as their outcome and significant differences with patients with obstructive coronary artery disease. The participating centers should have the availability to measure high-sensitivity cardiac troponin and perform coronary angiography.
Results: A total of 984 patients from 15 centers were included. Eighty-five patients (8.6%) had a final diagnosis of MINOCA at discharge. Median age was 65 years (53-63), 48 (51.8%) were women, 55 (64.7%) had hypertension, 44 (51.8%) had dyslipidemia, 9 (10.6%) were diabetics and 23 (27.1%) were smokers. Median high-sensitivity cardiac troponins on admission (expressed as multiples of the 99th percentile) were 2.42 times higher (0.85-10.21) and the ECG had no ischemic changes in 71.8% of the patients. Coronary angiography was normal in 72.9% of the patients and the rest of the cases had coronary artery stenoses < 50%. Sixteen patients underwent cardiac magnetic resonance imaging. The median GRACE score was 115 (98-139), which corresponds to intermediate risk. The event rate for the composite outcome of stroke/myocardial infarction or death was1.2%, and there were no bleeding events BARC ≥ type 2. The discharge prescription rate was 72.9% for aspirin, 27.1% for clopidogrel, 88.2% for statins, 67.1% for beta-blockers, and 22.4% for calcium channel blockers.
Conclusion: In this registry, patients with MINOCA represent a significant proportion of those with ACS. The rate of in-hospital complications, including mortality, was low. There seems to be a strong opportunity for further investigations to confirm the diagnosis, pathophysiological mechanisms, and treatment of MINOCA.

Key words: MINOCA - Myocardial Infarction with Non-obstructive Coronary Arteries - Acute Coronary Syndrome - Registry - Coronary Artery Disease

RESUMEN

Introducción: El infarto de miocardio sin obstrucciones coronarias significativas (MINOCA) es una conocida entidad que se ha redefinido recientemente al excluir la injuria miocárdica no isquémica. ReSCAR fue un registro prospectivo, multicéntrico de pacientes hospitalizados por síndrome coronario agudo (SCA) desde enero hasta agosto de 2022.
Objetivos: Un objetivo principal del registro fue definir la prevalencia de pacientes con MINOCA, sus características basales clínicas y paraclínicas y evolución intrahospitalaria. Los resultados del análisis respectivo son la base de esta publicación.
Material y métodos: Registro nacional prospectivo y multicéntrico de SCA. Diagnóstico de MINOCA de acuerdo con la Cuarta Definición Universal de Infarto de Miocardio. Análisis de las características basales, evolución y diferencias significativas respecto de los pacientes con coronariopatía obstructiva. Los centros participantes debían contar con determinación de troponina de alta sensibilidad y la posibilidad de realizar cinecoronariografía.

Rev Argent Cardiol 2024;92:108-116. http://dx.doi.org/10.7775/rac.v92.i2.20746

SEE RELATED ARTICLE: Rev Argent Cardiol 2024;92:97-98. http://dx.doi.org/10.7775/rac.v92.i2.20750

Received: 12/15/2023 – *Accepted:* 01/27/2024

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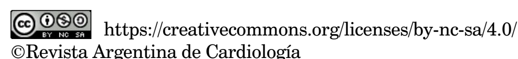
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Resultados: Se incluyeron 984 pacientes de 15 centros. Ochenta y cinco pacientes (8,6 %) tuvieron diagnóstico final de MINOCA al alta. Cuarenta y cuatro pacientes (51,8 %) eran mujeres, la mediana de edad fue de 65 años (53-63), 55 (64,7 %) pacientes eran hipertensos, 44 (51,8 %) dislipidémicos, 9 (10,6 %) diabéticos y 23 (27,1 %) fumadores. La mediana de troponina al ingreso (expresada como múltiplo del percentilo 99) fue de 2,42 (0,85-10,21) y el 71,8 % se presentó con un ECG sin cambios isquémicos. La angiografía coronaria fue normal en el 72,9 % de los pacientes y con lesiones menores de 50 % en el resto. Se realizó resonancia cardíaca a 16 pacientes. La mediana del score GRACE fue de 115 puntos (98-139), lo cual perfila un riesgo intermedio; con una tasa de eventos combinados de accidente cerebrovascular/infarto o muerte de 1,2 %, sin haberse registrado sangrados BARC 2 o más. La prescripción al alta de aspirina fue del 72,9 %, clopidogrel 27,1 %, estatinas 88,2 %, beta bloqueantes 67,1 % y antagonistas cálcicos 22,4 %.
Conclusión: En este registro, los pacientes con MINOCA representan una proporción significativa de aquellos con SCA. La tasa de complicaciones intrahospitalarias, incluida la mortalidad, fue baja. Impresiona existir una fuerte oportunidad para profundizar los estudios para confirmar este diagnóstico, sus mecanismos fisiopatológicos y su tratamiento.

Palabras clave: MINOCA - Infarto de miocardio sin lesiones coronarias - Síndrome coronario agudo - Registro - Enfermedad coronaria

INTRODUCTION

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is defined as a condition suggestive of myocardial infarction in the absence of obstructive coronary arteries on angiography (angiographically normal coronary arteries or coronary artery stenosis < 50%). This entity has gained renewed interest in recent years based on studies aimed at clarifying its pathophysiology and differentiating it from other causes of non-ischemic myocardial injury such as Takotsubo cardiomyopathy and myocarditis. (1) The diagnosis is often suspected during hospitalization and is confirmed later or not. Cardiology societies worldwide have agreed to use the term MINOCA to describe a working diagnosis for ischemic cardiomyopathy which encompasses various causes, including plaque rupture, coronary artery spasm, coronary embolism, spontaneous coronary artery dissection, and microvascular dysfunction. (2-5) The optimal treatment and prognosis for these patients are still uncertain.

Many studies that describe the characteristics of MINOCA are based on retrospective data and do not differentiate its diagnosis from other causes of non-ischemic myocardial injury. Therefore, the conclusions drawn from these studies may be erroneous. (6-8)

The aim of this study was to describe the characteristics and in-hospital outcome of MINOCA patients in high-complexity centers of Argentina.

METHODS

ReSCAR was a prospective cohort study conducted in high complexity medical centers in Argentina, mostly located in Buenos Aires metropolitan area. The study was conceived, designed and conducted by the Council on Cardiovascular Emergency Care of the Argentine Society of Cardiology to describe the spectrum of acute coronary syndromes (ACS), particularly the in-hospital features and one-year outcome. The protocol was designed with a focus on including variables for describing MINOCA.

The participating centers should have the availability to measure high-sensitivity cardiac troponins and perform coronary angiography in order to standardize the diagnosis of myocardial infarction according to the current criterion. (5) The Argentine Society of Cardiology invited all centers in Argentina to participate in the study.

Diagnosis of MINOCA

The diagnosis of MINOCA was assigned by the principal investigator of the center when the patient was discharged. The definition used was the one suggested by the Fourth Universal Definition of Myocardial Infarction which is currently shared by the Consensus Statement of the Argentine Society of Cardiology. (4,5)

MINOCA was considered a clinical-angiographic syndrome characterized by:

1- A rise and/or fall of high-sensitivity cardiac troponin values with at least one value above the 99th percentile upper reference limit and at least one of the following: symptoms of myocardial ischemia, new significant electrocardiographic changes, development of pathological Q waves, evidence of loss of viable myocardium or regional wall motion abnormality in imaging tests, or identification of intracoronary thrombus by angiography or autopsy.
2- Non-obstructive coronary artery disease: defined as absence of coronary artery stenosis ≥ 50%.
3- Absence of alternative diagnoses of myocardial injury (sepsis, pulmonary embolism, aortic dissection, etc.).

Sample size estimation

Given that previous registries have reported a prevalence of around 10% for MINOCA, (6,9,10) we planned to include 1000 ACS patients from January to August 2022. This would allow us to obtain approximately 100 patients with MINOCA for the analysis and comparison with other coronary syndromes.

Inclusion criteria

We included consecutive patients > 18 years of age who were admitted to the coronary care unit for an acute coronary syndrome (ACS) and a final diagnosis at discharge of ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina, type 2 myocardial infarction, or MINOCA. Patients with a diagnosis of ACS on admission and final diagnosis of myocarditis of Takotsubo were also included.

Data collection

Data were collected from the information recorded in an electronic case report form in the RedCap platform. (11) Access to the data was controlled by the group that organized the registry to ensure confidentiality.

The collected data included the patient's medical history, clinical information upon admission, laboratory tests, electrocardiogram, coronary angiography, and other tests conducted during hospitalization. In-hospital complications

and medications on admission and discharge were recorded. For data analysis, high-sensitivity cardiac troponins (T and I) are expressed as multiples of the 99th percentile (99px) to separate the values of the different cut-off points for each center and make them comparable. Analysis of the data corresponding to the pre-specified 12-month follow-up period is ongoing and was collected through telephone contact and medical records. For further information on the protocol, please refer to the already published ReSCAR registry. (12)

Statistical analysis

All the statistical calculations were performed using IBM SPSS 25.0 software package. Discrete variables were expressed as frequencies and percentages. Continuous variables were expressed as mean ± standard deviation, or median and interquartile range, according to their distribution. The chi square test or Fisher's exact test were used to compare the categorical variables, and continuous variables were analyzed using the Student's t test or the Mann-Whitney test according to their distribution. A type I error < 5% (two-tailed p value < 0.05) was considered statistically significant.

Ethical considerations

All the patients gave their informed consent before participating in the study. The consent was submitted for approval by the institutional review board of each center, which is under the regulations of the Central Review Board of the Argentine Society of Cardiology.

The investigators implemented measures to protect the confidentiality of all the information according to the Argentine Law on Protection of Personal Data No. 25326, so that the identity of the patients and all their personal data will remain anonymous and only the researchers and the members of the learning, teaching and research ethics committee would have access to these data, if required.

The study was conducted following national ethical standards (Law No. 3301 of the city of Buenos Aires, National Law for Good Clinical Practice in Research on Human Subjects, and the Declaration of Helsinki, among others).

RESULTS

A total of 984 patients from 15 centers were included between January and August 2022. Of the 104 patients (10.6%) without significant coronary artery stenoses, 85 (8.6%) had a final diagnosis of MINOCA.

Median age of MINOCA patients was 65 years (53-73) and 51.8% were women. The general characteristics of MINOCA patients are displayed in Table 1. Among coronary risk factors, 55 patients had hypertension (64.7%), 9 patients had diabetes (10.6%), 44 had dyslipidemia (51.8%), 23 were current smokers (27.1%), and 7 had a family history of cardiovascular disease (8.2%). Regarding women-specific risk factors (n= 43), 1 patient had a history of gestational diabetes (2.3%), 1 had a hypertensive disorder of pregnancy (2.3%), and median age of menopause was 52 years (48-55). Active or recent cancer was the most common comorbidity and was present in 5 patients (5.9%), while 4 patients had chronic kidney disease (4.7%). Almost a quarter (23.5%) of the patients had a history of coronary artery disease, which was associated with the presence of coronary artery stenoses <50% on coronary angiography. Ten patients had a history of myocardial infarction (11.8%) and 9 patients had undergone percutaneous coronary intervention (9.5%). Eight patients had a history of atrial fibrillation (9.4%) and 3 had heart failure (3.5%). Compared to patients with myocardial infarction and significant coronary artery obstructions, patients with MINOCA had a higher proportion of female gender (51.8% vs. 20.4%, p < 0.001), and lower prevalence of diabetes (10.6% vs. 26.8%, p<0.001), tobacco use (27.1% vs. 47.3%, p = 0.012) and previous myocardial infarction (11.8% vs. 24.7%, p = 0.006), but a a trend to higher prevalence of chronic angina (8.2 vs. 3.8%, p = 0.084).

On admission, 95.3% of the patients were hemodynamically stable and without heart failure. There were no ischemic changes in the electrocardiogram in 71.8% of the cases. Among abnormal electrocardiograms, T-wave changes were the most common (12.9%), followed by ST-segment depression (8.2%), and only 2.4% presented with ST-segment elevation. Median high-sensitivity cardiac troponin levels on admission were 2.42 times above the 99th percentile of the reference values (0.85-10.21). Median left ventricular ejection fraction was 60% (55-64%). Median GRACE score was 115 (98-138) and median CRUSADE score was 23 (14-31). Compared to patients with myocardial infarction with obstructive coronary arteries, patients with MINOCA presented with lower GRACE score (115 vs. 135, p < 0.001) (Table 2).

When the angiographic characteristics were analyzed, 62 patients (72.9%) had normal coronary arteries and 23 patients (27%) had coronary stenoses < 50%. Although the median troponin level was higher in patients with coronary artery obstructions than in those with normal coronary arteries, this difference was not statistically significant. Additionally, the proportion of patients with normal electrocardiograms was not statistically different between the two groups (Table 3).

The additional tests performed to patients with suspected MINOCA included cardiac magnetic resonance imaging in 16 patients (18.8%) during hospitalization and computed tomography coronary angiography in 8 (9.4%). Intracoronary spasm provocation test was performed in only one patient. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) were not performed in any patient. One patient underwent non-invasive assessment of endothelial dysfunction, and another patient underwent myocardial perfusion SPECT imaging.

The final diagnosis of the MINOCA mechanism assigned by the principal investigator of each center was microvascular dysfunction in 52 patients (61.2%), coronary spasm in 18 patients (21.5%), plaque accident in 6 patients (7.1%), coronary artery dissection in 3 patients (3.5%), and coronary embolism in 1 patient (1.2%). The mechanism was not assigned in 5 patients.

Median length of hospital stay was 3 days (2-4). Atrial fibrillation was the most common complica-

Table 1. General characteristics of the population with MINOCA

Variables	MINOCA (n = 85)	Myocardial infarction with obstructive coronary arteries (n = 621)	p
Age - years, median (IQR)	65 (53-73)	65 (57-74)	0.932
Female sex, n (%)	44 (51.8)	127 (20.4)	<0.001
BMI - kg/m^2, median (IQR)	27.8 (24.1-30.8)	27.7 (25.2-31.1)	0.564
Hypertension, n (%)	55 (64.7)	405 (65.3)	1
Diabetes mellitus, n (%)	9 (10.6)	167 (26.8)	<0.001
Dyslipidemia, n (%)	44 (51.8)	357 (57.4)	0.351
Smoking habits, n (%)	23 (27.1)	257 (41.3)	0.012
Family history, n (%)	7 (8.2)	56 (9)	1
CKD, n (%)	4 (4.7)	48 (7.7)	0.383
COPD, n (%)	2 (2.4)	39 (6.2)	0.215
Chronic inflammatory disease, n (%)	2 (2.4)	19 (3)	1
Cancer, n (%)	5 (5.9)	27 (4.3)	0.574
Depression, n (%)	3 (3.5)	22 (3.5)	1
Any previous coronary artery disease, n (%)	20 (23.5)	203 (32.6)	0.105
Previous myocardial infarction, n (%)	10 (11.8)	154 (24.7)	0.006
Previous coronary artery bypass graft surgery, n (%)	3 (3.5)	37 (5.9)	0.463
Percutaneous coronary intervention > 1 year, n (%)	6 (7.1)	112 (18)	0.008
Percutaneous coronary intervention within the last year, n (%)	2 (2.4)	40 (6.4)	0.217
Chronic angina, n (%)	7 (8.2)	24 (3.8)	0.084
Atrial fibrillation, n (%)	8 (9.4)	39 (6.2)	0.256
Stroke/TIA, n (%)	5 (5.9)	40 (6.4)	1
Heart failure, n (%)	3 (3.5)	24 (3.8)	1
Peripheral vascular disease, n (%)	3 (3.5)	44 (7)	0.356
Previous vascular disease, n (%)	23 (27.1)	241 (38.8)	0.041

BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; MINOCA: myocardial infarction with non-obstructive coronary arteries; TIA: transient ischemic attack

tion (4 patients). Two patients had recurrent angina or reinfarction, 1 patient had ventricular tachycardia/fibrillation (VT/VF) and 3 patients had signs of heart failure. There were no bleeding events BARC ≥ type 2. No deaths were reported. Compared to patients with myocardial infarction with obstructive coronary arteries, MINOCA patients had fewer ischemic events (death/infarction/stroke 1.2% vs. 7.9%, p=0,021) and a trend to fewer bleeding events BARC ≥ type 2 (0 vs. 4.2%, p = 0.061) during hospitalization (Table 4).

At hospital discharge, aspirin was prescribed to 62 patients (72.9%) and P2Y12 receptor inhibitors to 23 (27.1%) patients. Dual antiplatelet therapy was prescribed to 22 patients (22.9%) (Table 5).

DISCUSSION

Our study shows a prevalence of MINOCA of 8.6% in hospitalized patients with suspected ACS. We would like to highlight some of our findings.

First, in our registry, the prevalence of non-obstructive coronary arteries on coronary angiography among all patients hospitalized for ACS was 10.6%, which is similar to the one reported in other registries. Gehrie et al. found a prevalence of 10% in patients with non-ST-segment elevation ACS in a retrospective analysis of the CRUSADE registry. (13) In the analysis of MINOCA in the retrospective ACTION registry-GWTG (9) and the extensive meta-analysis of MINOCA by Pasupathy et al., the incidence reported was 6%. (6) In Argentina, the CONAREC XVII Registry on ACS found that 2.8% of patients had no coronary artery stenoses on angiography and 7.7% had moderate obstructions. (14) In all these registries, the term MINOCA is used as a working diagnosis, which means that it does not exclude conditions such as Takotsubo or myocarditis, but rather includes them as possible causes of MINOCA. In our registry, we attempted to exclude non-ischemic injuries and found a prevalence of MINOCA of 8.6%.

Second, half of the MINOCA patients in this registry are women. The proportion of women in this registry is similar to that of other registries, but differs from registries of myocardial infarction with significant epicardial lesions, where the proportion of women

Table 2. Characteristics on admission

Variables	MINOCA (n = 85)	Myocardial infarction with obstructive coronary arteries (n = 621)	p
HR - bpm, median (IQR)	78 (70-85)	76 (70-88)	0.833
SBP - mm Hg, median (IQR)	125 (115-140)	130 (120-150)	0.041
Killip & Kimball ≥class II - n (%)	4 (4.7)	97 (15.6)	0.005
LVEF (%), median (IQR)	60 (55-64)	53 (41-60)	<0.001
Hematocrit - %, median (IQR)	40 (38-43)	41 (37-44)	0.204
RDW -%, median (IQR)	13 (12-13.5)	13 (12.5-14)	0.065
White blood cell count/mm^3 - n, median (IQR)	8245 (6742-10787)	9388 (7532-11847)	0.009
Glycemia – mg/dL, median (IQR)	105 (95-117)	116 (100-139.7)	0.001
High-sensitivity cardiac troponin levels (in multiples of p99), median (IQR)	2.4 (0.8-10.2)	20.2 (4-125.3)	0.001
Creatinine levels – mg/dL, median (IQR)	0.89 (0.70-1.02)	1 (0.82-1.17)	<0.001
Creatinine clearance - mL/min, median (IQR)	88 (70-114)	84 (62.9-109.7)	0.144
GRACE score, median (IQR)	115 (98-139)	135 (113.5-159)	<0.001
CRUSADE score, median (IQR)	23 (14-31)	23 (13-35)	0.556
ECG on admission, n (%)			
No ischemic changes	61 (71.8)	164 (26.4)	0.001
ST-segment depression	7 (8.2)	87 (14)	
ST-segment elevation	2 (2.4)	238 (38.3)	
T-wave changes	11 (12.9)	85 (13.7)	
New Q waves	1 (1.2)	32 (5.2)	
LBBB/pacemaker rhythm	3 (3.5)	15 (2.4)	

HR: heart rate; IQR: interquartile range; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MINOCA: myocardial infarction with non-obstructive coronary arteries; RDW: red cell distribution width; SBP: systolic blood pressure.

Table 3. Comparison of troponin levels and ECG in MINOCA patients with or without coronary artery disease on angiography.

	Without obstructions	NS obstructions	p
N (%)	62 (72.9)	23 (27.1)	
Cardiac troponins*	2.1 (1.5-5.4)	3.3 (1.0-11.5)	0.483
No ischemic changes on ECG, n (%)	55 (88.7)	17 (73.9)	0.708
History of CAD, n (%)	10 (16)	10 (43.4)	0.002

*High-sensitive cardiac troponins expressed as multiples of p99. Median (P25-75)
CAD: coronary artery disease; ECG: electrocardiogram; MINOCA: myocardial infarction with non-obstructive coronary arteries; NS: non-significant.

is lower. (6,15,16) The age found in our registry is similar to that of patients with myocardial infarction with obstructive coronary arteries but differs from that described in other registries, where the age of MINOCA patients was lower than that of patients with significant coronary artery disease. (9,17)

Third, in our registry the prevalence of traditional coronary risk factors is lower than the one found in myocardial infarctions with epicardial coronary artery disease. It is worth noting that the prevalence of diabetes is lower, which is consistent with other MINOCA registries. (7,18) This registry also collected data on women-specific risk factors, such as hypertensive disorders of pregnancy, gestational diabetes, and menopause-related factors. The prevalence of these risk factors was lower than that described in other registries such as the VIRGO study, a registry of coronary syndromes in patients < 55 years with a special focus on nontraditional risk factors. (18) There may be a data collection bias related to the lack of routine asking about women-specific risk factors.

Fourth, most MINOCA patients presented as non-ST-segment elevation ACS with moderate elevation of cardiac troponins on admission and clinical stability. Although the risk estimated by the GRACE score was moderate, the rate of in-hospital events was low and there were no in-hospital deaths. Similarly, we could not confirm in our registry that the presence of cor-

Table 4. Complications during hospitalization

Variables	MINOCA (n = 85)	Myocardial infarction with obstructive coronary arteries (n = 621)	p
Acute kidney failure, n (%)	1 (1.2)	39 (6.3)	0.074
Contrast-induced nephropathy, n (%)	0	11 (1.8)	0.375
Heart failure, n (%)	3 (3.5)	75 (12.1)	0.015
Left ventricular assist device, n (%)	0	17 (2.7)	0.246
Need for MV, n (%)	0	33 (5.3)	0.024
Atrial fibrillation, n (%)	4 (4.7)	35 (5.6)	1
VF/VT, n (%)	1 (1.2)	32 (5.2)	0.164
Need for pacemaker implantation, n (%)	0	7 (1.1)	1
Reinfarction, n (%)	1 (1.2)	20 (3.2)	0.496
Recurrent angina, % (n)	1 (1.2)	20 (3.2)	0.496
Non-scheduled percutaneous coronary intervention, n (%)	0	9 (1.4)	0.609
Stroke/TIA, n (%)	0	6 (1)	1
Death/myocardial infarction/stroke, n (%)	1 (1.2)	49 (7.9)	0.021
Bleeding events ≥ BARC type 2, n (%)	0	26 (4.2)	0.061
Length of hospital stay in days, median (IQR)	3 (2-4)	4 (2-7)	<0.001
Mortality, % (n)	0	32 (5.2)	0.024

IQR: interquartile range; MV: mechanical ventilation; TIA: transient ischemic attack; VF: ventricular fibrillation; VT: ventricular tachycardia.

Table 5. Medication on admission and discharge

Medication	On admission	On discharge	p
Aspirin, n (%)	25 (29.4)	62 (72.9)	<0.001
Any P2Y12i, n (%)	5 (5.9)	23 (27.1)	<0.001
Clopidogrel	5 (5.9)	22 (25.9)	
Prasugrel	-	1 (1.2)	
Ticagrelor	-	-	
Oral anticoagulant agents, n (%)	8 (9.4)	12 (14.1)	0.476
ACEI/ARB/ARNI, n (%)	40 (47.1)	49 (57.6)	0.219
Beta blockers, n (%)	26 (30.6)	57 (67.1)	<0.001
Calcium channel blockers, n (%)	10 (11.8)	19 (22.4)	0.101
Nitrates, n (%)	2 (2.4)	7 (8.2)	0.637
Trimetazidine, n (%)	2 (2.4)	10 (11.8)	0.032
Statins, n (%)	33 (38.8)	75 (88.2)	<0.001

ACEI: angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; P2Y12i: P2Y12 receptor inhibitor

onary artery disease is associated with a worse outcome during hospitalization, as some registries have previously described. (19) The question of long-term outcomes remains, and we hope to answer it when we complete the analysis of the one-year follow-up.

Fifth, most MINOCA patients did not undergo additional tests during hospitalization to determine the etiology. This is particularly striking for cardiac magnetic resonance imaging, considered essential for the diagnosis of MINOCA, which was performed in only 18.8% of patients. It is possible that cardiac magnetic resonance imaging was not performed during hospitalization due to unavailability at the center or to avoid prolonging hospitalization for low-risk patients. It is also possible that the test was performed after discharge. Furthermore, it can be hypothesized that intravascular diagnostic tests or intracoronary spasm provocation tests are not widely available in our setting, and noninvasive methods for diagnosing coronary artery spasm or microvascular dysfunction are not widely used or known. Nevertheless, it is also true that the etiologic diagnosis of MINOCA begins during hospitalization and is often completed in the outpatient setting. The Argentine Consensus Statement on MINOCA, recently published, can assist in the initial management and diagnosis of these patients. (4) Due

to the low rate of tests performed during hospitalization, the population described in this registry may be more indicative of a working diagnosis than of a confirmed diagnosis of MINOCA.

However, the main etiologic diagnosis ascribed by the investigator of each center was microvascular dysfunction in 62.1% of the cases. According to several studies that further investigate the etiology of MINOCA using a combination of cardiac magnetic resonance imaging and intravascular imaging, at least half of MINOCA cases are due to plaque injury, followed by coronary artery spasm and cases of undetermined etiology, while spontaneous coronary artery dissection and embolism are less common. (19,20) The possible causes of MINOCA may still be unknown or confused with INOCA (ischemia without obstructive coronary artery disease), a condition in which microvascular dysfunction is very common.

Finally, there is little evidence on the optimal treatment for MINOCA after discharge from the index hospitalization. Dual antiplatelet therapy has not been shown to reduce events, and the use of statins, renin-angiotensin-aldosterone system antagonists, and beta-blockers may have a protective effect. (21-24) In our registry, the use of dual antiplatelet therapy at discharge was significantly higher than at admission, but was used in only 22.9% of patients, which is related to the etiologic diagnosis assigned. Secondary prevention with statins was high and, together with beta blockers, prescription was greater than on admission

The strength of our registry lies in its prospective description of MINOCA, providing data that are hard to obtain from retrospective analyses of registries designed with different objectives. Post-discharge monitoring of patients will provide data on long-term outcome. We expect that this study will help to generate hypotheses for future research to clarify the prognosis and optimal treatment of patients with MINOCA.

STUDY LIMITATIONS

Due to the requirement of signing an informed consent form and the nature of this registry, we cannot guarantee the consecutive inclusion of patients. Therefore, the prevalence found in our study may not accurately reflect reality. The involvement of centers primarily located in the Buenos Aires metropolitan area may result in data not representative of the entirety of Argentina. In addition, the interpretation of the coronary angiograms was the responsibility of the investigators at each center and not of a central group. In any case, we believe that the registry represents the characteristics of hospitalized patients in "real life".

CONCLUSIONS

In this registry, patients with MINOCA represent a significant proportion of those with ACS. The rate of in-hospital complications, including mortality, was low. There seems to be a strong opportunity for further investigations to confirm the diagnosis, pathophysiological mechanisms, and treatment of MINOCA.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Sources of funding

None.

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ORIGINAL ARTICLE

Myocardial Tissue Characterization Using Electron Density Imaging: Relationship with Sex and Cardiovascular Risk Factors

Caracterización del tejido miocárdico a través de imágenes de densidad electrónica: relación con el sexo y factores de riesgo cardiovascular

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ABSTRACT

Background: Electron density (ED) imaging might be able to detect myocardial tissue differences indistinguishable for conventional non-contrast computed tomography (CT).

Objectives: To evaluate whether there are differences in myocardial ED associated with sex, and if present, their relationship with cardiovascular risk factors or coronary calcification.

Methods: Patients were participants of a prospective single center observational study comprising asymptomatic subjects between 50 and 75 years old, referred for a low-dose chest CT. All images were obtained using a dual-layer detector spectral CT, and evaluated using conventional CT (120 kVp) and ED images.

Results: A total of 171 patients were included. Myocardial attenuation was not related to sex or coronary risk factors (all p>0.05), whereas the percent electron density relative to water (%EDW) was significantly higher among males (p<0.0001), and patients with diabetes (p=0.007), hypertension (p=0.004), and obesity (p=0.004). The extent of coronary artery calcification was unrelated to neither the myocardial attenuation, nor the myocardial ED. At univariate analysis, male sex was the only variable associated with a high %EDW (p=0.011), whereas age, diabetes, obesity, smoking, hypertension, and CACSIS (coronary artery calcification segment involvement score), were not. Logistic regression analysis including sex, obesity, diabetes, and hypertension in the model, identified male sex as the only independent predictor of a high %EDW (OR 2.51, 95%CI 1.23-5.34, p=0.016).

Conclusions: In this study, ED imaging identified myocardial tissue differences that conventional CT was unable to discriminate, with a higher %EDW in men and in patients with cardiovascular risk factors. Male sex was the only independent predictor of a high %EDW

Key words: Computed tomography - Dual energy - Spectral - Gender - Coronary calcification

RESUMEN

Introducción: Las imágenes de densidad electrónica (DE) podrían detectar diferencias miocárdicas tisulares no distinguibles mediante la tomografía computarizada (TC) convencional sin contraste.

Objetivos: Evaluar si existen diferencias de DE miocárdica asociadas al sexo, y de estar presentes, su relación con factores de riesgo cardiovascular o calcificación coronaria.

Material y métodos: Los pacientes pertenecían a un estudio prospectivo observacional de centro único que incluyó sujetos asintomáticos entre 50 y 75 años, derivados para realizar una TC de tórax de baja dosis. Todas las imágenes se obtuvieron mediante un equipo de TC espectral dual, y fueron evaluadas utilizando imágenes de TC convencional (120 kVp) y de DE,

Resultados: Se incluyó un total de 171 pacientes. La atenuación miocárdica no estuvo relacionada con el sexo o factores de riesgo coronarios (todos con p >0,05), mientras que el porcentaje de densidad electrónica respecto del agua (%EDW, por su sigla en inglés) fue significativamente mayor en la población masculina (p<0,0001), y en los pacientes con diabetes (p=0,007), hipertensión (p=0,004) y obesidad (p=0,004). La extensión de la calcificación coronaria no estuvo relacionada ni con la atenuación ni con la DE miocárdicas. En el análisis univariado, el sexo masculino fue la única variable asociada a un %EDW elevado (p=0,011), mientras que la edad, la diabetes, la obesidad, el tabaquismo, la hipertensión y el score CACSIS (score de calcificación de las arterias coronarias), no. Un modelo de regresión logística que incluyó sexo, obesidad, diabetes e hipertensión, identificó al sexo masculino como el único

REV ARGENT CARDIOL 2024;92:117-123. http://dx.doi.org/10.7775/rac.v92.i2.20752

Received: 02/02/2024 – *Accepted:* 03/14/2024

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predictor independiente de %EDW elevado (OR 2,51, IC 95% 1,23-5,34, p=0,016).
Conclusiones: En este estudio, las imágenes de DE identificaron diferencias en el tejido miocárdico que la TC convencional fue incapaz de discriminar, con un mayor %EDW en hombres y en pacientes con factores de riesgo cardiovascular. El sexo masculino fue el único predictor independiente de %EDW elevado

Palabras clave: Tomografía computarizada - Energía dual - Espectral - Género - Calcificación coronaria

INTRODUCTION

After decades of female underrepresentation in most clinical studies, there is an increasing interest in the evaluation of the distinctive cardiovascular phenotypes of men and women. (1)

Aside from a different risk factor profile, clinical presentation, and higher susceptibility to myocardial injury associated with psychological stress, women have less coronary calcification, higher rates of microvascular disease, and a more hypercoagulable profile, underscoring the role of nonobstructive disease among them. (2-4) Furthermore, independent of smaller (adjusted for body surface) epicardial coronary arteries, women have higher resting myocardial perfusion and myocardial blood volume compared with men. (5) Indeed, gender differences endure even among the elderly, with males displaying consistently higher coronary calcification and total coronary plaque burden despite showing, interestingly, a similar extent of extra-coronary calcification. (6,7)

To date, characterization of myocardial tissue using computed tomography (CT) requires iodinated contrast. Nonetheless, the electron density (ED) of the atoms comprising the tissues, normalized to pure water, can be directly estimated using dual-layer spectral computed tomography (CT), without modifications of acquisition protocols. (8) Previous studies have suggested an incremented value of (non-contrast) ED imaging over iodinated contrast assessment for tissue characterization, although to the best of our knowledge, data regarding myocardial ED has not been explored. (9-11)

Therefore, we hypothesized that ED imaging might be able to detect differences indistinguishable for conventional non-contrast CT. To confirm this, we evaluated sex-related differences in myocardial ED and whether, if present, these are related to cardiovascular risk factors or coronary calcification.

METHODS

Study Population

Patients were participants of a prospective single center observational study that explored the ability of whole-blood transcriptome screening test assisted by deep learning to detect coronary calcium, whose main analysis (transcriptome) will be reported independently. The study population comprised 200 asymptomatic volunteers (men between 40 and 75 years old and women between 50 and 75 years old), or patients referred for a low-dose chest CT scan for smoking. Main exclusion criteria comprised a history of heart, renal, or liver failure, previous myocardial infarction, previous coronary revascularization or peripheral vascular disease, active pulmonary disease, immunosuppressant treatment or malignancy under current treatment, and COVID-19 infection in the past three months. To avoid age differences, males younger than 50 were further excluded for the present investigation.

Image acquisition and analysis

All images were obtained with a dual-layer detector CT scanner (IQon Spectral CT, Philips Healthcare, Best, The Netherlands) using the following parameters: collimation 64 x 0.625 mm; tube voltage 120 kV; current 70-140 mA based on patient size; rotation time 270 ms; slice thickness 2.0 mm. Dose modulation (3D Modulation) and hybrid iterative reconstruction (iDose 5) were used in all cases. This scanner enables extraction of spectral data using dual-layered scintillation detectors, being the inner layer an yttrium-based garnet low density scintillator for detection of lower energies, and the outer layer a gadolinium oxysulphide high density scintillator for detection of higher energies. ED estimation using this scanner is based on a two-base model comprising the combination of Compton scatter-like (SC) and photoelectric-like effects, with a dominating SC component. Images were assessed using multiparametric side-by-side view of conventional CT (120 kVp) and ED images and were analyzed offline by a cardiac imaging expert who was blinded to all demographic and clinical data. All images were assessed using average multiplanar reconstructions of short axis views (assisted by adjacent landmarks including the anterior and posterior interventricular groove, and coronary veins and arteries), adjusting window´s width and level at the best discretion of the observer. Using the American Heart Association 16-segment model, regions of interest (ROIs) were placed at the sixteen myocardial segments (Figure 1) starting with those involving the lateral, anterior, and inferior walls, and finally the septal wall. Care was taken to avoid areas with uniform band-like artifacts. Subsequently, the mean Hounsfield units (HU) and mean percent ED relative to water (%EDW) were calculated. It is noteworthy that ROIs were automatically co-localized and identical in size and location in both displays (conventional and ED, Figure 1).

In addition, we evaluated the relationship between myocardial ED and the extent of coronary artery calcifications. For this purpose, we evaluated the presence of any calcification and scored each patient according to the number of vessels involved, and to the numbers of segments involved (CACSIS).(12)

Ethical considerations

The protocol of the study, in accordance with the declaration of Helsinki and later amendments, was approved by the ethics review board (CEI FLENI registration code 4230), and all patients provided their written informed consent.

Statistical analysis

Discrete variables are reported as counts (%) and continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR) for non-uniform

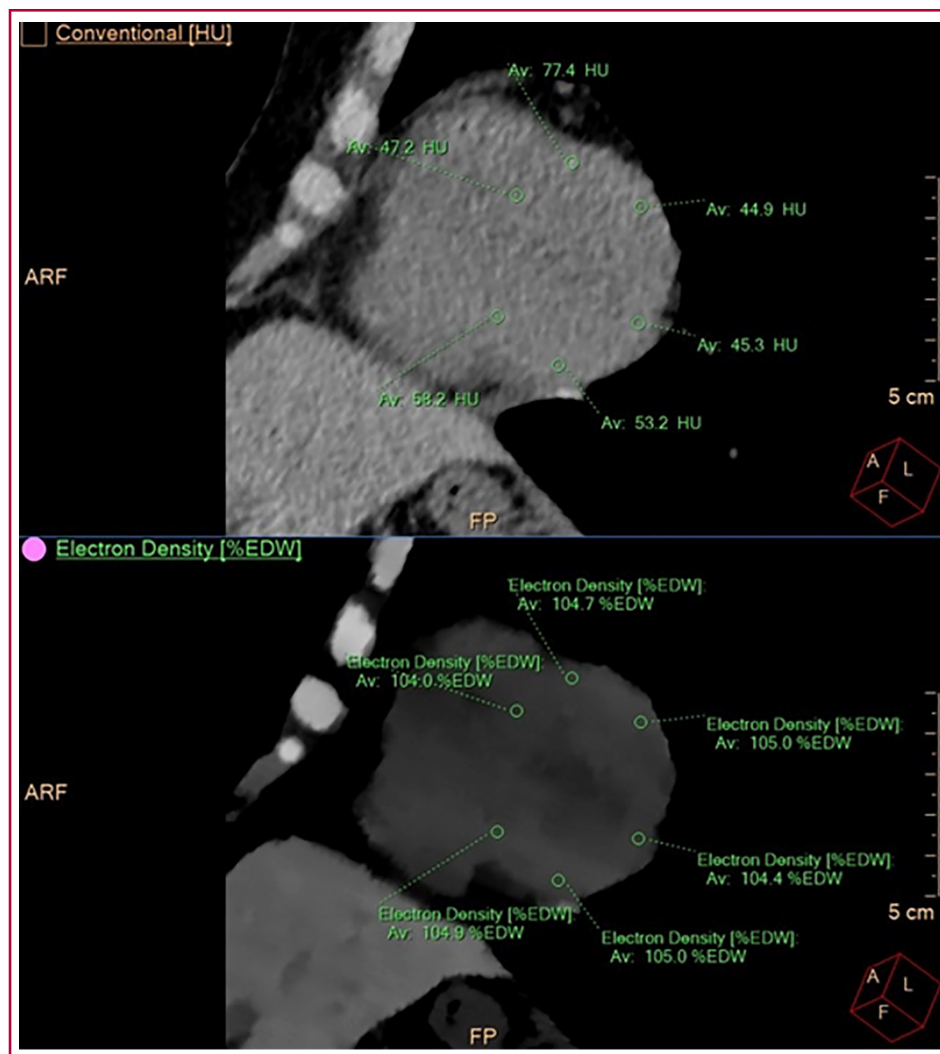

Fig. 1. Side-by-side short axis view of conventional CT (upper panel) and electron density (ED) imaging (lower panel). Mean Hounsfield units (HU) and percent ED relative to water (%EDW) calculated using regions of interest (ROI) placed at the sixteen ventricular segments. Note the exact co-localization and size of each ROI.

distributions. Comparisons between groups of continuous variables were performed using a t test for independent variables, one-way analysis of variance (ANOVA), or the Mann-Whitney U test; whereas comparisons of categorical variables were performed using Fisher exact test, and the chi square test (multiple groups). To identify independent predictors of an incremented %EDW, we built a multiple logistic regression model using the 75th percentile %EDW as dependent variable. Myocardial segments were re-evaluated by an independent cardiologist in a randomly selected subset of 20 cases (320 segments), and the agreement between observers was analyzed using intraclass correlation coefficients (ICC; two-way random effects model absolute agreement, and average measurement) with 95% confidence intervals. All statistical analyses were performed using SPSS software, version 22.0 (Chicago, Illinois, USA). A two-sided p value of less than 0.05 indicated statistical significance.

RESULTS

Two hundred patients were enrolled in the main study between June and October 2021, of which 29 men younger than 50 years old were excluded to attain a balanced age comparison, leading to a total of 171 patients (77 men and 94 women) in this analysis. Mean age was 60.2±6.8 years, without differences between groups (men 60.4±6.9 years, vs. women 60.0±6.8 years, p=0.714). We did not identify significant differences between groups regarding rates of diabetes (p=0.282), smoking (p=0.334), and hypercholesterolemia (p=0.076), whereas men showed a higher prevalence of hypertension (53% vs. 34%, p=0.012) and obesity (48% vs. 31%, p=0.034). Compared to women, men had larger extent of coronary calcification (coronary artery calcification segment involvement score, CACSIS: men 2.34±2.9, vs. women 1.38±2.3, p= 0.016).

Relationship between myocardial attenuation and %EDW, and risk factors

Myocardial attenuation levels (HU) were not related to sex or coronary risk factors (Table 1), whereas %EDW was significantly higher among males (104.5±0.2 %EDW, vs. 104.3±0.2 %EDW, p<0.0001). Despite the narrow differences, there was no overlap between the error bars based on 95% confidence intervals of the population mean (Figure 2).

Myocardial %EDW was also higher among pa-

Table 1. Myocardial attenuation levels (Hounsfield units, HU) and percent electron density relative to water (%EDW) according to sex, risk factors, and coronary artery calcification

	Myocardial HU	Myocardial %EDW
Sex		
Men (n=77)	46.2±2.2	104.5±0.2
Women (n=94)	45.7±2.6	104.3±0.2
p value	0.182	<0.0001
Diabetes		
Yes (n=25)	46.4±2.6	104.5±0.2
No (n=146)	45.9±2.4	104.4±0.2
p value	0.343	0.007
Hypercholesterolemia		
Yes (n=54)	45.6±2.4	104.4±0.2
No (n=116)	46.1±2.5	104.4±0.2
p value	0.220	0.722
Hypertension		
Yes (n=73)	45.9±2.3	104.5±0.2
No (n=98)	46.0±2.5	104.4±0.2
p value	0.653	0.001
Obesity		
Yes (n=66)	45.9±2.7	104.5±0.2
No (n=105)	46.0±2.3	104.4±0.2
p value	0.796	0.004
Smoking		
Yes (n=33)	45.6±2.1	104.4±0.2
No (n=138)	46.0±2.5	104.4±0.2
p value	0.323	0.503
Coronary calcification		
CACSIS 0 (n=82)	46.1±2.3	104.4±0.2
CACSIS 1-3 (n=51)	45.6±2.8	104.5±0.3
CACSIS ≥4 (n=38)	46.1±2.2	104.4±0.2
p value	0.556	0.382

CACSIS: coronary artery calcification segment involvement score
Continuous variables are presented as mean ± standard deviation

tients with diabetes (104.5±0.2 %EDW vs. 104.4±0.2 %EDW, p=0.007), hypertension (104.5±0.2 %EDW, vs. 104.4±0.2 %EDW, p=0.001), and obesity (104.5±0.2 %EDW, vs. 104.4±0.2 %EDW, p=0.004). Hypercholesterolemia (p=0.722), smoking history (p=0.503), and treatment with statins (p=0.184) were not related to the myocardial ED. After discrimination according to body mass index (BMI) categories (BMI <25 kg/m^2; 25-29.9 kg/m m^2 2; and ≥30 kg/m^2), myocardial attenuation levels were not related to sex among patients with normal weight (p=0.242), overweight (p=0.913), or obesity (p=0.445); whereas myocardial ED was significantly higher among males irrespective of the BMI (normal weight: 104.5±0.2 %EDW vs. 104.3±0.2 %EDW, p=0.046; overweight: 104.5±0.2 %EDW vs. 104.4±0.2 %EDW, p=0.002; and obesity: 104.6±0.3 %EDW vs. 104.4±0.2 %EDW, p=0.006). The extent of coronary artery calcification was unrelated to neither the myocardial attenuation (p=0.554), nor the myocardial ED (p=0.382). When discriminated in tertiles (Table 2), we identified a significant relationship between the myocardial %EDW and sex (p<0.0001), diabetes (p=0.038), and hypertension (p=0.049).

Regarding reproducibility, the interobserver reliability was modest when assessing the myocardial attenuation levels (ICC 0.58, 95%IC -0.07 - 0.83) and good by means of %EDW (ICC 0.86, 95%CI 0.64-0.94).

Predictors of high myocardial electron density

At univariate analysis, sex was the only variable associated with a high %EDW (p=0.011), whereas age (p=0.702), diabetes (p=0.154), obesity (p=0.073), smoking (p=0.454), hypertension (p=0.421), and CACSIS (p=0.842), were not. At multiple logistic regression analysis including sex, obesity, diabetes, and hypertension in the model, male sex was identified as the only independent predictor of a high %EDW (OR 2.51, 95%CI 1.23-5.34, p=0.016), whereas obesity (OR 1.97, 95%CI 0.91-4.14, p=0.0823), diabetes (OR 1.89, 95%CI 0.76-5.02, p=0.206), and hypertension (OR 1.53, 95%CI 0.74-3.46, p=0.284) remained outside the model.

DISCUSSION

The main finding of our study was the identification of significant sex-related differences in myocardial ED,

with male sex being identified as the only independent predictor of a high %EDW. Furthermore, myocardial ED was significantly higher in patients with cardiovascular risk factors, perhaps indicating a common pathophysiological process. Interestingly, attenuation levels estimated using conventional CT were unable to detect such associations.

Women's heart is not just a smaller kind of men's. As aforementioned, several studies have identified substantial phenotypical differences between men and women that exceed the most common structural and functional aspects, including the microstructural architecture even at a cellular, metabolic, and electrical level. (13-16)

Our findings are in line with the results of a large cohort of healthy biobank participants among whom the cardiovascular magnetic resonance radiomic profile was evaluated. In that study, both male sex and

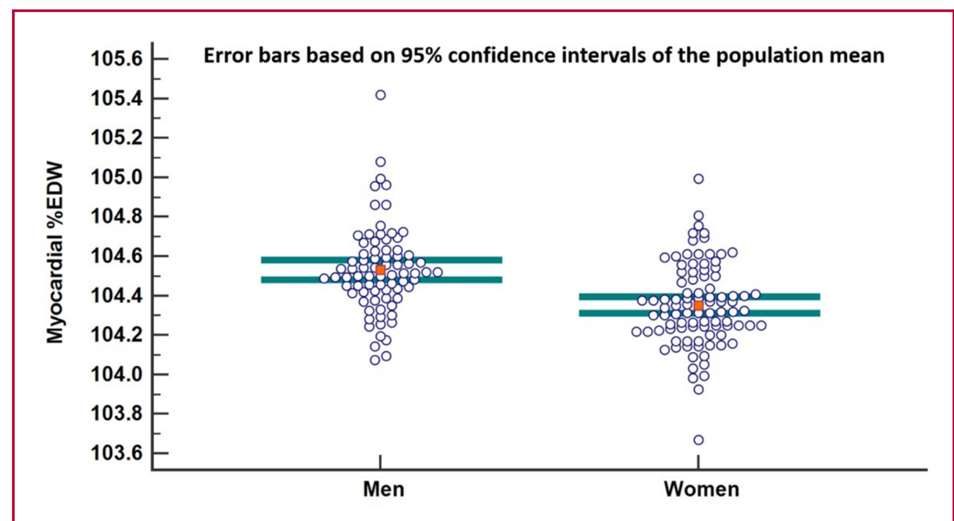

Fig. 2. Myocardial percent electron density relative to water (%EDW) discriminated by sex

Table 2. Frequency distribution of sex, risk factor, and coronary artery calcification according to myocardial electron density (%EDW) tertiles

	Lower tertile %EDW	Mid tertile %EDW	Upper tertile %EDW	p value
Sex				<0.0001
Men (n=77)	11 (14%)	31 (40%)	35 (46%)	
Women (n=94)	46 (49%)	28 (30%)	20 (21%)	
Diabetes				0.038
Yes (n=25)	3 (12%)	10 (40%)	12 (48%)	
No (n=146)	54 (37%)	49 (34%)	43 (30%)	
Hypercholesterolemia				0.674
Yes (n=54)	18 (33%)	21 (39%)	15 (28%)	
No (n=116)	39 (40%)	38 (33%)	39 (34%)	
Hypertension				0.049
Yes (n=73)	18 (25%)	25 (34%)	30 (41%)	
No (n=98)	39 (40%)	34 (35%)	25 (26%)	
Obesity				0.072
Yes (n=66)	18 (27%)	20 (30%)	28 (42%)	
No (n=105)	39 (37%)	39 (37%)	27 (26%)	
Smoking				0.464
Yes (n=33)	11 (33%)	14 (42%)	8 (24%)	
No (n=138)	46 (33%	45 (33%)	47 (34%)	
Coronary calcification				0.485
CACSIS 0 (n=82)	32 (39%)	26 (32%)	24 (29%)	
CACSIS 1-3 (n=51)	14 (28%)	17 (33%)	20 (39%)	
CACSIS ≥4 (n=38)	11 (29%)	16 (42%)	11 (29%)	

CACSIS: coronary artery calcification segment involvement score

cardiovascular risk factors were associated with a dimmer and less texturally complex myocardium. Notably, in keeping with our findings, Raisi-Estabragh et al. identified diabetes and hypertension as the risk factors with the closest associations with left ventricular features, but not smoking. (17) Of note, we did not find a relationship between the extent of coronary artery calcification and myocardial ED, although our findings did not address the effect of flow-limiting lesions in myocardial ED.

The dual-layer configuration of single-source dual energy CT scanners such as the one used in the present study allows simultaneously obtaining spectral data, and a significant reduction of image noise (reflected in this study by the exceedingly low standard deviation), without affecting the routine workflow of the CT scanner, and makes it compatible for retrospective reconstruction. (18,19) For decades, the main purpose of ED imaging was radiation therapy planning, although single-energy CT requires scanner-specific calibration curves for dose calculation performed by skilled medical physicists. (20) In turn, dual-energy CT allows direct calculation of the ED on a voxel basis. In a phantom study using the same dual-layer spectral CT scanner as in our study, Hua et al. demonstrated a high accuracy of ED measurements compared with the expected values, with a median deviation from all tissue inserts ranging from 0.1% to 1.1%. In keeping with our findings, such negligible error might explain to some extent the incremental value of ED over conventional CT to detect subtle differences between tissues that cannot be conveyed without using contrast-enhanced images. Notably, in the study of Hua el at. all soft tissue materials near water ED (adipose, brain, breast, and liver) were well separated, and results were not sensitive to acquisition or reconstruction parameters. (21)

The seemingly synchronic effect of male sex and cardiovascular risk factors might potentially be related to a shared pathophysiological process such as fibrosis, or water or fat content, although interpretation of our results in this regard should be cautious since they don't offer explanations about the underlying pathophysiological mechanisms related to observed differences. (8) In this regard, despite the significant differences between genders and the relationship with risk factors, it should be acknowledged that the clinical relevance of our results is uncertain. Nonetheless, if confirmed, our findings suggest that ED might become in the future a valuable unsophisticated tool for non-contrast CT myocardial tissue characterization.

It should be stressed that it is unclear whether the improved discrimination compared with conventional imaging was related to the intrinsic value of ED imaging, or to the almost lack of image noise and minimal error associated with such approach. (8) In this regard, a previous study has shown that compared with other spectral parameters such as the effective Z number, ED imaging has the lowest deviation (within 1%) from phantom inserts. (21) It should also be recognized that our results might be influenced by the challenging multiplanar reformatting and ROI placement in non-contrast images. Finally, despite the effect of motion artifacts for non-coronary imaging is mild, future studies are warranted in order to confirm our findings using ECG-gated ED imaging. (22,23)

In conclusion, ED imaging was able to identify myocardial tissue differences that conventional CT was unable to discriminate, with a higher %EDW in men and in patients with cardiovascular risk factors.

Conflicts of interest

Dr. Gastón A. Rodriguez-Granillo declares consulting fees from MultiplAI Health, Caristo Diagnostics, Fundacion INICIAR, and RDCom. Dr. Rosana Poggio is employee of MultiplAI Health. None of the other authors have conflicts of interest to declare related to the content of the manuscript.

(See conflicts of interest forms on the website).

Funding

MultiplAI Heath.

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ORIGINAL ARTICLE

Differential Functions of High-density Lipoproteins in Response to SARS-CoV-2 Infection

Diferencia en las distintas funciones de las lipoproteínas de alta densidad en respuesta a la infección por SARS-CoV-2

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ABSTRACT

Background: Post-COVID-19 syndrome (PCS), characterized by symptoms that persist for more than 4 weeks after initial infection, could increase cardiovascular risk. High-density lipoproteins (HDL) have antiatherogenic functions, such as the ability to promote reverse cholesterol transport (RCT) and antioxidant activity. In this regard, paraoxonase 1 (PON 1) plays a key role.
Objective: The aim of this study was to evaluate HDL functions in patients with PCS and compare them with asymptomatic patients (AP) and controls.
Methods: The study included 9 patients with PCS, 18 AP and 10 controls. Complete blood count, basic lipoprotein profile, apolipoproteins A-I and B, and inflammatory markers were measured using automated methods. PON 1 activity was evaluated by a spectrophotometric assay and the 3 steps of RCT, cellular cholesterol (efflux CCE), lecithin-cholesterol acyltransferase (LCAT) activity and cholesteryl ester transfer protein (CETP) activity were evaluated by radiometric assays.
Results: There were no differences in sex, age or general parameters. The AP group had higher PON activity than the control group (94±76 vs. 183±111 vs. 148±58 nmol/mL.min, in controls, AP and PCS, respectively; p=0.049). There were no differences in RCT. Cellular cholesterol efflux (r=-0.45; p=0.049) and CETP (r=-0.38; p=0.028) had a negative correlation with neutrophil-to-lymphocyte ratio. LCAT had an inverse correlation with ferritin (r=-0.34; p=0.046).
Conclusions: Increased antioxidant activity of PON 1 would represent a defensive mechanism against oxidative stress after infection. All the RCT steps had a negative correlation with inflammatory markers. Our findings may explain, at least in part, the link between COVID-19 and atherosclerosis.

Key words: Post Acute COVID 19 Syndrome – Cholesterol, HDL – Lipoproteins – Oxidative stress

RESUMEN

Introducción: El síndrome post COVID (SPC), que se caracteriza por síntomas que se extienden superando las 4 semanas post-infección, podría desencadenar aumento en el riesgo cardiovascular. Las lipoproteínas de alta densidad (HDL) presentan funciones antiaterogénicas, como su capacidad para promover el transporte inverso del colesterol (TIC) y su actividad antioxidante, en la que es clave la enzima paraoxonasa 1 (PON 1).
Objetivo: Evaluar funcionalidad de HDL en pacientes con SPC comparados con pacientes asintomáticos (PA) y controles.
Material y métodos: Se incluyeron 9 individuos con SPC, 18 PA y 10 controles. Se midieron el hemograma, el perfil lipoproteico básico, las apolipoproteínas A-I y B, y marcadores inflamatorios por métodos automatizados. La actividad de PON 1 se evaluó empleando un método espectrofotométrico y los 3 pasos del TIC, eflujo de colesterol (ECC), y actividades de lecitina:colesterol aciltransferasa (LCAT) y proteína transportadora de colesterol esterificado (CETP), por métodos radiométricos.
Resultados: No se observaron diferencias en sexo, edad, ni parámetros generales. El grupo PA presentó mayor actividad PON que los controles (94±76 vs. 183±111 vs. 148±58 nmol/mL.min, en controles, PA y SPC, respectivamente; p=0,04). No se observaron diferencias en el TIC. El ECC (r=-0,45; p=0,049) y CETP (r=-0,38; p=0,028) correlacionaron negativamente con el índice neutrófilos/linfocitos. LCAT correlacionó inversamente con la ferritina (r=-0,34; p=0,046).
Conclusiones: El incremento de PON 1 en el grupo PA representaría un mecanismo de defensa frente al estrés oxidativo post-infección. Todos los pasos del TIC mostraron una correlación negativa con marcadores inflamatorios. Nuestros resultados podrían explicar, en parte, el vínculo entre COVID y ateroesclerosis.

Palabras clave: Síndrome post COVID - HDL - Lipoproteínas - Estrés oxidativo

Rev Argent Cardiol 2024;92:124-129. http://dx.doi.org/10.7775/rac.v92.i2.20454

Received: 11/06/2023 – *Accepted:* 02/27/2024

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INTRODUCTION

The coronavirus disease described in December 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). (1) Post-COVID-19 syndrome (PCS) is a multisystemic disease characterized by signs and symptoms that develop during or after an acute infection and persist for more than 4 weeks after symptom onset. (2) The most common clinical symptoms are fatigue, dyspnea, chest pain, cough, myalgia, headache, and palpitations. (3) This condition can cause a significant decline in the quality of life of those affected. (4) It is estimated that at least 10% of infections result in PCS, affecting 65 million people worldwide. (5)

SARS-CoV-2 enters the host cells due to the interaction of the viral spike protein with the angiotensin-converting enzyme 2 (ACE2) receptor. (6) As a result, ACE2 is less available to catalyze the conversion of angiotensin II to angiotensin 1-7 and angiotensin II levels increase. Under this condition, angiotensin II binds the angiotensin II type 1 receptor (AT1R), which stimulates oxidized nicotinamide dinucleotide phosphate (NADPH) activity. This results in reducing O2 to superoxide and increasing the production of other reactive oxygen species (ROS). (7,8). This is the main mechanism leading to increased oxidative stress in patients with COVID-19 and is facilitated by the pro-inflammatory context, as the identification of the virus promotes the release of cytokines that recruit macrophages and neutrophils. These cells are responsible for the production of ROS and other mediators that contribute further to oxidative stress and cytokines synthesis. Cytokine release is prolonged and disproportionate and is known as cytokine storm, which is closely related to disease severity. (9,10) It can cause tissue damage and symptoms that persist beyond the acute stage of infection and may be responsible, at least in part, for the development of PCS. Increased oxidative stress impairs mitochondrial function and affects cell proliferation, extracellular matrix remodeling, and lung defensive mechanisms. (11) In this context, the role of antioxidants has become relevant and even proposed as therapy for PCS. (12,13)

Some patients, while they were suffering from COVID-19, had lower levels of high-density lipoprotein cholesterol (HDL-C), the only lipoprotein fraction with antiatherogenic properties. This decrease was associated with disease severity and exacerbated cytokine storm. (14,15) In addition, HDL-C levels were significantly associated with prolonged virus clearance time. (16,17) This highlights the potential antiviral role of HDL, which, in addition to promoting reverse cholesterol transport, has antithrombotic, antiapoptotic, anti-inflammatory, and antioxidant functions. The antioxidant activity of HDL is due to the paraoxonase (PON) 1 which is located on it and prevents low-density lipoprotein (LDL) from oxidation. (18) For these reasons, the evaluation of HDL function becomes relevant in a context of high oxidative stress and inflammation with high risk of cardiovascular disease such as PCS.

The aim of the present study was to assess the primary cardioprotective functions of HDL, including its antioxidant activity and its ability to facilitate reverse cholesterol transport. This process encompasses three steps: a) cellular cholesterol efflux, b) esterification of free cholesterol by the enzyme lecithin-cholesterol acyltransferase (LCAT), and c) cholesteryl ester transfer protein (CETP) transfer of cholesterol from HDL to apoB-containing lipoproteins in exchange for triglycerides, a process with therapeutic relevance. (19) Impairment of some HDL functions may be associated with slow clearance of SARS-CoV-2 from the body and progression to PCS.

METHODS

Study design and population

We conducted a cross-sectional, observational and collaborative study between Favaloro Foundation University Hospital and the Laboratory of Lipids and Atherosclerosis, School of Pharmacy and Biochemistry, University of Buenos Aires, between June 2021 and February 2022. The inclusion criteria included men and women between 20 and 60 years with a history of COVID-19 confirmed by polymerase chain reaction (PCR) between 4 and 12 weeks prior to inclusion and who signed the informed consent form. This period corresponds to the symptomatic PCS defined in the National Institute for Health and Care Excellence (NICE) 2020 guidelines. (2) Based on the presence of persistent symptoms, a group of patients with PCS (PCS group, n=9) was compared with a group of patients who had experienced the disease and subsequently evolved without any symptoms (AP group, n=18). A control group of patients with no diagnosis of COVID-19 was incorporated in the last year (control group, n=10). The following exclusion criteria were considered: symptoms prior to COVID-19, body mass index (BMI) > 35 kg/m2, presence of comorbidities (chronic kidney disease, type 1 or type 2 diabetes mellitus, chronic liver disease, chronic inflammation, structural or functional heart disease, lung disease), patients treated with ACE inhibitors, angiotensin II receptor antagonists, statins or corticosteroids, and pregnancy. The study protocol was approved by the Committee on Ethics of Favaloro Foundation and followed the recommendations of the Declaration of Helsinki and subsequent amendments.

Evaluation of the clinical and anthropometric characteristics

All the selected subjects underwent clinical examination, and their medical history was recorded. Weight and height were measured to calculate BMI. Blood pressure (BP) was measured three times with a certified sphygmomanometer (Welch-Allyn, USA), and the average of the last two determinations was considered. To verify the persistence of symptoms and to assess functional capacity, a 6-minute walk test was conducted, and the rating of perceived exertion was measured using the Borg scale. (20,21)

Samples

Blood samples were obtained from the antecubital vein after a 12-hour fast. Samples were collected in tubes containing clot accelerator and gel serum separator and in Na2EDTA tubes and centrifuged at 1500 rpm for 15 minutes. Serum and/or plasma samples was separated, as appropriate, and aliquots were stored at 4 ºC and -70 ºC.

Determination of general and specific biochemical parameters

Plasma levels of blood urea nitrogen and creatinine and complete blood count were determined in accordance with standard methods.

Characterization of the inflammatory status

High-sensitivity C-reactive protein (hs-CRP) and ferritin concentrations were determined by immunoturbidimetric assays on a COBAS c 501 analyzer (Roche S.A.Q. e I., Switzerland). Neutrophil-to-lymphocyte ratio was calculated as an inflammatory marker. (22)

Determination of lipids, liproproteins, and apolipoproteins

Plasma levels of triglycerides, total cholesterol, and HDL-C were measured according to standard methods. LDL-C was calculated using the Friedewald formula or the Sampson formula according to triglyceride levels. Apo B and apo A-I concentrations were determined by immunoturbidimetric assays on a COBAS c 501 analyzer (Roche, Basel, Switzerland).

Paraoxonase 1 activity

PON 1 activity was evaluated by a spectrophotometric assay using two substrates: paraoxon (paraoxonase activity itself, PON) and phenylacetate (arylesterase activity, ARE). Both activities were measured following a previously described method with minimal modifications. (23) The phenotypes for the Q192R genetic variant of the PON1 gene were estimated by the double substrate method. (24)

Evaluation of the ability of HDL to promote cellular cholesterol efflux

HDL was isolated by selective precipitation using 45% polyethylene glycol (6000) and 0.2 M Tris-HCl buffer (pH = 8.2). The ability of HDL to promote cellular cholesterol efflux was analyzed using the human monocyte cell line THP-1. (25)

Determination of lecithin cholesterol acyltransferase activity

LCAT activity was determined using a radiometric assay based on a modified version of the protocol of Aguilar-Espinoza et al. (26)

Determination of cholesteryl ester transfer protein

CETP was measured with a radiometric assay previously described with minimal modifications. (27)

Statistical analysis

The sample size was estimated using Open Epi software (MIT, USA) considering 80% power and an alpha level of 0.05. We chose PON activity as the dependent variable and used previous unpublished data from the group in similar populations. The sample size was estimated in 8 subjects per group. Quantitative variables were expressed as mean and standard deviation, or median and interquartile range (Q1-Q3), according to their distribution. The assumption of normal distribution of the population for each variable was evaluated using descriptive statistics (comparison of means and medians), graphics (histogram and quantile-quantile plot) and goodness-of-fit tests (Kolmogorov-Smirnov test and Shapiro-Wilk test). ANOVA or Kruskal-Wallis test was used to compare continuous variables according to data distribution. The correlations were evaluated using Pearson's correlation coefficient for parametric variable or Spearman's correlation coefficient for non-parametric variables. The differences in categorical variables were compared using the chi-square test. All the statistical calculations were performed using Infostat (National University of Cordoba, Cordoba, Argentina) and SPSS 26.0 software packages (Chicago, Illinois, USA) A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

There were no differences in the distribution of sex, age, height, weight, BMI, and BP among the 3 groups evaluated in the study (Table 1). Patients in the PCS group presented dyspnea (69%), palpitations (54%) and asthenia (46%) as the main symptoms. Consistent with these symptoms, subjects in the PCS group reported a higher score on the Borg scale in the 6-minute walk test (1.6 ± 1.0 vs. 1.2 ± 1.0 vs. 3.5 ± 1.9; control group, AP, and PCS, respectively; p=0.017). There were no significant differences in any of the general biochemical parameters or in the complete blood count (Table 1).

Furthermore, plasma levels of total cholesterol, LDL-C, HDL-C, triglycerides, Apo A-I or B did not differ significantly (Table 2). The inflammatory markers (hs-CRP, ferritin and neutrophil-to-lymphocyte ratio) were similar among the 3 groups (Table 3).

When the three steps of reverse cholesterol transport were analyzed, none of them showed significant differences (Figure 1). However, all three presented associations with other parameters. The results indicated a negative correlation between cellular cholesterol efflux and the neutrophil-to-lymphocyte ratio (r = -0.45; p=0.049), an inverse correlation between LCAT activity and the acute phase reactant ferritin (r = -0.34; p= < 0.046), while CETP activity demonstrated a positive correlation with triglyceride levels (r = 0.47; p < 0.01) and a negative correlation with the neutrophil-to-lymphocyte ratio (r = -0.38; p =0.028).

The AP group had higher PON activity than the control group, with no significant differences in ARE activity between the three groups (Figure 2). In addition, all groups showed a similar phenotypic distribution of the Q192R genetic variant of the PON1 gene, allowing for comparison between groups.

DISCUSSION

The results show that PCS is not associated with changes in reverse cholesterol transport in the groups analyzed. However, we observed a change in HDL antioxidant function represented by higher PON activity in patients who resolved symptoms compared to healthy controls. This function is particularly important during viral infections, since the performance and survival of immune cells is under redox control and depends on ROS levels (28) which are increased in PCS. Therefore, the increased PON activity could be explained as a defensive mechanism against increased oxidative stress. In fact, this has already been described in other conditions associated with increased oxidative stress such as physical activity. (29,30)

In addition to PON activity, ARE activity, which is not affected by genetic variants and is considered

a marker of PON 1 concentration, was also analyzed. (24) Therefore, the presence of increased PON activity with preserved ARE activity would indicate a specific increase in the intrinsic activity of the enzyme without changes in its concentration. This response, observed in patients whose symptoms have resolved and not in patients with PCS, may explain, at least in part, the persistence of symptoms in PCS patients. Indeed, previous studies have indicated that HDL may play an antiviral role, particularly in the context of COVID-19. (17) In addition, the antioxidant activity of HDL attributable to PON 1, as well as its general antiatherogenic properties, may have an influence in suppressing the replication of SARS-Co-V2. (17) Consistent with this, a previous study showed that PON1 Q192R polymorphism was associated with less severe COVID-19. (31)

It is worth noting that the inflammatory markers measured in our population were not elevated. However, there is a negative correlation between each step of reverse cholesterol transport and some of these markers. This would confirm the previously reported impact of persistent inflammation on HDL function and the development of atherosclerotic cardiovascular disease. (32,33) In fact, in a previous paper we showed the negative association between the presence of vascular-specific inflammation and reverse cholesterol transport in obese children and adolescents. (34)

Persistent symptoms in the PCS group were associated with a higher score reported on the Borg scale for the 6-minute walk test. This test has been widely used to measure functional exercise capacity, (35) which has been found to be impaired in patients after acute SARS-CoV-2 infection. (36) The discrepancy between symptoms and inflammatory markers may be attributed to the heterogeneity of these markers reported in different studies. As we have previously explained, persistent inflammation may play an important role in the development of PCS. (9,10) However, the evidence is inconclusive. A re-

Table 1. Anthropometric and biochemical parameters

Parameter	Control group	AP	PCS
Sex (F/M)	7/3	9/9	7/2
Age (years)	31 ± 10	36 ± 13	41 ± 11
BMI (kg/m²)	22.2 (20.5 – 22.5)	22.9 (20.6 – 30.4)	24.4 (23.4 – 30.9)
Urea (mg/dL)	36 ± 5	33 ± 8	30 ± 10
Creatinine levels (mg/dL)	0.90 (0.80 – 0.90)	0.85 (0.80 – 1.00)	0.80 (0.70 – 0.90)
Hematocrit (%)	41 ± 3	41 ± 4	40 ± 3
Hemoglobin (g/dL)	13.6 ± 1.3	13.9 ± 1.2	13.6 ± 1.2
Leucocytes (x103/mm³)	5.4 ± 1.1	6.7 ± 1.6	6.5 ± 1.3
Neutrophils (%)	52 ± 10	57 ± 8	54 ± 8
Lymphocytes (%)	38 ± 10	34 ± 11	34 ± 8
Eosinophils (%)	2 (2 – 3)	3 (2 – 4)	4 (2 – 5)

AP: asymptomatic patients; BMI: body mass index; F: female; M: male; PCS: post-COVID syndrome.
Variables are expressed as mean ± SD, or median and interquartile range (Q1-Q3), according to their distribution.

Table 2. Determination of lipids, lipoproteins and apolipoproteins

Parameter	Control group	AP	PCS
TC (mg/dL)	187 ± 21	183 ± 45	194 ± 31
LDL-C (mg/dL)	106 ± 19	110 ± 35	122 ± 27
HDL-C (mg/dL)	61 ± 13	54 ± 15	56 ± 13
TG (mg/dL)	79 (73 - 93)	80 (52 - 118)	81 (64 - 85)
Apo B (mg/dL)	82 ± 22	84 ± 35	91 ± 13
Apo A-I (mg/dL)	184 (162 – 228)	157 (140 - 171)	160 (149 – 171)
Apo B / Apo A-I	0.45 ± 0.14	0.57 ± 0.27	0.57 ± 0.12
non-HDL-C (mg/dL)	125 ± 21	129 ± 42	138 ± 27
TC / HDL-C	3.2 (2.8 – 3.4)	3.4 (2.9 – 4.0)	3.5 (3.3 – 3.9)
LDL-C / HDL-C	1.8 ± 0.6	2.2 ± 1.0	2.3 ± 0.7
TG / HDL-C	1.3 (1.1 – 1.7)	1.6 (0.9 – 2.4)	1.6 (1.1 – 1.8)

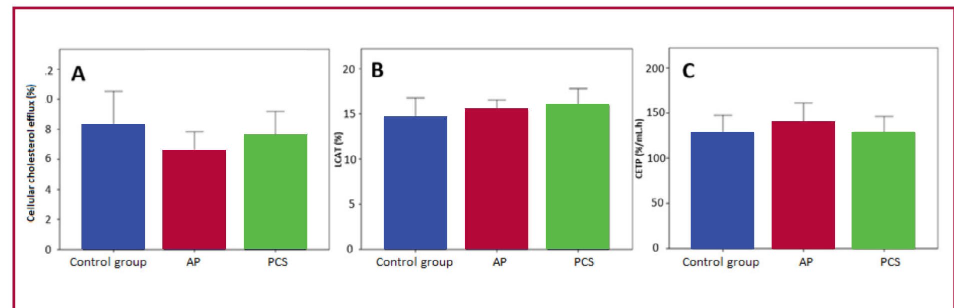
AP: asymptomatic patients; Apo: apolipoprotein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein; PCS: post-COVID syndrome; TC: total cholesterol; TG: triglycerides.
Variables are expressed as mean ± SD, or median and interquartile range (Q1-Q3), according to their distribution.

Table 3. Inflammatory markers. Determination of lipids, lipoproteins and apolipoproteins

Parameter	Control group	AP	PCS
Neutrophil-to-lymphocyte ratio	1.56 (0.91 – 2.18)	1.86 (1.26 – 2.21)	1.64 (1.41 – 1.93)
hs-CRP (mg/dL)	0.20 (0.19 – 0.20)	0.20 (0.19 – 0.20)	0.19 (0.19 – 0.20)
Ferritin (ng/mL)	51 (29 – 171)	140 (56 – 249)	78 (57 – 165)

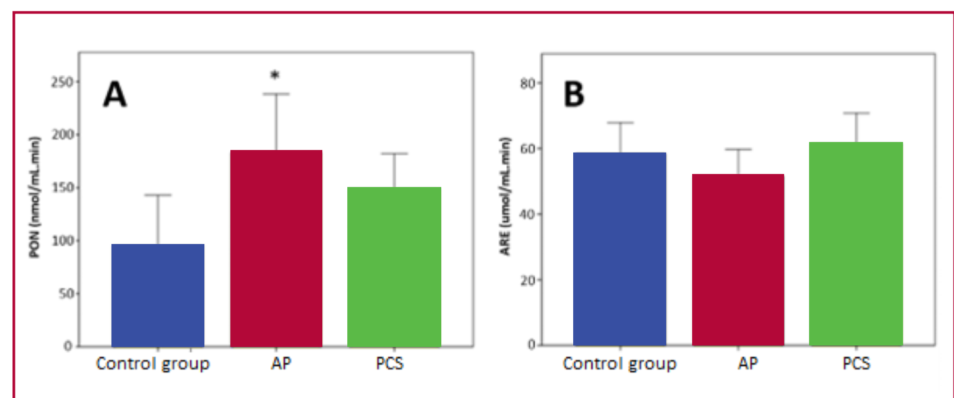
AP: asymptomatic patients; hs-CRP: high-sensitivity C-reactive protein; PCS: post-COVID syndrome. Variables are expressed as mean ± SD, or median and interquartile range (Q1-Q3), according to their distribution

Fig. 1. Evaluation of the three steps of reverse cholesterol transport. Panel A: cellular cholesterol efflux. Panel B: LCAT activity. Panel C: CETP activity



AP: asymptomatic patients; CETP: cholesteryl ester transfer protein; LCAT; lecithin-cholesterol acyltransferase; PCS: post-COVID syndrome.

Fig. 2. Paraoxonase 1 activity. Panel A: PON activity. Panel B: ARE activity.



AP: asymptomatic patients; ARE: arylesterase; PCS: Post-COVID syndrome; PON: paraoxonase.
*p=0.049 between AP and control group.

cent study demonstrated that persistent inflammation was present in approximately 60% of patients with PCS. (37) Furthermore, the persistence of inflammation would be determined by several factors, such as the severity of the acute infection, age, or BMI. (37) A meta-analysis analyzing 113 inflammatory markers in PCS reported that hs-CRP and ferritin were not elevated even in the presence of persistent inflammation. (38) The inflammatory status of patients with PCS would be defined by markers of low-grade inflammation such as interferon. (37,38) Thus, the diversity present in patients with PCS may explain the lack of differences in inflammatory markers found in our study. However, the presence of low-grade inflammation cannot be excluded, which may partly explain the negative association between inflammatory markers and HDL function observed in PCS patients.

CONCLUSIONS

Increased antioxidant activity of PON1 would represent a defensive mechanism against oxidative stress that only reaches statistical significance in the AP group. Consequently, the negative correlation between inflammatory markers and each step of reverse cholesterol transport indicates the potential for a detrimental effect of the inflammatory process on this crucial function of HDL. Our findings may explain, at least in part, the link between PCS and atherosclerosis.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Sources of funding

Project PIP N° 11220200102363 and project UBACyT N° 20020190100075BA.

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ORIGINAL ARTICLE

Participation of Chloride Channels in Cardiovascular and Kidney Health. Effects of High Chloride Diets on Blood Pressure in an Experimental Model of Saline Overload

Participación de los canales de cloruro en la salud cardiovascular y renal. efectos de dietas altas en cloro sobre la presión arterial en un modelo experimental de sobrecarga salina

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ABSTRACT

Background: Excessive consumption of salt (sodium chloride, NaCl) in the diet leads to the development of hypertension (HTN) and target organ damage. It is known that the ClC-K1 and ClC-5 channels are essential regulators of the chloride (Cl^-) anion, but the contribution of this anion to salt-harmful effects remains unknown.
Objective: The aim of this study was to evaluate the participation of Cl^- in the renal inflammatory and oxidative response and in the development of HTN.
Methods: Male Wistar rats were divided into four groups (n=8/group) and fed with different diets for 3 weeks: control (C group); NaCl 8% (NaCl group); high Na^+ diet: sodium citrate ($Na_3C_6H_5O_7$) 11.8% (Na group); high Cl^- diet: calcium chloride ($CaCl_2$) 3.80%, potassium chloride (KCl) 3.06% and magnesium chloride ($MgCl_2$) 1.30% (Cl group). Systolic blood pressure (SBP), renal function, oxidative stress and inflammation markers in the renal cortex, and renal expression of the chloride ClC-K1 and ClC-5 channels were assessed.
Results: An increase in SBP, glutathione peroxidase (GPx) activity, and renal expression of nuclear factor kappa B (NFkB) and angiotensin II type 1 receptor (AT1R) were observed in the NaCl and Cl groups ($p<0.05$). The production of thiobarbituric acid reactive substances (TBARS) increased in the experimental groups compared with C. The expression of Parkinson disease protein 7 (PARK7) decreased in the Cl group compared with C ($p< 0.05$). The NaCl and Cl groups showed increased expression of ClC-K1, while ClC-5 was reduced in the NaCl group compared with C ($p<0.05$)
Conclusion: Cl- would be co-responsible together with Na^+ in triggering oxidative and inflammatory kidney damage and increasing blood pressure. This indicates the importance of reducing the intake of both ions as a non-pharmacological preventive measure for the prevention and control of HTN. The role of ClC-K1 and ClC-5 channels as mediators of this process remains to be confirmed.

Keywords: Chloride Anion – Sodium Cation – Sodium Chloride – Arterial Hypertension – Chloride Channels.

RESUMEN

Introducción: El consumo excesivo de sal (cloruro de sodio, NaCl) en la dieta conduce al desarrollo de hipertensión arterial (HTA) y daño de órgano blanco. Se sabe que los canales ClC-K1 y ClC-5 son reguladores esenciales del anión cloruro (Cl^-), pero la contribución de este anión a los efectos deletéreos de la sal es aún desconocida.
Objetivo: El objetivo de este trabajo fue evaluar la participación del Cl^- en la respuesta inflamatoria y oxidativa renal y en el desarrollo de HTA.
Material y métodos: Ratas Wistar macho se dividieron en cuatro grupos (n=8/grupo) y se alimentaron con diferentes dietas durante 3 semanas: control (grupo C); NaCl 8 % (grupo NaCl); dieta alta en Na^+: citrato de sodio ($Na_3C_6H_5O_7$) 11,8 % (grupo Na); dieta alta en Cl^-: cloruro de calcio ($CaCl_2$) 3,80 %, cloruro de potasio (KCl) 3,06 % y cloruro de magnesio ($MgCl_2$) 1,30 % (grupo Cl). Se determinó la presión arterial sistólica (PAS), función renal, marcadores de estrés oxidativo y de inflamación en corteza renal, y la expresion renal de los canales de cloruro ClC-K1 y ClC-5.

Rev Argent Cardiol 2024;92:130-138. http://dx.doi.org/10.7775/rac.v92.i2.20753

Received: 12/05/2023 – *Accepted:* 02/12/2024

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Resultados: Se observó un aumento de la PAS, actividad de glutatión peroxidasa (GPx) y expresión renal de factor nuclear kappa B (NFkB) y receptor de angiotensina II tipo 1 (AT1R) en los grupos NaCl y Cl ($p<0,05$). La producción de sustancias reactivas del ácido tiobarbitúrico (TBARS) aumentó en los grupos experimentales con respecto a C. La expresión de la proteína de Parkinson 7 (PARK7) disminuyó en el grupo Cl en comparación con C ($p< 0,05$). Los grupos NaCl y Cl mostraron una mayor expresión de ClC-K1, mientras que ClC-5 se redujo en el grupo NaCl en comparación con C ($p<0,05$).
Conclusión: El Cl^- sería corresponsable, junto con el Na^+, de desencadenar daño oxidativo e inflamatorio renal y aumentar la presión arterial; por ello se deduce la importancia de reducir la ingesta de ambos iones como medida preventiva no farmacológica para la prevención y control de la HTA. El rol de los canales ClC-K1 y ClC-5 como mediadores de este proceso queda aún por confirmarse.

Palabras clave: Anión cloruro – Catión sodio – Cloruro de sodio – Hipertensión arterial – Canales de cloruro.

INTRODUCTION

Excessive consumption of sodium chloride (NaCl) in the diet is a risk factor for the development of hypertension (HTN) and target organ damage. In the kidney, salt overload induces oxidative stress and inflammation, independently of the blood pressure value. Clinical studies suggest that blood pressure is not increased by a high Na^+ diet in the absence of chloride anion (Cl^-), (1-3) since sodium bicarbonate does not have the same pressor effect as NaCl in hypertensive people. (2,4) The most recent studies suggest that chloride may have a more specific role in "salt-sensitive" hypertension, independent of the hypertensive effect of sodium. (5-7)

On the other hand, it is known that chloride channels closely regulate the concentrations of this anion in both the intracellular and extracellular compartments. These channels are classified into four groups: family of chloride channels (ClCs), calcium-activated chloride channels (CaCCs), cystic fibrosis transmembrane conductance regulators (CFTR) and γ-aminobutyric acid type A (GABAA) receptors. ClCs constitute a large family of voltage-gated channels and is the family of chloride channels most involved in the development of HTN. (8-14) They include nine subtypes: ClC-1 to ClC-7, ClC-K1, and ClC-K2. (15) It has recently been shown in vitro that high concentrations of NaCl decrease the expression levels of ClC-5. (16) Finally, it is known that high concentrations of NaCl are associated with an increase in the renal expression of the ClC-K1 channel. (17) However, it is unknown what effects a diet rich in chlorides has on the expression of these channels.

The aim of this work was to evaluate whether the Cl^- anion, in addition to the Na^+ cation, would be involved in the renal inflammatory and oxidative response and in the development of HTN.

METHODS

Animals and diets

Male, 7-week-old Wistar rats with average body weight (BW) of 155-165 g at the beginning of the diet were used. They were divided into a control group and three experimental groups (n=8/group) and were fed different equimolar diets and ad libitum tap water for 3 weeks:

1) Control: normal sodium and chloride diet (C Group);
2) NaCl 8% W/W: high-sodium and high chloride diet (NaCl Group);
3) High in Na^+ without Cl^-: high-sodium and normal chloride diet (sodium citrate, $Na_3C_6H_5O_7$, 11.8% W/W) (Na Group);
4) High in Cl- without Na+: high chloride and normal sodium diet (calcium chloride, $CaCl_2$, 3.80%; potassium chloride, KCl, 3.06% and magnesium chloride $MgCl_2$, 1.30% W/W) (Cl Group).

The diets were prepared by the Nutrition Chair of the Faculty of Pharmacy and Biochemistry, of the University of Buenos Aires (UBA).

Assessment of systolic blood pressure (SBP)

Systolic blood pressure was assessed at time 0 (baseline), and at weeks 1, 2 and 3 using the plethysmographic method in the rat's tail.

Assessment of urinary and plasma parameters and evaluation of renal excretory function

After 3 weeks of diet, the animals were housed in metabolic cages for two days: one for acclimatization and another for 24-hour urine collection to measure diuresis, urinary concentrations of Na^+ and Cl^- (mEq /L) and creatinine (mg/dL).

On the day of euthanasia, while under anesthesia, blood was drawn from the retroocular sinus. Plasma concentrations of Na^+, Cl^-, creatinine, glucose and urea were measured using an autoanalyzer. Plasma osmolarity (mOsm/kg) was estimated as: 2*natremia (mEq/L) + 1/18*glycemia (mg/dL) + 1/6*uremia (mg/dL).

Creatinine clearance (CrCl) was calculated according to:

CrCl = (urine creatine/serum creatinine) * diuresis/time/BW.

The filtered load (FL) and the parameters of renal excretory functionality, urinary excretion (UE) and fractional excretion (FE) of the different ions, were determined, based on the following standard formulas:

FLNa = CrCl * serum sodium
UENa = diuresis * urinary sodium
FENa = (UENa/FLNa)*100
FLCl = ClCr * serum chloride
UECl = diuresis * urinary chloride
FECl = (UECl/FLCl)*100

Diuresis, CrCl, FL, and UE were normalized by the BW of each rat and are expressed in mL/day/kg, mL/min/kg or mEq/day/kg, while FE is expressed as percentage (%).

Euthanasia, kidney removal and sample processing

Both kidneys were removed under anesthesia. The renal cortex was dissected, homogenized in phosphate buffered saline (7.6 mM KH_2PO_4, 42.4 mM K_2HPO_4, 150 mM NaCl, pH: 7.40) and centrifuged at 600 g for 20 minutes at 4°C. In the supernatant, thiobarbituric acid reactive substances (TBARS), and activity and expression of the antioxidant enzyme glutathione peroxidase (GPx) were assessed. Protein expression was eval-

uated using the Western Blot technique and protein content was measured by the Lowry method. (18)

Assessment of TBARS and enzymatic activity

TBARS content was assessed fluorometrically in renal cortex homogenates. (19) Results are expressed as TBARS nmol of malondialdehyde (MDA) equivalents/mg protein.

GPx activity was measured spectrophotometrically following the enzymatic oxidation of NADPH at 340 nm in the presence of 1 mm glutathione (GSH), 1 mm sodium azide (NaN^3), 0.15 mm nicotinamide adenine dinucleotide phosphate (NADPH) and 0.25 units (U)/mL of glutathione reductase. The results are expressed in μmol oxidized NADPH/mg protein/min, which is equivalent to μmol oxidized glutathione (GSSG)/mg protein/min). (20)

Western Blot

To assess the expression of the nuclear factor kappa B (NFkB) protein, glutathione peroxidase (GPx), angiotensin II type 1 and 2 receptors (AT1R, AT2R), Parkinson disease protein 7 (PARK7), ClC-5 and ClC-K1, 120 μg of proteins were diluted in sample buffer and separated by electrophoresis in acrylamide gels under denaturing conditions (SDS 10%). Then, they were electrotransferred to a nitrocellulose membrane. Subsequently, the membranes were blocked for 1 h at room temperature with 3% nonfat dry milk diluted in tris buffered saline (TBS)-Tween. They were incubated overnight at 4°C with the corresponding primary antibodies, which were diluted 1:1000 in phosphate buffered saline (PBS). After 1 h of incubation with the respective secondary antibodies conjugated with horseradish peroxidase (1:2000), and 1 h of incubation with Streptavidin-Peroxidase (1:2000), the proteins were revealed using a chemiluminescence kit. The bands obtained were analyzed using the ImageJ program. The results were normalized to values of β-actin, β-tubulin, or glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

Kidney histology

The kidneys were fixed in 10% formaldehyde to subsequently follow the conventional histological technique consisting of paraffin embedding, 7-μm thick tissue sections with a microtome and staining with hematoxylin-eosin (H-E). Then, the histological preparations were qualitatively analyzed with a bright-field optical microscope coupled to a digital camera (Nikon).

Statistical analysis

The results are expressed as mean ± standard error of the mean (SEM). A two-way analysis of variance (ANOVA) and the Tukey test were used to analyze the data using the InfoStat program. Differences with $p < 0.05$ were considered statistically significant.

Ethical considerations

The experimental protocol was approved by the Institutional Committee for the Care and Use of Laboratory Animals (CICUAL) of the Faculty of Pharmacy and Biochemistry of the University of Buenos Aires (UBA) under resolution N°1881/2019. The procedures were carried out following the instructions of the “Guide for the care and use of laboratory animals”. (21)

RESULTS

Time evolution of systolic blood pressure

Control rats remained normotensive during the 3 weeks of treatment. SBP increased in the three experimental groups from the second week onwards. The differences were statistically significant with respect to baseline and the C group values for the NaCl and Cl^- diets (Table 1).

The NaCl group reached the highest SBP values in the second and third week, while the increases in the Cl and Na groups were lower than those reached in the NaCl group. As can be seen in Table 1, SBP in the Na group showed a lower elevation with respect to the other two experimental groups, but without reaching significant differences with respect to the C group.

Plasma and urinary parameters

Regarding serum creatinine, sodium, chloride, and plasma osmolarity (estimated from serum sodium, glucose, and urea), no significant differences were observed in any of the groups. Compared with the C group, urinary creatinine decreased in the other three groups, and urinary sodium increased in the high sodium diet groups (NaCl and Na) and decreased in the Cl^- group. The urinary sodium/chloride index, which evaluates urinary equimolarity between the two ions, increased significantly in the Na group, and reached values very close to equimolarity in the Cl group (Table 2).

Diuresis increased in the three groups with respect to C, while CrCl decreased in the NaCl and Na groups. In the NaCl and Na groups, UENa, FENa, UECl and FECl increased compared with the C group (Table 2).

Compared with the NaCl group, an increase in UENa and a decrease in UECl were observed in the Na group. Similarly, in the Na group, FECl was lower than FENa.

The Cl group did not show significant differences with respect to the C group, but it did show significant differences compared with the NaCl and Na groups, with a lower urinary and fractional excretion of both ions (Table 1).

Oxidative stress and inflammation markers in the renal cortex

TBARS increased in the renal cortex in the experimental groups compared with the C group (Figure 1 A). On the other hand, while GPx protein expression was not modified in any group, the activity of this enzyme increased in the NaCl and Cl groups with respect to C and Na groups (Figure 1 B).

Increased renal expression of p50-NFkB and AT1R was observed in the NaCl and Cl^- groups compared with the other two groups (Figures 1C and D, respectively). The expression of AT2R was significantly reduced in the NaCl and Cl groups (Figure 1E). The expression of PARK7 was decreased in the Cl group compared with the C group (Figure 1F). Finally, while ClC-5 was significantly reduced in the NaCl group compared with the C group (Figure 2A), the NaCl and Cl groups showed higher expression of ClC-K1 (Figure 2B)

Histological characteristics of the renal parenchyma

Figure 3 shows representative microphotographs of the histological characteristics of the renal parenchy-

Table 1. Time evolution of systolic blood pressure and parameters of renal excretory functionality

	Systolic blood pressure (mm Hg)			
	Control	NaCl	Na	Cl
Week 0	122±3	127±3	122±3	114±4
Week 1	121±5	142±5	141±8	146±4
Week 2	129±5	168±7*&§	141±9$&	151±4*&
Week 3	125±9	164±8*&§	133±4$&	152±7*&Δ
Parameters of renal excretory functionality				
Diuresis (mL/day/kg)	10 ± 2	78 ± 14*	92 ± 15*	51 ± 21Δ
CrCl (mL/min/kg)	3.55 ± 0.55	2.21 ± 0.29*	2.41 ± 0.19*	3.01 ± 0.53
UENa (mEq/día/kg)	1.2 ± 0.3	22.9 ± 4.3*	34.4 ± 6.2*$	1.1 ± 0.3$Δ
FENa (%)	0.15 ± 0.04	5.24 ± 1.74*	6.82 ± 0.97*	0.15 ± 0.03$Δ
UECl (mEq/día/kg)	1.4 ± 0.3	26.5 ± 5.1*	7.8 ± 1.5*$	1.1 ± 0.3$Δ
FECl (%)	0.27 ± 0.07	8.39 ± 2.70*	2.23 ± 0.33*$@	0.24 ± 0.04$Δ

Cl-: chloride; CrCl: creatinine clearance; FE: fractional excretion; UE:urinary excretion; Na :sodium; NaCl:sodium chloride
* p<0.05 vs. control; $ p<0.05 vs. NaCl; @ p<0.05 vs. FENa; Δ p<0.05 vs. Na; & p<0.05 vs. t=0; § p < 0.05 vs. 1st week.

Table 2. Plasma and urinary parameters

	Plasma and urinary parameters			
	Control	NaCl	Na	Cl
Serum creatinine (mg/dL)	0.56 ± 0.04	0.64 ± 0.04	0.62 ± 0.03	0.63 ± 0.04
Serum sodium (mEq/L)	151 ± 5	144 ± 2	147 ± 3	144 ± 2
Serum chloride (mEq/L)	102 ± 2	100 ± 1	101 ± 3	99 ± 1
Serum urea (mg/dL)	27 ± 1	38 ± 4*	49 ± 4*$	22 ± 2*$Δ
Plasma osmolarity (mOsm/kg)	319 ± 9	311 ± 4	321 ± 7	306 ± 5
Urinary creatinine (mg/dL)	316 ± 42	52 ± 17*	22 ± 4*	71 ± 24*Δ
Urinary sodium (mEq/L)	117 ± 31	293 ± 41*	360 ± 43*	26 ± 11*$Δ
Urinary chloride (mEq/L)	145 ± 37	345 ± 48*	83 ± 8*$	29 ± 12*$Δ
Urinary Na+/Cl- index	0.77 ± 0.09	0.84 ± 0,05	4.30 ± 0.23*$	0.99 ± 0.26Δ

Cl: chloride; Na:sodium; NaCl: sodium chloride
* p<0.05 vs. control; $ p<0.05 vs. NaCl; Δ p<0.05 vs. Na.

ma from the 4 experimental groups, using H-E technique. The qualitative histological analysis shows that the animals of the NaCl and Cl groups exhibited more pronounced tubulointerstitial changes characterized by tubular dilation compared with the C group. In addition, both groups also exhibited urinary space dilation with respect to the C group. Finally, the Na group evidenced the presence of less pronounced changes compared with the other two experimental groups.

DISCUSSION

Temporal evolution of systolic blood pressure

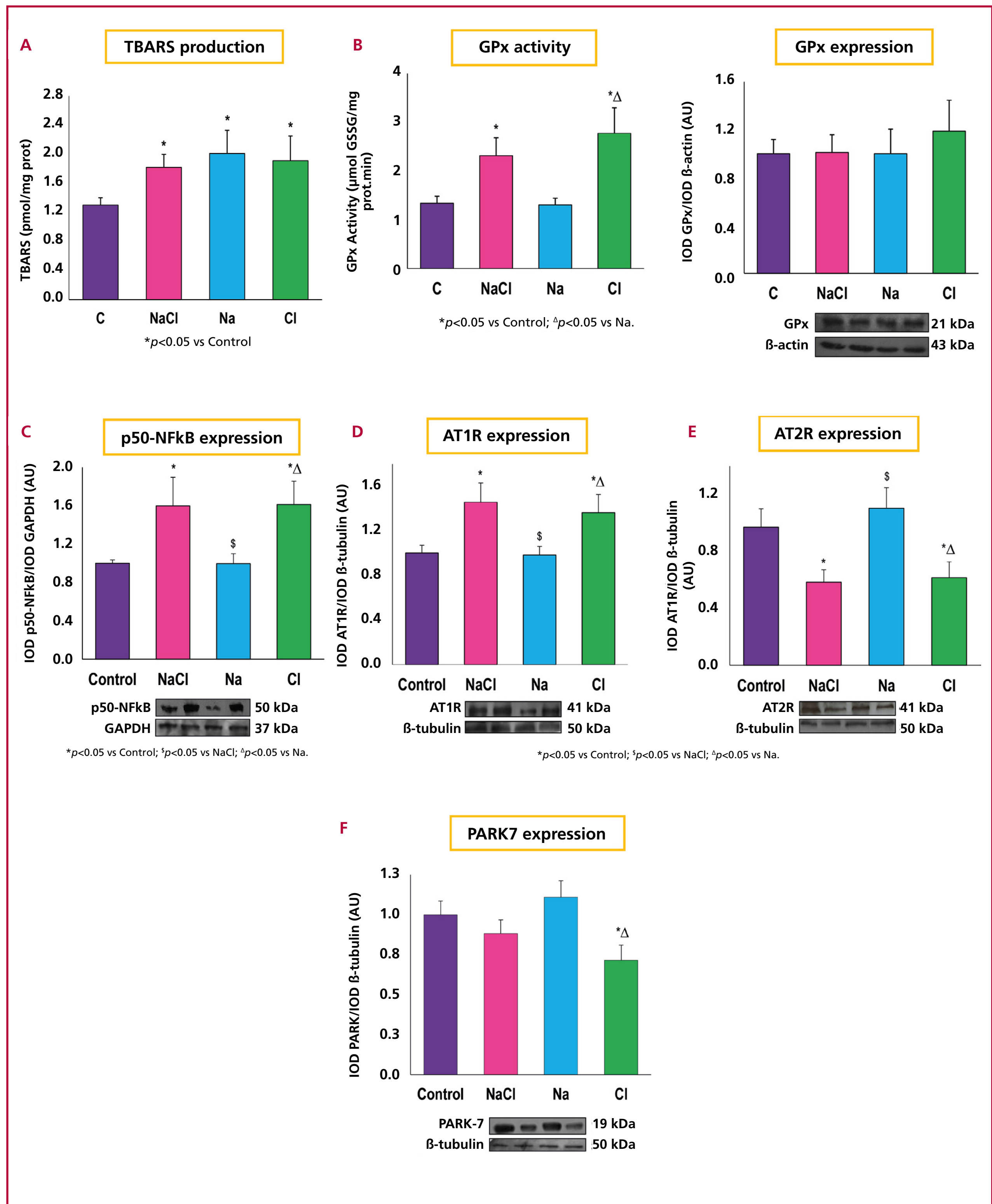
The results of this study suggest that NaCl overload is associated with HTN. Increased SBP is also related to chloride overload, since the Cl group attained pressure values over 140 mmHg, above the Na group. The Cl^- anion is a NaCl component that could have a more specific role in salt-sensitivity, and that could be even more significant than Na^+. (14) Other studies carried out in *Dahl* "salt-sensitive" rats demonstrated that, throughout several weeks, HTN developed in animals consuming NaCl, but not in those fed with sodium bicarbonate ($NaHCO_3$) or other Na^+ salts. (22-24)

On the other hand, the overeating of "non-sodium" chloride salts, that is accompanied by a lower urinary excretion of Cl^- than that produced in the presence of Na^+, could be related with a selective Cl- accumulation in the organism, leading to the development of "salt-sensitive" HTN. (25-27)

Plasma and urinary parameters

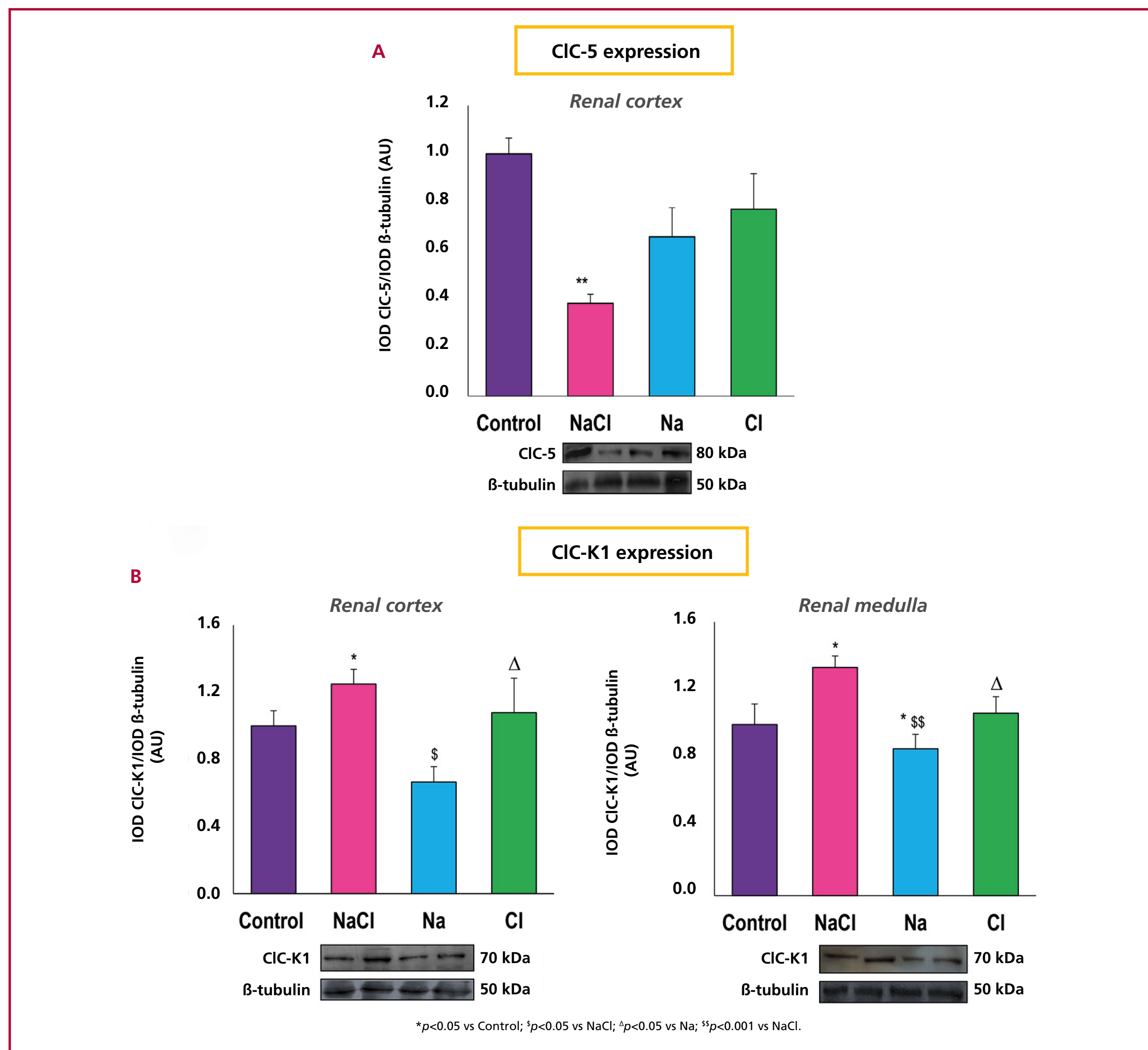
The absence of changes in the plasma concentrations of sodium and chloride and osmolarity are evidence of the biological efficiency of physiological mechanisms to compensate for a possible hypernatremia and/or hyperchloremia, and to preserve plasma osmolarity.

Natriuria and urinary chloride increased in the NaCl group with respect to the C group, and the Na^+/Cl^- index was similar in both groups. In the Na group it is possible that the secretion and excretion of bicarbonate increases with respect to the other groups, a result consistent with the Na^+/Cl^- urinary index, suggesting that Cl^- is not the main counterion of excreted Na^+. The objective of HCO_3^- secretion is to compensate for the metabolic alkalosis in the animals receiving Na+ citrate and, as a consequence, Cl^- reabsorption would be increased and its excretion decreased, since the Cl^-/HCO_3^- exchanger would present greater



Cl: chloride; Na : sodium; NaCl: sodium chloride; AU: arbitrary units
* p<0.05 vs. Control; $ p<0.05 vs. NaCl; Δ p<0.05 vs. Na.

Fig. 1. Oxidative stress and inflammation markers in the renal cortex. A) TBARS: Thiobarbituric acid reactive substances . B) GPx: Glutathione peroxidase. C) p50-NFkB: Nuclear factor kappa B; GAPDH: glyceraldehyde 3-phosphate dehydrogenase D) AT1R : Angiotensin II type I receptor E) AT2R: Angiotensin II type 2 receptor . F) PARK7: Parkinson disease protein 7.



Cl: chloride; Na: sodium; NaCl: sodium chloride
#p<0.0001 vs. Control; *p<0.05 vs. Control; $p<0.05 vs. NaCl; Δp<0.05 vs. Na; #p<0.001 vs. NaCl.

Table 2. Renal expresión of ClC-5 and ClC-K1 chloride channels

expression in the apical membranes of the distal, convoluted, collector, cortical and connector tubule cells, independently of the Na^+ cation. (14) The low urinary chloride in the Cl^- group is striking compared with the control rats, suggesting that it is also necessary to eliminate Na^+ as a counterion for its excretion.

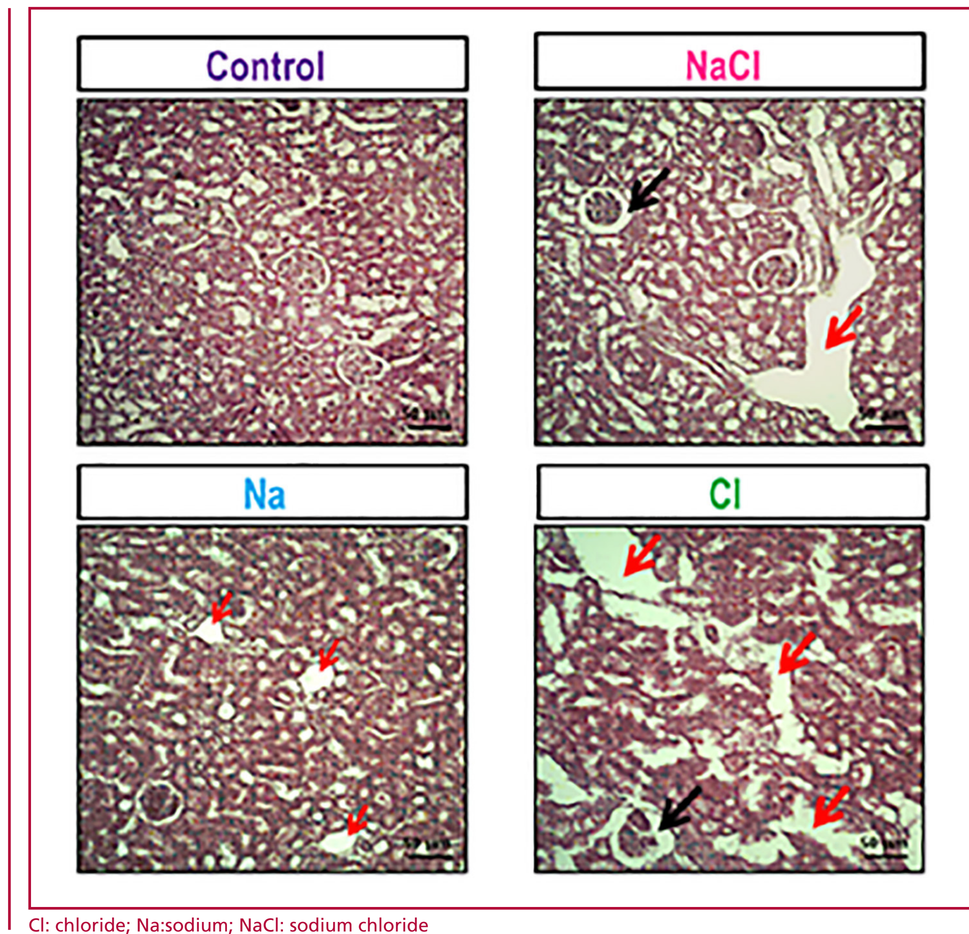
These results indicate that the Cl^- anion would be accumulating in some compartment, such as the skin, since its plasma levels continue to be normal. (26,27)

Oxidative stress and inflammatory markers in the kidney

Na^+, Cl^- or both ions overload in the diet was associated with an increase of lipid peroxidation in the renal cortex, represented by increased TBARS production. The prooxidant state in these cells is characterized by increased production of reactive oxygen species (ROS). Despite GPx protein expression was not affected, its activity was increased. Its regulation is related with post- translational modifications taking place in the active site of the enzyme, independently that its expression varies or not. (28)

Cl^- can convert to hypochlorous acid (HOCl) in the presence of hydrogen peroxide (H_2O_2), a reaction catalyzed by the myeloperoxidase enzyme (MPO). (29) The reactions of oxidative damage to the biomolecules are predominantly associated in most cases with secondary reactive nitrogen species (RNS) as peroxynitrite ($ONOO^-$) and HOCl. HOCl formation is also known

Fig. 3. Histological images representative of the renal parenchyma stained with H-E. Scale bar=50 μm. Red arrows indicate tubulointerstitial changes and black arrows urinary space dilation.



Cl: chloride; Na:sodium; NaCl: sodium chloride

to be associated with tissue damage. (30,31) On the other hand, ROS are known to contribute to the activation of proinflammatory signaling pathways such as NF-kB. (32) To study the participation of the Cl^- anion in the renal inflammatory response, the expression of inflammatory markers such as p50-NFkB and AT1R was evaluated.(33-35) The present study showed that the levels of p50-NFkB and AT1R expression were significantly increased in the NaCl and Cl groups, which also suggest a proinflammatory state at the renal level compared with excess sodium.

On the other hand, it has been shown that PARK7, also called DJ-1 has antioxidant activity eliminating H_2O_2 and regulating the expression of several antioxidant enzymes, as superoxide dismutase (SOD). (36,37) Increased PARK7 levels were expected to increase. However, we have observed that their expression decreases in the Cl group compared with the C group. It has been demonstrated that AT1R interacts with PARK7, which could support the hypothesis that AT1R is negatively regulating it. (38) Nevertheless, further findings are still needed to elucidate this hypothesis.

ClC-5 and ClC-K1 chloride channels

The ClC-5 channel participates in the endosome acidification of kidney, intestine, and liver tissues. ClC-5 is mainly expressed in intracellular vesicles of the proximal tubule and plays a key role in exocytosis. (10) Endosomal acidification is principally achieved through the active transport of H^+ by a vacuolar-type ATPase H^+. Since the active transport of H^+ is electrogenic, it requires the concurrent movement of chloride anions towards the endosomal compartments. (39) In vitro studies have recently shown that high NaCl concentrations decrease its levels of expression. (16) Currently, however, the involved specific mechanisms are unknown. Our results confirm that in excess NaCl reduces ClC-5 expression in the renal cortex compared with the C group, but not in the Cl and Na groups, suggesting an important role in the reabsorption of both ions in the renal proximal tubule. (40) The mechanism by which Cl- and Na^+ jointly reduce the expression of ClC-5 in the renal cortex is as yet unknown.

The ClC-K1 channel participates in the epithelial transport of chloride in the kidney and in the mechanisms of urinary concentration. (12) It is known that high concentrations of NaCl are associated with an increased expression of ClC-K1 in the ascending thin limb of Henle's loop, (17) but the effects of a diet rich in chlorides on the expression of this channel is unknown. Our results indicate that the NaCl and Cl groups present a higher renal expression of ClC-K1.

These findings suggest that the ClC-K1 channel has an important role in maintaining the homeostasis of the chloride anion and water by promoting its excretion.

CONCLUSION

Taken together, these results support the hypothesis that the Cl^- anion together with the Na^+ cation would be co-responsible for triggering renal oxidative damage and increasing blood pressure. Therefore, further studies are necessary to test the importance of reducing the intake of both anions as a preventive non-pharmacological measure to avoid and control HTN. Our results put in evidence the participation of ClC-K1 and ClC-5 channels as mediators of this process.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Funding

Part of the study was funded by the following grants: PICT 2021-I-A-00607 and PIP CONICET 2022-2024.

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BRIEF ARTICLE

Prognostic Value of Various Hemodynamic Parameters in Pulmonary Hypertension

Utilidad de diversos parámetros hemodinámicos como marcadores pronósticos en la hipertensión pulmonar

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ABSTRACT

Background: Pulmonary hypertension (PH) is associated with high morbidity and mortality and its prognosis is determined by the right ventricular function and right ventricular-pulmonary artery coupling. Several hemodynamic parameters have been proposed to better characterize the risk for adverse disease progression.
Objective: The aim of this study was to determine the predictive ability of various hemodynamic parameters that can be calculated during RHC to predict serious events.
Methods: In this retrospective multicenter and descriptive cohort study of patients with PH, hemodynamic variables values were divided as high or low risk based on the 2022 European guidelines, or mean or median values in our population.
Results: A total of 324 patients with PH were included; mean age was 61.5 years and 69% were women; 62.1 % of the patients were in Group 1 and 19.2 % in Group 3. In a median (IQR) follow-up of 23(14-44) months, the event rate (death or hospitalization for heart failure) was 60.6% and all-cause mortality was 24.5%. The cut-off values associated with risk for the different hemodynamic variables were: cardiac index (CI) 2.72 L/min/m², systolic volume index (SVI) 33.1 ml/m², pulmonary vascular resistance (PVR) 6 Wood units (WU), pulmonary artery pulsatility index (PAPI) 3.76, right ventricle systolic work index (RVSWI) 11.6 g.m/m², and pulmonary arterial compliance 1.84 mL/mm Hg. Elevated PVR was associated with a higher rate of composite events, while high-risk CI, SVI, PVR, and compliance were associated with higher mortality at follow-up.
Conclusions: While CI and SVI are adequate predictors of risk, PVR and compliance demonstrate similar or even better risk prediction in patients with PH. Additional research is necessary to validate these parameters during follow-up.

Key words: Pulmonary hypertension - Prognosis - Hemodynamics - Pulmonary vascular resistance

RESUMEN

Introducción: La hipertensión pulmonar (HP) se asocia con elevada morbimortalidad y su pronóstico está determinado por la función del ventrículo derecho y el acople ventrículo-arterial pulmonar. Diversos parámetros hemodinámicos han sido propuestos para caracterizar el riesgo de evolución adversa.
Objetivos: Determinar la capacidad de predicción de eventos graves, de diversos parámetros hemodinámicos medidos por cateterismo derecho.
Material y métodos: Estudio multicéntrico, descriptivo, de cohorte retrospectiva de pacientes con HP. Se dividió a los datos hemodinámicos en alto o bajo riesgo según lo definido por las recomendaciones europeas de 2022, o según media o mediana de nuestra población.
Resultados: Fueron incluidos 324 pacientes con HP, con edad media 61,5 años y 69% de sexo femenino; 62,1 % de los pacientes del Grupo 1 y 19,2 % del Grupo 3. La tasa de eventos (muerte o internaciones) en un seguimiento mediano de 23 (RIC 14-44) meses fue 60 % y la mortalidad global 24,5 %. Los valores de corte para definir riesgo de las diferentes variables fueron: índice cardíaco (IC) 2,72 L/min/m², índice de volumen sistólico (IVS) 33,1 mL/lat./m², resistencia vascular pulmonar (RVP) 6 unidades Wood (UW), índice de pulsatilidad de la arteria pulmonar (IPAP) 3,76, índice de trabajo sistólico del ventrículo derecho (ITSVD) 11,6 g.m/m², compliance vascular pulmonar 1,84 mL/mmHg. La RVP elevada se asoció a mayor frecuencia de eventos combinados, mientras que valores de alto riesgo de IC, IVS, RVP y compliance presentaron asociación con mayor mortalidad en el seguimiento.

Rev Argent Cardiol 2024;92:139-143. http://dx.doi.org/10.7775/rac.v92.i2.20745

Received: 10/01/2023 – *Accepted:* 12/07/2023

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Conclusiones: Si bien el IC y el IVS presentaron una adecuada predicción de riesgo, variables como la RVP y la compliance mostraron similar, e incluso mejor predicción de eventos graves en HP. Se necesitan nuevos estudios que validen estos parámetros en el seguimiento.

Palabras clave: Hipertensión pulmonar - Pronóstico - Hemodinamia - Resistencia pulmonar

INTRODUCTION

Pulmonary hypertension (PH) is a multifactorial entity due to multiple causes and is defined as a complex hemodynamic condition characterized by a mean pulmonary arterial pressure (mPAP) > 20 mm Hg. Regardless of the underlying cause (such as left heart disease, respiratory disease, or pulmonary vascular disease), PH is always associated with high morbidity and mortality, and its occurrence always worsens the clinical course of patients.

Its prognosis is determined by the ability of the right ventricle (RV) to adapt to the progressive excessive pressure load of the pulmonary circulation (RV-pulmonary artery coupling). In this sense, several hemodynamic parameters have been proposed to better characterize this issue. The 2022 European Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension identify several prognostic hemodynamic parameters in patients with pulmonary arterial hypertension, including right atrial pressure (RAP), cardiac index (CI), central venous oxygen saturation (SvO_2), and stroke volume index (SVI). (1,2) These parameters have been validated during follow-up, especially CI and SvO_2. (3,4)

There are other hemodynamic parameters of right ventricular function and RV-pulmonary artery coupling that can be measured during right heart catheterization (RHC). These include pulmonary vascular resistance (PVR), pulmonary arterial compliance, RV systolic work index (RVSWI) (5,6) or pulmonary artery pulsatility index (PAPI). (7,8) Although PVR is widely used as a hemodynamic parameter in pulmonary arterial hypertension (PAH) and even as a clinical endpoint in most current clinical trials, recent European recommendations do not consider it a prognostic marker. The REVEAL registry only uses a cutoff value of 5 Wood units (WU) with little hierarchy within the score based on baseline characteristics. (9) This may be due to the fact that some studies have failed to demonstrate its prognostic value. (10,11)

However, we lack information on the prognostic value of the different measurements of right ventricular function and pulmonary circulation that can be obtained in the catheterization laboratory. In this context, the aim of this study was to determine the predictive ability of various hemodynamic parameters that can be calculated during RHC to predict serious events such as death or hospitalization due to worsening pulmonary hypertension.

METHODS

The Pulmonary Hypertension Working Group consists of a multidisciplinary team working in 5 centers in the Autonomous City of Buenos Aires and the Greater Buenos Aires Area (Sanatorio de la Trinidad Quilmes, Centro Gallego de Buenos Aires, Sanatorio Dupuytren, Sanatorio Trinidad Ramos Mejía and Sanatorio Mater Dei). We performed a retrospective cohort analysis of our registry which included consecutive patients recorded in the work group database who underwent RHC between January 2011 and May 2023. All the patients signed an informed consent form to undergo RHC and authorized the anonymous use of the result of the test for research purposes. All patients with PH, defined as mPAP > 20 mmHg at rest, were included in the analysis. Patients were classified into PH groups 1 to 5 according to international recommendations. Group 1 patients with PAH were subdivided into idiopathic PAH, associated with connective tissue diseases, congenital heart disease, human immunodeficiency virus (HIV) infection or drugs, and portopulmonary hypertension, following the same recommendations.

Cardiac index was calculated according to the formula:

$$CI = CO / BSA$$

where CI: cardiac index, CO: cardiac output, BSA; body surface area

Stroke volume index was calculated according to the formula:

$$SVI = CI / HR$$

where SVI: stroke volume index, CI: cardiac index, HR: heart rate

Pulmonary vascular resistance was calculated according to the formula:

$$PVR = (mPAP - PAWP) / CO$$

where PVR: pulmonary vascular resistance, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure; CO: cardiac output

Pulmonary artery pulsatility index was calculated according to the formula:

$$PAPI = (sPAP - dPAP) / RAP$$

where PAPI: pulmonary artery pulsatility index, sPAP: systolic pulmonary artery pressure, dPAP: diastolic pulmonary artery pressure; RAP: right atrial pressure

Pulmonary arterial compliance was calculated according to the formula:

$$C = SV / (sPAP - dPAP)$$

where C: compliance, SV: stroke volume, sPAP: systolic pulmonary artery pressure, dPAP: diastolic pulmonary artery pressure

Finally, RVSWI was calculated according to the formula:

$$RVSWI = (mPAP - RAP) * SVI * 0.0136$$

where RVSWI: right ventricular systolic work index, mPAP: mean pulmonary arterial pressure, RAP: right atrial pressure, SVI: stroke volume index

The values of the hemodynamic variables were defined as high or low risk as stated by the 2022 ESC (European Society of Cardiology) recommendations. Low risk was defined as CI > 2.5 L/min/m² and SVI > 38 mL/m². For variables not defined by the guidelines, we used the mean or median values of our population, according to their distribution. Quantitative variables with normal distribution are expressed as mean ± standard deviation (SD) and those with non-normal distribution are expressed as median and interquartile range (IQR). The incidence of events (death, hospitalization due to worsening PH, or need for dose escalation of a specific therapy) was assessed and compared in the high-risk and low-risk groups for each variable using the chi square test and logistic regression analysis with calculation of odds of the occurrence of events (odds ratio).

RESULTS

A total of 324 patients with PH documented by RHC were prospectively included in the registry. Mean age was 61.5 ± 17.6 years and 69.0% were men. Median (IQR) follow-up was 23 (14-44) months. The patients were classified as follows: 62.1% in Group 1, 8. 7% in Group 2, 19.2% in Group 3, 7.7% in Group 4, and 2.1% in Group 5. In group 1, the etiologies were idiopathic PAH in 57.1%, associated with connective tissue diseases in 26.1%, associated with congenital heart disease in 12.8%, portopulmonary hypertension in 1.9%, associated with HIV in 1.4%, and associated with drugs in 0.4%. The event rate (death or hospitalization for heart failure) was 60.6% and all-cause mortality was 24.5%. The mean ± SD values or median (IQR) values of the hemodynamic variables of the sample were: CI 2.72 ± 0.72 L/min/m², SVI 33.1 ± 12.4 mL/m², PVR 6 (3.7-9.8) WU, PAPI 3.76 (2.5-5.8), RVSWI 11.6 (8.6-16.5) g.m/m², and pulmonary arterial compliance 1.84 (1.09-3.03) mL/mm Hg. Tables 1 and 2 show the event rates for each hemodynamic variable in the low-risk and high-risk groups. The rate of combined events was higher in high-risk patients, although statistically significant only in patients with PVR > 6 WU (OR 1.99, 95% CI 1.17-3.38, p = 0.006). Mortality was also higher in the high-risk groups, with statistical significance for the variables CI (OR 1.8, 95% CI 1.38-3.31, p = 0.038), SVI (OR 3.46, 95% CI 1.51-8.92, p = 0.001), PVR (OR 2.75, 95% CI 1.45-5.34, p < 0.001) and compliance (OR 5.95, 95% CI 2.17-18.86, p < 0.001).

Table 1. Baseline characteristics

Age (years)	61.5±17.6
Female sex, (%)	67.6
Diagnosis (%)	
Group 1	62.1
Idiopathic	57.1
Associated with connective tissue diseases	26.1
Associated with congenital heart diseases	12.8
Portopulmonary	1.9
Associated with HIV infection	1.4
Associated with drugs	0.4
Group 2	8.7
Group 3	19.2
Group 4	7.7
Group 5	2.1
NYHA FC (%)	
I / II	48.6
III / IV	51.4
6MWT (m),	360 (210-440)
Hemodynamic parameters	
RAP (mm Hg)	9 (6-13)
mPAP (mm Hg)	42.5 ± 14.9
PAWP (mm Hg)	12 ± 4.3
CO (L/min)	4.81± 1.32
CI (L/min·/m²)	2.72 ± 0.72
PVR (WU)	6 (3.7-9.8)
Specific medical treatment (%)	
PDE5 inhibitors	81.8
Endothelin receptor antagonists	51.8
Prostanoids	29.6
Combination therapy	62.7

6MWT: 6-minute walking test; CI: cardiac index; CO: cardiac output; HIV: human immunodeficiency virus; mPAP: mean pulmonary arterial pressure; NYHA FC: New York Heart Association functional class; PAWP: pulmonary arterial wedge pressure; PDE5: phosphodiesterase 5; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WU: Wood Units Quantitative variables are presented as mean ±SD or median (IQR) according to their distribution.

DISCUSSION

The present study represents the analysis of hemodynamic variables with the largest number of patients carried out by a PH working group in our country and confirms the importance of measuring and calculating hemodynamic parameters to determine the patients' prognosis. We decided to include the hemodynamic variables with the best correlation to RV-pulmonary artery coupling and RV work, namely CI and SVI, as SvO_2 is a surrogate of CI and RAP is also influenced by the volume overload present in these patients. This study confirms that estimates of CI and SVI are strongly associated with mortality at follow-up. These findings support the concept that RV function and RV-pulmonary artery coupling have a significant impact on patients' survival. However, our analysis questions the need for including other variables in determining prognosis. Beyond the known association of IVS with prognosis, PVR and pulmonary arterial compliance demonstrated an excellent association with the event rate, even greater than the variables suggested by international recommendations. Although the cause of this finding has not been established, a possible hypothesis is that both compliance and PVR continuously worsen from the onset of the disease to the later stages. (12,13) In

Tabla 2. Event rates for each hemodynamic variable

Hemodynamic variable (cut-off point used)	Events in Low risk (%)	Events in High risk (%)	Odds ratio (95% CI)	p value
Cardiac index (2.5 L/min·/m²)	59.8	62.0	1.09 0.59-1.70)	0.726
SVI (33.1 mL/m²)	50.7	63.1	1.66 (0.92-3.01)	0.066
PVR (6 WU)	51.2	67.6	1.99 (1.17-3.38)	0.006
PAPI (3.76)	55.8	65.2	1.48 (0.88-2.47)	0.110
Compliance (1.84 mL/mm Hg)	53.5	67.4	1.79 (0.91-3.54)	0.067
RVSWI (11.6 g.m/m²)	56.2	62.8	1.31 (0.77-2.23)	0.274

PAPI: pulmonary artery pulsatility index; PVR: pulmonary vascular resistance; RVSWI:right ventricular systolic work index; SVI: stroke volume index.

Tabla 3. Mortality for each hemodynamic variable

Hemodynamic variable (cut-off point used)	Low risk (%)	High risk (%)	Odds ratio (95% CI)	p value
Cardiac index (2.5 L/min·/m²)	20.5	31.7	1.80 (1.01-3.31)	0.038
SVI (33.1 mL/m²)	11.2	30.5	3.46 (1.51-8.92)	0.001
PVR (6 WU)	15.2	33.1	2.75 (1.45-5.34)	< 0.001
PAPI (3.76)	23.5	25.5	1.11 (0.62-2.01)	0.698
Compliance (1.84 mL/mm Hg)	7.1	31.3	5.95 (2.17-18.86)	< 0.001
RVSWI (11.6 g.m/m²)	21.4	28.5	1.46 (0.79-2.69)	0.189

PAPI: pulmonary artery pulsatility index; PVR: pulmonary vascular resistance; RVSWI: right ventricular systolic work index; SVI: stroke volume index.

contrast, cardiac output and stroke volume remain normal due to compensatory mechanisms, only to worsen in advanced stages of PH. (14) In this sense, the absence of association between PAPI and RVSWI and the incidence of events can be explained because both variables not only do not decrease in the initial stages, but also tend to increase during these stages, only to decrease in the final stages of PH. This makes their behavior unpredictable and poorly related to the severity of the disease. (15)

These parameters can be very useful in the assessment of the prognosis of PH in entities other than those in group 1. The European guidelines support this assertion by establishing specific medical treatment for PAH in patients with left heart failure or pulmonary parenchymal disease (groups 2 and 3), as long as PVR is > 5 WU. This implies that there is an underlying acknowledgment of the correlation between elevated PVR and the severity of the disease. In addition, in recent years, several clinical trials in PAH have included PVR as a pathophysiologic endpoint to determine the presence or absence of clinical benefit from treatment without considering other hemodynamic variables. (16-18) Both situations, in addition to the findings of not only our study but also others that suggest similar conclusions, underscore the prognostic significance of PVR and compliance as hemodynamic markers. This explains their usefulness both for diagnosis and during follow-up. In fact, an analysis of the REVEAL registry shows that patients with PVR < 5 WU have a 5-year survival rate >70%, while those with higher PVR have a survival rate < 60%. (19)

Our study has some limitations. First, most patients had idiopathic PAH or PAH associated with connective tissue disease, with few patients associated with congenital heart disease, less than in other registries, who usually present with hemodynamic parameters different from the general population with PAH. Second, the hemodynamic variables used as risk parameters are recommended for patients with group 1 pulmonary hypertension, whereas our registry included patients from all groups. This is because most of these risk parameters have been defined based on expert recommendations with little scientific evidence to support them, and are suggested mainly for patients with idiopathic or heritable PAH or associated with drugs. Additionally, they are commonly used for all the groups in clinical practice worldwide, since groups 2 to 5 lack their own risk parameters.

Finally, we did not analyze whether the improvement of worsening of the hemodynamic parameters during follow-up affected the event rate, as indicated by the risk variables recommended by the guidelines. Further follow-up of patients will be required to demonstrate this question.

CONCLUSIONS

Our registry showed that hemodynamic variables used routinely in patients with PH adequately predicted the risk of events. Although RVSWI and PAPI did not have a strong association with events, parameters

such as PVR and compliance demonstrated similar or even better risk prediction at follow-up compared to the variables currently used in practice. Additional research is necessary to determine the prognostic significance of different hemodynamic variables for monitoring patients over time.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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BRIEF ARTICLE

Preliminary Data of the Hypertrophic Cardiomyopathy Registry in Nonspecialized Centers of Argentina. Exploring Behind the Veils of Common Practice

Datos preliminares del registro de miocardiopatía hipertrófica en centros no especializados en Argentina. Explorando detrás de los velos de la práctica cotidiana

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is the most common genetic disease caused by cardiac sarcomere protein mutations, with considerable prevalence and different clinical presentation, varying from asymptomatic to heart failure and sudden death. Some patients are followed-up in nonspecialized centers, and it is necessary to know data that show the reality of their diagnosis, treatment, and prognosis.
Objective: The aim of this study was to know the clinical characteristics, and diagnostic and therapeutic strategies when HCM is managed in centers not specialized in this disease.
Methods: This was a national, cross-sectional, multicenter study, with quantitative analysis of patients with confirmed or highly probable HCM.
Results: A total of 95 patients were recruited, mostly men, with hypertension (40%) and dyslipidemia (22%) as main risk factors. A low proportion of comorbidities was observed: chronic obstructive pulmonary disease (6%), prior myocardial infarction (5%), prior stroke (1%) and chronic kidney failure (1%). The main symptoms were dyspnea (47% and angina (27%), and the most used diagnostic methods were echocardiogram (97%) and cardiac magnetic resonance imaging (71%). The most frequent localization was septal, with 37% of hypertrophic obstructive cardiomyopathy.
The genetic test, performed in 33% of patients, was positive in more than half of cases. It was not performed in the rest of the patients, mainly due to lack of health coverage.
Conclusions: These findings are in agreement with international registries. Based on our findings, emphasis should be placed in improving the access to more complex diagnostic studies and optimizing the resources in a fragmented health system.

Key words: Hypertrophic cardiomyopathy – Registry – Nonspecialized centers – Clinical practice

RESUMEN

Introducción: La miocardiopatía hipertrófica (MCH) es la enfermedad genética cardiovascular más común, causada por mutaciones en proteínas del sarcómero cardíaco, con una prevalencia considerable y clínica variable, desde asintomática hasta insuficiencia cardíaca y muerte súbita. Existen pacientes seguidos en centros no especializados, y es necesario conocer datos que puedan mostrar la realidad de su diagnóstico, tratamiento y pronóstico.
Objetivo: Conocer las características clínicas, estrategias diagnósticas y terapéuticas al abordar la MCH en centros no especializados en la patología.
Material y métodos: Estudio de corte transversal, multicéntrico, de alcance nacional, con análisis cuantitativo, de pacientes con MCH confirmada o altamente probable.
Resultados: Se registraron 95 pacientes, mayormente hombres, con hipertensión arterial (40 %) y dislipidemia (22 %) como principales factores de riesgo. Se observó baja proporción de comorbilidades: enfermedad pulmonar obstructiva crónica (6%), infarto de miocardio previo (5 %), accidente cerebro vascular previo (1 %) e insuficiencia renal crónica (1 %). Los síntomas principales fueron la disnea (47 %) y el ángor (27 %), y los métodos diagnósticos más usados fueron el ecocardiograma (97 %) y la resonancia cardíaca (71 %). La localización más frecuente fue septal, con 37 % de tipo obstructivo.
El test genético, realizado en un 33 %, fue positivo en más de la mitad de los pacientes. No se realizó en el resto de los casos principalmente por falta de cobertura.

Rev Argent Cardiol 2024;92:144-150. http://dx.doi.org/10.7775/rac.v92.i2.20751

Received: 12/20/2023 – *Accepted:* 02/05/2024

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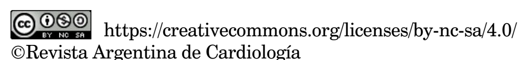
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Conclusiones: Los hallazgos son concordantes con los de registros internacionales. Con base a nuestros hallazgos, se resalta la necesidad de mejorar el acceso a estudios diagnósticos más complejos y optimizar recursos en un sistema de salud fragmentado.

Palabras clave: Miocardiopatía hipertrófica - Registro - Centros no especializados - Práctica clínica

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic disease affecting the heart, with an approximate prevalence of 1 in 200/500. (1,2) Its etiology lies in the mutation of a series of genes that codify proteins of the cardiac sarcomere, developing left ventricular hypertrophy (LVH), myofibrillar disarray and myocardial fibrosis. (3,4) Clinical manifestations are variable, from absence of symptoms to heart failure and sudden death. (5,6)

This entity is a veritable diagnostic challenge, as there are infiltrative cardiomyopathies that behave as phenocopies. (5,7)

Currently, pharmacological treatments, implantable devices and surgeries are recommended, improving survival and quality of life. (8-10)

An important number of patients with suspected HCM is followed -up in centers not specialized for the disease. We consider that the data derived from these patients can contribute to reflect in a more comprehensive way the reality of this disease.

We present the first report of the ongoing Hypertrophic Cardiomyopathy Registry in nonspecialized centers in Argentina

OBJECTIVES

The aim of the study was to know the clinical characteristics of patients, and the diagnostic and therapeutic strategies applied by clinical cardiologists in nonspecialized centers to conditions highly compatible with HCM.

METHODS

This was a national, cross-sectional, multicenter study in patients with confirmed or highly probable HCM, with the participation of clinical cardiologists attending outpatient clinics of nonspecialized centers.

Patients ≥18 years old with confirmed or highly probable diagnosis of HCM established by imaging or laboratory studies (Doppler echocardiography, late gadolinium-enhancement magnetic resonance imaging and/or genetic test), as considered by the clinical cardiologists following them up, were included in the study. Patients with diseases or situations that generated secondary ventricular hypertrophy: hypertension (HTN), valvular diseases, infiltrative cardiomyopathies, athletes, etc, and patients with HCM followed-up in specialized centers, were excluded from the study. A specialized center was defined as a center specialized only in cardiology and/or cardiomyopathies specific outpatient clinics.

Data collection was performed through the REDCap platform of the Argentine Society of Cardiology from June 1 to September 30, 2023.

Statistical analysis

Qualitative variables are presented as frequencies and percentages and quantitative variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR 25%-75%), according to their distribution. The analysis of discrete variables was performed using the chi-square test of Fisher´s exact test, as appropriate, and continuous variables were analyzed with the t test or the Mann Whitney test, according to their distribution. A two-tail $p<0.05$ was considered significative. The R statistical software package was used to perform the analyses.

Ethical considerations

The protocol was approved by the Research Committee of Autonomous City of Buenos Aires Government. An informed consent was waived as it was a study with anonymized data, without personal information.

RESULTS

A total of 95 patients distributed in 8 provinces were included in the study. Mean age was 50 years, with predominance of male sex (58%). The prevalence of cardiovascular risk factors was: HTN 40%, dyslipidemia 22%, obesity 15% and diabetes 14%. A low proportion of comorbidities was observed: chronic obstructive pulmonary disease in 6% of cases, prior myocardial infarction in 5%, prior stroke in 1% and chronic kidney failure in 1%. (Table 1)

A third of patients consulted for the first time with presumptive or confirmed diagnosis of HCM, 37% for some symptom and 27% for a routine control. As shown in Figure 1, dyspnea and angina were the most frequent symptoms, followed by palpitations and syncope. Among patients with dyspnea, 41% were in functional class III/IV, representing 9.5% of all patients.

Regarding diagnostic studies, 96% of patients had an electrocardiogram (90% with sinus rhythm, 91% with signs of left ventricular hypertrophy), 96% an echocardiogram, 71% cardiac magnetic resonance (CMR), and 66% 24-hour ECG Holter monitoring. A genetic test was performed in 33% of patients, coronary angiography in 22%, exercise stress-echo in 13% and coronary computed tomography angiography in 7%. (Figure 2)

Both in the echocardiogram and CMR, LVH was most frequently observed in the interventricular septum (67% and 51%, respectively), and in the apex (9% and 13%, respectively). A significant difference was observed in left ventricular ejection fraction (LVEF) quantification by echocardiography compared with CMR, with median (IQR 25%-75%) of 61% (55%-67%) vs. 67% (65%-74%), respectively, $p<0.001$. An obstructive gradient (>30 mmHg) of the left ventricular outflow tract (LVOT) was detected at rest in 35 patients (37%) with a mean of 43±26 mmHg at rest and 62±39 mmHg with Valsalva maneuver ($p<0.001$).

The genetic test was positive in approximately half of the cases in which it was performed (52%). At the

time of data collection for the registry, the result was pending in 1 out of 3 patients. The most prevalent genetic alterations identified were TNNT2 (5 patients), MYH7 (5 patients) and MYBPC3 (4 patients). Interrogation of the reasons for not requesting the genetic test revealed that in 19 cases the healthcare plan did not cover the test, in 16 cases the center did not have access to the test, in 12 cases the physicians never request it, in 4 cases the test was refused by the patient and in 12 cases for other causes.

Family members were studied in 44% of cases, by means of echocardiogram (41 cases), CMR (15 cases) and genetic test (14 cases).

Medication consisted mostly of betablockers (91%), calcium channel blockers (41%), angiotensin converting enzyme system inhibitors/angiotensin II receptor antagonists (ACEI/ARAII, 47%) and statins (37%).

Table 1. Baseline data

Characteristic (n=95)	%
Age, years, mean (SD)	50 (15)
Male sex	58
Cardiovascular risk factors	
HTN	40
DLP	22
SM	8
DM	14
Obesity	15
History of stroke	1
History of AMI	5
COPD	6
CKD	1

AMI: acute myocardial infarction; DM: diabetes mellitus; DLP: dyslipidemia; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HTN: hypertension; SD: standard deviation; SM: smoking.

Figure 3 describes the medication the patients were receiving prior to consultation and that added during follow-up.

Regarding invasive treatments, among the 22 patients who consulted with confirmed HCM diagnosis or for a second opinion, 45% had some previous invasive treatment: 23% implantable cardioverter defibrillator (ICD), 18% myectomy, 4% pacemaker and 4% alcohol ablation. During follow-up 22 patients required new invasive treatments: ICD 18%, pacemaker 3%, resynchronization therapy 1% and septal myectomy 4%.

DISCUSSION

The present study represents the first approach for the care of patients with HCM in nonspecialized centers of Argentina. Although most cardiologists who follow-up these patients are concentrated in Buenos Aires and Autonomous City of Buenos Aires, there is representation in other provinces: Santa Fe, Formosa, Catamarca, Tucumán, Río Negro, Mendoza and Chubut (see Appendix).

Great progress has been achieved in the field of HCM, both in imaging diagnosis as treatments, providing patients a life expectancy similar to that of the general population. (11) Knowledge of the data of the real world in this rare disease is important to identify the impact of these new strategies. An outstanding example is the Hypertrophic Cardiomyopathy Registry (HCMR), the largest prospective and multicenter study, with 2755 patients from 44 centers in 6 countries, which in addition to clinical data, included CMR characteristics, genotypification and biomarkers. (12-14) In our setting there is no history of registry of these patients with focus on nonspecialized centers. Among the most important findings of our registry, we noticed that patients were diagnosed at an age simi-

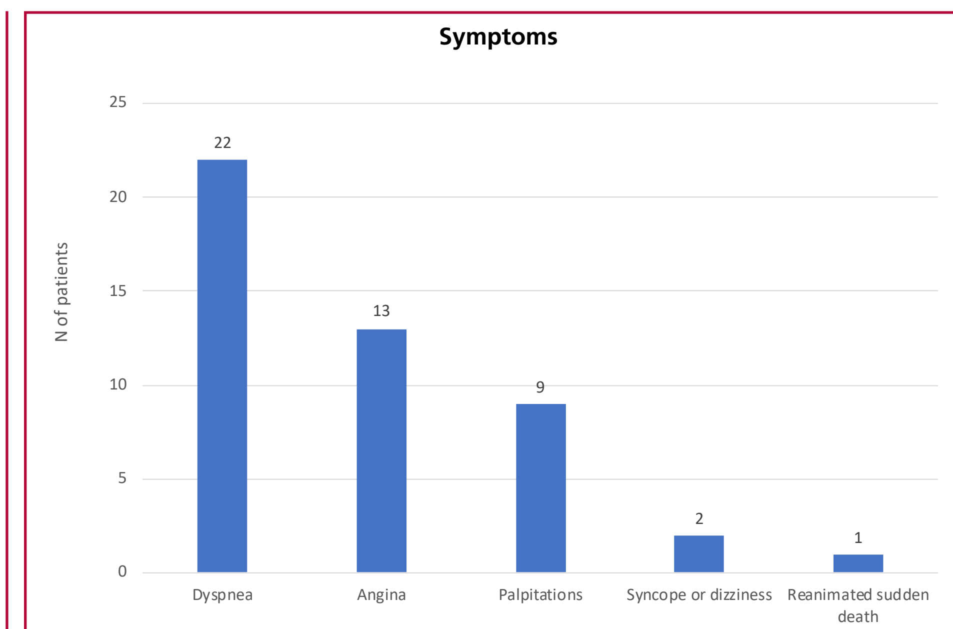
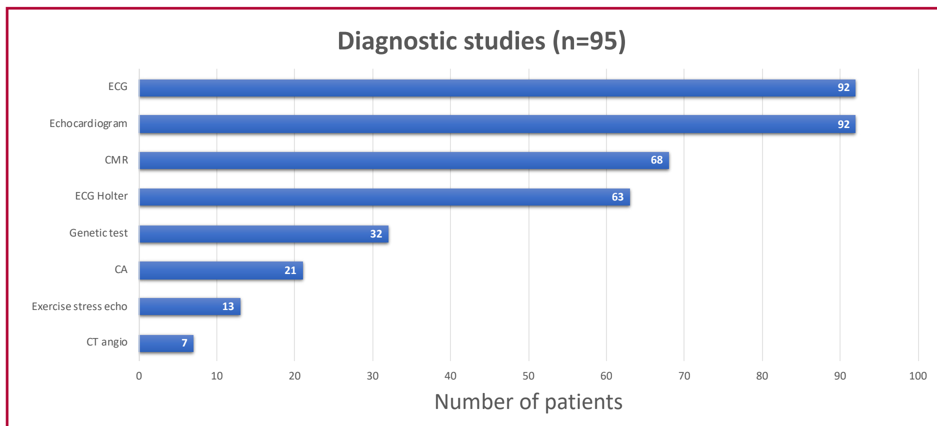
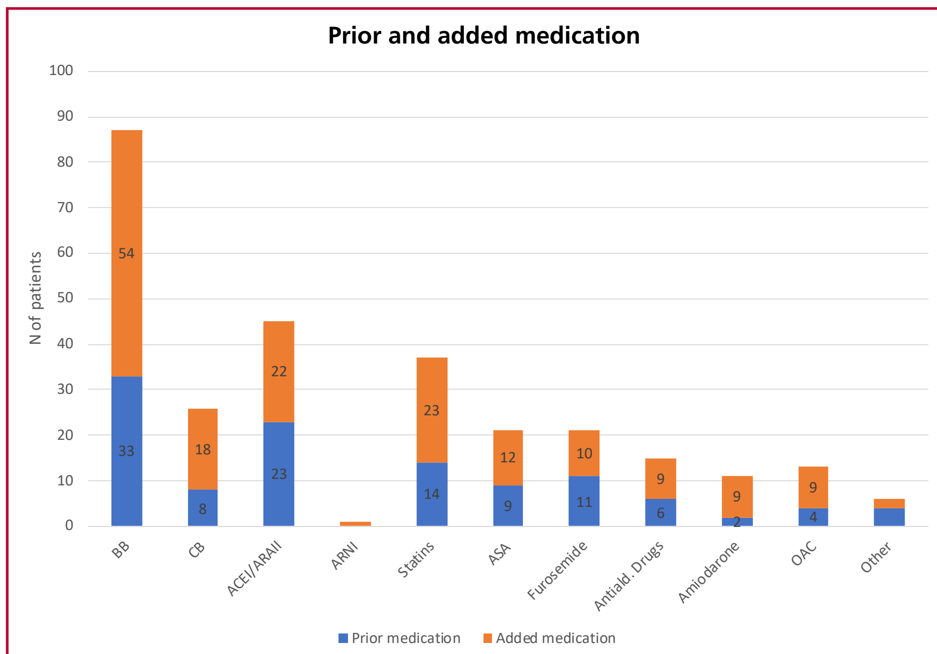


Fig. 1. Consultation symptoms (n=95).



CA: Coronary angiography; CMR: Cardiac magnetic resonance; CT angio: CT angiography; ECG: Electrocardiogram.

Fig. 2. Studies performed



ACEI: angiotensin-converting enzyme inhibitors; ARA II: angiotensin II receptor antagonists Antiald: antialdosterone drugs; ARNI: angiotensin receptor-neprilysin inhibitor; ASA: acetylsalicylic acid; BB: betablockers; CB: calcium channel blockers; OAC: Oral anticoagulation.

Fig. 3. Prior and added medication

lar to that observed in the HCMR, with a similar proportion of hypertensive cases, though with a greater share of diabetics. (12)

Dyspnea was the predominant symptom, and more than 25% of patients were diagnosed after a routine consultation, strongly indicating the high level of suspicion that should be adopted for the diagnosis of this pathology, as many present asymptomatic or oligosymptomatic.

One of the most important contributions of the present registry refers to requested studies. The most frequent are ECG and echocardiogram, in probable relationship to their ample availability in the territory. ECG Holter monitoring was used in 66% of cases, similar to the HCMR (60%). However, exercise echo-stress was scarcely requested, in approximately 1 out of 10 patients, contrary to the suggestion of the 2023 ESC guideline on the management of cardiomyopathies, which recommends it as a IB indication at the time of evaluating the LVOT gradient. (5,15,16)

If we analyze the echocardiographic data, we can observe that the percentage of patients with LVOT obstruction was higher in our registry compared to the HCMR (37% vs. 18%). However, the mean gradient at rest was lower in our study (43±26 mmHg vs. 69±31 mmHg). These trends require an additional validation through the inclusion of a larger number of patients. In the case of CMR, it should be pointed out that a not negligible percentage of patients with highly probable HCM diagnosis lack this study (3 out of 10). This is

another data that contradicts the HCMR, where 9 out 10 patients have undergone the study. (12,17)

Nevertheless, the CMR findings are similar, the septal and apical locations being the most frequent and mean LVEF showing similar values (67% vs. 64%). (12,13) An interesting aspect is the variability of LVEF and cardiac mass quantification by echocardiography and CMR, probably related with the spatial resolution of the latter. The genetic test has not performed in 2 out of 3 patients, and the most common reason for not requesting it by the follow-up physician is lack of resources or health coverage. (18)

Regarding pharmacological treatment, use of betablockers and calcium channel blockers was greater in our registry compared with the HCMR (91% vs. 57% and 27% vs. 18.7%, respectively), which could be due to the difference in patients with LVOT obstruction and in functional class III/IV (37% vs. 18% and 9.5% vs. 7.2%). The same trend is observed in the use of ACEI/ARAII and statins (47% vs. 23.7% and 37% vs. 27%). It should be pointed out that 48% of patients did not present with pharmacological treatment prior to consultation with the follow-up physician. (12)

Invasive treatments in HCM are part of the mainstays in the management of these patients, especially in those who continue to be symptomatic despite the pharmacological treatment or are at risk of sudden death. (5,19,20). In our registry, 1 out of 10 admitted patients, already had some treatment prior to the first consultation with the treating physician, the most important being ICD. One-fourth of patients required intensive care during follow-up, with predominance of implantable devices. The low rate of myectomy and alcohol ablation should be pointed out, despite the percentage of obstructive type and functional class III/IV patients.

The specially fragmented healthcare system in Argentina, in addition to the inequity of resources available in different provinces of our territory, might explain the differences with other countries. This point could help us optimize the resources in this type of disease.

As limitations, the sample size of this registry is not representative of all the Argentine territory. Moreover, it has weaknesses inherent to retrospective registries with voluntary participation, which might generate reporting biases.

CONCLUSIONS

The present registry is the first study of patients with HCM in Argentina which provides data of the real world in the care of patients in nonspecialized centers. Dyspnea and chest pain were the most frequent symptoms of clinical presentation. The ECG and echocardiogram stand out as the pillars for diagnostic suspicion, and in this sense, there is a space for improvement for the access to more complex studies. Pharmacological treatment is in agreement with that established by international guidelines.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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APPENDIX

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OPINION ARTICLE

MULTISTARS AMI. A New Constellation or Just Stardust?

MULTISTARS AMI. ¿Una nueva constelación o solo polvo estelar?

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The MULTISTARS AMI study was presented at the 2023 Congress of the European Society of Cardiology and simultaneously published in the New England Journal of Medicine. (1) It was an open-label, randomized study to evaluate an immediate multivessel coronary angioplasty strategy versus a staged multivessel coronary angioplasty strategy. All the patients had acute ST-elevation myocardial infarction (STEMI) and multivessel disease. The staged strategy consisted of performing culprit lesion angioplasty during the index procedure and completing angioplasty on the rest of lesions from 19 to 45 days later. Large previous studies documented the benefits of complete staged revascularization in this context, (2,3) with reduced incidence of infarction or death upon remote progression, and the study was designed to see whether immediate revascularization was a non-inferior or eventually superior alternative.

The authors concluded that in hemodynamically stable patients with STEMI and multivessel disease, *immediate multivessel coronary angioplasty was non-inferior versus staged angioplasty* for the primary endpoint i.e., the risk of a combination of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemic revascularization, or heart failure hospitalization at a 1 year.

Remarkably, as clearly shown in Figure 1, the combined primary event in the immediate group was half reduced, with statistical significance for both non-inferiority and superiority.

Why immediate angioplasty was never concluded to be superior to the staged strategy and only non-inferiority was claimed?

This is a mystery, as the results appear to be very strong in terms of the advantages of immediate angioplasty and no investigator would deny its superiority, unless there was some barrier or criticism, which is not explicit in this case. According to the protocol design, if the primary endpoint analysis via the log-rank test was significant for non-inferiority, a similar superiority analysis would follow, (4) which is a common methodology aspect.

The table 1 below summarizes the events.

We believe that a possible rationale for the authors' (or reviewers') decision may be two major weaknesses of the trial design, which prevents a firm answer to the research question.

Sui Generis Non-Inferiority Study

The COMPLETE study, (2) which showed the advantage of multivessel angioplasty, rather than limiting to the culprit vessel during the acute stage of the ST segment elevation infarction, considered progression to death or myocardial infarction as long-term comparative events in 4,000 patients. The logical design of a non-inferiority trial is to compare a new procedure or strategy against those validated by the original studies to show that there is no loss of the advantage gained in those studies, which would require a trial with at least the same sample size maintaining the combined death/infarction endpoint. (5) The MULTISTARS AMI design did not consider the events taken into account in the COMPLETE study, but a combined outcome including infarction, death, and also the need for revascularization, stroke, and heart failure hospitalization. However, this combined endpoint was changed during the course of the trial due to challenging patient enrollment. Therefore, this is a non-inferiority study of two strategies on previously untested events, with a sui generis design, of just 840 patients. Showing that the immediate strategy was non-inferior or superior to the staged strategy across an endpoint designed for this trial does not ensure whether the benefit over mortality and infarction upon follow-up was maintained, which had been confirmed by the COMPLETE study. In other words, this trial shows that the immediate strategy is non-inferior and even superior to the staged strategy for evaluated events, but this is not applicable to events remote from the original study, given the low number of cases, the low rate of events, and the brief follow-up.

Rev Argent Cardiol 2024;92:151-154. http://dx.doi.org/10.7775/rac.v92.i2.20749

Received: 12/11/2023 – *Accepted:* 01/04/2024

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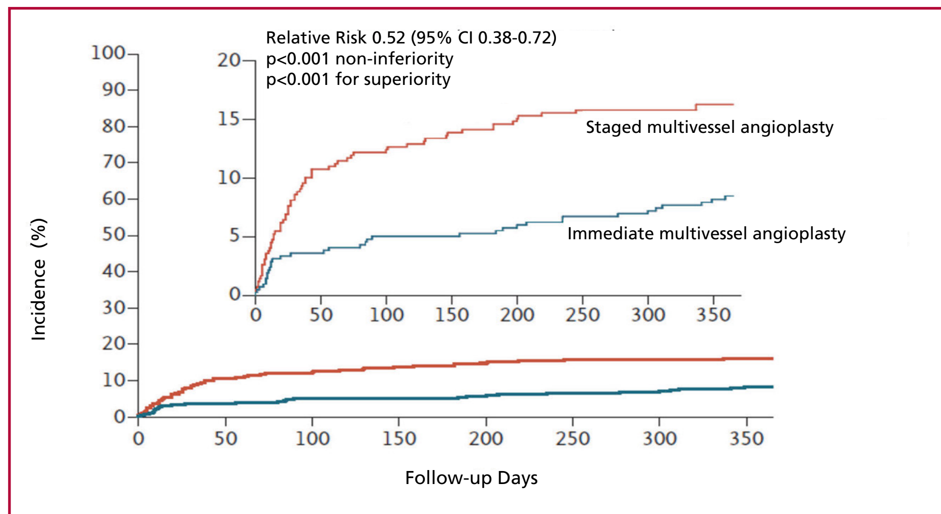


Modified from Stähli BE et al. N Engl J Med. 2023: 389:1368-1379.

Fig. 1. Progress of cumulative incidence for the combined endpoint in MULTISTARS AMI study. The large difference between both groups was already present before 50 days, with few subsequent changes.

Table 1.

Primary and secondary endpoints	Immediate Group (n=418)	Staged Group (n=422)	Relative Risk (95% CI)
Primary endpoint at 1 year			
	n (%)	n (%)	0.52 (0.38-0.72)
All-cause death, non-fatal myocardial infarction, stroke, unplanned ischemic revascularization, or heart failure hospitalization	35 (8.5)	68 (16.3)	
Secondary endpoints at 1 year			
	n (%)	n (%)	
All-cause death	12 (2.9)	11 (2.6)	1.10 (0.48-2.48)
Non-fatal myocardial infarction	8 (2.0)	22 (5.3)	0.36 (0.16-0.80)
Stroke	5 (1.2)	7 (1.7)	0.72 (0.23-2.26)
Unplanned ischemic revascularization	17 (4.1)	39 (9.3)	0.42 (0.24-0.74)
Heart failure hospitalization	5 (1.2)	6 (1.4)	0.84 (0.26-2.74)

What is a clinical trial relevant event?

The COMPLETE study considered two combined co-primary endpoints. The first combined endpoint considered as events related death or infarction during long-term follow-up. The second combined endpoint considered related death, infarction, or the need for long-term revascularization (Figure 2).

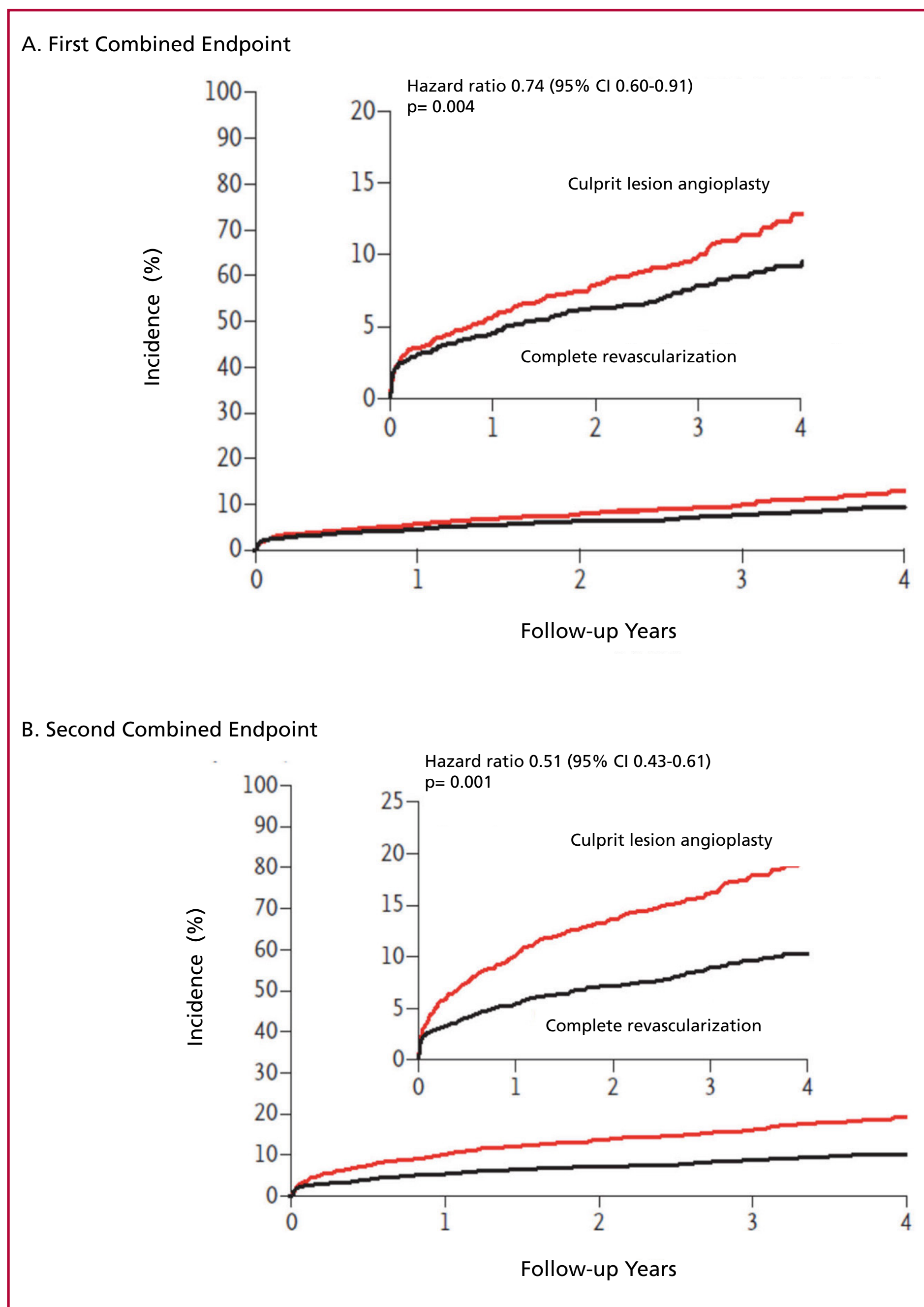
In the MULTISTARS AMI study, the curves are very different: every advantage is gained over the first few weeks, and then curves show parallel progression, which has a simple explanation.

Mortality in this trial was very low, and also the incidence of initial spontaneous infarction was very low during progression, with no differences between both strategies in the two cases. Nonfatal myocardial infarctions, excluding periprocedural ones, occurred in 5 patients (1.2%) in the immediate group and in 8 patients (1.9%) in the stage group (hazard ratio 0.62; 95% CI 0.20-1.89). The entire event difference was based on the rate of periprocedural infarctions and the revascularization indication.

Periprocedural myocardial infarction

The authors reported infarctions divided into 4a, overall post-angioplasty infarctions, and 4b, related to stent thrombosis. The incidence of stent thrombosis was similar in both groups (3 in the immediate and 2 in the staged group), but periprocedural infarction diagnosis was 0 in the immediate group and 12 in the staged group. The authors explain that it is difficult to diagnose a new enzyme elevation during the acute phase to be able to establish a procedure-related infarction, while, when angioplasty involves normalized enzyme levels, after several weeks, any elevated enzymes might induce the diagnostic assumption and be confirmed by minor clinical data, particularly infarctions with no new ST-segment elevation. The incidence of a new ST segment elevation infarction was 3 in the immediate group and 4 in the staged group, while the incidence of non-ST segment elevation infarction was 5 and 17, respectively. The periprocedural infarction diagnosis has been one of the most controversial and amended items in the proposed global definition of

Fig. 2. Cumulative incidence of events in the COMPLETE study.



2A. First combined co-primary endpoint of cardiovascular death or infarction. Divergence among curves is very slow in terms of infarction/death, with very little incidence in the first few months and increasing incidence upon progression.
2B. Second combined co-primary secondary endpoint of cardiovascular death, infarction, or need for deferred revascularization. Progression curves show an early separation that significantly increases over progression.
Modified from Mehta SR et al. N Engl J Med 2019; 381: 1411-21.

infarction, (6) and the Society for Cardiovascular Angiography and Interventions (SCAI) (7) suggests that 7-fold enzyme elevation thresholds confirm this diagnosis. Previous studies of acute coronary syndrome with non-ST segment elevation showed that spontaneous infarctions were associated, as expected, with higher mortality and a 4- or 5-fold relative risk (RR), while, paradoxically, periprocedural infarctions in the three classic studies (RITA 3, FRISC II and ICTUS) had HR 0.66 (95% CI 0.36-1.20), with a trend towards lower non-significant mortality. (8)

Different periprocedural infarction criteria affect the event rate reported by treating physicians versus central events evaluation committees, as observed in the PARAGON (9) and CHAMPION studies, (10) the latter showing three times the incidence of infarc-

tion. To summarize, periprocedural infarction, in this particular case, difficult to diagnose in the immediate group and overdiagnosed in the deferred staged group, may not be considered an adequate event for comparison. In addition, there is no pathophysiological hypothesis to explain that a deferred angioplasty might increase the rate of periprocedural infarction, which leads to the suspicion of a non-clinically relevant overdiagnosis, as commonly observed in intervention studies for acute coronary syndrome, as explained above. (11)

We ignore what led to "ischemia-guided" unplanned interventions

As this is an open-label study, a detailed description of the reasons leading to the decision of an unplanned ischemia-guided intervention would have been of much interest. Two reasons can be mentioned: angina recurrence, or ischemia findings upon stress tests. The revascularization rate was 17 (4.1%) in the immediate group versus 39 (9.3%) in the staged group. Unfortunately, the study has not provided any information in this sense, either in the original population or in the appendix. Had there been an indication for recurrent resting angina, it might be considered an event, but if findings of induced ischemia had been the indication in most cases, no event would be involved, but simply a logical and inevitable result of deferring the procedure, with no risks involved. Similar findings on this decision were reported by another non-inferiority trial with the same design. (12)

In summary:

COMPLETE, the original study, showing the benefits of complete revascularization versus limiting just to the culprit vessel in cases of ST-segment elevation infarction, deferred procedures at two different times, on the day after baseline and after several weeks, with similar benefits for both over remote progression of severe events, such as spontaneous infarction or death. This study, MULTISTARS AMI, does not provide any information on whether performing the procedure on the first day is non-inferior or superior to the staged approach in terms of relevant events, such as spontaneous infarction, death, or hospitalizations due to heart failure, as a result of the small sample size, the low rate of events similar to those in previous studies, the different combined endpoint composition, and the brief follow-up. It only shows that the immediate procedure will lead to fewer periprocedural infarction diagnoses and less common ischemia-induced revascularization, which are not relevant events to guide clinical behavior, as claimed above. Given these weaknesses, we believe that the authors (or reviewers) tried not to claim that the immediate strategy should be the standard-of-care for acute myocardial infarction and preferred eclectic "non inferiority" when it was clearly superior for their events. In other words, a study with a very limited contribution to the clinical decision.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Funding

No funding has been received for this paper.

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SCIENTIFIC LETTER

Antiaggregation Strategy post Coronary Angioplasty with Stent in a Patient with Severe Thrombocytopenia

Estrategia de antiagregación post angioplastia coronaria con stent en un paciente con trombocitopenia grave

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Dual antiplatelet therapy is a key element in the pharmacological treatment of coronary heart disease. It consists in the combination of aspirin (ASA) and a P2Y12 platelet inhibitor. This therapy reduces ischemic and stent thrombosis risk, but on the other hand, it increases bleeding risk. The combination of drugs and treatment duration is still today under constant debate. Scores such as the PRECISE DAPT score, the PARIS risk score, or the DAPT score are tools that are used in medical practice as a guide for decision making, although they do not include platelet count. On the other hand, the ARC-HBR (Academic Research Consortium for High Bleeding Risk) score includes as a criterion moderate to severe thrombocytopenia (platelet count less than 100 000/mm^3), which implies a risk of bleeding greater than or equal to 4% in 1 year, and that can sometimes be the greatest limitation of dual antiplatelet therapy. Patients with severe thrombocytopenia are usually excluded from the research studies giving origin to these scores, so decisions in this regard are subject to the experience of the treating medical team.

We present the case of a 52-year-old male patient, with a diagnosis of acute lymphocytic leukemia (ALL) associated with synchronous clear cell renal carcinoma and a history of acute myocardial infarction (AMI) in 2016, which required angioplasty with a bare metal stent (BMS) in the right coronary artery (RCA). He had an ongoing hospitalization for severe pancytopenia due to his oncohematological disease. Admission laboratory tests revealed hematocrit 22%, hemoglobin 7.9 g/dL, platelet count 25 000/mm^3, leukocytes 1190/mm^3, and unremarkable results for the remaining tests. He was asymptomatic for angina or anginal equivalents with an electrocardiogram (ECG) without pathological findings.

Prior to targeted treatment, a myocardial perfusion test with pharmacological stress was requested. At a dose of 30 mcg/kg/min of dobutamine, severe and extensive ischemia was evident in the middle and apical anterior, basal, and middle anteroseptal, basal and middle inferoseptal and inferoapical segments, compatible with the territory of the left anterior descending (LAD) artery. Results showed summed stress score (SSS) 28, summed rest score (SRS) 4, and summed differential score (SDS) 24, with dilation of the left ventricle (LV), radiotracer uptake in the right ventricle (RV) and drop in left ventricular ejection fraction (LVEF) after stress (45% to 32%).

A coronary angiography (CA) was performed with prior platelet infusion, which revealed LAD artery subocclusion and severe in-stent restenosis of the RCA. The case was discussed in an interdisciplinary meeting with Hematology given the high ischemic risk that would have prevented him from receiving onco-specific treatment, as well as facing its eventual complications (infectious, hemorrhagic, among others). As a consequence, revascularization was decided. Percutaneous transluminal coronary angioplasty (PTCA) was performed with insertion of a BMS in the LAD artery, without subsequent antiplatelet therapy given the very high hemorrhagic risk. The patient developed infectious and oncological complications, so he was transferred to the general ward. On the seventh day after stent placement and with 44 000 platelets/mm^3, ASA treatment at a dose of 100 mg per day was initiated. The rest of the hospitalization progressed without cardiovascular events, and without bleeding episodes up to discharge 26 days after admission. Five months after hospitalization, he continues antiplatelet therapy only with ASA, without presenting any intercurrences.

The case presented here raises a controversy that exceeds the guidelines present in the literature. Platelets in myelodysplastic syndromes often have abnormal concentrations or are dysfunctional, with

Rev Argent Cardiol 2024;92:155-156. http://dx.doi.org/10.7775/rac.v92.i2.20759

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high bleeding risk, even with platelet values over 100 000/mm^3. As in other hematological processes, (1) there are no recommendations on antiplatelet treatment for patients with severe thrombocytopenia due to myelodysplastic syndrome, who suffer an acute coronary syndrome or stable coronary disease.

In this type of patients, an angiographic study should be considered as a first measure since this procedure already presents a great challenge. The European cardio-oncology guideline is clear on preventive measures to reduce the risk of bleeding including, among other, platelet transfusion if they are below 20 000/mm^3, radial access, careful hemostasis, and low doses of heparin, between 30-50 IU/kg, (2) all actions that were carried out in our patient.

Regarding double antiplatelet therapy, expert agreements suggest starting it with platelet values above 30 000/mm^3, as well as opting for a type of stent that allows shortening its duration. (3) The European cardio-oncology guideline recommends using aspirin starting at 10 000 platelets/mm^3, and clopidogrel at 30 000 platelets/mm3 (there are experts who recommend cut-off values of 30 000 and 50 000 platelets/mm^3, respectively). (2) Our patient had less than 30 000 platelets/mm^3. In this sense, we have not found any similar reported case of severe thrombocytopenia.

The greatest evidence regarding thrombocytopenia and antiplatelet scenarios is provided by contradictory opinion articles. On the one hand, in patients with chronic coronary syndrome (CCS), they suggest stopping antiplatelet therapy and avoiding angioplasty if there is a platelet count of less than 50 000/mm^3. This consideration was considered in the discussion regarding our patient, but it could not be respected. (4) In patients with platelets between 50 000 and 100 000/mm^3, monotherapy with clopidogrel and proton pump inhibitor (PPI) is suggested, based on randomized studies, which mostly used second-generation drug-eluting stents (DES). Finally, in patients with CCS, symptomatic despite triple antianginal therapy, PTCA is reasonable when evaluating the risk-benefit ratio. If carried out, the suggestion is second-generation DES rather than BMS, and subsequent double antiplatelet therapy with ASA and clopidogrel for one month, and then continuing with clopidogrel as monotherapy, associated with PPI. The indication for second-generation DES arises from the evidence that demonstrates a lower rate of early stent thrombosis compared with BMS, considering dual antiplatelet therapy with the usual recommendations (duration and composition), a situation that is far from the scenario presented in our case, and that, in fact, would not be advisable to follow given the high ischemic risk that would arise if one did not comply with conventional treatment. (4)

On this issue, evidence has shown that DES reduces early restenosis and ischemia associated with the index lesion, when compared with BMS, but has failed to demonstrate superiority with respect to late thrombosis. (5,6) Therefore, BMS are reserved for patients who cannot receive double antiplatelet therapy for more than a month given the risk of bleeding, (6) and, as in our patient, in scenarios in which the standard double antiplatelet therapy cannot be administered. This type of stent presents the challenge of the risk of thrombosis during the first month, but once this period is over, the risk of late thrombosis would be reduced and thus the need for dual antiplatelet therapy, making simple antiplatelet treatment a more reasonable goal in these cases.

In conclusion, the evidence is scarce and divergent, so we sustain that the behavior to be adopted should be individualized, and of multidisciplinary decision, until more studies are developed

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

(See conflicts of interest forms on the website).

Financing
None.

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SCIENTIFIC LETTER

Emergency Cardiac Transplantation in Patient with Arrhythmogenic Cardiomyopathy and Electrical Storm

Trasplante cardíaco de emergencia en paciente con miocardiopatía arritmogénica y tormenta eléctrica

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Arrhythmogenic cardiomyopathy (ACM) is a genetic disease of the cardiac muscle characterized by the progressive substitution of muscle cells by fibrous and adipose tissue, generally affecting the right ventricle (RV), with variable involvement of the left ventricle (LV), which causes ventricular dysfunction and predisposition to potentially fatal arrhythmias and sudden death. It is associated with dominant autosomal inheritance and irregular penetrance, involving genes encoding desmosomal proteins. Both its diagnosis and clinical management represent a challenge. (1)

This is the case of a 27-year-old male patient, with history of frequent ventricular extrasystoles (VES) in 2018, electrocardiogram with negative T waves in leads III, aVF, V2-V6, observed in a presurgical study. ECG-Holter monitoring evidenced 17 183 VES, bigeminies and triplets, during the day. The echocardiogram showed moderate left ventricular systolic function impairment, ejection fraction 40%, global hypokinesia, dilation and marked RV dysfunction, and cardiac magnetic resonance with inferior subepicardial, free wall and right ventricular outflow tract delayed enhancement, moderate left ventricular impairment and interventricular dyssynchrony, compatible with arrhythmogenic cardiomyopathy with biventricular involvement. These findings led to implantable cardioverter defibrillator (ICD) insertion as primary prevention of sudden death. Subsequently he was hospitalized in another institution for effective ICD shock, with evidence of multiple episodes of ventricular tachycardia (VT), and treated with betablocker and antiarrhythmic agents, sotalol at maximum doses and amiodarone, which had to be suspended for hyperthyroidism.

The patient consulted at our institution for frequent palpitations followed by ICD shock on two occasions. On admission, he was lucid, clinically stable, well perfused, without signs of congestion, no signs of pulmonary congestion, oxygen saturation at ambient air 98%, and no alterations in laboratory tests. Monitoring revealed repeated palpitations and sustained VT. (Figure 1) Due to confirmed ventricular arrhythmia and two ICD shocks in the last 24 hours, an electrical storm was diagnosed and a protocol with lidocaine and magnesium sulphate was initiated, with reversion to sinus rhythm.

The reading of ICD records was performed, and multiple episodes of sustained VT were ratified, with effective electrical cardioversion on two occasions and antitachycardia therapies on repeated circumstances.

A computed tomography angiography was performed for possible ischemic trigger, which ruled out coronary heart disease. Jointly with Electrophysiology, the possibility of radiofrequency ablation was evaluated by cardiac magnetic resonance, which confirmed right ventricular dilation with markedly increased volumes, severe systolic function impairment, and transmural fibrosis and thinning of the entire free wall. Severe thinning precluded ablation due to the high risk of ventricular rupture and cardiac tamponade.

The patient evolved with multiple episodes of electrical storm and resumption of the lidocaine protocol. Due to refractory response, orotracheal intubation, mechanical respiratory support and deep sedation was decided to decrease the adrenergic stimulus. He presented an episode of ventricular fibrillation, with cardiopulmonary resuscitation and external cardiac defibrillation that returned spontaneous circulation, followed by low cardiac output syndrome requiring the initiation of inotropic support with milrinone and levosimendan.

Because of his torpid evolution, the patient was evaluated for heart transplantation and subsequent incorporation into the waiting list in Emergency B

Rev Argent Cardiol 2024;92:157-159. http://dx.doi.org/10.7775/rac.v92.i2.20761

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condition. Mexiletine was initiated, which resolved a large proportion of the arrhythmic density, achieving extubation. Orthotopic bicaval heart transplantation was performed, without immediate postoperative complications. The native heart was sent for anatomo-pathological study, which established extensive adipose substitution and muscle bundles disorganization, with foci of myocyte necrosis, and final diagnosis of ACM with biventricular involvement. (Figure 2)

An endomyocardial biopsy was performed prior to discharge. It presented grade 2R cellular rejection with no evidence of antibody-mediated rejection, and was treated with high doses of corticoids with clinical and histopathological resolution. He subsequently completed his hospitalization uneventfully.

Arrhythmogenic cardiomyopathy is a rare hereditary heart disease, potentially fatal, that requires clinical care and a comprehensive therapeutic approach. The current diagnosis is based on the 2010 Task Force criteria, consisting of structural disorders in imaging and histopathological studies, conduction and repolarization disorders in the electrocardiogram, presence

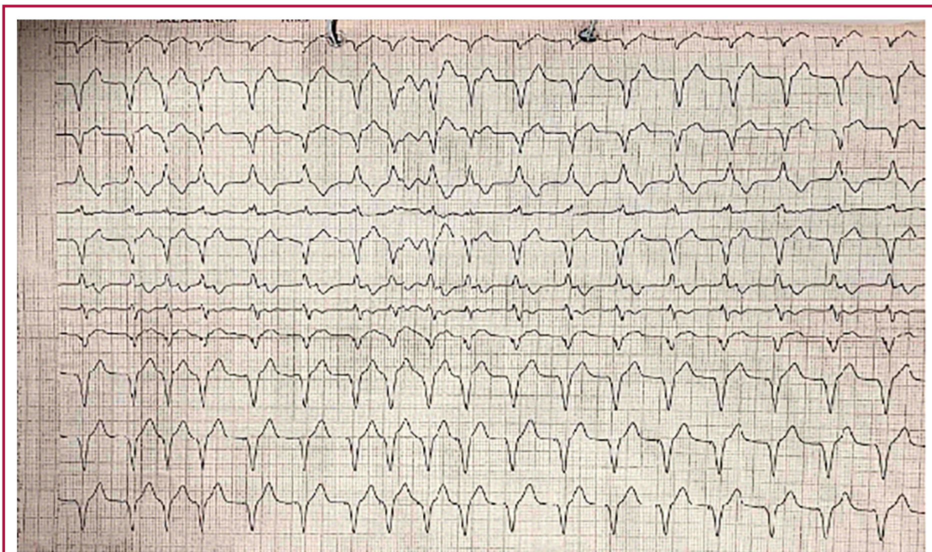

Fig. 1. Episode of ventricular tachycardia

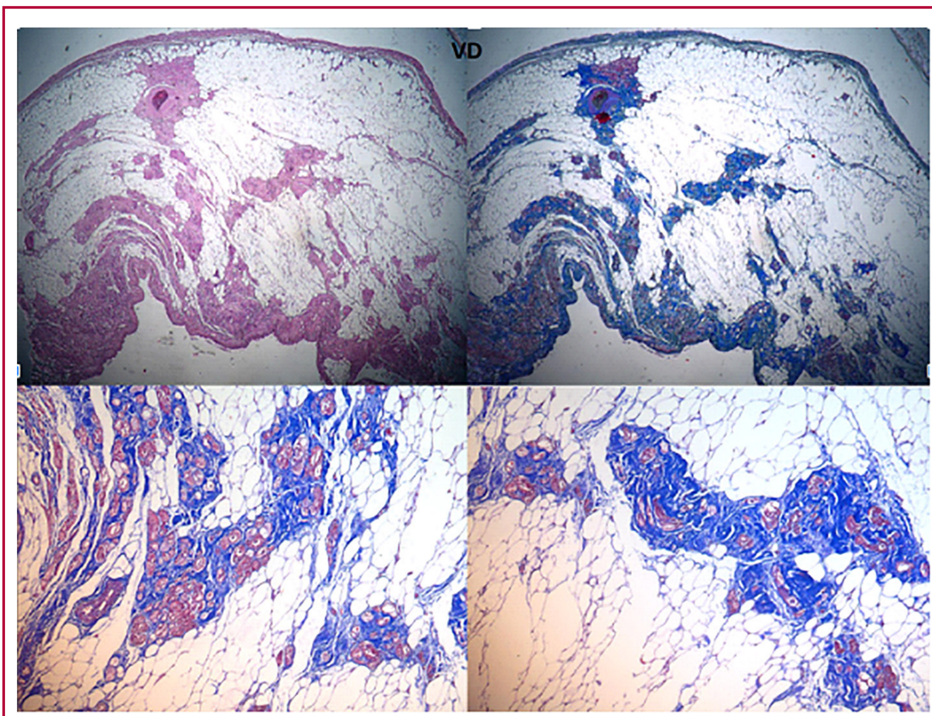

Fig. 2. Pathological anatomy of the native heart. Adipose substitution, disorganization, and myocyte fibrosis.

of ventricular tachycardia with complete left ventricular bundle branch block morphology in the electrocardiogram or Holter monitoring and family history, especially in first degree relatives with confirmatory genetic test. (1).

Electrical storm is defined by three or more episodes of sustained ventricular arrhythmia, antitachycardia therapy or ICD shock in the course of 24 h, which predisposes to decompensated heart failure and increased mortality. An initial management with preferably non-selective betablockers is suggested, combined with amiodarone. In case of treatment refractoriness, deep sedation and intubation with mechanical respiratory assistance should be considered to decrease the psychological stress and the pro-arrhythmogenic sympathetic tone. Catheter ablation is associated with reduction of arrhythmia and electrical storm recurrence in patients suitable for this procedure. (2)

According to the 2012 Johns Hopkins registry, including 1000 patients with ACM, only 18 received heart transplantation between 1995 and 2009. They presented at a young age, with left ventricular involvement and 94% survival at one-year post-transplantation. In 13 of these patients, the cause for transplantation was symptomatic heart failure and only in 5, refractory ventricular arrhythmia. (3)

The Nordic registry of cardiac transplantation in patients with ACM, published in 2017, reported 31 transplantations between 1988 and 2014. Compared with a non-transplanted control group with ACM, the only independent risk factor that predicted transplantation was the emergence of the first symptom before 35 years of age. Ninety percent were transplanted for heart failure, compared with 10% for arrhythmia, and with 91% survival at 5 years. (4)

Current heart transplantation guidelines do not provide specific recommendations for ACM due to its low frequency, and because only a small proportion of this population needs to be considered for this procedure. (5) However, the inclusion of patients with refractory ventricular arrhythmias is recommended.(6)

Ethical considerations
Not applicable.

Conflicts of interest
None declared.
(See conflicts of interest forms on the website).

Financing
None.

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SCIENTIFIC LETTER

"Flip" Syndrome, a new Mechanism of Lead Macrodislodgement of Cardiac Stimulation Devices

Síndrome de flip, un nuevo mecanismo de macrodesalojo de electrodos de dispositivos de estimulación cardíaca

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Lead dislodgement and subsequent dysfunction are among the rarest complications after implantation of a permanent cardiac device, such as a pacemaker, with an incidence of 1.7%. (1) Its advent may be related to external manipulation of the device, inadequate fixation in the muscular plane, and a large pocket area/ generator area ratio, among others. (1) Multiple macrodisplacement and rotation syndromes of the device and leads, including reel, twiddler and ratchet syndromes, have been described.

We present the case of a 64-year-old woman who was admitted to the emergency department with 10 hours of chest pain, palpitations, and "vibrations" in the chest, and without other symptoms. The patient had a history of coronary and ischemic heart disease, which triggered heart failure with reduced left ventricular ejection fraction (26%).

Five months before the current admission, she had been fitted with a dual-chamber implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death, through access by cephalic vein dissection. The leads were fixed to the muscle plane with separate nonabsorbable sutures over the fixation drums, and the device was fixed to the muscle plane with a nonabsorbable suture, without complications. However, the patient mentioned a burning sensation in the pocket of the device every night and, consequently, she performed a "massage" with counterclockwise and clockwise rotating movements on the generator casing. Additionally, she did not attend device review appointments after the implantation. Her physical examination presented no significant findings.

The initial electrocardiogram showed a pacemaker rhythm in DDD mode with adequate atrial stimulation, ventricular sensing failure, and frequent pseudofusions. A transthoracic echocardiogram exposed the right ventricle without a lead inside it. The chest X-ray showed lead displacement; the atrial lead was located in the right atrium under traction and the ventricular lead was in the superior vena cava (Figure 1a). Additionally, the leads were observed coiled around the casing. Interestingly, a 180-degree rotation of the device in its sagittal axis was evident; the rotation was later on confirmed by comparing the connector location with the X-ray taken in the immediate postoperative period of the implant (Figure 1b). Therefore, it was suspected that lead dislodgement corresponded to a mixed mechanism, including ratchet. and reel syndromes. The device was examined, revealing a normal battery and dysfunction due to defects in sensing and capture of the atrial and ventricular leads. No arrhythmias or shocks were recorded as active vibratory alerts, so the symptoms were not related to device shock.

The patient was subsequently transferred to the coronary care unit.

Explantation and implantation of the ICD and repositioning of the leads under fluoroscopic guidance was scheduled for the next day.

During the procedure, the previously described findings on the chest X-ray were confirmed. These included a 180º ICD displacement in the sagittal axis with the device brand directed towards the posterior region (at the time of implantation this area had been positioned towards the anterior region), the casing fixation point was loose, there was lead retraction with clockwise rotation in the ICD short axis (reel) and a cogwheel mechanism on the fixing cap (ratchet).

An obvious deterioration of the leads and their endocardial fixation mechanisms was also documented, making their complete removal necessary. Given the extensive vascular stenosis, it was decided to insert a single ventricular lead, so the resulting device had a

Rev Argent Cardiol 2024;92:160-162. http://dx.doi.org/10.7775/rac.v92.i2.20756

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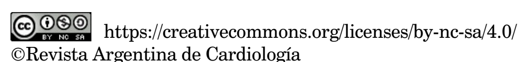
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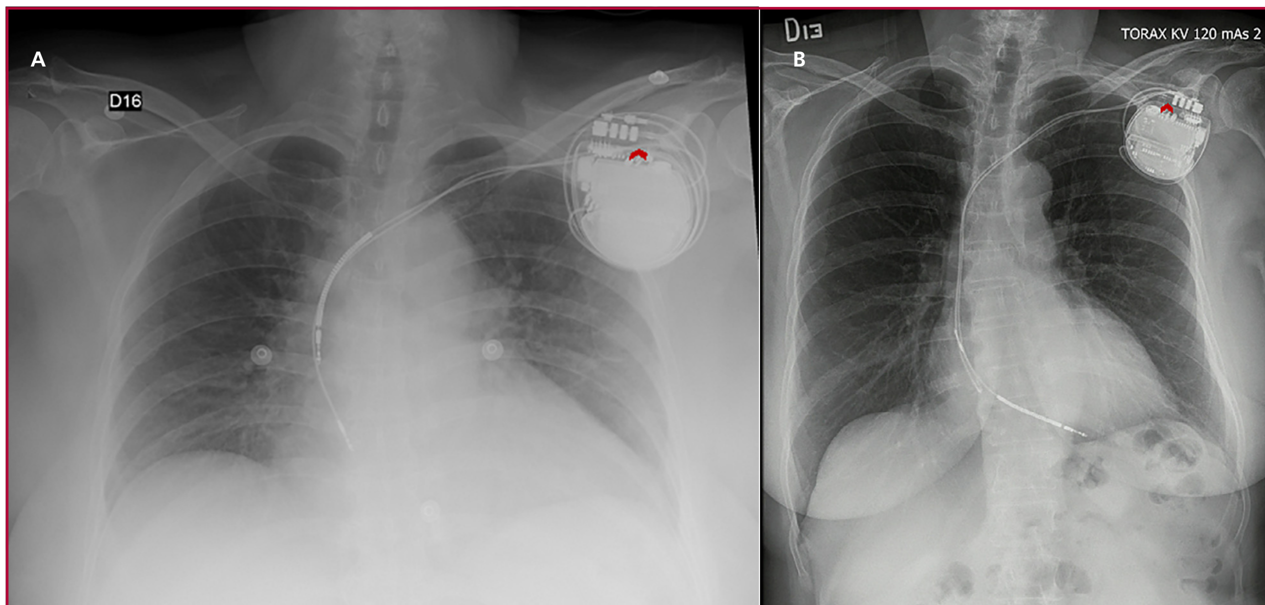

Fig. 1. A. Initial chest X-ray upon arrival to the emergency room. Lead displacement is evident; the atrial lead is in traction in the right atrium and the ventricular lead is observed in the superior vena cava. Reel and ratchet syndromes are confirmed. The lead connectors are seen laterally directed (arrowhead), so a 180° rotation of the device in its sagittal axis is suspected. **B.** Chest x-ray in the immediate postoperative period after ICD implantation, five months before arrival at the emergency room. The lead connectors are seen medially directed (arrowhead).

unicameral configuration. The procedure ended without complications. The post-procedure chest X-ray showed adequate lead and generator positioning, so the patient was discharged within the next 24 hours.

Three different syndromes have been described in the literature (Figure 2):

• Twiddler syndrome produced by the rotation of the generator on its long (axial) axis, which would correspond to the X axis in the Cartesian coordinate system, with lead coiling or twisting (characteristically in the form of a braid). This results in lead dislodgement or fracture, and, consequently, device dysfunction. (2)

• Reel syndrome occurs due to rotation of the pacemaker generator on its transverse axis (short axis), which would correspond to the Z axis in the Cartesian coordinate system, with subsequent coiling (reel) of the pacemaker leads around the generator.

• The ratchet mechanism is produced by an initial lead retraction, followed by a ratchet (cogwheel) mechanism. It is caused by the progressive retraction of the leads from their fixing protections, without twisting or wrapping around the device. Furthermore, it is associated with a lateral displacement of the generator in the frontal plane. (1)

In our patient, it was considered that performing repetitive massage in the area of the device to relieve

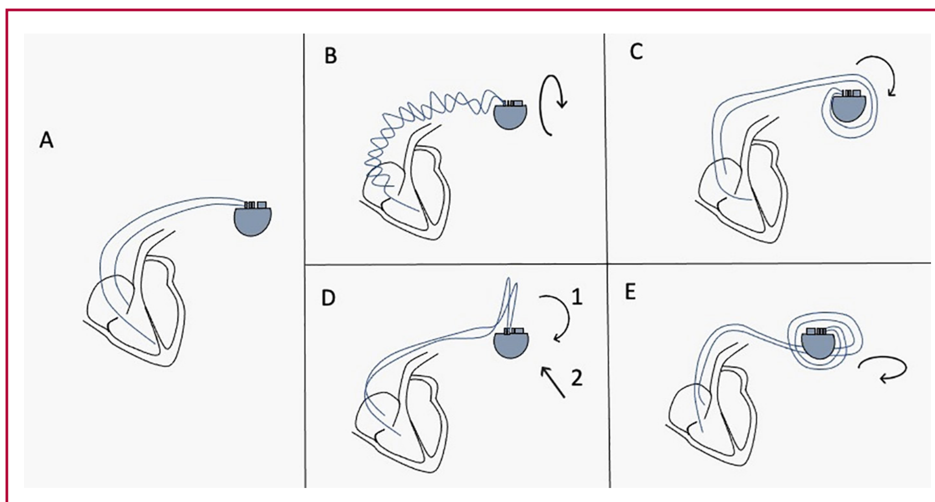

Fig. 2. A. Normal arrangement of leads and generator. **B.** Twiddler mechanism. **C.** Reel mechanism. **D.** Ratchet mechanism. **E.** New mechanism described with rotation in the sagittal axis of 180°: flip mechanism.

the "burning" sensation caused the progressive rotation of the generator. Although coiling of the leads around it, known as reel syndrome, and the lateral displacement of the generator along the frontal plane, known as ratchet syndrome, can explain lead dislodgement and device dysfunction, in this particular case a different mechanism was observed. This was a macrorotation not previously reported in the literature, where the generator is flipped 180 degrees on its sagittal axis, which would correspond to the Y axis in the Cartesian coordinate system. As a result, the brand letters were oriented towards the posterior region, favoring lead retraction and dislodgement (Figure 2). Therefore, it is proposed to call this phenomenon "flip" syndrome or mechanism.

Diagnosis is made by chest X-ray and treatment depends on the underlying mechanism. In the case of the reel syndrome, lead repositioning is the most common strategy. On the other hand, in the twiddler syndrome, leads are replaced in most cases due to the higher frequency of fracture/damage. Additionally, in some specific cases the device pocket can be remodeled. Several strategies have been proposed to prevent device rotation, such as creating a small pocket, subpectoral implantation of the device, use of nonabsorbable or polyester fixation sutures, and the use of active fixation leads and even immobilization of the upper limb in the first week after implantation. (4)

In conclusion, this case emphasizes the importance of device care recommendations and timely and close follow-up of patients in the first 2 to 3 months after device implantation, or remote monitoring that allows early detection of device dysfunction, in order to identify risk behaviors and thus avoid complications such as those described in our patient. In addition, we described a macrorotation mechanism of the device in its sagittal axis, not previously reported in the literature, which we propose to call "flip" syndrome or mechanism.

Ethical considerations
Informed consent was obtained from the patient.

Conflicts of interest
None declared.

(See conflicts of interest forms on the website).

Financing
None.

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SCIENTIFIC LETTER

Dengue Fulminant Myocarditis with ECG Brugada Type 1 Pattern

Miocarditis fulminante por dengue, con patrón de Brugada tipo 1 en el ECG

LISANDRO PÉREZ VALEGA[1,2], TOMÁS MULLINS[2,3], LUCIANA OLIVERA[2,3], SEBASTIÁN CARAVAGIO[2,4]

Dengue is a viral disease caused by an arbovirus transmitted by arthropods, specifically by the bite of the female *Aedes aegypti* mosquito. It predominates in tropical and subtropical areas, and is one of the main public health problems in Central and South America. There are 4 serotypes of the virus: DEN-1, DEN-2, DEN-3 and DEN-4.

Most infections are benign or oligosymptomatic. Other cases may present with fever, headache, retro-ocular pain, myalgia, arthralgia and marked asthenia. Only on very few occasions are serious symptoms seen. This occurs when the patient had a previous infection with a serotype, and is reinfected with a different serotype. It is in these situations that the symptoms of dengue syndrome with shock, or hemorrhagic shock appear, presenting with thrombocytopenia, increased vascular permeability and in very few situations fulminant organ dysfunction (myocarditis or hepatitis).

In Argentina and countries in the region, especially Brazil, there is currently a dengue epidemic with alarming numbers of new infections. That is why we decided to present this clinical case, given the importance of this disease in endemic areas.

This is an 18-year-old patient, with no relevant pathological history, who reports starting on February 16 of this year with fever, general malaise and watery diarrhea without mucus, pus or blood. He progresses with marked asthenia in the following days, and on February 21 he adds mucous membranes and skin pallor, sweating, precordial pain and a presyncopal episode, so he is taken to the emergency room of a nearby hospital. Upon admission, they describe a patient frankly hypotensive, with blood pressure 60/40 mmHg, heart rate 60 bpm, temperature 38ºC, O_2 saturation 99% at room air, and glucometer assessment 87 mg/dL. Figure 1 presents the admission ECG.

A few hours after being admitted to that institution he presents a sudden loss of consciousness with a tonic-clonic seizure. Electrocardiographic changes of Brugada type 1 syndrome are reported, which leads to request a referral to our clinic.

He is admitted to the coronary care unit with hypotension that does not improve with expansion with crystalloids, precordial pain and slowed capillary filling (greater than 3 seconds) with ECG evidencing a Brugada type 1 pattern, (Figure 2). Laboratory tests reveals ultrasensitive troponin T at 1532 pg./mL, CPK 1178 U/L; B peptide (BNP) 218 pg./mL; metabolic acidosis with pH 7.18, pCO_2 58 mmHg, $pO_2$99 mmHg, bicarbonate 21 mEq/L, base excess 7.1 mmol/L, O_2 saturation at room air 96%, lactic acid 9.3 mmol/L; hematocrit 55%, leukocytes 7260/mm^3, platelets 131.000/mm^3, blood glucose 167 mg/dL, urea 38 mg/dL, creatinine 1 mg/dL, KPTT 36 sec, prothrombin 47%, and SGOT 108 U/L. The rest of the hepatogram is normal.

The echocardiogram shows severe global hypokinesis, with left ventricular ejection fraction estimated at 10%, mild pericardial effusion without chamber collapse, and no evidence of valvular disease.

The condition is interpreted as cardiogenic shock in a young patient without previous diseases and a 5-day persistent fever. Our first suspicion is myocarditis of viral origin, so we request serologies for multiple viruses that can cause this entity. Infusion of noradrenaline and dobutamine is started with poor response, and mechanical ventilatory assistance is decided. Four hours after admission to the coronary care unit, the patient develops refractory hypotension and pulseless electrical activity, and despite advanced cardiopulmonary resuscitation maneuvers, he dies.

Five days after death, a positive dengue result is received, both for the NS1 antigen and the PCR for DEN-2.

We present a case of fulminant myocarditis due to dengue, with fatal outcome, in a young patient with no pathological history, who was admitted with a pre-

Rev Argent Cardiol 2024;92:163-165. http://dx.doi.org/10.7775/rac.v92.i2.20764

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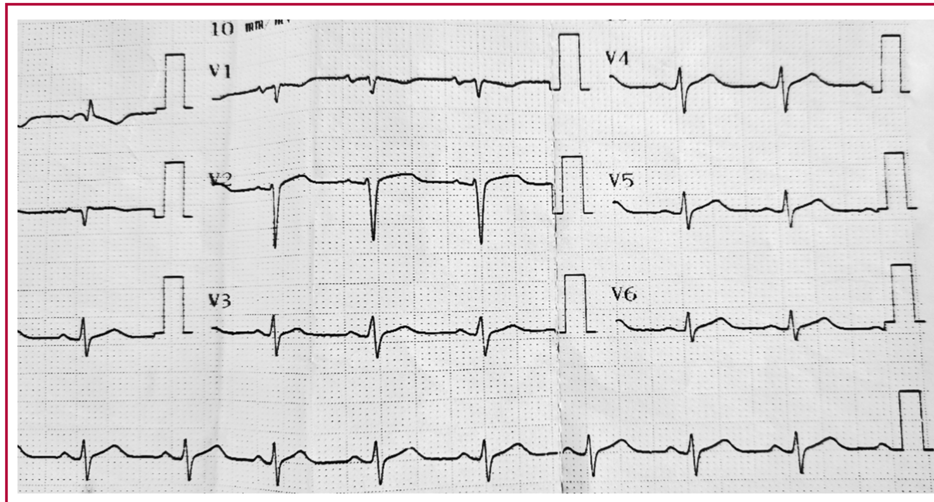

Fig. 1. Admission ECG in the Hospital that referred the patient

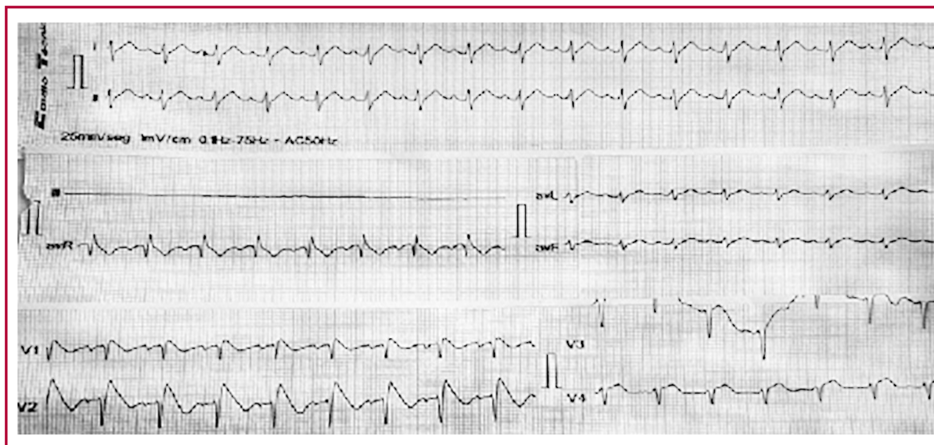

Fig. 2. ECG upon admission to our clinic showing Brugada type I pattern.

viously unknown Brugada type 1 pattern. There was no history of sudden death or diagnosis of this syndrome in the family. For all this, we considered that it could be an expression of Brugada type 1 pattern in the context of fever. We did not find in the literature any report of Brugada and dengue association.

In most cases, dengue is a self-limited disease and resolves in 5 to 7 days. However, a low percentage of patients experience the severe form, with cardiovascular impact evidenced by arrhythmias and myocarditis. (1)

According to Sud et al. the prevalence of myocarditis due to non-severe dengue without alarm symptoms is 9.7%, in non-severe dengue but with alarm symptoms it is 21%, and for severe dengue it is 46.6%. (2)

A meta-analysis of 12 studies and 2795 patients on the incidence of myocarditis in dengue defined it at around 21%. It should be noted that the patients were hospitalized, the mortality rate was low, and the sample was very heterogeneous. (3)

In another review carried out by the Inter-American Society of Cardiology (NET-Heart Project) in 120 patients hospitalized for dengue in India, 12.5% had cardiovascular manifestations, the most frequent being bradyarrhythmias (6.6%), with sinus bradycardia as the most prevalent. In 3.3% of cases, echocardiography reported systolic dysfunction, 1.6% had pericardial effusion and 1% had atrial fibrillation. In this same review it was seen that between 3.3% and up to 24% of patients hospitalized for dengue may have changes on the echocardiogram that suggest myocarditis. (4)

An extensive review of the literature showed that up to 87% of dengue cases may have ECG changes (negative T waves, ST segment depression, T wave inversion, bundle branch blocks, etc.). It is interesting to note that the Brugada pattern is not described. (5) The appearance of Brugada pattern has traditionally been linked to febrile symptoms, but, we repeat, there is no description of its appearance in the context of dengue fever. (6)

Since we are going through a serious dengue epi-

demic, we consider it is very appropriate to know the cardiovascular damage caused by this virus. At the same time, we present a novel and extremely rare association of fulminant myocarditis due to dengue that presents with a Brugada type 1 ECG pattern. At no time did the patient present arrhythmias, and the arrest rhythm was not tachycardia or ventricular fibrillation, but rather pulseless electrical activity, so we do not believe that the Brugada pattern had a role in the fatal outcome.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Financing

None.

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William Harvey (IV)
De Motu Cordis. (Third part)

William Harvey (IV)
De Motu Cordis. (Tercera parte)

JORGE C. TRAININI[MTSAC,]

We continue with the analysis of *De Motu Cordis*

Chapter X. "The first hypothesis about the amount of blood that passes from the veins to the arteries and the existence of a circular movement of the blood is freed from objections and confirmed by experience"

Harvey presents arguments and experiments that prove his first hypothesis regarding the blood circuit. Thus, in the practice of vivisection in snakes and fish, he details that if the vena cava near the heart is compressed, the overlying vein, the heart and the aorta are left without blood. If, however, the aorta is occluded, the heart becomes engorged.

Chapter XI. "Confirmation of the second hypothesis"

The second hypothesis proposed by Harvey refers to the fact that the blood transported to the periphery by the arteries is much greater than that necessary for nutrition. When referring to "*the veins being the return route to the heart,*" he must have reasoned about a necessary interconnection between arteries and veins. To settle this gap he speaks of "*porosities of the flesh*" ("*carnis porositates*"). Despite not being able to know the microscopic structure of the capillaries that were to be discovered by Malpighi in 1661, he successfully used the concept by saying "*blood passes from the arteries to the veins in the same way as it was already said that in the thorax it passes from the veins to the arteries*."

He uses the ligatures on the arm to support the return of blood. Thus, a loose ligation stops the blood in the veins, engorging it in its distal portion. On the other hand, a very tight ligation will stop blood in both directions, arterial and venous, making the radial pulse disappear. With this he shows that blood flows towards the center through the veins and towards the periphery through the arteries.

The application of bleeding with moderate pressure on the arm had always shown venous engorgement. The Galenic paradigm explained this with the assumption that the "*vis attractiva*" of the vein was stimulated by the ligation, or after phlebotomy by the "*horror vacui*" ("*horror of emptiness*") that the blood would have, the latter a concept of Erasistratus in Alexandria (3rd century BC). Harvey deduces that this mechanism of pressure would bring enough blood from the arteries to the venous network to make it plethoric. Therefore, with this use of ligature experimentation he demonstrates the error of the ancients and the true nature of circulation.

Chapter XII. "The confirmation of the second hypothesis allows us to recognize the existence of a circular movement of blood"

There is a reference that blood is driven by the force of the heart and only comes from it. He uses the method of calculation again when he states that if a phlebotomy is performed and blood is let out for half an hour "*lipothymia and syncope will occur... and if we then calculate how many ounces of blood pass through a single arm*" we will be able to know how much passes through the rest of the organism, resulting in the amount that circulates far exceeding the nutritional needs of the parts. He also expresses that as the phlebotomy diverts blood to the outside, the cardiac impulse is lost. That last statement is a clear demonstration that blood pressure varies and is not constant.

Chapter XIII. "The confirmation of the third hypothesis demonstrates the existence of a circular movement of blood"

Harvey's third hypothesis was the understanding of the venous valves function. Robert Boyle (1626-1691) infers that this was the initial subject in the original idea of blood circulation, referring to it with these words: "*I remember asking our famous Harvey, shortly before his death, what motives had suggested the idea of blood circulation to him. He answered me that this idea arose in his mind when he recognized that the venous valves in many parts of the body are*

Rev Argent Cardiol 2024;92:166-168. http://dx.doi.org/10.7775/rac.v92.i2.20748

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placed in such a way that they give free passage to the blood towards the heart, preventing its flow in the opposite direction. This fact led him to think that perceptive nature would not have placed so many valves in the veins without a certain purpose. Since blood cannot flow in the veins towards the extremities because of the interposed valves, their purpose seemed to be that the blood sent through the arteries would return through the veins whose valves do not oppose this direction of its course".

In any case, the analysis of *De Motu Cordis* reveals that its author has not undermined to this venous valve function the importance of the rest of the topics discussed, which correspond to the problems that Harvey was solving and that were impediments to the true knowledge of circulation.

While in Padua, he became aware of the venous valves through his teacher Fabrizio d'Aquapendente, who had studied them thoroughly from a morphological point of view in his book *De venarum ostiolis* (Padua, 1603). Regarding their function, Fabrizio was oriented towards the regularization of peripheral blood volume, in order to avoid its accumulation in the hands and feet, which did not contradict the system set up by Galen. Harvey does not refer to those who studied venous valves before his teacher (Estienne, Vesalius, Cannano, Amatus Lusitanus, Colombo, Alberti); he even gives ownership of the drawings to Fabrizio "*or perhaps to Jacobo Silvio, as claims the wise Riolanus.*"

The fundamental thing about all this is that Harvey was able to understand the meaning through what he called the third hypothesis to confirm the blood circuit. He thus expresses that the veins are "*so that (the blood) flows from the extremities to the center, since such a movement easily opens the most tenuous valves, and the opposite closes them.*" To make the understanding of this mechanism clearer, he establishes an analogy with the sigmoid valves: "*... it is clear that the valves of the veins have the same function as the three sigmoid valves that are arranged in the orifices of the aorta and the arteriosus vein, that is, to close perfectly to prevent the blood that passes through them from refluxing*". Furthermore, in the practice of dissection he verified that it is not possible to introduce a stylet along the vein against the current, due to the valves' closure.

To further clarify his position, he carries out experiments with ligatures on the arms, visualizing the valves at regular sections of the venous path and the centripetal direction of the blood flow, by pressing and decompressing the engorged path with a finger.

Chapter XIV. "Conclusion of the demonstration of the circular movement of blood"

After demonstrating his three hypotheses that confirm the circulatory idea, he succinctly summarizes the blood circuit. Upon reaching the arterial end he expresses that its path "*... is suggested by the porosities of the flesh and by the veins themselves.*" This expression of "*porosities of the flesh*" does not imply the discovery of capillaries made later by Marcelo Malpighi (*De pulmonibus observationes anatomicae*, Bologna, 1661), but simply the need to glimpse a passage between arteries and veins in the periphery.

Chapter XV. "The circular movement of blood is confirmed by plausible reasons"

He details the driving character of the heart, which he calls the "*life principle.*" Following Aristotle, mentioned repeatedly in this chapter, he finds "innate heat" in the heart, expressing that "*it is necessary for the blood to return again to the source and origin to replenish both heat and spirits.*" He also finds in the perpetual movement of circulation the ability to prevent blood from clotting.

The description he makes of the "*muscular pump*" that helps venous expression in the limbs, facilitating its return, is very interesting; adding that "*due to the movement of the limbs and the compression of the muscles, it is prone and inclined to move (the blood in the veins) from the periphery to the center.*"

Chapter XVI. "The circular movement of the blood is demonstrated by its consequences."

He intelligently applies the concept of circulation to pathology (spread of rabies, syphilis) and therapeutics (medicinal absorption of colocynth, aloes, cantharides, garlic and cordials). Likewise, he wonders about the meaning of the different pulses, because, since Galen it had been accepted that each disease had a pulse.

Chapter XVII. "The movement and circulation of blood are confirmed by what appears in the heart and what results from anatomical dissection."

He makes a description of the ventricles, including their internal conformation, distinguishing the right from the left by their function. In this way he explains the difference in thickness of each ventricular wall: (the left ventricle) "*... has walls three times stronger and more robust than that of the right*", later adding the functional concept of its cause: "*since it must carry the blood further, throughout the body.*" He determines that the heart has a muscular structure by reporting "not without foundation did Hippocrates consider in his book *De Cordis* that the heart is a muscle."

Next, he reviews the use of the sigmoid and atrioventricular valves. Regarding the mitral valve he says "*Those of the left ventricle are two (the leaflets) in the shape of a miter*", an analogy with the papal hat already proposed by Vesalius.

There is also an essay on the explanation of the pulse, which he considers as an epiphenomenon of cardiac impulse. He also relates the thickness of the arterial tunic to the difference in pulse, determining that this tunic is thicker the closer it is to the heart:

"*the closer the arteries are to the heart, the more their constitution differs from those of the veins, and the more robust and ligamentous they are.*" He astutely establishes that the more distal the artery, the lower the driving force. The expression "*sometimes we feel the pulse in the teeth, in the tumors and in the fingers*" must be understood as a precursor statement of the capillary pulse.

Similarly, a reference is made to the "*arterial vein*" with the structure of an artery and the "*venous artery*" of a vein. This nomenclature may have originally been due to Andrea Cesalpino.

The completion of this last chapter and therefore of the book maintains the same fidelity to the work based on reasoning and experimentation to demonstrate blood circulation, appealing to both deep observation and an anatomy in movement. His final words are clear "*... when practicing vivisection (the circulatory phenomena) shed a lot of light... the explanation of all of them and the causes by which they are thus constituted, is extremely difficult unless it fits our way of seeing.*"

The Importance of Evaluating Remodeling

La importancia de evaluar el remodelado

JUAN A. MOUKARZEL [1, MTSAC], JOAQUÍN PEIRANO[2], MARIANA DAICZ[2]

Adverse left ventricular remodeling is a myocardial maladaptive process characterized by morphological changes in the structure and shape of the chamber with subsequent impaired function.

It is a common cause of heart failure occurring in up to 30% of anterior infarctions and 17% of inferior infarctions, according to some series. (1)

From a pathophysiological perspective, the process involves a sequence that could be divided in two stages: an early acute stage in the site of acute myocardial infarction (AMI), and a second late stage of remodeling at least a month after the event. The latter is potentially reversible and includes both structural and biochemical changes, occurs in sites other than site of infarction, and involves viable cardiomyocytes. (2)

As a result, noninfarcted remote myocardial tissue becomes hypertrophic and undergoes adaptive dilatation in response to increased wall stress; this is not necessarily the case in all infarctions and is not necessarily progressive. (3,4)

The connection among extensive infarction, remodeling, and the rate of cardiovascular events is well known. It has been interesting to read the article *Left Ventricular Remodeling After Infarction: A Perspective from Gated-Spect Myocardial Perfusion Imaging*, where L. San Miguel et al. (5) evaluate risk factors associated with adverse remodeling after a non-extensive infarction. This model identifies diabetes as a risk factor independently associated with adverse remodeling in less extensive infarctions.

While no clinical endpoints were evaluated, pathophysiological evidence supports this finding and identifies diabetes as a factor related to adverse remodeling.

As suggested by this article, gated-SPECT myocardial perfusion at rest is an accessible, less complex method with a shorter time of acquisition than magnetic resonance imaging, and can be used to evaluate adverse remodeling through the association between necrotic burden and left ventricular ejection fraction.

While this is a retrospective work sensitive to potential unidentified confounders, it suggests, like many others, the importance of more aggressive treatment for heart failure in diabetic patients.

This information, together with other method-related aspects –such as AMI localization and degree of motility–, provide a wider view for clinical cardiologists when considering other variables and, therefore, enable enhancement of the relevant treatment for the benefit of the patient.

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Rev Argent Cardiol 2024;92:169-170. http://dx.doi.org/10.7775/rac.v92.i2.20762

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AUTHORS' REPLY

We deeply appreciate our colleagues' interest in our article. As above stated, the association between diabetes and left ventricular remodeling has been described in previous articles. Our report from a nuclear cardiology department database was our modest contribution and shows that SPECT myocardial perfusion imaging may provide valuable information on this subject. We believe that these concepts may specially help colleagues who are unable to perform other more complex cardiologic images.

Lucas San Miguel MTSAC,

N-acetyl Cysteine and Post-infarction Remodeling

N-acetil cisteína y remodelado post infarto

MARÍA FLORENCIA PÉREZ[1, 2], JUAN MANUEL PÉREZ[3], JOAQUÍN PÉREZ[1]

Ischemic cardiomyopathy is the main cause of worldwide mortality. Despite progress in the strict control of risk factors and in anti-ischemic and antithrombotic treatment, patients suffering from acute myocardial infarction (AMI) present with a worse prognosis. A concept supporting the unfavorable outcome of these patients is cardiac remodeling following the irreversible loss of cardiac muscle, with the resulting increase in the risk of heart failure and sudden death. (1)

Pathophysiologically, during AMI there is an increase of oxidative stress, triggered by the over production of oxygen-derived free radicals (2) which are deleterious for the cardiomyocytes and lead to a reduction of their viability, greater hypertrophy, and ventricular remodeling. (3)

In their interesting study, M Rodriguez et al. used an experimental AMI model in rabbits with the aim of reducing this oxidative stress by increasing antioxidant species, through N-acetyl cysteine (NAC) administration in animals with AMI induced by ligation of the left coronary artery. (4) N-acetyl cysteine is a precursor of cysteine, an amino acid catabolized by gamma-glutamyl cysteine synthetase producing glutathione, the main endogenous antioxidant system of the organism against oxidative stress. (5)

After a 28-day follow-up period, the AMI group treated with NAC significantly reduced non-infarcted zone thinning, left ventricular (LV) dilation, the increase of LV diastolic pressure and ejection fraction impairment.

The results of this study support the importance of targeting post AMI ventricular remodeling and suggest that antioxidant therapy, as NAC administration, could provide significant benefits to improve the prognosis of patients, with a favorable effect in the initial stages of cardiac remodeling. However, studies in humans, applicable to the general population, as well as randomized clinical trials, are necessary to extend this knowledge and reproduce these results.

These findings highlight the need to continue the research in this field to develop new therapeutic strategies that benefit the affected population.

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Rev Argent Cardiol 2024;92:170-171.. http://dx.doi.org/10.7775/rac.v92.i2.20763

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AUTHORS' REPLY

On behalf of the research team, I wish to express our most sincere thanks to Drs. María Florencia Pérez, Juan Manuel Pérez and Joaquín Pérez, for their interest and thorough and valuable comments on our study: *Administration of N-acetylcysteine Attenuates Post-Myocardial Infarction Remodeling*. Their observations and analysis enrich our publication.

As mentioned in the article, post myocardial infarction remodeling refers to the structural changes that take place in the heart after a myocardial infarction (MI), affecting its geometry. In its chronic evolution, it provokes progressive functional impairment and heart failure, significantly affecting patient quality of life and increasing the long-term risk of adverse events. Management of ventricular remodeling includes strategies to reduce the working load of the heart, improve the contractile function and prevent complications. However, even with available therapeutic resources, an unfavorable outcome occurs in a high number of patients. Therefore, it is necessary to develop new strategies to modify this harmful situation.

Oxidative stress increasingly emerges as a pathophysiological mechanism of myocardial injury, involved in different pathological processes. Recent experimental animal and clinical studies, have pointed out that during post MI remodeling and heart failure, oxidative stress due greater oxygen-derived free radical production plays a key role, in both early as late stages. The search for alternative therapies that decrease myocardial damage caused by oxidative stress have led to consider N-acetylcysteine as an antioxidant agent. Its use as such in other medical areas is a very active field of research. Though studies in the cardiovascular area are scarce, the results are promising.

The search for new therapeutic resources can start knowing the mechanisms involved in the development and/or maintenance of pathological processes, as attempted in our study. Unfortunately, this type of work usually goes unnoticed or does receive careful attention. However, preclinical findings frequently set the foundations for future clinical progress and improved patient care.

As expressed by Dr. Pérez et al., human studies are necessary to confirm our results and benefit the affected population. Nevertheless, their comment endorsing the importance of targeting ventricular remodeling after an acute myocardial infarction encourages us to persist in a more detailed study of this field and to continue exploring the afore-mentioned and new strategies.

Manuel Rodríguez [MTSAC]

LETTER TO THE EDITOR

Low-density Lipoprotein Cholesterol (LDL-C) and Atherosclerotic Cardiovascular Disease: is More Evidence Necessary to Attribute its Causal Role?

Colesterol asociado a lipoproteína de baja densidad (cLDL) y enfermedad cardiovascular aterosclerótica: ¿es necesaria más evidencia para atribuir su rol causal?

PABLO CORRAL[1, MTSAC,] , AUGUSTO LAVALLE COBO[2, MTSAC,]

Atherosclerosis can be defined as a chronic and progressive disease of the elastic arteries, characterized by the accumulation and retention of cholesterol in apolipoprotein B (ApoB) containing lipoproteins, mainly low-density lipoproteins, in the subendothelial space of these arteries. This concept seems so simple that Jan Borén and Kevin Jon Williams chose "a triumph of simplicity" as part of the title of an interesting review that describes the aforementioned. (1) Accordingly, William Clifford Roberts, modifying one of the phrases that brought Bill Clinton to the presidency of the United States at the beginning of the last decade of the 20th century, titled an editorial "*It's Cholesterol, Stupid*" in which he used four arguments to explain the causal role of cholesterol associated with low-density lipoproteins (LDL-C) in atherosclerosis. (2) In his review, Borén claims that it is a fact, not a hypothesis, that elevated cholesterol levels transported by lipoproteins with Apo B have a causal role in the genesis of atherosclerosis, and that lowering LDL-C also reduces the risk of cardiovascular events. Similarly, Clifford Roberts implies something similar when he quotes the word cholesterol "hypothesis" in the development of atherosclerosis.

This view of atherosclerosis is not universally accepted, it has its detractors, and this has motivated the publication of new studies, which seem to contribute to Jan Borén's "triumph of simplicity".

Along these lines, a study published in JAMA, some months ago, adds to the body of evidence that for years has supported the causal role of LDL-C in the development of atherosclerotic cardiovascular disease (ASCVD). This interesting study analyzed the impact on a group of people with variations in two genes (APOB -apolipoprotein B- and PCSK9 – proprotein convertase subtilisin/kexin type 9) related to lipid metabolism, more precisely in reference to LDL-C levels. (3)

For this analysis, two large databases were considered (the National Heart, Lung, and Blood Institute -NHLBI- and the UK Biobank), with a total number of 209 537 analyzed individuals. (3)

The analysis found in 0.4% of participants (n=801) a variant or mutation in the APOB or PCSK9 genes, associated with a decrease in the LDL-C level (47 mg/dL on average) compared with individuals without the genetic variant. Carriers of the genetic variant had an average of 80 mg/dL LDL-C, whereas non-carriers had an average of 128 mg/dL LDL-C. After a mean follow-up of 21.5 years, the incidence of coronary events reported was 8.6% in mutation carriers and 16% in non-carriers, which corresponds to a reduction of 49% in the adjusted risk of developing coronary heart disease. Interestingly, this result was observed despite an 8-fold greater use of statins and other lipid-lowering agents in the group not carrying the variants. (3) (Figure)

This finding is in line with previous studies of similar characteristics and design, which analyzed the impact of having a genetic variant associated with lower levels of LDL-C and the benefit in terms of decreased risk of atherosclerotic cardiovascular events. (4-6)

When we refer to the consistency of studies and scientific evidence, we observe that once again science shows us the preponderant and central role of LDL-C in the genesis and progression of ASCVD, which unfortunately continues to be the first cause of morbidity and mortality in Argentina and across the world. (7)

From the first purely epidemiological studies, through genetic evidence (Mendelian randomization

Rev Argent Cardiol 2024;92:172-174. http://dx.doi.org/10.7775/rac.v92.i2.20477

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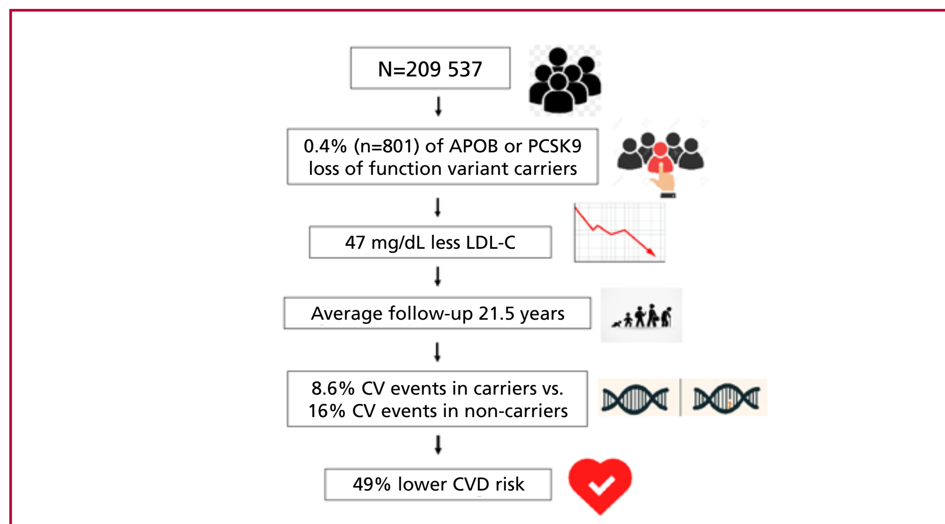

Fig. 1. Prognostic impact of a genetic variant associated with LDL-C decrease.

CVD: cardiovascular disease

studies and genetic disorders of lipid metabolism) and finally the evidence derived from pharmacological intervention, science has shown us concordance, until now irrefutable, of this causal association between LDL-C and CVD of atherosclerotic origin. And it is the accumulated atherogenic load of LDL-C over the years (mg/dL/years) that determines the risk of suffering from atherosclerosis, which is difficult to observe when it is <5000 mg/dL/years. (8) For more than five years now, a reduction in the risk of cardiovascular events in studies with non-statin drugs such as ezetimibe, PCSK9 inhibitors and recently bempedoic acid has been found in pharmacological intervention studies. This last study included a population of patients at high cardiovascular risk but without established cardiovascular disease, with partial or total intolerance to statins. A benefit was observed in a proportion similar to that expected for equivalent reductions in LDL-C levels with statins. (9-12) Once again this reinforces that, regardless of the pleiotropic effect that each pharmacological group may have, the final common pathway responsible for most of the benefit is explained by the reduction of plasma levels of LDL-C and ApoB.

The benefit then of being aggressive in terms of beginning lipid-lowering therapy (*the sooner, the better*) and in terms of intensity (*the lower, the better*) is evidenced again in the observational study that we present, with an unquestionable methodology and design, and with clear implications when assessing the potential beneficial effect of reducing LDL-C levels in our patients. (3)

The above mentioned clearly adds to the basic and elementary recommendation of adopting a healthy lifestyle in which we can include an adequate diet, systematic physical activity, avoiding smoking and maintaining a good rest, among other actions. The synergy of these two strategies clearly has the power to modify the natural course of ASCVD and in this way combat the number one cause of morbidity and mortality in our country and worldwide. (13)

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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JORGE THIERER[MTSAC,]

Is percutaneous coronary intervention useful in non-flow-limiting vulnerable plaques? PREVENT trial

Park SJ, Ahn JM, Kang DY, Yun SC, Ahn YK, Kim WJ, et al. Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial. **Lancet 2024;403:1753-65. https://doi.org/10.1016/S0140-6736(24)00413-6**

Rupture and thrombosis of lipid-rich coronary atherosclerotic lesions (known as vulnerable plaques) have been described as the most common cause of acute coronary syndrome and sudden cardiac death. Vulnerable plaques often have no hemodynamic consequence and do not limit flow. On intravascular imaging they are recognized as thin-cap fibroatheromas, containing a large plaque and a lipid-rich necrotic core, separated from the lumen by a thin fibrous cap. We know that vulnerable plaques increase the risk of major adverse cardiac events. Until now, clinical practice guidelines recommend the use of pharmacological treatment (antiplatelet agents, high-intensity statins) for vulnerable plaques, but do not consider percutaneous coronary intervention (PCI), unless they limit flow or have caused an acute coronary syndrome. Theoretically, PCI could seal and passivate vulnerable plaques, reducing the risk of acute coronary events. Until now, a single randomized trial in 182 patients showed that PCI of vulnerable plaques could enlarge the coronary lumen and thicken the fibrous cap in 2 years, but this study was not powered to demonstrate clinical outcomes (major adverse cardiac events in 4.3% with PCI vs 10.7% with exclusive medical treatment at 2 years, p=0.12). It is not clear whether it is advisable to revascularize vulnerable plaques without hemodynamic repercussion, that is, they do not generate ischemia.

The multicenter, open-label, randomized, controlled PREVENT trial was conducted at 15 hospitals in South Korea, Japan, Taiwan, and New Zealand. Its objective was to evaluate the effects of PCI on major adverse cardiovascular events in patients with vulnerable, high-risk, non-flow-limiting plaques identified by intracoronary imaging. It included patients with stable coronary artery disease or acute coronary syndromes undergoing cardiac catheterization. Flow-limiting lesions, with a fractional flow reserve (FFR) ≤0.80, and lesions causing acute coronary syndrome were treated with PCI with drug-eluting stents before randomization. All untreated, non-culprit lesions, which were clearly not responsible for the presenting clinical syndrome, with a stenosis ≥ 50% by visual estimation were functionally evaluated by FFR. Any intermediate, non-flow-limiting lesion with FFR >0.80 and non-culprit was evaluated with gray-scale intravascular ultrasonography (IVUS), radiofrequency IVUS, a combination of gray-scale intravascular IVUS with near-infrared spectroscopy or optical coherence tomography (OCT). Vulnerable plaques were defined as lesions with at least two of the following four characteristics: a minimum luminal area <4 mm^2, defined by IVUS or OCT; a plaque burden >70% by IVUS; a lipid-rich plaque defined by near-infrared spectroscopy, or a thin-cap fibroatheroma detected by radiofrequency IVUS or OCT. The main exclusion criteria included previous surgical or stent revascularization, three or more target lesions, or two lesions in the same artery, highly calcified or angulated lesions, or bifurcation lesions requiring treatment with two stents. Initially, resorbable scaffolds were used; when they were withdrawn from the market, everolimus-eluting cobalt-chromium metal stents were used. Patients with one or two vulnerable non-flow-limiting plaques were randomly assigned (1:1) to a strategy of PCI plus optimal medical therapy or optimal medical therapy alone. After PCI, dual antiplatelet therapy was administered for 6 or 12 months depending on clinical presentation and anatomical complexity. Treatment with high-dose statins was recommended. Clinical follow-up was performed 1, 6, 12, and 24 months after randomization and every year thereafter.

The primary endpoint was a composite of cardiovascular death, target vessel myocardial infarction, or target vessel revascularization due to ischemia, or hospitalization for unstable or progressive angina, at 2 years after randomization. Secondary endpoints were the individual components of the primary composite endpoint, death from any cause, any myocardial infarction, any revascularization, stent or scaffold thrombosis, stroke, bleeding events, and the combination of death from all causes, myocardial in-

Rev Argent Cardiol 2024;92:175-180. http://dx.doi.org/10.7775.rac.v92.i2.20760

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farction, or repeated revascularization. To calculate the sample size, an incidence of the primary endpoint at 2 years of 8.5% in the preventive PCI group and 12% for the medical treatment alone group was assumed, which implies a relative risk reduction of 30%. With 1600 patients included there would be a power of 80%, with a two-tailed p value of 5%, assuming a loss to follow-up and a crossover rate of 7%. Between September 2015 and September 2021, 5,627 patients were assessed for eligibility; 3,562 patients had intermediate non-flow-limiting lesions (FFR >0.80) that were evaluated with intracoronary imaging. Vulnerable plaques were found in 1608 (45%), and 1606 patients were included in the trial, with 1672 qualifying lesions; 803 patients with 831 lesions in the preventive PCI plus optimal medical treatment group and 803 patients with 841 lesions in the optimal medical treatment alone.

The median age was 65 years (interquartile range 58-71); 73% were men, 31% had diabetes, 84% had stable coronary artery disease, 12% unstable angina, and 4% a myocardial infarction within 1 week. Vulnerable plaques were assessed by grayscale IVUS in 95% of patients; radiofrequency IVUS was used in 71%, near-infrared spectroscopy in 42%, and OCT in 5%. Regarding the predefined criteria for plaque vulnerability, in 97% of the patients a minimum luminal area <4 mm^2 was verified, in 96% a plaque load >70%, in 11% a high lipid content and in 5% thin-cap fibroatheromas. Eighty-nine percent had at least two defined images characteristic of vulnerable plaque.

PCI of non-flow-limiting lesions was performed in 91% of the 803 patients assigned to preventive PCI, with bioabsorbable scaffolds in 33%, and with cobalt-chromium everolimus-eluting metallic stents in 67%. In the preventive PCI group, 9% crossed to receive medical treatment only. In the medical therapy group, 1% switched to PCI. The use of dual antiplatelet therapy was higher in the PCI group. More than half of the patients in both groups received high-intensity or moderate-intensity statins plus ezetimibe. The mean LDL cholesterol was 64±21 mg/dL in both groups at the last follow-up.

The 2-year follow-up was completed in 97% of patients. The median duration of follow-up was 4.3 years. The maximum duration of follow-up was 7.9 years in both groups. At 2 years, the primary endpoint occurred in 0.4% of patients in the preventive PCI group and 3.4% in the optimal medical therapy group, $p=0.0003$. The effect was directionally consistent for each component of the primary composite endpoint. The composite risk of death from all causes, myocardial infarction, or any revascularization was also lower. The number needed to treat with preventive percutaneous coronary intervention was 45.4 to prevent one primary endpoint event in 2 years and 87.7 to prevent cardiac death or target vessel myocardial infarction in 2 years. Stroke and hemorrhagic events did not differ between the two groups. The per-protocol and real-treatment analysis yielded similar results.

The concept of preventive PCI to render vulnerable high-risk plaques passive assumes that neointimal development over the stent or scaffold would functionally thicken the fibrous cap, reducing the risk of rupture. We know that a high plaque burden, a small minimum lumen area, a high lipid content, and a thin fibrous cap are associated with future cardiac events, and the risk increases with the number of adverse features present. Currently, clinical guidelines recommend PCI only for flow-limiting lesions or those responsible for acute coronary syndromes. However, studies have shown that cardiovascular events arise from vulnerable plaques, whether or not they are flow-limiting. The PREVENT trial challenges conventional wisdom by demonstrating reduced risk of major events with preventive PCI in commonly untreated lesions.

Importantly, patients in both groups were treated with optimal medical therapy and strict control of risk factors, achieving low LDL concentrations.

We can cite several limitations. First, the trial was open, which introduces observation bias. It is true that this does not apply to hard endpoints such as death or heart attack, but it does not rule out that some components of the cotreatment could differ. In fact, there was a difference in the use of double antiaggregation, and it is striking that the main body of the publication does not quantify this difference. The low incidence rate of the primary endpoint (in the medical treatment arm 3.4% at 2 years when expected 8.5%) may be due to the fact that the majority of patients had chronic coronary syndromes and the excellent control of risk factors.

But it is essential to highlight that the very concept of vulnerability is under discussion. Plaque vulnerability is a dynamic condition: some vulnerable plaques could stabilize without events, while stable plaques could transition and become vulnerable later, and plaques of different maturity often coexist. Up to three-quarters of vulnerable plaques could evolve to a more stable phenotype. Less than 5% of vulnerable plaques evolve with major events. In contrast, more than 95% of autopsies of patients with sudden death show myocardial hypertrophy and fibrosis. The phenomenon of plaque erosion (endothelial desquamation adjacent to the atherosclerotic plaque, without rupture of the fibrous cap) appears to be a more frequent phenomenon than traditional rupture. While rupture occurs in plaques with the characteristics evaluated in the trial and is accompanied by red thrombi rich in blood cells and fibrin, erosion occurs in lesions with the fibrous cap intact,

lower lipid content, and white thrombi rich in platelets. Viewed in this way, it is clear that our ability to predict events and which of all the manifestations of atherosclerotic disease in a particular patient will be responsible for a serious event seems illusory. The concept of vulnerable patient (vulnerable plaque, with vulnerable blood, prone to thrombotic phenomena, and vulnerable myocardium, with structural alterations that predispose to malignant ventricular arrhythmia) implies a much broader vision of cardiovascular risk. In this sense, strict metabolic control and lifestyle modification emerge as probably more cost-effective behaviors.

REDUCE-AMI trial: lack of evidence about the benefit of treating with beta-blockers patients with myocardial infarction and preserved left ventricular ejection fraction.

Yndigegn T, Lindahl B, Mars K, Alfredsson J, Benatar J, Brandin L, et al. Beta-Blockers after Myocardial Infarction and Preserved Ejection Fraction. **N Engl J Med 2024;390:1372-81. https://doi.org/10.1056/NEJMoa2401479**

Clinical trials from the 1980s and 1990s demonstrated that long-term beta-blocker therapy after acute myocardial infarction (AMI) reduces mortality by approximately 20%. These trials primarily involved patients with large infarcts and low left ventricular ejection fraction (LVEF), and this occurred at a time before the routine use of percutaneous coronary interventions, dual antiplatelet therapy, high-intensity statin therapy, and renin angiotensin aldosterone system antagonists. A meta-analysis by S. Bangalore et al. in 2014 suggested that in the era of modern reperfusion strategies, beta-blockers did not significantly reduce mortality. Data are lacking on the effect of long-term treatment with beta-blockers in patients with AMI and preserved LVEF. Divergent conclusions have emerged from extensive observational studies and meta-analyses of such studies. Despite this, current guidelines recommend the use of beta blockers after an AMI.

The REDUCE-AMI trial investigated whether long-term beta-blocker treatment in patients with AMI and preserved LVEF reduces a composite endpoint of death from any cause or new AMI. It was a prospective, randomized, open-label, pragmatic, registry-based clinical trial, conducted in Sweden (38 centers), Estonia (1 center), and New Zealand (6 centers). It enrolled patients between 1 and 7 days after an AMI who had undergone coronary angiography and who had LVEF ≥50% on echocardiogram. They also had to have documented obstructive coronary artery disease (stenosis ≥50%, or a fractional flow reserve ≤0.80 at any time before randomization). The main exclusion criterion was indication or contraindication for treatment with beta-blockers. Randomization was carried out using a web-based system. The beta-blockers used were metoprolol (at least 100 mg daily) as the first option and bisoprolol (at least 5 mg daily) as an alternative. Patients were required to continue beta-blocker treatment after discharge until a contraindication appeared. Patients randomly assigned to the group without beta-blockers were discouraged from using them unless there was a compelling indication.

The primary endpoint was a composite of death from any cause or new AMI. Secondary endpoints were death from any cause, death from cardiovascular causes, new AMI, and hospitalization for atrial fibrillation or heart failure as primary diagnoses. Safety endpoints were hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or pacemaker implantation; hospitalization for asthma or chronic obstructive pulmonary disease (as primary diagnosis), and hospitalization for stroke. The data were obtained from different national registries. The bulk of the information comes from the Swedish SWEDEHEART registry.

To calculate the sample size, it was assumed that the annual incidence of the primary end point would be 7.2% in the group without beta-blockers, and that these would reduce the risk by 16.7% (1.2% absolute risk reduction per year, considered the least important difference to detect). During the trial, total event counts by blinded adjudicators indicated an actual event rate of 3% per year. The sponsor and the steering committee then modified the assumptions: they assumed 25% the minimum important difference to detect a lower risk, which corresponds to a 0.7% absolute risk reduction. With a power of 80% and a 2-tailed p value <0.05, it was calculated that 379 events of the primary endpoint would be necessary, which was expected to occur after including 5000 patients.

From September 2017 to May 2023, 5020 patients were randomized, 95.4% in Sweden. The median age was 65 years, 22.5% were women, and 35.2% had an ST-segment elevation AMI; 46.2% had hypertension, 14% diabetes, 7.1% had previous AMI. Near 11 % of patients were already receiving beta blockers. The median systolic blood pressure was 150 mm Hg; 55.4% had one-vessel disease, 27% had two-, and 16.6% had three-vessel or left main coronary artery disease. Percutaneous coronary intervention (PCI) was performed in 95.5% and coronary artery bypass grafting in 3.9%. At discharge, 97.4% were receiving aspirin, 95.8% a P2Y12 receptor inhibitor, 80.2% a renin angiotensin system inhibitor or antagonist, and 98.5% a statin.

Of the 2508 patients assigned to beta-blockers, 62.2% received metoprolol (a median dose of 100

mg daily) and the rest received bisoprolol (a median dose of 5 mg daily).

The median follow-up was 3.5 years (interquartile range, 2.2 to 4.7) in each trial arm. The primary endpoint occurred at 2.4% per year in the beta-blocker arm and at 2.5% per year in the non-beta-blocker arm (HR 0.96, 95% CI 0.79-1.16; p=0 ,64). There was also no reduction in the incidence of each of the secondary end points. Adjustment for age, diabetes, or prior AMI did not change the results. There was no difference in the incidence of safety endpoints.

The REDUCE-AMI trial calls into question the conduct of prescribing beta-blockers to all patients with AMI, since it points out that in patients with AMI and LVEF ≥ 50% there is no clear benefit from the intervention. Although it does not rule out a small beneficial or harmful effect, the time-to-event curves were overlapping throughout follow-up and there was no difference in the primary endpoint or each of the secondary endpoints, making a clinically relevant difference very improbable. It is interesting to remember that also in the case of heart failure with preserved LVEF, the benefit of beta-blockers is under discussion, and appears reduced compared to other interventions.

But we want to make some observations. The doses of beta-blockers used in this trial were lower than in previous trials. Fourteen percent of those assigned to the no-beta-blocker group crossed arms and were taking beta-blockers after 1 year of follow-up. We cannot rule out the possibility that this crossover may have contributed to the null effect of the intervention. And we want to highlight that included patients had a high median systolic blood pressure, high prevalence of one-vessel disease, two-thirds an AMI without ST- segment elevation, and almost universal use of PCI. That is, a population with low risk of events, with a very low pretest probability of obtaining benefit from beta-blocker treatment. Although the favorable effect of these drugs in patients with LVEF ≤ 40% is clear (a fact confirmed by different meta-analyses in the context of AMI or heart failure), we should not even extrapolate the results of PREVENT trial to patients with AMI. and LVEF between 41% and 49%, where some analyzes suggest benefit. Other ongoing trials (including BET-AMI and REBOOT) are examining long-term treatment with beta-blockers in patients with AMI and a broader definition of preserved LVEF, with a cut-off value of 40%. Presumably, the lower the LVEF of the patients included, the greater the benefit of the treatment.

One last comment about the design: a pragmatic (reduction of procedures complexity) and registry-based trial (easily accessible data), as a way to facilitate the investigation of clinically relevant topics, with lower costs.

No impact of empagliflozin on the prognosis of acute myocardial infarction: the EMPACT-MI trial

Butler J, Jones WS, Udell JA, Anker SD, Petrie MC, Harrington J et al. Empagliflozin after Acute Myocardial Infarction. **N Engl J Med 2024;390:1455-66. https://doi.org/10.1056/NEJMoa2314051**

In recent decades, the treatment of acute myocardial infarction (AMI) has experienced a series of advances that have significantly reduced in-hospital and long-term mortality: antiplatelet agents, early reperfusion treatment (with fibrinolytics and now mainly with coronary angioplasty), the use of neurohormonal antagonists (renin-angiotensin system inhibitors or antagonists, beta-blockers, of mineralocorticoid receptor antagonists) and statins in high-intensity treatment. For a decade, sodium-glucose cotransport 2 inhibitors (SGLT2i) or gliflozins have demonstrated strong effects in patients with diabetes, heart failure or renal failure on cardiovascular adverse events, and specifically heart failure progression of renal dysfunction and cardiovascular mortality. So, it was expected that the study of SGLT2i effect in AMI patients would be considered. Let us remember that patients experiencing an AMI, or a very recent AMI were excluded from studies with gliflozins in diabetes, heart failure or kidney failure. The mechanisms by which these drugs could be beneficial in AMI are multiple: decrease in sodium entry into the myocardial fiber, increase in mitochondrial calcium content, attenuation of reperfusion injury and cell necrosis, reverse remodeling, energy improvement by promoting the consumption of ketone bodies, decreased fibrosis, reduction of epicardial fat and improvement in diastolic function. In addition, the attenuation of endothelial dysfunction, the improvement of coronary flow, the decrease in oxidative stress, the attenuation of inflammatory phenomena and neurohormonal activation, the promotion of autophagy, the decrease in glomerular hyperfiltration, the restoration of tubuloglomerular feedback, and the increase in the production of erythropoietin and the oxygen supply to the tissues. In different observational studies on the use of gliflozins in patients with AMI, publication bias led us to know generally positive results, especially in patients with AMI and diabetes, in whom reduction of the in-stent restenosis, the size of the AMI and even cardiovascular mortality were advocated.

After the publication of the randomized trials EMMY (empagliflozin vs placebo in patients with large AMI, in which the use of the drug generated a decrease in the values of natriuretic peptides and a slight increase in the left ventricular ejection fraction, LVEF) and DAPA -MI (dapagliflozin vs placebo in AMI patients without diabetes, generally with

LVEF < 50%, in which the drug did not demonstrate a clear effect on hard clinical endpoints, only a reduction in diabetes incidence and weight) , we now know the results of the EMPACT-MI trial.

EMPACT-MI was a randomized, multicenter, parallel-group, placebo-controlled clinical trial designed to evaluate the safety and efficacy of empagliflozin in patients at high risk of developing heart failure after AMI with or without ST-segment elevation. The AMI had to have occurred within 14 days prior to admission to the study and coincide with signs and/or symptoms of pulmonary congestion requiring treatment, or new development of ventricular dysfunction, with LVEF <45%. Additionally, the presence of at least one enrichment factor was required: age ≥65 years; that the new LVEF was <35%; myocardial infarction prior to the current one; estimated glomerular filtration rate <60 ml/min/1.73 m^2; atrial fibrillation; type 2 diabetes; elevated natriuretic peptides; uric acid ≥ 7.5 mg/dL; systolic pulmonary pressure ≥ 40 mm Hg; patient not revascularized for AMI, and without plans to do so; 3-vessel coronary lesion; peripheral vascular disease. Patients with a history of heart failure or reduced LVEF before the index AMI, those with estimated glomerular filtration rate <20 ml/min/1.73 m^2, patients with cardiogenic shock, and those who planned to start treatment with SGLT2i were excluded.

The primary endpoint was a composite of time to first hospitalization for heart failure or death from any cause. Secondary endpoints hierarchically established were the times to all hospitalizations for heart failure or death from any cause; all unscheduled cardiovascular hospitalizations or death from any cause; all hospitalizations from any cause or death from any cause; all hospitalizations due to AMI or death from any cause. It was established that the trial would continue until 532 events of the primary end point were recorded, which would ensure, with an annual incidence of the primary end point in the placebo arm of 12.5% and a relative reduction of 23% with empagliflozin, a power of 85% with a 2-tailed p value of 0.05. Considering an annual loss of 1% of the included patients, it was estimated that 3312 patients were necessary, with an inclusion period of 12 months and a similar follow-up period. The analysis was done by intention to treat. It was proposed that if the inclusion of patients was slower than expected, or the event rate lower than expected, the number of included patients could be increased to 5000. This was accompanied by an extension of the inclusion and follow-up periods. Despite everything, it finally became necessary, to reach the desired power, to include 6500 patients.

Between the end of 2020 and March 2023, 6522 patients at 451 centers in 22 countries were randomly assigned to empagliflozin at a dose of 10 mg daily or placebo. The median age was 64 years; 75.1% were men, 74.3% corresponded to AMI with ST-segment elevation. Sixty-nine percent had a history of high blood pressure, 31.7% of diabetes. 78.3% of patients met the inclusion criterion of LVEF <45%, and 56.9% met the criterion of congestion requiring treatment. There was an overlap of both criteria in 35.6% of the cases. In 75.8% of the patients in whom there was accurate measurement of LVEF, the average was 40%.

Near 29 % of patients had one enrichment criterion, 28.1% 2, 20.7% three, the rest between 4 and 7. The most frequent enrichment factors were age ≥65 years, diabetes type 2 and 3-vessel injury. The median from admission to randomization was 5 days. In 89.3% of the cases, a revascularization procedure was performed (almost all of them coronary angioplasty) and in 10.7%, thrombolytics were used. Treatment at discharge consisted of renin angiotensin system inhibitors/antagonists or sacubitril valsartan in 82% (most cases an angiotensin converting enzyme inhibitor), beta blockers in 86%, and mineralocorticoid receptor antagonists in 47.2%; loop diuretics in 37.8% and some diuretic in 64.7%. Ninety-eight percent received antiplatelet therapy, 90% dual antiplatelet therapy, and 94.7% received statins.

In a median follow-up of 17.9 months, the annual incidence of the primary end point was 6.6% in the placebo arm and 5.9% in the empagliflozin arm (HR 0.90; 95% CI 0.76-1,06; p=0.21). There were no differences in any of the subgroups considered (according to age, LVEF; diabetes, kidney function, blood pressure, congestion, etc.). The analysis of the composite primary endpoint components shows no difference in the annual incidence of mortality (3.8% vs 3.6%) and suggests an effect on the incidence of hospitalization for heart failure (3.4% in the placebo, 2.6% in the empagliflozin arm, HR 0.77; 95% CI 0.60-0. 98). It should be clarified, however, that hospitalization for heart failure was not a prespecified individual endpoint. Statistical significance was not reached in any secondary endpoint. The total number of hospitalizations for heart failure (an exploratory endpoint) was significantly reduced, from 207 to 148 (RR 0.67; 95% CI 0.51-0.89).

Although DAPA-MI and EMPACT-MI trials share common characteristics (patients of similar age, with equivalent prevalence of male sex and ST-segment elevation infarctions, and, in general, similar treatments, close to perfection), EMPACT-MI included more ill patients: patients with diabetes were not ruled out, the LVEF and the glomerular filtration rate were somewhat lower. But most importantly: the annual mortality rate and the annual incidence of hospitalization for heart failure in the placebo arm doubled those of DAPA-MI trial. However, as in this case, the SGLT2i did not modify the incidence of the

composite primary endpoint, basically because all-cause mortality (more than half of the primary endpoint events) did not change with the gliflozin, most likely due to the excellent treatment instituted, which makes it very difficult for a specific intervention to generate an additional and significant reduction in mortality. The effect on hospitalization for heart failure was not a prespecified endpoint, so, from a methodological point of view, it is only enough to generate hypotheses. As it is highly unlikely that studies like those cited will be repeated, we will have to rely on post hoc analysis to act. In this sense, patients who we know benefit most from gliflozins (kidney dysfunction, diabetes, persistent heart failure) may eventually be candidates for treatment after AMI. It is clear that there is no room in the information available for a universal indication of gliflozins, but undoubtely there are patients who are candidates to be treated. Clinical trials have not been able to give us a definitive answer.

The SAC on the go

La SAC en movimiento

Dear Colleagues,

This year we are celebrating the 90th anniversary of the Argentine Journal of Cardiology and the 87th anniversary of the Argentine Society of Cardiology. Also, next October we are celebrating the 50th anniversary of the Argentine Congress of Cardiology, one of the most important scientific events in the world.

Thanks to the effort and commitment of our cardiology community, we have become a highly respected society all over the world, and I am very proud of the position held by the SAC in various congresses and activities.

In addition to our long-standing bonds with the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC), I would like to highlight our close relationship with similar associations in Latin America, in particular, Cardiology Societies from Uruguay, Paraguay, Chile, Brazil, Venezuela, and Peru. We share the same strategy in terms of our cardiology perspective and the commitment to work together and become stronger in order to boost our academic and research capabilities.

At the end of June, the most remarkable Imaging Congress will be held in our country, and in August we are having our 1st Argentine Congress on Cardiometabolic Prevention and Hypertension.

Our biannual medical training course includes more than 400 students from all over the country and this year is incorporating interns and lecturers from Uruguay and Paraguay Cardiology Societies.

Ten interdistrict conferences have been planned this year. The first of them was held in the province of Formosa and was very successful. It is worth underscoring the effort and spirit of our SAC País District to find a place for our Society across the Argentine territory. Also, in March, the Heart and Women Area organized the 1st LATAM Symposium on Cardiac Obstetrics in La Rioja, with the massive involvement of colleagues, nurses, medicine students and community.

The SAC Young Area has been working hard to gather together young cardiologists taking part in different national and international activities through their own inter-societal bonds. Jointly with the Area of "International Young Members", they organize scientific activities with young people from the Spanish Society of Cardiology (SEC), the ACC, the ESC, and Latin America.

Today, Friday April 19th, while writing this letter, I was informed that we have reached 1000 registrations to our different courses. This is the result of the hard work by the Continuous Medical Education office, with the involvement of the various Areas and Councils to develop these courses, which reflects the high level of commitment and academic quality of all members.

WikiCardio has already become a worldwide source of information. Following the agreement signed with the World Heart Federation, it was translated into 49 languages using an artificial intelligence program. We continue to undertake to update and change its contents.

Two international grants, one being part of our agreement with the ACC and the New York Chapter and the other provided by the SAC, will allow the younger members of our community to experience major training at some high-complexity sites abroad. In addition, 6 grants will be given to interns from all over the country taking our Biennial SAC Course, who will be selected according to merit to rotate in their preferred sites in Buenos Aires.

In May we are having a contest to assign 6 grants to the best research works in the country and will also reward the best paper published in the Argentine Journal of Cardiology in the past year.

Thanks to the Press Department, the SAC's and the Argentine Cardiology Foundation's views in terms of medical or political subjects have become known to the population.

But I would not like this letter to conclude just with a mention to the outstanding work by all our members.

Someone once told me that creativity and resilience are a good antidote to the despair and depression caused by different variables. I am certain of that, and I believe my colleagues are too. I have provided objective evidence in that respect.

At a time of, and I am quoting here, "reshaping of policies in our country", there is one policy in particular that was not dealt with before the elections and is not heard of at present: how are we going to care about the Argentinians' health, and how are we going to boost and upgrade the work done by healthcare workers.

Rev Argent Cardiol 2024;92:181-182. http://dx.doi.org/10.7775/rac.v92.i2.20758

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These are times of confrontation, and this is often useless for our purposes as citizens and healthcare professionals. We know that health has been deprived from funds for many years, but that seems to be a profitable business for some. Obviously, not for us.

We have two choices: either we continue to complain, or we undertake to at least try to change things. Our Society has decided and confirmed with actions that we are going for the second choice. We have met with the Ministry of Public Health and funders. We are working on health policies together with all cardiology societies and colleges in Argentina, as well as with (more than 50) societies from other fields. We would like to discuss this with all health authorities and players in Argentina. We do not want to be mere observers. Our objectives are: 1) to achieve equal access to health care for the entire population; 2) to help create a sustainable system once and for all; and 3) to upgrade our professional work.

We need to achieve these goals as a team. Otherwise, we shall be left with scarcity of healthcare workers and poor professional quality. We would not like for just 2 factors –money and luck– to decide the future of our population in terms of health.

Greetings to all of you.

Víctor Mauro MTSAC,
President of the Argentine Society of Cardiology