Argentine Journal of Cardiology
Revista Argentina de Cardiología

AUGUST 2025 - Vol 93 N° 4

www.sac.org.ar

Indexed in SciELO, Scopus, Embase, LILACS, Latindex, Dialnet and DOAJ.
Included in U.S. National Library of Medicine (NLM)
Board in the Núcleo Básico de Revistas Científicas Argentinas of CONICET

ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
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 93 N° 4 AUGUST 2025
Scientific and administrative address
Azcuénaga 980 - (1115) Buenos Aires - Argentina / Tel.: +54-11-4961-6027/8/9 / Fax: +54-11-4961-6020 / e-mail: revista@sac.org.ar
web site: www.sac.org.ar / http://ppct.caicyt.gov.ar/index.php/rac
Editorial and graphic production
Graphic design - digital edition
CF Brand Design & Communication - e-mail: estanislao@cfdisenografico.com.ar / www.cfdisenografico.com.ar

VOL 93 Nº 4
AUGUST 2025

Summary

EDITORIAL

Advantages and Limitations of Killip and Kimball Class A on Admission for Deciding Early Discharge in ST-Segment Elevation Myocardial Infarction. ARGEN-IAM-ST Registry

Ventajas y limitaciones de la clase Killip y Kimball A al ingreso para decidir el alta precoz en el infarto agudo de miocardio con elevación del segmento ST. Registro ARGEN-IAM-ST

JAVIER GUETTA[1,MTSAC]

In this issue of the Argentine Journal of Cardiology, Dr. José Macías et al. take an interesting look at the prognostic value of Killip & Kimball (KK) class A .(1) They argue that this category does not guarantee a hospital stay free of adverse events, mainly for two reasons: first, because despite having a low individual mortality rate, its high prevalence means that its impact on overall mortality is not negligible; and second, because approximately 5% of patients classified as KK A on admission develop heart failure (HF) during hospitalization, and among them, 20% die before discharge.

The KK classification has been a useful tool since its development, providing a simple but valuable resource for prognostic information in patients with ST-segment elevation myocardial infarction (STEMI). Its usefulness is attributed both to its inherent prognostic value and its simplicity, as it is based exclusively on physical examination. (2,3)

The researchers conducted a retrospective analysis of the prospective, observational, and continuous ARGEN-IAM-ST registry, focusing on the in-hospital evolution of patients admitted in KK class A. A total of 7304 patients were included between March 2015 and October 2024, excluding 174 due to lack of data and 90 due to mechanical complications. Median age was 60 years, and 80% were men. KK class A was the most prevalent finding, (77.6%, n=5666 patients), probably attributable to the implementation of better medical treatments and early reperfusion. Classes B, C, and D accounted for 14%, 1.4%, and 7%, respectively. Overall mortality was 7.3%, and mortality among patients with KK A was 2.6%, representing 28% of the registry total mortality.

A total of 311 patients (5.5%) with KK A at admission developed HF during the course of their illness, with a mortality rate of 21%. In contrast, the mortality rate for those who did not develop HF was 1.5% (OR = 17.7; 95% CI: 12.1-24.3; $p < 0.001$). This means that presenting with KK class A and not developing HF during hospitalization has a high negative predictive value (98.5%) for in-hospital mortality.

The independent variables associated with the development of HF were: age >70 years, female sex, diabetes, left anterior descending artery involvement, longer time from onset of pain to consultation, and failed primary percutaneous coronary intervention (PCI). The model showed moderate discriminatory power (C statistic 0.68). (1)

Despite its simplicity and clinical usefulness, the KK classification has limitations, such as subjectivity in the auscultation of crackles or a third heart sound (S3), which depends on the skill of the examiner and may overlap with other concomitant conditions, such as pneumonia, chronic obstructive pulmonary disease (COPD), or acute respiratory distress syndrome (ARDS). (4) Therefore, physical examination should be considered a complementary method. At this point, there is emerging evidence on the contribution of artificial intelligence to improve our semiological skills. (5)

On the other hand, several authors have supplemented the KK classification with natriuretic peptide testing or lung ultrasound. A new scale that combined the latter with KK class, called the LUCK classification, showed that the absence of pulmonary congestion detected by ultrasound conferred a negative predictive value for in-hospital mortality of 98.1% (95%

Rev Argent Cardiol 2025;93:251-252. https://doi.org/10.7775/rac.v93.i4.20924

SEE RELATED ARTICLE: Rev Argent Cardiol 2025;93:255-262. https://doi.org/10.7775/rac.v93.i4.20909

Correspondence: Emiliano Salmeri. E-mail: emilianosalmeri@yahoo.com.ar

[1] Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno (CEMIC), Autonomous City of Buenos Aires, Argentina

CI 93.1-99.5%). The area under the ROC curve of the LUCK classification for in-hospital mortality was 0.89 ($p = 0.001$), compared with 0.86 ($p < 0.001$) for the traditional KK classification. The LUCK classification reclassified patients in 18% of cases. (5) Other studies using lung ultrasound also found that most reclassification was at the expense of patients KK A and B, reflecting the difficulty in correctly detecting mild forms of HF. (6–9)

Beyond these considerations, the value of this analysis, that was carried out in the most representative registry in our field with a cohort of more than 7000 patients, lies in the practicality of its implementation.

Another noteworthy aspect is that it provides a different perspective, focusing the analysis on HF as an evolving event in patients who were classified as KK A. Years ago, in the early 1990s, Carlos Bertolasi's group at Argerich Hospital proposed the use of the Peel and KK indices both in the first hours of evolution and at the time of discharge, calling them "admission" and "discharge" or "stay," respectively. With regard to the latter, the experience of the Coronary Care Unit at Argerich Hospital in 580 patients showed an excellent correlation between stratification at discharge and mortality one year after the infarction, establishing the concept that risk stratification is a continuous process throughout the patient's evolution. (10)

In conclusion, the present study by Macías et al., based on the robust ARGEN-IAM-ST registry, provides an invaluable contribution to the contemporary management of STEMI. Their analysis reinforces a fundamental principle: risk stratification is a dynamic process and does not depend on a single condition at admission. By demonstrating that a subgroup of patients in class KK A, identifiable by simple clinical predictors, has a significant risk of developing HF and mortality, the study challenges complacency and advocates for intensive and prolonged monitoring even in patients who appear to be at lower risk. This finding does not invalidate the usefulness of the KK classification, but rather contextualizes and enriches it. Thus, this study transcends the academic realm to offer practical and crucial guidance for optimizing the safety of early discharge, improving clinical outcomes in our population.

Conflicts of interest

None declared

(See authors conflicts of interest forms on the website).

REFERENCES

1. Macias J, Charask A, Castillo Costa Y, Delfino F, D'Imperio H, Quiroga W. Advantages and limitations of Killip and Kimball A status on admission in the decision to discharge early in ST-segment elevation myocardial infarction. Argen-IAM-ST Registry. Rev Argent Cardiol 2023;93:255-62. https://doi.org/10.7775/rac.es.v93.i4.20909

2. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two-year experience with 250 patients. Am J Cardiol 1967;20:457–64. https://doi.org/10.1016/0002-9149(67)90023-9

3. Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA, TopolEJ. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. JAMA. 2003;290:2174–81. https://doi.org/10.1001/jama.290.16.2174

4. Arts L, Lim EHT, van de Ven PM, Heunks L, Tuinman PR. The diagnostic accuracy of lung auscultation in adult patients with acute pulmonary pathologies: a meta-analysis. Sci Rep 2020;10:7347. https://doi.org/10.1038/s41598-020-64405-6.

5. Kelshiker MA, Bächtiger P, Mansell J, Kramer DB, Nakhare S, Almonte MT, et al. Triple cardiovascular disease detection with an artificial intelligence-enabled stethoscope (TRICORDER): design and rationale for a decentralized, real-world cluster-randomized controlled trial and implementation study. BMJ Open 2025;15:e098030. https://doi.org 10.1136/bmjopen-2024-098030.

6. Carreras-Mora J, Vidal-Burdeus M, Rodríguez-González C, Simón-Ramón C, Rodríguez-Sotelo L, Sionis A, et al. Killip scale reclassification according to lung ultrasound: Killip pLUS. Eur Heart J Acute Cardiovasc Care. 2024;13:566-69. https://doi.org/10.1093/ehjacc/zuae073.

7. Araujo GN, Silveira AD, Scolari FL, Custodio JL, Marques FP, Beltrame R, et al. Admission Bedside Lung Ultrasound Reclassifies Mortality Prediction in Patients With ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Imaging 2020;13(6):E010269. https://doi.org/10.1161/CIRCIMAGING.119.010269.

8. Gargani L. Lung ultrasound: a new tool for the cardiologist. Cardiovascular Ultrasound 2011;9:6. https://doi.org/10.1186/1476-7120-9-6.

9. Scali MC, Zagatina A, Simova I, Zhuravskaya N, Ciampi Q, Paterni M, et al; Stress Echo 2020 study group of the Italian Society of Cardiovascular Echography (SIEC). B-lines with lung ultrasound: the optimal scan technique at rest and during stress. Ultrasound Med Biol 2017;43:2558–66. https://doi.org/10.1016/j.ultrasmedbio.2017.07.007

10. Bertolasi C, et al. Clinical Cardiology. Editorial Intermédica, 1991. Pp. 1838-41

EDITORIAL

Beyond LDL Cholesterol

Más allá del colesterol LDL

EMILIANO SALMERI[1, 2, MTSAC]

If we had to succinctly summarize the key reasons why LDL cholesterol (LDL-C) became the central focus in the management of atherosclerotic dyslipidemia, three core arguments would stand out beyond dispute. The first is the compelling clinical benefit derived from therapeutic interventions—across various drug classes and their combinations—that consistently reduce major adverse cardiovascular events (MACE). These outcomes clearly illustrate the significance of targeting LDL-C.(1-3) The second pillar lies in the well-established linear relationship demonstrating that each 1 mmol/L reduction in LDL-C corresponds to a 22% decrease in MACE risk, a figure that is both intuitive and impactful.(4) Finally, and no less importantly, the absence of a J-shaped curve—together with the broad scientific consensus on the causal relationship between LDL-C and atherosclerosis—reinforces the safety and efficacy of aggressive lipid lowering. This understanding has been crucial in recognizing that intensive treatment prolongs life by directly addressing a core mechanism of the disease. (5) Thus, LDL-C control has become deeply embedded in all clinical practice guidelines and continues to serve as the foundation for setting precise therapeutic targets based on individual cardiovascular risk profiles.

However, the story does not end there—and that is precisely where the work of Pacce O et al., published in this issue of the Revista Argentina de Cardiología (RAC), becomes relevant: it intellectually invites us to look beyond the LDL-C value. (6) The central value of this publication lies in its contribution—based on local evidence—to highlight the importance of not overlooking the broad universe of pro-atherogenic particles that exist beyond LDL-C, even when LDL-C levels are adequately controlled. This is, in essence, an exploration into the world of residual risk and its clinical relevance, with non-HDL cholesterol (non-HDL-C) serving as the vehicle for that journey. Much has already been written about the descriptive capacity of lipid-related residual risk attributed to both non-HDL-C and apolipoprotein B (ApoB) when considering MACE or vascular events.

Although ApoB appears to offer greater discriminatory power for overall atherosclerotic risk (7) and exhibits lower biological variability, (8-10) this study reaffirms that non-HDL-C remains a clinically relevant parameter. Indeed, its cost-neutral nature—requiring no additional resources beyond the standard lipid panel—and its reasonable correlation with ApoB (11) make it a valuable tool, especially in low- and middle-income countries such as Argentina. Moreover, by the end of the article, the strong association between non-HDL-C and short-term MACE in secondary prevention patients—those we encounter daily in our clinical practice—is once again clearly exposed. In this light, the extensive body of work by authors such as Børge Nordestgaard on the clinical impact of triglyceride-rich lipoproteins and remnant cholesterol seems to come alive once again in our region. (12-15)

In conclusion, the article by Pacce O et al. contextualizes the clinical utility of assessing non-HDL-C in the management of our patients—particularly in a country as diverse as Argentina, where financial and technological resources are not always available to support large-scale implementation of even low-cost strategies. It is yet another call to action: to take the initiative in establishing clinical practice guidelines that incorporate treatment goals beyond LDL-C alone, without diminishing its well-established pathophysiological and therapeutic relevance.

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

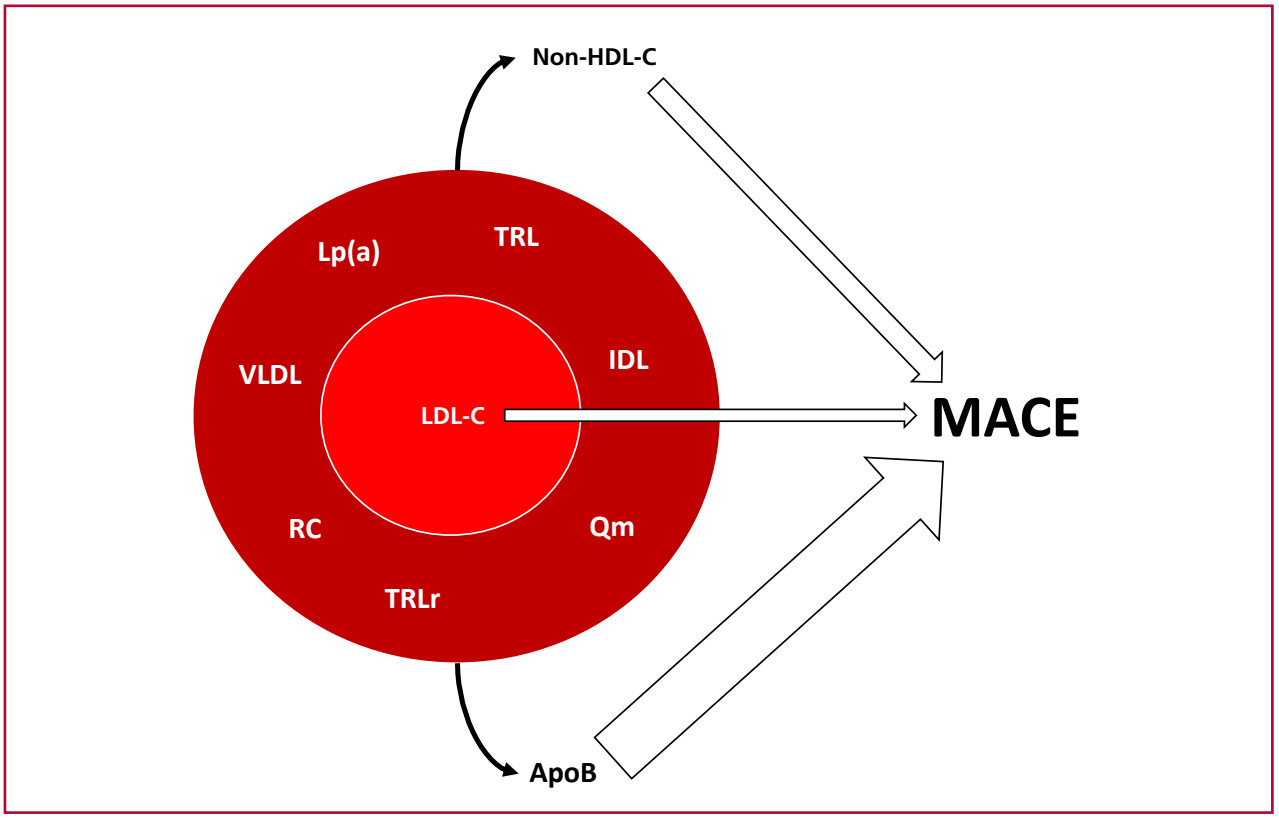
Rev Argent Cardiol 2025;93:253-254. https://doi.org/10.7775/rac.v93.i4.20913

SEE RELATED ARTICLE: Rev Argent Cardiol 2025;93:263-269. https://doi.org/10.7775/rac.v93.i4.20910

Correspondence: Emiliano Salmeri. E-mail: emilianosalmeri@yahoo.com.ar

[1] Former director of the Epidemiology and Prevention Council of the Argentine Society of Cardiology
[2] Coordinator of the Cardiology Service at Clínica OCMI, Autonomous City of Buenos Aires, Argentina

Fig 1. Lipid species and their impact on MACE



ApoB: apolipoprotein B; IDL: intermediate-density lipoproteins; LDL-C: LDL cholesterol; Lp(a): lipoprotein a; non-HDL-C: non-HDL colesterol; Qm: chylomicrons; RC: remnant colesterol; TRL: triglyceride-rich lipoproteins; TRLr: triglyceride-rich lipoprotein remnant; VLDL: very low-density lipoproteins

REFERENCES

1. Redel-Traub G, Smilowitz NR, Xia Y, Berger JS. Systematic review and meta-regression on the duration of LDL-C lowering and major adverse cardiovascular events. Vasc Med 2022;27:375-6. https://doi.org/10.1177/1358863X221098459

2. Khan SU, Khan MU, Virani SS, Khan MS, Khan MZ, Rashid M, et al. Efficacy and safety for the achievement of guideline-recommended lower low-density lipoprotein cholesterol levels: a systematic review and meta-analysis. Eur J Prev Cardiol 2022;28:2001-9. https://doi.org/10.1093/eurjpc/zwaa093

3. Koskinas KC, Siontis GC, Piccolo R, Mavridis D, Räber L, Mach F, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. Eur Heart J 2018;39:1172-80. https://doi.org/10.1093/eurheartj/ehx566

4. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81. https://doi.org/10.1016/S0140-6736(10)61350-5

5. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459-2472. https://doi.org/10.1093/eurheartj/ehx144

6. Pacce O, Vargas Parraga E, Fiori Anabella E, Janches Quiñones J, Cardozo D, Villarreal R, y cols. Beyond LDL Cholesterol: Value of non-HDL Cholesterol as a Predictor of Atherosclerotic Cardiovascular Events in Patients with ST-segment Elevation Myocardial Infarction. Rev Argent Cardiol 2025;93:263-9. https://doi.org/10.7775/rac.v93.i4.20910

7. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–88. https://doi.org/10.1093/eurheartj/ehz455

8. Pischon T, Nöthlings U, Boeing H. Apolipoprotein B Versus Non–High-Density Lipoprotein Cholesterol in Cardiovascular Risk Assessment: Current Evidence and Clinical Implications. J Am Coll Cardiol 2023;81:123-34.

9. Johannesen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. J Am Coll Cardiol 2021;77:1439-50. https://doi.org/10.1016/j.jacc.2021.01.027

10. Katsi V, Argyriou N, Fragoulis C, Tsioufis K. Apolipoprotein B and non–HDL cholesterol for cardiovascular risk assessment: Emerging evidence and clinical implications. Eur Heart J 2023;44:1-10.

11. Welsh P, Sattar N. To ApoB or Not to ApoB: New Arguments, but Basis for Widespread Implementation Remains Elusive. Clin Chem 2023;69:3-5. https://doi.org/10.1093/clinchem/hvac183

12. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res 2016;118:547-63. https://doi.org/10.1161/CIRCRESAHA.115.306249

13. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013;61:427–36. https://doi.org/10.1016/j.jacc.2012.08.1026

14. Johansen MØ, Nielsen SF, Afzal S, Vedel-Krogh S, Davey Smith G, Nordestgaard BG. Remnant cholesterol and myocardial infarction in normal weight, overweight, and obese individuals from the Copenhagen General Population Study. Clin Chem 2021;67:276–87. https://doi.org/10.1093/clinchem/hvaa290

15. Langsted A, Madsen CM, Nordestgaard BG. Contribution of remnant cholesterol to cardiovascular risk. J Intern Med 2020;288:116–27. https://doi.org/10.1111/joim.13059

ORIGINAL ARTICLE

Advantages and Limitations of Killip and Kimball Class A at Admission in Early Discharge Decision-Making in ST-Segment Elevation Acute Myocardial Infarction. ARGEN-IAM-ST Registry

Ventajas y limitaciones de la condición Killip y Kimball A de ingreso en la decisión de alta precoz en el infarto agudo de miocardio con elevación del segmento ST. Registro Argen-IAM-ST

JOSÉ MACÍAS[1], ADRIÁN CHARASK[1, MTSAC], YANINA CASTILLO COSTA[1, MTSAC], FLAVIO DELFINO[1, MTSAC], HERALDO D'IMPERIO[1, MTSAC], WALTER QUIROGA[1], MAURO QUIROGA[1], STELLA MACÍN[1], MARIANO ADAMOWSKI[1], JUAN GAGLIARDI[1, MTSAC]

ABSTRACT

Background: Patients admitted to the coronary care unit with ST-segment elevation myocardial infarction (STEMI) without heart failure (HF) are classified as Killip and Kimball class A (KK A). They usually have a favourable prognosis and are often considered for early discharge. However, this initial assessment may be insufficient, as not all patients experience an uncomplicated clinical course. From a practical perspective, progressive HF is often used as a risk marker for mortality.
Objectives: 1. To determine the incidence of KK class A at admission in patients with STEMI and its role in overall mortality. 2. To establish the incidence of HF during the clinical course of patients classified as KK A at admission and its characterization. To analyze the negative predictive value of the absence of HF during the clinical course on mortality.
Methods: Retrospective analysis of the ARGEN-IAM-ST registry. This prospective observational study was conducted from March 2015 to October 2024. All patients enrolled in the registry were analyzed. HF was considered a complication and defined according to the treating physician's criteria.
Results: From March 2015 to October 2024, 7304 patients were enrolled, with a median age of 60 years (interquartile range, IQR, 52-67); 80% were male. According to the Killip and Kimball classification, 77.6% of patients were class A, 14% class B, 1.4% class C, and 7% class D. The overall mortality rate was 7.3%. For KK A patients, in-hospital mortality was 2.6%, representing 28% of the overall in-hospital mortality rate.
During hospitalization 5.4 % of KK A patients developed progressive HF, and 21% of these patients died. In contrast, among patients who did not develop HF, only 1.5% died (OR 17.77, 95% CI, 12.09-24.35; p<0.001). The absence of progressive HF in KK A patients had a high negative predictive value for mortality (98.5%). Independent variables related to progressive HF in KK A patients were age >70 years, female sex, diabetes, left anterior descending artery involvement, longer symptom-to-door time, and failed primary percutaneous coronary intervention.
Conclusions: Although mortality in KK A patients at admission is low, its contribution to overall mortality is elevated due to its high prevalence at presentation. The absence of HF during the clinical course identifies a group at a very low risk for mortality, supporting safe early discharge.

Keywords: ST-segment elevation acute myocardial infarction - Killip and Kimball - Early discharge

RESUMEN

Introducción: Los pacientes que ingresan a la unidad coronaria con un infarto agudo de miocardio con elevación del segmento ST (IAMCEST) sin insuficiencia cardíaca (IC) constituyen la subcategoría A de la clasificación de Killip y Kimball (KK A). Suelen presentar un excelente pronóstico, y se considera en ellos el alta temprana. Sin embargo, la evaluación inicial puede ser insuficiente, ya que no todos los pacientes evolucionan de manera benigna. Desde un punto de vista práctico frecuentemente se utiliza a la IC evolutiva como un marcador de riesgo para mortalidad.

Rev Argent Cardiol 2025;93:255-262. https://doi.org/10.7775/rac.v93.i4.20909

SEE RELATED ARTICLE: Rev Argent Cardiol 2025:93:251-252. https://doi.org/10.7775/rac.v93.i4.20924

Received: 04/23/2025 – *Accepted:* 07/04/2025

Correspondence: José Macías. México 1467, Ciudad Autónoma de Buenos Aires, Argentina. Email: joseig.89escritor@hotmail.com

[1] On behalf of the researchers of ARGEN-IAM-ST Registry
Argentine Society of Cardiology and Argentine Federation of Cardiology

Objetivos: 1. Determinar la incidencia de la subcategoría KK A al ingreso en pacientes con IAMCEST, y su participación en la mortalidad global. 2. Establecer la incidencia de IC durante la evolución de los pacientes clasificados como KK A al ingreso y su caracterización. Analizar el valor predictivo negativo de la ausencia de IC durante la evolución sobre la mortalidad.
Material y métodos: Análisis retrospectivo del registro ARGEN-IAM-ST, un estudio prospectivo y observacional, en el periodo comprendido entre marzo de 2015 y octubre de 2024. Se incluyó el total de los pacientes ingresados al registro. La IC fue considerada como complicación y definida según criterios del médico tratante.
Resultados: Desde marzo de 2015 a octubre de 2024 se registraron 7304 pacientes con una mediana de edad de 60 años (rango intercuartílico, RIC, 52-67), el 80 % de sexo masculino. La distribución de acuerdo a la clasificación de Killip y Kimball fue 77,6%, 14%, 1,4% y 7% para las categorías A, B, C, D respectivamente. La mortalidad total fue de 7,3%. La mortalidad intrahospitalaria de los pacientes con KK A fue de 2,6%, un 28% de la mortalidad global.
El 5,4% de los pacientes KK A desarrollaron IC evolutiva, de los cuales el 21% falleció; de aquellos que no desarrollaron IC durante la internación, falleció solo el 1,5 % (OR 17,77 IC 95%, 12,09-24,35; p<0,001). La ausencia de desarrollo de IC evolutiva en los pacientes KK A tuvo un elevado valor predictivo negativo para mortalidad: 98,5%. Las variables independientemente asociadas a IC evolutiva en los pacientes con KK A fueron: edad mayor de 70 años, el sexo femenino, la diabetes, el compromiso de la arteria descendente anterior, un mayor tiempo desde el dolor a la consulta, y la angioplastia coronaria (ATC) primaria fallida.
Conclusiones: Si bien la mortalidad de los pacientes que ingresan en KK A es baja, su contribución nominal a la mortalidad total es elevada debido a que es la forma de presentación más frecuente. La ausencia de IC en la evolución selecciona un grupo de muy bajo riesgo de mortalidad que permite asegurar un alta temprana.

Palabras clave: Infarto agudo de miocardio con elevación del segmento ST - Killip y Kimball - Alta precoz

INTRODUCTION

Patients suffering from acute myocardial infarction with ST-segment elevation (STEMI) have a high hospital mortality rate, which, according to various records, ranges from 7% to 9%, (1–3), is higher in patients with heart failure (HF) at admission, (4) and depends on the treatment received. (5–7)

Since the 1967 work by Thomas Killip and John Kimball (KK), who described the clinical characteristics of patients with STEMI, prognosis has improved thanks to coronary reperfusion strategies. As a result, the percentage of patients classified as Killip and Kimball class A (KK A) has increased dramatically from 33% to 78%, making it the most common clinical presentation at hospital admission in patients with STEMI. However, few studies have analyzed complications or hospital mortality specifically in this patient subgroup.

In the era of reperfusion therapy, a decrease in complications in patients with STEMI has been observed, enabling earlier hospital discharge. (10,11) In countries such as the United States, the average length of hospitalization is three days, International guidelines recommend early discharge (on the third day) in low-risk patients, with conditions such as age <70, left ventricular ejection fraction (LVEF) >45%, 1- or 2-vessel disease, successful coronary angioplasty, and absence of arrhythmias. (12) Despite this, early discharge is not always implemented, even in eligible patients.

Objectives:

1. To determine the incidence of the KK class A at admission in patients with STEMI and its role in overall mortality.
2. To establish the incidence of HF during the clinical course of patients classified as KK A at admission and its characterization. To analyze the negative predictive value of the absence of HF during the clinical course on mortality.

METHODS

This study was conducted as a retrospective analysis of the ARGEN-IAM-ST continuous registry, a prospective and observational registry of hospitalized STEMI patients. The study was performed from March 2015 to October 2024, and its design focused on assessing the hospital clinical course of patients with KK A admitted to the coronary care unit.

The inclusion criteria were patients classified as Killip and Kimball classes A, B, C, or D, according to the original Killip and Kimball classification. A total of 264 patients were excluded: 174 due to missing data, and 90 because of mechanical complications. HF was classified as a hospital complication. The diagnosis of HF was based on the treating physician's criteria according to the Killip and Kimball classification. Bleeding was defined as follows: minimal: non-intracranial, with a decrease in hemoglobin (Hb) <3 mg/dL; minor: non-intracranial with a decrease in Hb between 3 and 5 mg/dL; major: intracranial bleeding or a decrease in Hb >5 mg/dL.

Statistical analysis

Quantitative variables with normal distribution were expressed as mean and standard deviation (SD), while those with non-normal distribution were reported as median and interquartile range (IQR). To perform the statistical analysis of these variables, the Student's t-test, Mann-Whitney U test, or analysis of variance (ANOVA) were used as appropriate.

Qualitative variables were expressed as frequencies and percentages, and the statistical analysis was performed using the chi-square test or Fisher's exact test, as appropriate.

A contingency table was created to explore an association between the presence or absence of HF and the clinical course in patients with KK A at admission.

The search for independent predictors of progressive HF and the assessment of the incidence of progressive HF on the occurrence of events were conducted using multiple logistic regression analysis, including variables that were statistically significant in the univariate analysis. The association with events was expressed as odds ratio (OR) with its 95% confidence interval (95% CI). A p value <0.05 was considered statistically significant. To assess the usefulness of the overall model (Table 2), the omnibus test was used,

Table 1. Baseline characteristics of patients according Killip and Kimball classification at admission

Variable	KK A (n=5666)	KK B (n=1020)	KK C (n=107)	KK D (n=511)	p
Age, years	60 (52-68)	63 (55-72)	64 (56-74)	64 (57-74)	<0.001
Female sex	20	23	29	29	<0.001
Diabetes mellitus	26	31	34	34	<0.001
Hypertension	52	58	66	65	<0.001
Dyslipidemia	37	38	43	36	0.601
Smoking	31	34	35	35	0.061
Prior AMI	37	54	59	39	<0.001
Symptom-to-door time, min	119 (55-240)	129 (60-300)	152 (60-323)	120 (53-300)	0.004
Reperfusion therapy	91	88	84	87	<0.001
Ischemic total time (PCI), min	305 (185-573)	345 (198-660)	524 (271-901)	400 (212-722)	<0.001
Ischemic total time (FBL), min	180 (105-290)	220 (120-327)	170 (112-266)	180 (104-329)	0.399
Reperfusion therapy: Primary PCI Fibrinolytics Both	80 13 7	 76 13 11	74 16 9	77 11 12	<0.001
Door-to-balloon time, min	77 (44-135)	80 (43-130)	102 (60-198)	85 (50-141)	0.004
Multivessel disease	32	41	46	52	<0.001
Successful PCI	98	95	90	84	<0.001
Bleeding: Minimal Minor Major	2 0.7 0.5	3 0.9 0.8	7.5 5 0.9	6 3 1.4	<0.001

AMI: acute myocardial infarction; FBL: fibrinolytics; KK: Killip and Kimball; PCI: percutaneous coronary intervention.
Qualitative variables are expressed as percentage rounded to the nearest whole number. Quantitative variables are expressed as median and interquartile range.

and a ROC curve was generated. The statistical analysis was performed using the statistical software JAMOVI (version 2.3.28.0).

Ethical considerations

The protocol was reviewed and approved by the Bioethics Committee of the Argentine Society of Cardiology. This registry does not require signed informed consent. This decision is left to each participating institution.

RESULTS

From March 2015 to October 2024, 7304 patients were admitted for STEMI, with a median age of 60 years (IQR 52-67), 80% were male. According to Killip and Kimball classification, 77.6% of patients were class A (n=5666), 14% class B (n=1020), 1.4% class C (n=107), and 7% class D (n=511).

Table 1 shows the baseline characteristics of patients according to KK classification at admission. KK A patients were significantly younger, less likely to be female, had lower prevalence of diabetes, hypertension, prior acute myocardial infarction (AMI) location, and shorter symptom-to-door time. They also had a lower prevalence of multivessel disease but a higher use of primary percutaneous coronary intervention (PCI) as their revascularization method. The rate of successful primary PCI was higher in this group.

Among KK A patients, 311 (5.4%) developed progressive HF during hospitalization. Their baseline characteristics resembled those of patients with KK class >A (Table 2). In a multiple logistic regression model, the independent variables associated with progressive HF were age >70 years, female sex, diabetes, anterior descending artery involvement, symptom-to-door time, and failed primary PCI (area under the ROC curve 0.68, 95% CI 0,61-0,74) (Table 3).

Total in-hospital mortality was 7.3% (n=532). Among patients with KK A, in-hospital mortality was 2.6%, accounting for 28% of total deaths (Figure 1). Among the 311 KK A patients who developed progressive HF, in-hospital mortality was 20,9% (n=65), while it was only 1.5% (n=82) among the 5355 patients who did not (OR 17.77, 95% CI 12.09-24.35; p<0.001). In the multivariate analysis in KK A patients, the development of HF was an independent predictor of hospital mortality (OR 4.79; 95% CI 2.74-8.36 p<0.001).

DISCUSSION

The Killip and Kimball (KK) classification, proposed in 1967, (8) continues to be a valid and widely used tool for risk stratification in STEMI patients. Despite the time elapsed and therapeutic advances, its simplicity, reproducibility, and prognostic value have preserved

Table 2. Baseline characteristics of Killip and Kimball class A patients according to the presence or absence of progressive heart failure

Variable	HF (n=311)	Non-HF (n=5355)	p
Age, years	64 (56-74)	60 (52-67)	<0.001
Female sex	28	19	< 0.001
Diabetes mellitus	32	25	<0.001
Hypertension	59	52	0.001
Dyslipidemia	41	37	0.101
Smoking	31	34	0.551
Prior AMI	47	36	<0.001
Symptom-to-door time, min	120 (60-300)	116 (55-240)	<0.001
Reperfusion therapy	91	91	0.991
Ischemic total time (PCI), min	377 (203-818)	300 (183-568)	<0.001
Ischemic total time (FBL), min	200 (110-324)	180 (105-285)	0.512
Reperfusion therapy: Primary PCI Fibrinolytics Both	 75 17 8	 81 12 7	0.033
Door-to-balloon time, min	83 (48-150)	77 (44-135)	0.255
Culprit vessel: LADA	60	43	<0.001
Successful PCI	91	98	< 0.001
Bleeding Minimal Minor Major	 4 3 2	 2 0.5 0.4	<0.001

AMI: acute myocardial infarction; FBL: fibrinolytics; HF: heart failure; LADA: left anterior descending artery;min: minutes; PCI: percutaneous coronary intervention.
Qualitative variables are expressed as percentage rounded to the nearest whole number. Quantitative variables are expressed as median and interquartile range.

its clinical utility. However, the patient profile has changed considerably since its original publication. (9) In particular, there is now a higher proportion of patients admitted to KK class A, a phenomenon attributable to the positive impact of adjuvant therapies, especially early reperfusion treatment. (13,14)

In our study, we observed that the vast majority of STEMI patients were admitted to KK class A. This subcategory, despite its low individual mortality, represents a significant proportion of AMI-related deaths: approximately one in three occurs in this group. This finding, in line with our first objective, highlights that initial classification in KK class A does not guarantee an event-free hospital course. In fact, the high prevalence of this subcategory has a significant impact on overall AMI mortality, a fact that, although little explored in previous studies, is essential for an adequate understanding of population risk.

Likewise, in addressing our second objective, we identified that approximately 5% of patients admitted to KK class A developed HF during hospitalization. Among them, 21% died before discharge, underscoring the adverse prognostic impact of HF as a hospital complication. (15) The progression to HF in this subgroup, initially considered low risk, highlights the need for continuous clinical monitoring and more sensitive risk stratification strategies. (16,17) In this regard, multivariate analysis allowed us to identify independent predictors for the development of HF, which are similar to those in the PAMI II study and the Zwolle score. (18-23) However, the model discriminatory power was moderate, with a C-statistic of 0.68, indicating the need to optimize predictive tools for this population.

On the other hand, patients who did not develop HF during hospitalization had a very favorable outcome, with a low event rate, which translates into a high negative predictive value. This observation supports the consideration of this subgroup for early discharge strategies, (24-28) in line with international guidelines (Class IIa recommendation). (29,30) Additionally, clinical detection of HF may be complemented by B-type natriuretic peptide (BNP) testing, (31) which has proven useful for early identification of ventricular dysfunction even in the absence of overt clinical signs, as shown by the GREAD NETWORK registry. (32)

Multiple studies have confirmed that HF at admission is associated with a worse prognosis in the context of acute coronary syndrome. (4,15) However, our

Fig. 1. Mortality rate according to Killip and Kimball classification at admission (bar chart). Percentage impact of deaths according to Killip and Kimball classification on overall mortality for myocardial infarction (pie chart).

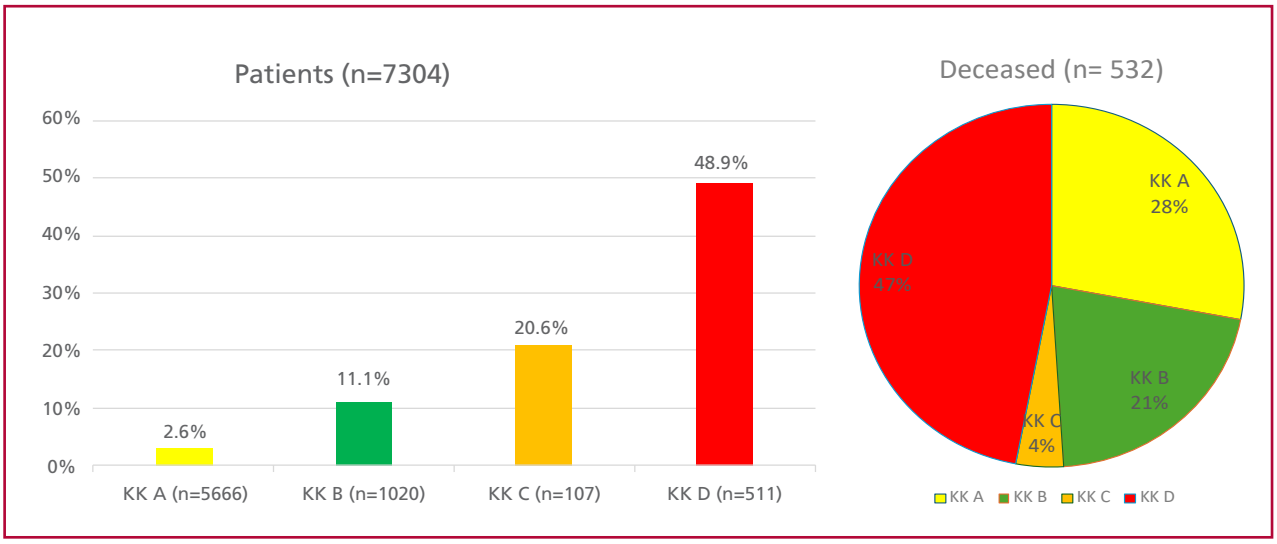
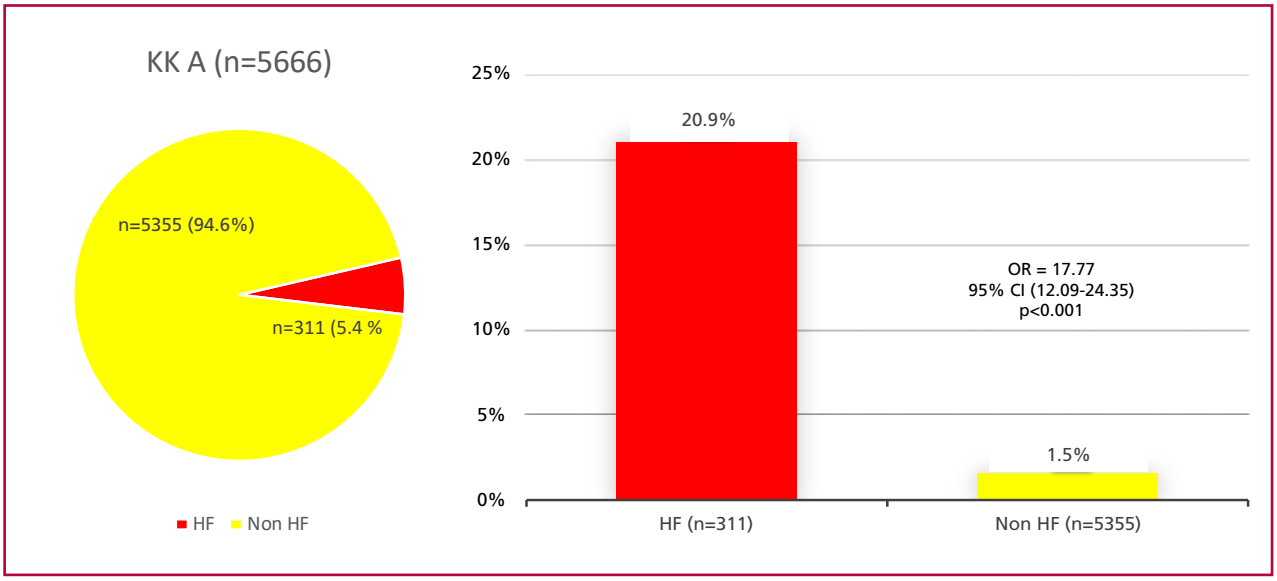


Fig. 2. Incidence (A) and mortality (B) of heart failure (HF) complicating patients with KK A at admission



study offers a different perspective, shifting the focus to HF as a progressive event in patients classified as KK A at admission. This view contrasts with previous studies from the ARGEN-IAM-ST registry, which focused exclusively on patients with KK class B, C, or D at admission, (33–36) leaving a gap in understanding the clinical course of those initially considered low risk.

Finally, our findings allow us to assess the epidemiological burden of KK A patients on overall STEMI mortality and highlight that HF onset during hospitalization is a critical event with significant prognostic implications. Conversely, the absence of HF is associated with a favorable outcome, which has important clinical implications for decision-making regarding early discharge and outpatient follow-up. This information emphasizes the importance of a dynamic approach to risk stratification that considers both the initial clinical presentation and the hospital clinical course.

Limitations

Due to the design of the ARGEN-IAM-ST registry, we were unable to determine the exact timing of HF onset. However, we can estimate this indirectly, as most complications in our local clinical context occur within

Table 3. Multivariate analysis of the development of progressive heart failure

Variable	OR	95% CI	p
Age >70	2.06	1.51-2.81	<0.001
Female sex	1.65	1.20-2.26	0.001
Diabetes mellitus	1.71	1.27-2.31	<0.001
Culprit vessel: LADA	1.88	1.26-2.81	0.001
Symptom-to-door time, min	1.04	1.03-1.06	0.022
Failed PCI	4.20	2.42-7.28	<0.001

HF: heart failure; LADA: left anterior descending artery; PCI: percutaneous coronary intervention; OR: odds ratio

Table 4. Multivariate analysis of mortality

Variable	OR	95% CI	p
Age >70	1.71	1.01-2.88	0.043
Progressive HF	4.79	2.74-8.36	0.001
Major bleeding	9.21	2.60-32.62	<0.001
Failed PCI	3.99	1.73-9.21	<0.001
LVEF <35%	4.93	2.43-9.99	<0.001
Dyslipidemia	2.12	1.30-3.44	0.002

HF: heart failure; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; OR: odds ratio

the first three days. A study conducted at Hospital Argerich showed that all complications, without exceptions, occurred within the first 48 hours. (37,38)

CONCLUSIONS

KK A at admission remains a valid criterion for identifying patients who will have a favorable hospital course following STEMI. However, close monitoring in the coronary care unit is essential to detect patients who will develop heart failure, as they constitute a high-risk group for early discharge.

Conflicts of interest

None declared.

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

REFERENCES

1. Martins E, Magne J, Pradel V, Faugeras G, Bosle S, Cailloce D, et al. The mortality rates in registries of patients with STEMI are highly affected by inclusion criteria and population characteristics. Acta Cardiol 2021;76:504-12. https://doi.org/10.1080/00015385.2020.1848970

2. D´ Imperio H, Gagliardi J, Charask A, Zoni R, Quiroga W, Castillo Costa Y, et al. Acute ST-segment Elevation Myocardial Infarction in Argentina. Data from the continuous ARGEN-IAM-ST registry. Rev Argent Cardiol 2020;88:289-98.

3. Bertomeu V, Cequier Á, Bernal JL, Alfonso F, Anguita MP, Muñiz J, et al. In-hospital Mortality Due to Acute Myocardial Infarction. Relevance of Type of Hospital and Care Provided. RECALCAR Study. Rev Esp Cardiol 2013;66:935-42. https://doi.org/10.1016/j.recesp.2013.06.008

4. Desta L, Jernberg T, Löfman I, Hofman-Bang C, Hagerman I, Spaak J, et al. Incidence, Temporal Trends, and Prognostic Impact of Heart Failure Complicating Acute Myocardial Infarction. JACC Heart Fail 2015;3:234-42. https://doi.org/10.1016/j.jchf.2014.10.007

5. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995–2014. Eur Heart J 2017;38:3056-65. https://doi.org/10.1093/eurheartj/ehx515

6. Zeymer U, Ludman P, Danchin N, Kala P, Laroche C, Sadeghi M, et al. Reperfusion therapies and in-hospital outcomes for ST-elevation myocardial infarction in Europe: the ACVC-EAPCI EORP STEMI Registry of the European Society of Cardiology. Eur Heart J 2021;42:4536-49. https://doi.org/10.1093/eurheartj/ehab342

7. Danchin N, Popovic B, Puymirat E, Goldstein P, Belle L, Cayla G, et al. Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmaco-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme. Eur Heart J 2020;41:858-66. https://doi.org/10.1093/eurheartj/ehz665

8. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. Am J Cardiol 1967;20:457-64. https://doi.org/10.1016/0002-9149(67)90023-9

9. Ferrero L, Cosco OPD, Grieve SM, Bravo LD, González MB, Nebreda C, et al. Correlation between the Killip-Kimball classification and the mortality of patients with AMI, 55 years after its creation. Rev Fed Argent Cardiol 2022;51:115-9.

10. Gong W, Li A, Ai H, Shi H, Wang X, Nie S. Safety of early discharge after primary angioplasty in low-risk patients with ST-segment elevation myocardial infarction: A meta-analysis of randomized controlled trials. Eur J Prev Cardiol 2018;25:807-15. https://doi.org/10.1177/2047487318763823

11. Asad ZUA, Khan SU, Amritphale A, Shroff A, Lata K, Seto AH, et al. Early vs Late Discharge in Low-Risk ST-Elevation Myocardial Infarction Patients Treated With Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Cardiovasc Revasc Med 2020;21:1360-8. https://doi.org/10.1016/j.carrev.2020.04.030

12. Rossello X, Dan GA, Dweck MR, Galbraith M, Hinterbuchner L, Jankowska EA, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur heart J 2023;44:3730-26 https://doi.org/10.1093/eurheartj/ehad191

13. Charask A, Gagliardi J, Tajer C, Castillo Costa Y, D´Imperio H,

Marturano MP, et al. Acute Myocardial Infarction Mortality in Continuous ARGEN-IAM-ST Registry. Its Relationship with Different Reperfusion Therapies. Rev Argent Cardiol 2021;89:312-20. https://doi.org/10.7775/rac.es.v89.i4.20412

14. Echanove Errazti I, Antonio Velasco Rami J, Ridocci Soriano F, Pomar Domingo F, Vilar Herrero V, Martínez Alzamora N, et al. The evolution of hospital mortality from acute myocardial infarction during last 15 years.Impact of reperfusion therapy. Rev Esp Cardiol 1999;52:547-55.

15. Zoni CR, D'Imperio H, Zapata G, Charask A, Macín SM, Castillo Costa Y, et al. Heart failure at admission complicating ST-elevation myocardial infarction in a middle-income country. Experience of the ARGEN-IAM-ST Registry. Curr Probl Cardiol 2024;49:102076. https://doi.org/10.1016/j.cpcardiol.2023.102076

16. De Luca G, Suryapranata H, Van'T Hof AWJ, De Boer MJ, Hoorntje JC, Dambrink JHE, et al. Prognostic Assessment of Patients With Acute Myocardial Infarction Treated With Primary Angioplasty: Implications for Early Discharge. Circulation https://doi.org/10.1161/01.CIR.0000131765.73959.872004;109:2737-43.

17. Raposeiras-Roubín S, Abu-Assi E, Cabanas-Grandío P, Agra-Bermejo RM, Gestal-Romarí S, Pereira-López E, et al. Walking Beyond the GRACE (Global Registry of Acute Coronary Events) Model in the Death Risk Stratification During Hospitalization in Patients With Acute Coronary Syndrome. JACC Cardiovasc Interv 2012;5:1117-25. https://doi.org/10.1016/j.jcin.2012.06.023

18. Nan JZ, Jentzer JC, Ward RC, Le RJ, Prasad M, Barsness GW, et al. Safe Triage of STEMI Patients to General Telemetry Units After Successful Primary Percutaneous Coronary Intervention. Mayo Clin Proc Innov Qual Outcomes 2021;5:1118-27. https://doi.org/10.1016/j.mayocpiqo.2021.09.009

19. Ebinger JE, Strauss CE, Garberich RR, Bradley SM, Rush P, Chavez IJ, et al. Value-Based ST-Segment–Elevation Myocardial Infarction Care Using Risk-Guided Triage and Early Discharge. Circ Cardiovasc Qual Outcomes 2018;11:e004553. https://doi.org/10.1161/CIRCOUTCOMES.118.004553

20. Grines CL, Marsalese DL, Brodie B, Griffin J, Donohue B, Costantini CR, et al. Safety and Cost-Effectiveness of Early Discharge After Primary Angioplasty in Low Risk Patients With Acute Myocardial Infarction. J Am Coll Cardiol 1998;31:967-72. https://doi.org/10.1016/S0735-1097(98)00031-X

21. Parr CJ, Avery L, Hiebert B, Liu S, Minhas K, Ducas J. Using the Zwolle Risk Score at Time of Coronary Angiography to Triage Patients With ST-Elevation Myocardial Infarction Following Primary Percutaneous Coronary Intervention or Thrombolysis. J Am Heart Assoc 2022;11:e024759. https://doi.org/10.1161/JAHA.121.024759

22. Tralhão A, Ferreira AM, Madeira S, Borges Santos M, Castro M, Rosário I, et al. Applicability of the Zwolle risk score for safe early discharge after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. Rev Port Cardiol 2015;34:535-41. https://doi.org/10.1016/j.repc.2015.04.006

23. Banga S, Gumm DC, Kizhakekuttu TJ, Emani VK, Singh S, Singh S, et al. Left Ventricular Ejection Fraction along with Zwolle Risk Score for Risk Stratification to Enhance Safe and Early Discharge in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention: A Retrospective Observational Study. Cureus. 2019;11:e5272. https://doi.org/10.7759/cureus.5272

24. Millone LG, Garay S, Bruno LM, Konicoff M, Rossa V, Contreras AE. Early discharge after ST-elevation myocardial infarction and short-term cardiovascular events. Rev Fed Arg Cardiol. 2020;49:99-102.

25. Telayna JM, Telayna JM, Krause S, Fernandez H, Baratta S. Early Discharge in Acute ST-segment Elevation Myocardial Infarction Treated with Primary Angioplasty: Uncontrolled Intervention Study in Argentina. Rev Argent Cardiol. 2023;91:317-24. hhttp://dx.doi.org/10.7775/rac.v91.i5.20668

26. Noman A, Zaman AG, Schechter C, Balasubramaniam K, Das R. Early discharge after primary percutaneous coronary intervention for ST-elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2013;2:262-9. https://doi.org/10.1177/2048872612475231

27. Rathod KS, Comer K, Casey-Gillman O, Moore L, Mills G, Ferguson G, et al. Early Hospital Discharge Following PCI for Patients With STEMI. J Am Coll Cardiol 2021;78:2550-60. https://doi.org/10.1016/j.jacc.2021.09.1379

28. Yndigegn T, Gilje P, Dankiewicz J, Mokhtari A, Isma N, Holmqvist J, et al. Safety of early hospital discharge following admission with ST-elevation myocardial infarction treated with percutaneous coronary intervention: a nationwide cohort study. EuroIntervention 2022;17:1091-9. https://doi.org/10.4244/eij-d-21-00501

29. Seto AH, Shroff A, Abu-Fadel M, Blankenship JC, Boudoulas KD, Cigarroa JE, et al. Length of stay following percutaneous coronary intervention: An expert consensus document update from the society for cardiovascular angiography and interventions. Catheter Cardiovasc Interv2018;92:717-31. https://doi.org/10.4244/eij-d-21-0050110.1002/ccd.27637.

30. Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes. J Am Coll Cardiol 2025; S073510972410424X. https://doi.org/10.1016/j.jacc.2024.11.009

31. Schellings DAAM, Adiyaman A, Giannitsis E, Hamm C, Suryapranata H, Ten Berg JM, et al. Early Discharge After Primary Percutaneous Coronary Intervention: The Added Value of N-Terminal Pro–Brain Natriuretic Peptide to the Zwolle Risk Score. J Am Heart Assoc 2014;3:e001089. https://doi.org/10.1161/JAHA.114.001089

32. Ganovska E, Arrigo M, Helanova K, Littnerova S, Sadoune M, Kubena P, et al. Natriuretic peptides in addition to Zwolle score to enhance safe and early discharge after acute myocardial infarction: A prospective observational cohort study. Int J Cardiol 2016;215:527-31. https://doi.org/ 10.1016/j.ijcard.2016.04.148

33. Castillo Costa Y, Frontera E, Mauro V, D'Imperio H, Charask A, Macin SM, et al. Prognostic value of the shock index in myocardial infarction. Data from Argentine Registry of ST-segment elevation infarct (ARGEN IAM-ST).. Medicina (B. Aires) 2022;82:104-10.

34. Castillo Costa Y, Delfino F, Palacio S, Charask A, Mauro V, Macín S, et al. ARGEN-IAM-ST Registry: older adults with infarction: Are they all the same?. Medicina (B. Aires) 2024;84:682-8.

35. Castillo Costa Y, Caccavo A, Charask A, Moreno K, Cassano C, Gagliardi J. characteristics of adults older Than 75 Years in the arGen-ia M-sT registry. Rev Argent Cardiol 2019;87:47-51.

36. Arazi HC, Zapata G, Marturano MP, Pellizón OA, D´Imperio H, Lescano AJ, et al. Primary angioplasty in Argentina. Results from ARGEN-IAM-ST registry. MEDICINA (B. Aires). 2019;79:251-6

37. Bono LA, Puente LJ, Szarfer J, Estrella LM, Doppler EM, Llobera MEN, et al. In-hospital complications of acute myocardial infarction. Incidence and timing of their occurrence. MEDICINA (B. Aires). 2021;81:978-985

38. Bertolasi C, Bruno C, Ramos A, et al. Cardiología Clínica. Intermédica. 1991; 1833-41.

Participating centers and investigators:

Province	Center	Investigators
Ciudad Autónoma de Buenos Aires	Clínica Bazterrica	Adrián Charask, Yanina Castillo Costa
Ciudad Autónoma de Buenos Aires	Clínica Santa Isabel	Víctor Mauro, Flavio Delfino
Ciudad Autónoma de Buenos Aires	Hospital Dr. Teodoro Álvarez	Marcos Tomasella
Ciudad Autónoma de Buenos Aires	Hospital Gral. de Agudos Dr. Cosme Argerich	Juliana Taretto, Jeanette Lacusant
Ciudad Autónoma de Buenos Aires	Hospital de Clínicas José de San Martín	Víctor López
Ciudad Autónoma de Buenos Aires	Hospital Gral. de Agudos "Juan A. Fernández"	Mariano Merlo
Ciudad Autónoma de Buenos Aires	Hospital César Milstein	Sol Sucheck
Ciudad Autónoma de Buenos Aires	Hospital Rivadavia	Fernando Di Tommaso
Ciudad Autónoma de Buenos Aires	Sanatorio Güemes	Joaquín Perea
Ciudad Autónoma de Buenos Aires	Sanatorio Sagrado Corazón	Diego Costa
Ciudad Autónoma de Buenos Aires	Sanatorio de la Trinidad Mitre	Sebastián Mrad
Buenos Aires (Adrogué)	IMA Adrogué	Roxana Palacio
Buenos Aires (Caseros)	Sanatorio Modelo de Caseros	Eugenio Korolov
Buenos Aires (Florencio Varela)	Hospital El Cruce	Heraldo D´Imperio, Mariano Adamowski
Buenos Aires (Malvinas Argentinas)	Hospital Malvinas Argentinas	Víctor Zerna
Buenos Aires (Olavarría)	Hospital Municipal Dr. Héctor M Cura	Nora Zeberio
Buenos Aires (Quilmes)	Sanatorio Modelo Quilmes	Adrián Hrabar
Buenos Aires (Quilmes)	Sanatorio de la Trinidad Quilmes	Rene Feijoo, Adrián Lescano
Catamarca (San Fernando del Valle de Catamarca)	Sanatorio Pasteur	María Marturano
Córdoba (Nueva Córdoba)	Sanatorio Allende	Valentina Belluzo, Yesica Bofer
Córdoba (Córdoba)	Hospital Córdoba	Mauro Quiroga
Corrientes (Corrientes)	Instituto de Cardiología JF Cabral	Stella Maris Macín, Mariela Onocko
Entre Ríos (Libertador San Martín)	Sanatorio Adventista del Plata	Ramiro Ayala
Jujuy (San Salvador de Jujuy)	Sanatorio Los Lapachos	Augusto Barbosa
Mendoza (Mendoza)	Hospital Central de Mendoza	Leonardo Ripa, Javier Ortego
Mendoza (San Rafael)	Hospital Teodoro J. Schestakow	Leonardo Schiavone
Neuquén (Neuquén)	Clínica Pasteur SA	Esteban Frontera
Salta (Salta)	Hospital San Bernardo	Rocío Rodríguez
Santa Fé (Rosario)	Hospital Clemente Álvarez de Rosario	María Rosa Siegel
Santa Fe (Rosario)	Instituto Cardiovascular de Rosario	Alejandro Meirino, Fernando Bagnera
Santa Fe (Rosario)	Instituto de Cardiología Dr. González Sabathie	Lautaro Jiménez
Santa Fe (Santa Fe)	Sanatorio de Diagnóstico y Tratamiento	Miguel Hominal
Santa Fe (Santa Fe)	Sanatorio Santa Fe	Brenda Filippon
Tucumán (San Miguel de Tucumán)	Centro Modelo de Cardiología	Lorena López

ORIGINAL ARTICLE

Beyond LDL Cholesterol: Value of non-HDL Cholesterol as a Predictor of Atherosclerotic Cardiovascular Events in Patients with ST-segment Elevation Myocardial Infarction

Más allá del colesterol LDL: valor del colesterol no-HDL como predictor de eventos cardiovasculares ateroscleróticos en pacientes con infarto de miocardio con elevación del segmento ST

ORNELLA PACCE[1], ELENA VARGAS PARRAGA[1], ANABELLA E. FIORI[1], JULIA JANCHES QUIÑONES[1], DANIELA CARDOZO[1], RICARDO VILLARREAL[1, MTSAC], ÁLVARO SOSA LIPRANDI ÁLVARO[1,2, MTSAC], JOAQUÍN PEREA[1,2, MTSAC]

ABSTRACT

Background: In cardiovascular disease (CVD), lowering low-density lipoprotein cholesterol (LDL-C) remains the primary therapeutic goal to reduce major adverse cardiovascular events (MACE). Evidence from intervention studies shows that reducing LDL-C by at least 50% from baseline significantly decreases MACE risk. However, in clinical practice, even when target LDL-C levels are achieved, a residual risk persists, leaving patients vulnerable to recurrent events. Non-HDL cholesterol (cholesterol not associated with high-density lipoproteins, non-HDL-C) comprises all plasma lipoproteins except HDL-C, and denotes the serum cholesterol of all lipoproteins carrying apolipoprotein B.
Objective: To determine the role of non-HDL-C and remnant cholesterol (RC) as predictors of recurrent atherosclerotic cardiovascular events in patients with ST-segment elevation myocardial infarction (STEMI).
Methods: We conducted a retrospective cohort study at a high-complexity center in the city of Buenos Aires. The data analyzed were obtained from an institutional database. Follow-up was performed through the review of electronic medical records. Kaplan–Meier survival curves and Cox regression models were used for MACE prediction. A p-value < 0.05 was considered statistically significant.
Results: A total of 403 patients were included. During the first year of follow-up, MACE occurred in 23.5% (n=95) of patients, most frequently within the first 3 months. Patients with MACE had higher non-HDL-C (102 mg/dL vs. 84 mg/dL, $p<0.001$) and RC (29 mg/dL vs. 22 mg/dL, $p<0.001$) levels, with no significant differences in LDL-C
Conclusion: In this study, both non-HDL-C and RC were independent predictors of MACE after adjustment for LDL-C.

Keywords: STEMI - LDL cholesterol - non HDL cholesterol - M remnant cholesterol - Residual risk

RESUMEN

Introducción: En el contexto de la enfermedad cardiovascular (ECV), el control de la hipercolesterolemia con la reducción del colesterol LDL, (colesterol asociado a lipoproteínas de baja densidad, c-LDL), ha sido en los últimos años el objetivo principal de las diferentes terapéuticas para reducir el riesgo de eventos adversos cardiovasculares mayores (MACE, por su sigla en inglés); este criterio se basa en diversos estudios de intervención que demostraron que una reducción de al menos el 50% del valor basal del c-LDL se asocia a una disminución significativa de los MACE; sin embargo, en la práctica clínica existe un riesgo residual no abordado con la terapia hipolipemiante actual, que expone a una alta tasa de eventos recurrentes a pesar de encontrarse el c-LDL en valores objetivo. El colesterol no-HDL (colesterol no asociado a lipoproteínas de alta densidad, c-no-HDL), comprende todas las lipoproteínas plasmáticas excepto c-HDL, y denota el colesterol sérico de todas las lipoproteínas portadoras de apolipoproteína B.
Objetivo: Evaluar el rol del c-no-HDL y colesterol remanente (CR) como predictores de reincidencia de eventos cardiovasculares en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST).
Material y métodos: Se realizó un estudio de cohorte retrospectivo en un centro de alta complejidad de la Ciudad Autónoma de Buenos Aires. Los datos analizados fueron obtenidos de una base de datos institucional. El seguimiento se realizó a través de la revisión de la historia clínica electrónica. Para el análisis estadístico se utilizaron curvas de sobrevida de Kaplan Meier y modelo de regresión de Cox para generar modelos de predicción de MACE. Se consideró estadísticamente significativo un valor de $p < 0,05$.

Rev Argent Cardiol 2025;93:263-269. https://doi.org/10.7775/rac.v93.i4.20910

SEE RELATED ARTICLE: Rev Argent Cardiol 2025:93:251-252. https://doi.org/10.7775/rac.v93.i4.20913

Received: 01/29/2025 – *Accepted:* 04/04/2025

Correspondence: Ornella Pacce. Research Department, Sanatorio Güemes, Francisco Acuña de Figueroa 1228, 7mo Piso, CP 1180AAX, Autonomous City of Buenos Aires, Argentina. E-mail: ornepacce@gmail.com

[1] Department of Cardiology, Sanatorio Güemes, Autonomous City of Buenos Aires, Argentina
[2] Research Department, Sanatorio Güemes, Autonomous City of Buenos Aires, Argentina

Resultados: Fueron incluidos 403 pacientes. Se observó en el primer año de seguimiento una incidencia de MACE de 23,5% (n=95), el mayor número de eventos en los 3 primeros meses. Los pacientes con MACE tenían valores más elevados de cno-HDL (102 mg/dL vs. 84mg/dL, p<0,001) y CR (29 mg/dL vs. 22 mg/dL, p<0,001); no hubo diferencias estadísticamente significativas en cuanto al c-LDL.
Conclusión: En este estudio tanto el c-no-HDL como el CR se comportaron como predictores independientes de MACE tras ajustar por el valor de c- LDL.

Palabras clave: IAMCEST - Colesterol LDL - Colesterol no-HDL - Colesterol remanente- Riesgo residual

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide (1) and ranks first among the causes of disability in people > 50 years of age according to the Global Burden of Disease Study (2019). (2) Hypercholesterolemia remains one of the major determinants of attributable risk for CVD and cerebrovascular disease. (3)

In Argentina, the INTERASPIRE registry found that, during follow-up, 55% of the population who had a first coronary event did not meet the cholesterol bound to low-density lipoproteins (LDL-C) targets established by clinical practice guidelines. (4) It is known that the key event that triggers atherogenesis is the retention of LDL-C and other cholesterol-rich lipoproteins. These lipoproteins carry the cholesterol within the artery wall, thereby playing a pivotal role in the formation of atherosclerotic plaque and the subsequent development of CVD. Increased LDL-C concentration is causally related to atherosclerotic cardiovascular disease, and reducing the number of LDL-C particles and other lipoproteins containing apolipoprotein B (apoB) as much as possible decreases the occurrence of major adverse cardiovascular events (MACE). (5,6) The current problem is that despite optimal control of LDL-C levels through lifestyle changes and lipid-lowering treatment, patients who survive a first CVD event are at high risk of recurrence. (7) This can be attributed to the failure to consider residual cardiovascular risk due to elevated levels of other atherogenic particles: non-HDL cholesterol (non-HDL-C), remnant cholesterol (RC), and lipoprotein(a) [Lp(a)]. (8,9)

Non-HDL-C comprises all plasma lipoproteins except HDL-C: LDL-C, triglyceride-rich lipoproteins (TRL), which include intermediate-density lipoproteins (IDL), very low-density lipoproteins (VLDL), chylomicrons, remnant TRL, and Lp(a). This parameter indicates the total amount of lipoproteins containing apolipoprotein B. (10) Non-HDL-C has been shown to be more effective for estimating the risk of atherosclerotic cardiovascular disease when compared to LDL-C. This may be due to the fact that it encompasses all proatherogenic cholesterol particles. (10) It is also a superior predictor of risk in patients with metabolic disorders, including hypertriglyceridemia, diabetes mellitus (DM), and obesity.

In secondary prevention, the desirable value of non-HDL-C is < 85 mg/dL for patients with very high CV risk associated with DM, acute coronary syndrome (ACS), familial hypercholesterolemia (FH), recurrent events, and panvascular disease. For patients without these conditions, the desirable value is < 100 mg/dL. (12,13) RC is the cholesterol content of TRLs, and can be estimated as total cholesterol minus LDL-C minus HDL-C. Like non-HDL-C, RC is a causal factor in CVD and has been shown to have the potential to predict CVD independently of LDL-C levels. (12) The evidence from randomized clinical trials supports the hypothesis that elevated levels of these particles are associated with an increased risk of myocardial infarction (MI) and all-cause mortality. (14,15)

It is also known that the residual risk in these patients is multifactorial and is not only related to lipid factors but also to the persistence of other risk factors such as increased body mass index (BMI), hypertension (HTN) and diabetes mellitus (DM). (8,9) The primary objective of this study is to determine the role of non-HDL-C and RC as predictors of recurrent atherosclerotic cardiovascular events in patients with ST-segment elevation myocardial infarction (STEMI).

METHODS

Study design and population

We conducted a retrospective cohort study at a high-complexity center in the city of Buenos Aires. Patients > 18 years who were hospitalized due to STEMI with evidence of type 1 MI as demonstrated by invasive coronary angiography were included in the study. The diagnosis of STEMI was based on the fourth universal definition of MI, (16) with patients presenting with electrocardiographic changes consistent with ST-segment elevation at the J point in at least two contiguous leads, > 0.25 mV in men < 40 years, > 0.20 mV in men > 40 years or older, or > 0.15 mV in women in leads V2-V3 and/or > or equal to 0.10 mV in all leads.

Total cholesterol (TC), HDL-C, and triglyceride (TG) levels were measured in venous blood samples obtained within the first 12 hours following hospital admission. Samples were obtained in a fasting state (minimum 8 hours) when possible, but, this condition was not recorded. LDL-C was estimated using the Friedewald formula: LDL-C = TC – HDL-C – (TG/5), expressed in mg/dL. Non-HDL-C was calculated as the difference between TC and HDL-C, and RC was calculated using the formula TC – HDL-C – LDL-C. Given the elevated cardiovascular risk exhibited by these patients, the therapeutic targets were defined as LDL-C of <55 mg/dL or a reduction of at least 50% from baseline levels.

The primary outcome was a composite of unstable angina and major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal stroke, or nonfatal MI during the first 12 months of follow-up after the index event. Follow-up was mainly performed through electronic medical records. Those patients who were not followed up at our institution were contacted by telephone calls.

Statistical analysis

All the statistical calculations were performed using RStudio version 1.4.1106 (The R Foundation for Statistical Computing, Viena, Austria). Continuous variables are expressed as mean and standard deviation, or median and interquartile range (IQR), according to their distribution. Qualitative variables are presented as absolute frequencies and percentages. 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-Withney test, depending on the distribution of the sample. Cox regression analysis was used to identify independent predictors of cardiovascular events during follow-up. All models were adjusted for age, sex, HTN, DM, smoking habit, RC, LDL-C, and non-HDL-C. Survival curves were estimated using the Kaplan- Meier method. A p-value < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

A total of 403 patients with STEMI were included; median age was 64 years (IQR 55-73) and 78.8% were male. The main cardiovascular risk factors among the patients included were DM (16%), HTN (43%), dyslipidemia (29%) and current smoking (12%). Median values of LDL-C , HDL-C , TG, and non-HDL-C were 64 mg/dL, 36 mg/dL, 114 mg/dL, and 87 mg/dL, respectively. During the average follow-up period of 12 ± 3 months, adherence to statin treatment was 97.8%

Events at follow-up according to the change in non-HDL-cholesterol

The cardiovascular outcome occurred in 95 patients (23.5%) during follow-up.

Patients who developed MACE had higher levels of TC, TG,non-HDL-C and RC. There were no differences in LDL-C levels. The characteristics of the population and their relationship with the occurrence of events can be seen in Table 1. In a stratified analysis, patients who experienced events during follow-up had higher non-HDL-C and RC levels compared to those without events, despite having the LDL-C target value (Figure 1).

Multivariate analysis: independent predictors of major cardiovascular events

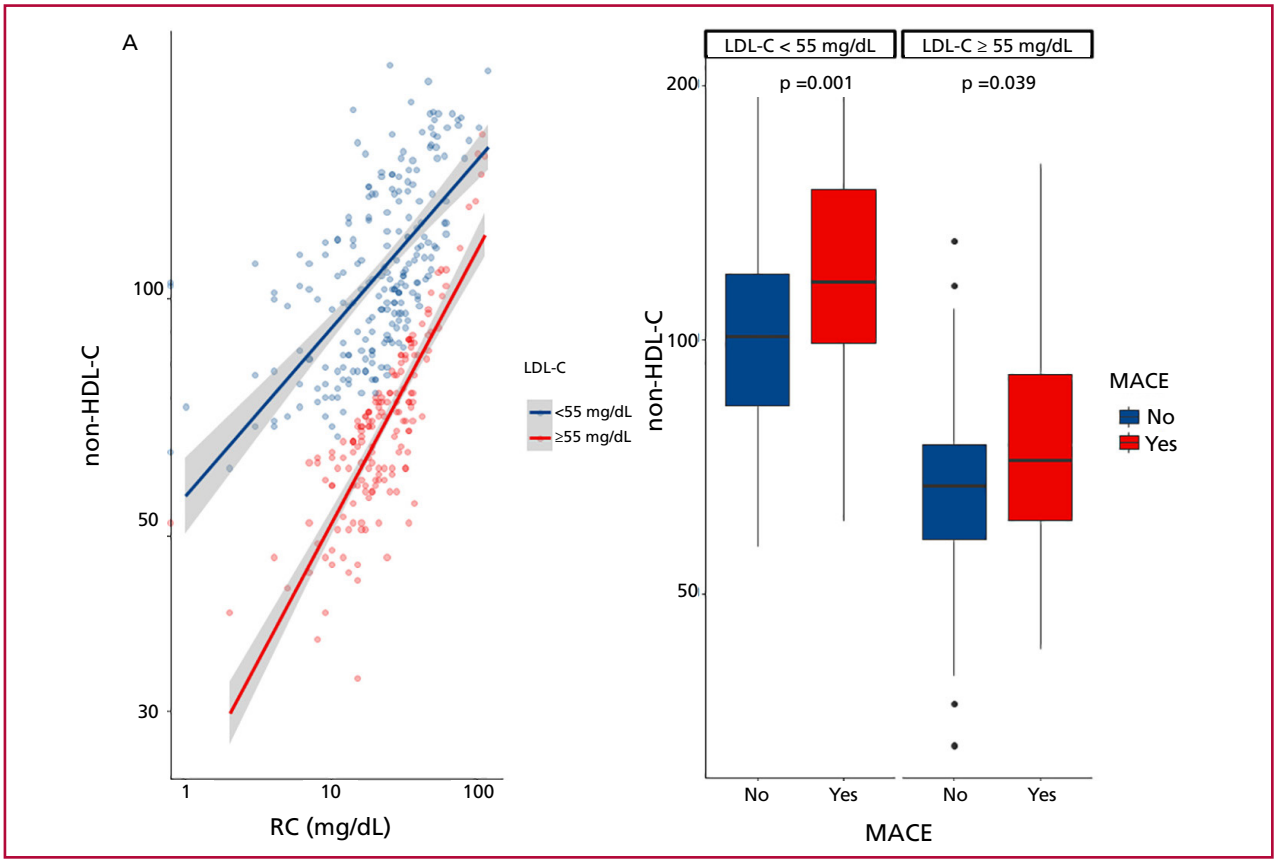
Two prediction models were adjusted for Cox multiple regression, one with the LDL-C variable and the other with the non-HDL-C variable. The hazard ratio (HR) for LDL-C was 1.15 (95% CI: 0.94-1.39, p=0.166), while the HR for non-HDL-C was 1.45 (95% CI: 1.21-

Table 1. Baseline characteristics of the population and relationship with major adverse cardiovascular events (MACE)

		MACE		
Variables	Total	No	Yes	p
Patients	403 (100)	308 (76.5)	95 (23.5)	
Male	316 (78.8)	250 (81.7)	66 (69.5)	0.016
Age, years	64 (55-73)	63 (54.71)	67.50 (57, 77)	0.009
DM	67 (16.6)	54 (17.5)	13 (13.7)	0.470
TBQ	50 (12.4)	46 (14.9)	4 (4.2)	0.009
DLP	118 (29.3)	84 (27.3)	34 (35.8)	0.143
HTN	175 (43.4)	127 (41.2)	48 (50.5)	0.139
Adherence to statins	394 (97.8)	303 (98.4)	91 (95.8)	0.274
LDL-C	64 (50-85)	64 (50–80)	65 (52-94)	0.327
HDL-C	36 (30-44)	35 (30-42)	39 (30-48)	0.151
TG	114 (84-69)	109.50 (79-160)	140 (100-196)	<0.001
TC	124 (103-49)	121 (102-140)	138 (118-177)	<0.001
Non-HDL-C	87 (70-110)	84 (69-105)	102 (75-135)	<0.001
RC	22 (13-33)	20 (14-31)	29 (17-48)	<0.001
Follow-up in months	4 (1-10)	6 (1-11)	1 (1-4)	<0.001

Qualitative variables are presented as frequency and percentage. Quantitative variables are presented as median and interquartile range or mean
DLP: dyslipidemia; DM: diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; HTN: hypertension; LDL-C: low-density lipoproteins cholesterol; Non-HDL-C: cholesterol not associated with high-density lipoproteins; RC: remnant cholesterol; TBQ: tobacco use; TC: total cholesterol;TG: triglycerides

Fig. 1. A: shows the relationship between RC and non-HDL-C according to LDL-C levels. Both groups exhibit a positive linear association between the two variables. However, the slope corresponding to the group with LDL-C < 55 mg/dL (blue line) is above the red line, indicating that, for the same RC value, these patients had higher levels of non-HDL-C. **B:** shows the comparison of non-HDL-C levels according to the occurrence of events (MACE), stratified by LDL-C levels. In both strata, patients who experienced events (red) had significantly higher levels of non-HDL-C compared to those without events (blue), with statistically significant differences.



LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events; non-HDL-C: non-high-density lipoprotein cholesterol; RC: remnant cholesterol.

1.73, p < 0.001) (Figure 2). Patients with non-HDL-C levels within the target range had higher event-free survival at follow-up (p=0.001) (Figure 3).

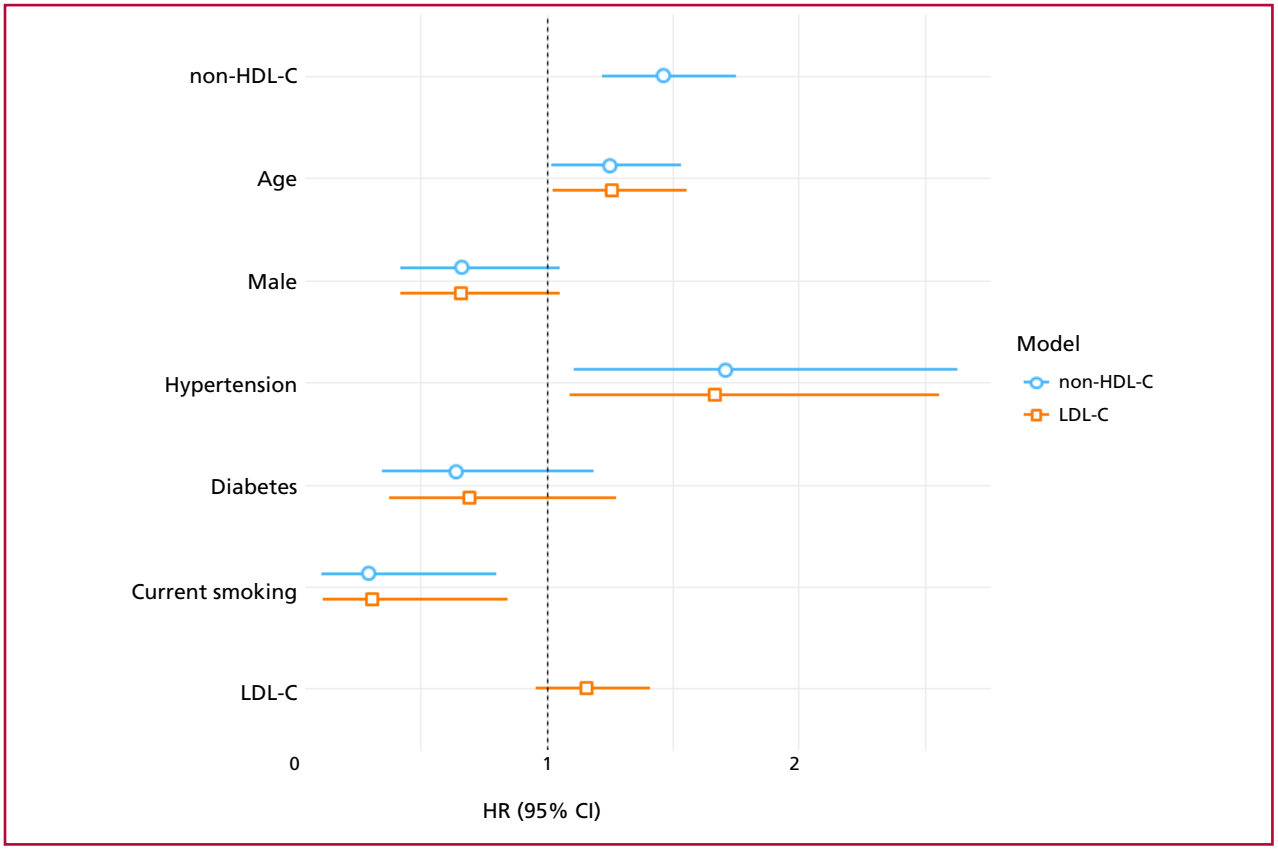
DISCUSSION

During the first year of follow-up after the index event, 23.5% of the patients included experienced MACE. There were no significant differences in the occurrence of events according to LDL-C levels. Conversely, patients with MACE did not achieve non-HDL-C and RC target levels, with median values of 102 mg/dL and 29 mg/dL, respectively. Furthermore, non-HDL-Cl was identified as an independent predictor of MACE during follow-up, in contrast to LDL-C, which did not demonstrate such an association.

In the SWEDEHEART registry, (17) which included 56 262 patients with MI as their first cardiovascular event, 17% of patients experienced MACE during follow-up. The efficacy of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab and evolocumab, compared with placebo, in reducing LDL-C and decreasing MACE was evaluated in two clinical trials (ODYSSEY and FOURIER). Despite achieving critical levels of LDL-C reduction (with medians of 38 mg/dL and 30 mg/dL, respectively), the incidence of MACE during follow-up in patients receiving monoclonal antibodies was 9.5% and 12.6%, respectively. (18,19) In our cohort, median LDL-C in patients with a new event during follow-up was 64 mg/dL, very close to the target value suggested by international guidelines.

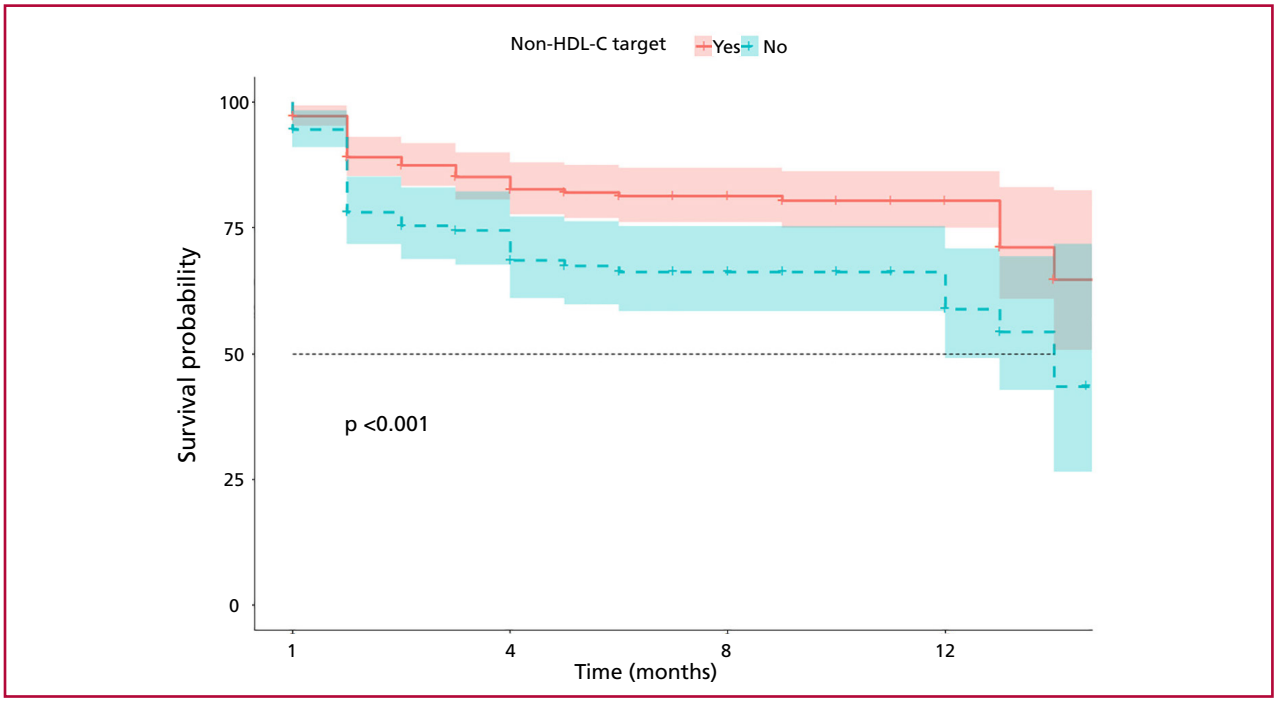
The meta-analysis by Boekholdt et al. (20) showed a strong association between LDL-C and non-HDL-C values as predictors of MACE at follow-up, but the association was stronger for non-HDL-C. Even in those patients who achieved LDL-C targets but did not do so for non-HDL-C, the HR was 1.32 (95% CI 1.17-1.50; p < 0.001). In the aforementioned Swedish registry, (17) baseline non-HDL-C levels were measured at the time of admission and at 1-year follow-up.The cumulative

Fig. 2. Cox regression model for major adverse cardiovascular events (MACE)



95% CI: 95% confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol

Fig. 3. Major adverse cardiovascular events (MACE) according to non-HDL-C target



non-HDL-C: non-high-density lipoprotein cholesterol

incidence rates by quartile of non–HDL-C reduction showed a clear separation of the survival curves. This finding demonstrates that a greater reduction in non-HDL-C (≥ 85 mg/dL) was associated with a lower rate of adverse events at follow-up. Patients in the quartile with the greatest reduction exhibited a 37 % decrease in the risk of MACE (HR 0.63; 95 % CI 0.57-0.68), as well as a 21 % reduction in the risk of all-cause mortality and a 49 % reduction in the risk of nonfatal MI ($p < 0.001$). In addition, the risk of MACE at one year of follow-up was significantly lower in patients who achieved the non-HDL-C target earlier and maintained it during the first year of follow-up (HR 0.80; 95% CI 0.74–0.86). These results underscore the importance of initiating treatment and achieving non-HDL-C targets early after the index event to optimize long-term clinical outcomes. These findings are similar to those observed in our study, in which non-HDL-C performed as an independent predictor of events with a HR of 1.45 (95% CI 1.21-1.73, $p < 0.001$).

Two randomized clinical trials analyzed discrepancies between apoB, non-HDL-C, and LDL-C levels to assess residual risk of MI. Elevated levels of apoB and non-HDL-C, but not of LDL-C levels, were associated with an increased risk of MI and all-cause mortality. In contrast, elevated LDL-C with discordant low apoB or non-HDL-C levels, did not show such an association. (7,21-23) Although our study did not include apoB measurement, these findings underscore the importance of considering other lipid parameters in addition to LDL-C for better assessment of the residual risk in our patients.

In our study, LDL-C did not result a significant predictor of events; yet, its clinical role remains fully valid. LDL-C remains a primary therapeutic target in the field of cardiovascular prevention, with substantial evidence from multiple studies and registries supporting its intensive reduction. According to the leading international guidelines, such as those of the American College of Cardiology (ACC) and the European Society of Cardiology (ESC/EAS), it is recommended that patients at very high cardiovascular risk achieve LDL-C levels of less than 55 mg/dL. (6,24) Therefore, our findings should not be interpreted as a disregard of the clinical importance of LDL-C. Rather, they should be seen as a call to broaden the focus to include other relevant lipid parameters in the assessment of residual risk.

Study limitations

Our study has several limitations that deserve consideration. First, given the retrospective nature of the study, complete information on lipid-lowering treatment, medication adjustment during follow-up, and patient adherence was not available. These data were collected from the electronic medical record and by telephone contact in specific cases. Second, patient recruitment and follow-up were limited to a single center, so our results represent the reality of the participating center. Third, LDL-C was estimated using the Friedewald formula, which is a methodological limitation that can lead to loss of diagnostic accuracy in the presence of moderate or high hypertriglyceridemia. This situation, which is common in patients with high cardiovascular risk, could have led to an underestimation of the actual LDL-C value, particularly in those cases with TG levels ≥ 200 mg/dL. Finally, we did not include the baseline lipid profile, which prevented us from calculating the absolute and percent reductions of the different lipid fractions during follow-up.

CONCLUSION

Our study highlights that, even with LDL-C levels close to the targets recommended by the guidelines, a significant percentage of patients still face a high risk of major cardiovascular events. Non-HDL-C proved to be a key marker for identifying this residual risk, underscoring the need to consider it as a complementary tool for optimizing prevention and management strategies in these patients.

Conflicts of interest

None declared.

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

REFERENCES

1. Giunta G, Lavalle Cobo A, Brandani L, Lobo M, Forte E, Masson G, y cols. Consenso de Prevención Cardiovascular. Rev Argent Cardiol 2023;91 (Suplemento 3): 1-190. https//doi.org/10.7775/rac.es.v91.s3

2. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024;403:2100-32. https://doi.org/10.1016/S0140-6736(24)00367-2.

3. Goldstein JL, Brown MS. A century of cholesterol and coronaries: From plaques to genes to statins. Cell [Internet] 2015;161:161-72. https://doi.org/10.1016/j.cell.2015.01.036

4. McEvoy JW, Jennings C, Kotseva K, De Bacquer D, De Backer G, Erlund I, et al. Variation in secondary prevention of coronary heart disease: the INTERASPIRE study. Eur Heart J 2024;45:4184-96. https://doi.org/10.1093/eurheartj/ehae558

5. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81. https://doi.org/10.1016/S0140-6736(10)61350-5

6. Guía ESC/EAS 2019 sobre el tratamiento de las dislipemias: modificación de los lípidos para reducir el riesgo cardiovascular. Rev Esp Cardiol 2020;73:403.e1-403.e70. https://doi.org/10.1016/j.recesp.2019.10.031

7. Li T-Y, Zhu P, Song Y, Tang X-F, Gao Z, Gao R-L, et al. Discordance analysis for apolipoprotein and lipid measures for predicting myocardial infarction in statin-treated patients with coronary artery disease: a cohort study. J Geriatr Cardiol 2023;20:845-54. https://doi.org/10.26599/1671-5411.2023.12.001

8. Badimon L, Vilahur G, Padro T, Mendieta G. ¿Qué es el riesgo cardiovascular residual? Etiología, lípidos e inflamación. Rev Esp Cardiol Supl 2023;23:5-8. https://doi.org/10.1016/S1131-3587(23)00008-0

9. Zamorano JL, Cequier Á. New approaches in residual cardiovascular risk. Introduction. Rev Esp Cardiol Supl 2023;23:1-4. https://doi.org/10.5565/rev/rubrica.343

10. Brunner FJ, Waldeyer C, Ojeda F, Salomaa V, Kee F, Sans S, et al. Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardio-

vascular Risk Consortium. Lancet 2019;394:2173-83. https://doi.org/10.1016/S0140-6736(19)32519-X
11. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, et al. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J 2022;43:716-99. https://doi.org/10.1093/eurheartj/ehab892
12. Cegla J. National Institute for Health and Care Excellence guidelines for lipid management. Heart .2023;109:661-7. https://doi.org/10.1136/heartjnl-2022-321414
13. Björnson E, Adiels M, Taskinen M-R, Burgess S, Chapman MJ, Packard CJ, et al. Lipoprotein(a) is markedly more atherogenic than LDL. J Am Coll Cardiol 2024;83:385-95. https://doi.org/10.1016/j.jacc.2023.10.039
14. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008;51:724-30. https://doi.org/10.1016/j.jacc.2007.10.038
15. Mora S, Wenger NK, DeMicco DA, Breazna A, Boekholdt SM, Arsenault BJ, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: The treating to new targets (TNT) study. Circulation 2012;125:1979-87. https://doi.org/10.1161/CIRCULATIONAHA.111.088591
16. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA ey al.; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651. https://doi.org/10.1161/CIR.0000000000000617. Erratum in: Circulation. 2018;138(20):e652. https://doi.org/10.1161/CIR.0000000000000632.
17. Schubert J, Leosdottir M, Lindahl B, Westerbergh J, Melhus H, Modica A, et al. Intensive early and sustained lowering of non–high-density lipoprotein cholesterol after myocardial infarction and prognosis: the SWEDEHEART registry. Eur Heart J 2024;45:4204-15. https://doi.org/10.1093/eurheartj/ehae576
18. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107. https://doi.org/10.1056/NEJMoa1801174
19. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22. https://doi.org/10.1056/NEJMoa1615664
20. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non–HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: A meta-analysis. JAMA 2012;307:1302. https://doi.org/10.1001/jama.2012.366
21. Johannesen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. J Am Coll Cardiol 2021;77:1439-50. https://doi.org/10.1016/j.jacc.2021.01.027
22. Hansen MK, Mortensen MB, Warnakula Olesen KK, et al. Non-HDL cholesterol and residual risk of cardiovascular events in patients with ischemic heart disease and well-controlled LDL cholesterol: a cohort study. The Lancet Regional Health – Europe 2024;36:100774. https://doi.org/10.1016/j.lanepe.2023.100774
23. Langsted A, Madsen CM, Nordestgaard BG. Contribution of remnant cholesterol to cardiovascular risk. J Intern Med 2020;288:116-27. https://doi.org/10.1111/joim.13059
24. Grundy SM, Stone NJ, Bailey AL, et al. 2018 HA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol. J Am Coll Cardiol. 2019;73:3168-209. https://doi.org/10.1016/j.jacc.2018.11.002

ORIGINAL ARTICLE

Analysis of Myocardial Flow Reserve in Patients with Transthyretin Cardiac Amyloidosis. Its Relationship with Cardiac Amyloid Distribution and Global Longitudinal Strain

Análisis de la reserva de flujo miocárdico en pacientes con amiloidosis cardíaca por transtiretina. Su relación con la distribución de amiloide cardíaco y el strain longitudinal global

MARÍA VICTORIA CARVELLI[1, MTSAC], ALEJANDRO MERETTA[1,MTSAC], MAGALI GOBBO[1, MTSAC], MARIANA CORNELI[1], ANA SPACCAVENTO[1], MARÍA DEL ROSARIO RODRÍGUEZ[1], DANIEL ROSA[1], PABLO ELISSAMBURU[1, MTSAC], JUAN PABLO COSTABEL[1, MTSAC], NÉSTOR PÉREZ BALIÑO[1, MTSAC], OSVALDO MASOLI[1, MTSAC]

ABSTRACT

Background: Transthyretin cardiac amyloidosis (ATTR-CA) is a disease characterized by the abnormal accumulation of amyloid protein in cardiac tissue, affecting ventricular function and global longitudinal strain (GLS).
Amyloid protein has a high affinity for Tc99m-labeled diphosphonate tracers. Cadmium zinc telluride (CZT) detector-equipped devices allow for evaluation of hydroxy methylene diphosphonate (HMDP) distribution due to their high resolution.
Myocardial perfusion imaging with Tc99m- MIBI using CZT technology devices allow simultaneous assessment of myocardial flow reserve (MFR).
Objectives: The aim of this study was to evaluate MFR in patients with ATTR-CA and analyze its relationship with amyloid deposition distribution and GLS.
Methods: Patients with ATTR-CA confirmed by cardiac scintigraphy with grade 3 uptake according to Perugini scale, and absence of monoclonal gammopathy were included. Doppler echocardiography with GLS assessment, myocardial perfusion with Tc99m-MIBI, and MFR estimation were performed. Amyloid distribution was analyzed by single-photon emission computed tomography (SPECT) and segmented polar maps, calculating the percent uptake in each coronary territory.
Results: Twenty-two male patients with mean age of 78 ± 7 years were studied. Median total amyloid distribution in the left ventricle was 88% (interquartile range, IQR, 81–97). In the left anterior descending artery territory, the median value was 94% (IQR 91–100), in the circumflex artery territory 94% (IQR 91–98), and in the right coronary artery territory100%. Median left ventricular ejection fraction was 56% (IQR 45–67.5) by echocardiography and 52.5% (IQR 39–57) by triggered SPECT, with no significant differences. Median GLS was –8.16 (IQR –9.67 to –6.27). No ischemia or necrosis was observed in the perfusion studies. Median MFR was 1.81 (IQR 1.33–2.02), with stress flow of 1.22 mL/min/g (IQR 0.95–1.74) and rest flow of 0.77 mL/min/g (IQR 0.64–0.91). No significant association was found between amyloid deposition, MFR, and GLS.
Conclusions: Myocardial flow reserve is reduced in patients with ATTR-CA, suggesting microvascular dysfunction. However, no association was found between the extent of amyloid deposit, MFR, and GLS, indicating the possible involvement of additional pathophysiological mechanisms.

Keywords: Cardiac amyloidosis - Myocardial flow reserve - Echocardiogram with GLS-CZT-SPECT assessment

RESUMEN

Introducción: La amiloidosis cardíaca por transtiretina (AC-TTR) es una enfermedad caracterizada por la acumulación anormal de proteína amiloide en el tejido cardíaco, que afecta la función ventricular y el *strain* longitudinal global (SLG).
La proteína amiloide posee alta afinidad por los trazadores con difosfonatos marcados con Tc99m. Los equipos con detectores de cadmio zinc telurio (CZT) permiten una evaluación de la distribución del hidroximetilendifosfonato (HMDP) debido a su alta resolución. Las imágenes de perfusión miocárdica (PM) con MIBI Tc99m realizadas en equipos con CZT permiten al mismo tiempo la evaluación de la reserva de flujo miocárdico (RFM).
Objetivos: Evaluar la RFM en pacientes con AC-TTR y analizar su relación con la distribución del depósito amiloide y el SLG.
Material y métodos: Se incluyeron pacientes con AC-TTR confirmada por centellograma cardíaco con captación grado 3 en la escala de Perugini y ausencia de gammapatía monoclonal. Se realizaron ecocardiografía Doppler con valoración del SLG, perfusión miocárdica con Tc99m-MIBI y estimación de la RFM. La distribución amiloide se analizó mediante tomografía por emisión de fotón único (SPECT, por su sigla en inglés) y mapas polares segmentados, calculando el porcentaje de captación en cada territorio coronario.

Rev Argent Cardiol 2025;93:270-277. https://doi.org/10.7775/rac.v93.i4.20906

Received: 02/03/2025 – *Accepted:* 06/30/2025

Correspondence: María Victoria Carvelli. E-mail: mariavictoriacarvelli@gmail.com

[1] Instituto Cardiovascular Buenos Aires (ICBA), Autonomous City of Buenos Aires, Argentina.

Resultados: Se estudiaron 22 pacientes masculinos con edad promedio de 78 ± 7 años. La distribución total de amiloide en ventrículo izquierdo mostró mediana de 88% (rango intercuartílico, RIC, 81–97). La mediana fue 94% (RIC 91–100) en territorio de la arteria descendente anterior, 94% (RIC 91–98) en el de la circunfleja y 100% en el de la coronaria derecha. La mediana de fracción de eyección del ventrículo izquierdo fue 56% (RIC 45–67,5) por ecocardiografía y 52,5% (RIC 39–57) por SPECT gatillado, sin diferencias significativas. El SLG presentó mediana de –8,16 (RIC –9,67 a –6,27). No se observaron isquemia ni necrosis en los estudios de perfusión. La RFM mediana fue 1,81 (RIC 1,33–2,02), con flujo en estrés de 1,22 mL/min/g (RIC 0,95–1,74) y en reposo de 0,77 mL/min/g (RIC 0,64–0,91). No se encontró asociación significativa entre depósito amiloide, RFM y SLG.
Conclusiones: La RFM se encuentra reducida en pacientes con AC-TTR, lo que sugiere disfunción microvascular. Sin embargo, no se halló asociación entre la magnitud del depósito amiloide, la RFM y el SLG, lo que indica la posible participación de mecanismos fisiopatológicos adicionales.

Palabras clave: Amiloidosis cardíaca - Reserva flujo miocárdico - Ecocardiograma -Strain longitudinal global-CZT - CZT- SPECT

INTRODUCTION

Transthyretin-related cardiac amyloidosis (ATTR-CA) is an infiltrative cardiomyopathy caused by extracellular amyloid protein deposition in cardiac tissue, compromising its structure, ventricular function, and global longitudinal strain (GLS). (1-3)

ATTR-CA is an underdiagnosed disease. However, there are clinical, electrocardiographic, and echocardiographic variables that are easily accessible in routine clinical practice and can facilitate early detection.

Previously considered a rare disease, diagnosis was made invasively through histological confirmation. However, in the last decade there has been a paradigm shift, driven by the emergence of specific treatments, which has led to research into non-invasive diagnostic methods. (4)

Currently, cardiac scintigraphy with phosphonates is considered a non-invasive biopsy due to its high sensitivity and specificity for diagnosis. It is combined with the assessment of free light chains in blood and urine, allowing for the exclusion of combined or alternative forms of amyloidosis, in particular light chain cardiac amyloidosis (AL-CA).

The amyloid protein has a high affinity for Tc99m-labeled diphosphonate tracers. Devices with cadmium zinc telluride (CZT) detectors evaluate the distribution of hydroxymethylene diphosphonate (HMDP) due to its high resolution. (2,5)

In parallel, it has been postulated that amyloid deposition may affect coronary microcirculation. Myocardial flow reserve (MFR), understood as the ability of the coronary circulation to increase blood flow in response to increased metabolic demand, may be altered by mechanisms related to amyloid infiltration. As amyloid proteins accumulate in the walls of blood vessels and cardiac tissue, their vasoconstrictive and proinflammatory effect may compromise adequate microcirculatory dilation, limiting the heart's ability to adapt to physiological variations. (6,7)

Gamma cameras with CZT detectors have emerged as a noninvasive and accurate alternative for assessing MFR. This method allows the acquisition of dynamic images in order to evaluate the integrated vasodilatory response of the coronary tree through myocardial flow measurement and MFR calculation. (8-10)

The primary objective of this study was to evaluate MFR in patients with ATTR-CA and, as a secondary objective, to correlate this parameter with cardiac amyloid distribution and GLS.

METHODS

Study design

This was a single-center, prospective cohort study.

Population

Twenty-two patients with ATTR-CA diagnosed with Grade 3 uptake HMDP on cardiac scintigraphy according to Perugini scale and negative light chains in blood and urine were consecutively included. In all cases, the diagnosis was established exclusively by noninvasive methods, without the need for endomyocardial biopsy.

Patients with known epicardial coronary artery disease were excluded. All participants were not receiving specific treatment at the time of evaluation.

Imaging studies

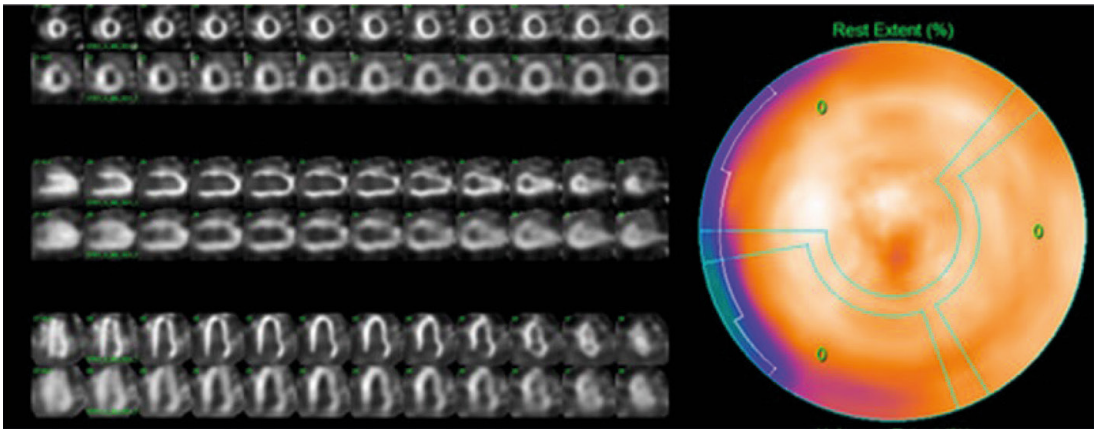
Conventional echocardiography and myocardial perfusion imaging (MPI) were performed, and Tc99m MIBI was used to assess MFR.

Images with diphosphonates were used to evaluate the degree of overall left ventricular involvement, expressed as percentage, as well as the territorial distribution of amyloid substance. This quantification was performed using polar maps automatically generated by the CZT system software. Uptake values were expressed as relative percentage of total activity in the left ventricle, segmented by coronary territory. (Figure 1)

Scintigraphy was performed one hour after intravenous injection of 20 mCi of HMDP-Tc99m. Images were acquired with a dual-head ADAC camera under the following protocol: 1) Planar images (anterior and left anterior oblique): Matrix 128×128 million counts; 2) Gated single-photon emission computed tomography (Gated SPECT): Matrix 64×64 with 30 seconds per frame. The images were processed with Vecsa's VEXWIN software.

The report was prepared independently by two experienced cardiologists (AM, OM). Discrepancies were resolved by consensus. The degree of cardiac uptake in relation to bone tissue was assessed using two methods: A) Semi-quantitative, following Perugini scale (Figure 2), where cardiac uptake was compared with that of the sternum: grade 0 = no uptake, I = cardiac uptake less than the sternum, II = cardiac uptake similar to the sternum, III = cardiac uptake greater than the sternum, and B) Quantitative: heart-to-lung ratio defined as the number obtained by dividing the number of counts at the level of the heart silhouette by the number of counts in a contralateral area of equal size. (11) (Figure 3)

Fig. 1. The image on the right shows a polar map expressing the distribution of amyloid tissue. The images on the left show tomographic images.



The MFR was determined as the ratio between absolute coronary flow (mL/min/g) during dipyridamole-induced pharmacological vasodilation and flow at rest. A stress flow value greater than1.8 mL/min/g and and MFR ≥ 2 are considered normal. (12) (Figure 4).

All patients underwent MPI with MFR assessment using Tc99m-MIBI, with pharmacological stress using dipyridamole and CZT-SPECT acquisition in a one-day protocol, approximately one week after the cardiac scintigraphy with HMDP. Regular medication was not suspended. Patients were instructed to avoid caffeine and proton pump inhibitors for at least 24 hours prior to the study. In addition, a minimum fasting period of two hours prior to the procedure was required.

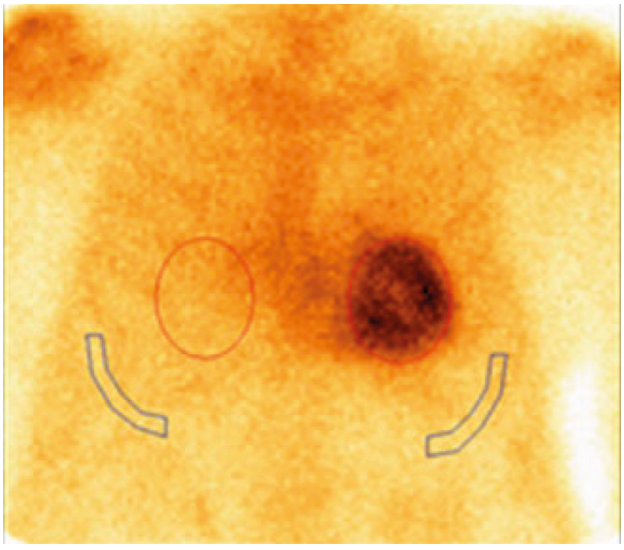
Baseline hemodynamic values were initially obtained, after which 7 mCi of Tc99m-MIBI were injected at rest and dynamic images were obtained to determine baseline MFR, followed by conventional myocardial perfusion images. At 60 minutes, 0.56 mg/kg of intravenous dipyridamole were administered over 4 minutes, followed by 21 mCi of Tc99m-MIBI, and hemodynamic values and dynamic images were obtained again to determine MFR after stress.

A cardiac color Doppler echocardiogram was also performed to determine ventricular function and GLS. A Philips Affinity C50 ultrasound machine was used. The studies were performed by two operators (PE, MC) with a 5 MHz Matrix transducer to acquire two-dimensional images at a frame rate of 60 to 70 per second. The evaluation of chamber diameters and thicknesses, left atrial area, as well as transvalvular flows with the respective assessments of systolic and diastolic function, was achieved according to the American Society of Echocardiography guidelines.(13) In addition to conventional echocardiographic assessment, GLS was analyzed; from four, three, and two chamber apical views. Processing of 2D strain images was done offline at a workstation.

Statistical Analysis

Categorical variables are presented as percentages and continuous variables as median with their interquartile range (IQR). The normality of continuous variables was assessed using the Shapiro-Wilk test. Since the MFR variable did not have a normal distribution ($p < 0.05$), Spearman's correlation coefficient was used to analyze the correlations between parameters of interest. A p value <0.05 was considered significant. StatsDirect version 3.3.5 was used for the analyses.

Fig. 2. Anterior view of cardiac scintigraphy with grade 3 Perugini uptake



Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki (14) and approved by the institutional teaching and research committee and by an independent ethics committee.

RESULTS

Twenty-two male patients with mean age of 78 ± 7 years, and history of hypertension (82%), dyslipidemia (73%), diabetes (23%), smoking (59%), heart failure (68%), and atrial fibrillation (59%) were included in the study.

Fig. 3. Anterior view of cardiac scintigraphy with one region of interest (ROI) located in the cardiac silhouette and another in the contralateral region. The heart-to-lung ratio yields a value of 3.03.

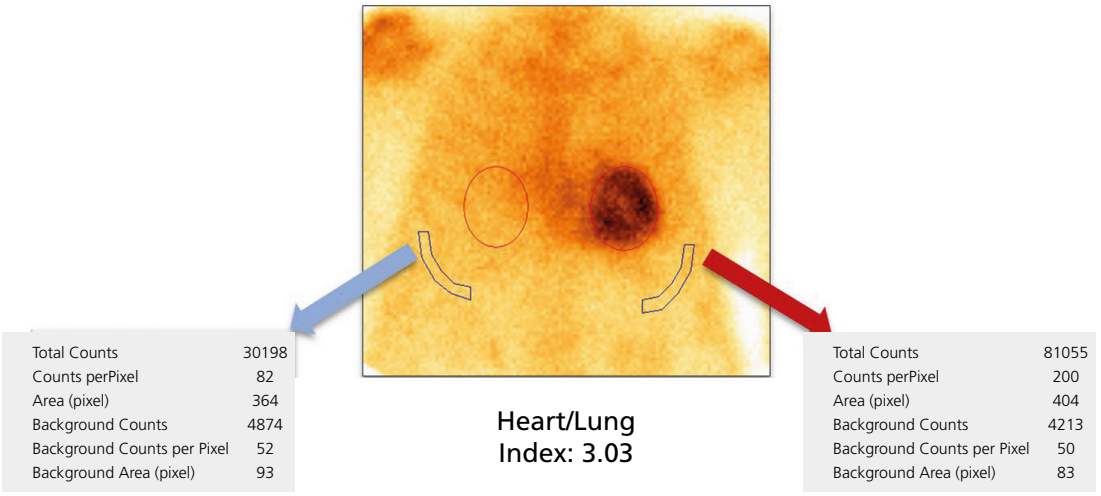
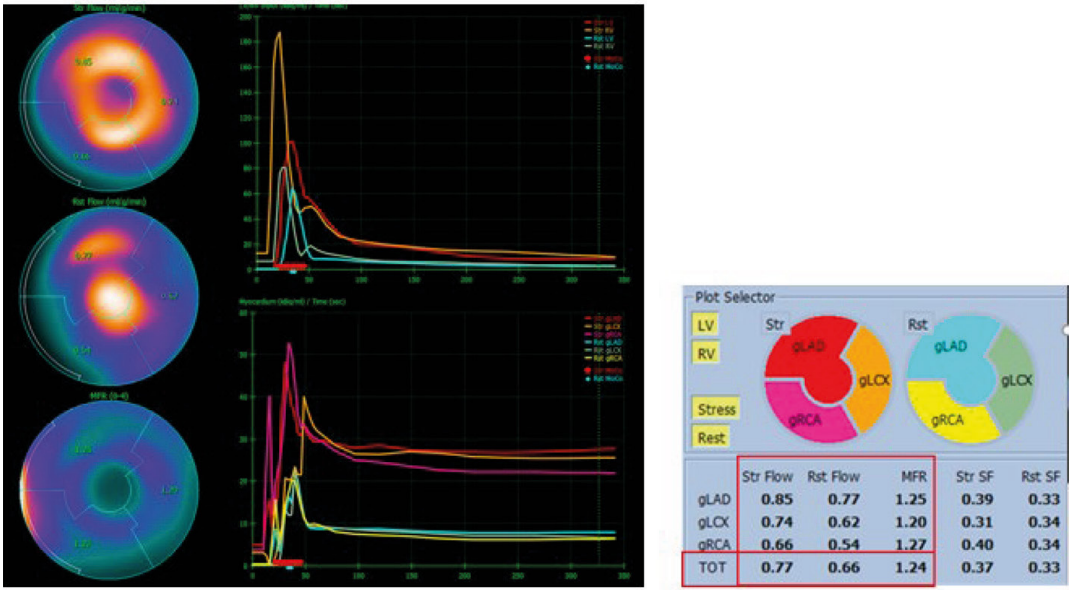


Fig. 4. The image on the left shows myocardial flow curves both at rest and during pharmacological stress with dipyridamole. The image on the right shows flow quantification, with peak flow under dipyridamole of 0.77 mL/min/g and at rest of 0.66 mL/min/g, defining a MFR value of 1.24.



MFR: myocardial flow reserve

Total amyloid involvement in the left ventricle, assessed by SPECT imaging with reconstruction into polar maps, showed a median of 88% (IQR 81%-97%). Territorial quantification of TTR deposition was performed by segmenting the polar maps according to the standardized distribution of the three main coronary territories. A median uptake of 94% (IQR 91%-100%) was observed in the left anterior descending artery territory, 94% (IQR 91%-98%) in the circumflex territory, and 100% in the right coronary territory.

Median left ventricular ejection fraction was 56% (IQR 45%-67.5%) by echocardiography and 52.5% (IQR 39%-57%) by triggered SPECT, with no statistically significant differences between the two methods.

Median GLS was –8.16 (IQR –9.67 to –6.27).

Myocardial perfusion studies showed no evidence of ischemia or necrosis.

Median MFR was 1.81 (IQR 1.33-2.02) with a peak flow of 1.22 mL/min/g (IQR 0.95-1.74) under stress and 0.77 mL/min/g (IQR 0.64-0.91) at rest

Table 1 shows the individual results of myocardial flow during stress and at rest (mL/min/g), myocardial flow reserve calculated as the ratio between the two, total amyloid deposit extent expressed as percentage,

Table 1. Individual results of myocardial flow under stress and at rest (mL/min/g), myocardial flow reserve (stress/rest), total amyloid deposit extent (%), and global longitudinal strain (GLS)

Patient	Total stress	Total rest	Total reserve	Total extent	GLS
1	2.29	0.88	2.62	78	-8.54
2	0.95	0.55	1.83	93	-6.27
3	1.23	0.65	1.82	88	-5.74
4	1.65	0.83	1.89	84	-9.6
5	0.61	0.33	1.88	99	-6.46
6	0.82	0.64	1.33	96	-2.87
7	0.79	0.50	1.71	68	-6.2
8	0.95	0.64	1.47	77	-6.23
9	2.12	1.13	1.80	80	-9.67
10	1.99	0.74	2.61	92	-5.48
11	1.18	0.90	1.30	82	-7.06
12	1.35	0.67	2.06	99	-8.33
13	1.12	0.86	1.31	100	-6.41
14	0.77	0.66	1.24	97	-8.65
15	1.74	0.75	2.41	100	-12.3
16	1.74	1.08	1.61	88	-9.67
17	1.16	0.91	1.23	84	-12.98
18	1.95	0.92	2.02	91	-6.41
19	1.22	0.94	1.30	81	-6.4
20	1.41	0.80	1.82	81	-11.75
21	1.62	0.97	1.67	85	-12.96
22	1.21	0.46	2.81	100	-9.69

and GLS in the 22 patients with ATTR-CA.

We found no asociation between MFR, amyloid deposit extent, and SLG, with Spearman's correlation coefficients between -0,03 and 0,25, non significant in any case (Figure 5), nor any specific anatomical location of the deposits (Figure 6).

DISCUSSION

In our study, most patients with ATTR-CA had decreased MFR with abnormal peak flow values. We found no association between MFR, cardiac amyloid distribution, and GLS.

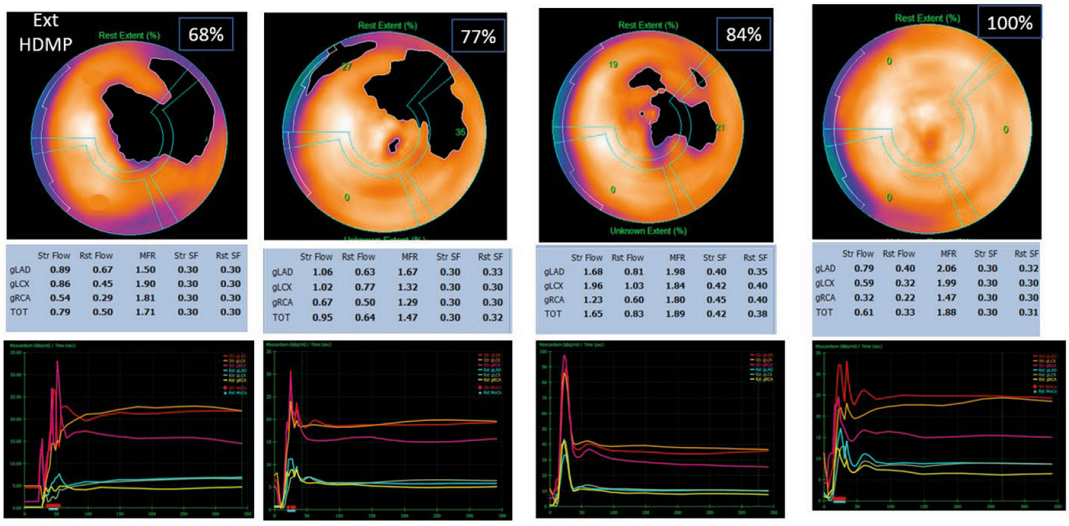
The characteristic GLS pattern in cardiac amyloidosis (CA), described as a "Japanese flag," has traditionally been attributed to the predominant accumulation of amyloid deposits in the basal and mid regions of the ventricle. However, in our study, we observed a homogeneous distribution of deposits, without a specific anatomical preference. (15)

There are no studies in the literature evaluating MFR using CZT cameras. Although there are a few studies addressing MFR, these have been conducted using other methods, such as positron emission tomography (PET), echocardiography, and cardiac resonance imaging. Most of these studies include heterogeneous populations, consisting of patients with ATTR-CA and AL-CA, and some consist solely of case reports, which limits the extrapolation of their findings. (16-20)

One of the most relevant studies supporting the role of microvascular dysfunction in cardiac amyloidosis is the prospective study by Dorbala et al., which included a cohort of 21 patients with confirmed diagnosis, 15 with AL-CA and 6 with ATTR-CA, including hereditary and senile forms. All patients were free from significant epicardial coronary artery disease and were compared with a control group with hypertensive left ventricular hypertrophy. Myocardial perfusion at rest and under stress, as well as MFR, were assessed by N-13 ammonium PET and echocardiography. The findings were consistent: patients with CA had significantly reduced myocardial flow at rest and under stress, markedly decreased MFR (1.19 vs. 2.23; $p<0.0001$), and minimum increased coronary vascular resistance. (20)

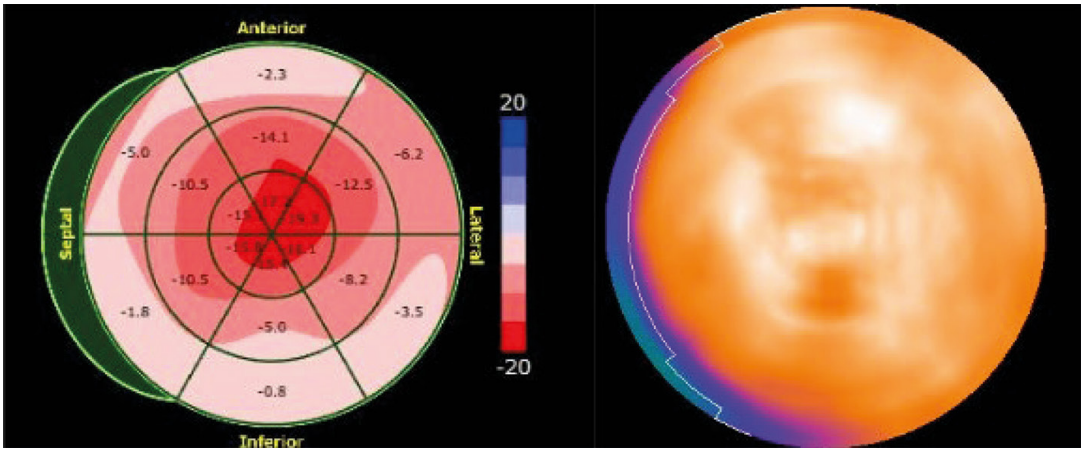
A study by Clemmensen et al. specifically evalu-

Fig. 5. Polar maps show the percentages of HMDP extension with their corresponding MFR values, demonstrating that there is no correlation between the two parameters.



HMDP: hydroxymethylene diphosphonate; MFR: myocardial flow reserve

Fig. 6. Patient's GLS with apical preservation pattern. The homogeneous distribution of HMDP is observed in the same patient. .



GLS: global longitudinal stress; HMDP: hydroxymethylene diphosphonate

ated MFR in patients with CA compared with healthy subjects. This prospective cohort included 27 patients with CA, 13 with AL-CA, 9 with hereditary ATTR-CA and 5 with wild-type ATTR-CA. All underwent MFR measurement by transthoracic Doppler echocardiography, evaluating flow in the anterior descending artery during physical exertion in the semi-supine position. The results showed a marked reduction in MFR in patients with CA, with average values of 1.7 vs. 3.9 in the control group ($p<0.001$). This alteration was consistently observed in the three variants of amyloidosis included in the study, with no significant differences between them. (19)

It is postulated that the underlying pathophysiological mechanisms of microvascular dysfunction in patients with CA could be classified into three main categories: a toxic mechanism, in which the release of free radicals induced by the amyloid substance generates microcirculatory dysfunction; a vascular mechanism, characterized by the deposition of amyloid in the blood vessel wall; and an extravascular mechanism associated with perivascular and interstitial amyloid deposition. Although these three mechanisms may coexist, the abnormal peak flow values observed in our population suggest microvascular compromise due to extrinsic compression, attributed to interstitial amyloid protein deposition. (15,20,21)

In a recent study that included autopsies performed on patients diagnosed with CA, the histopathological distribution of different types of amyloidosis was analyzed. The findings revealed that in patients with AL-CA the pattern of amyloid fibril deposition was predominantly perivascular. In contrast, in patients with ATTR-CA the predominant pattern was intersti-

tial. These results reinforce what we observed in our population. (22)

The study by Mustafa Bulut et al. proposes that chronic systemic inflammation is responsible for the decrease in MFR in patients with systemic amyloidosis. To verify this hypothesis, MFR was assessed by echocardiography and compared with systemic inflammatory diseases and a control group without disease. The results show that the subgroup of patients with systemic amyloidosis had significantly lower MFR values than other patients with chronic inflammatory diseases without amyloidosis and individuals in the control group. (23)

Published studies have documented a decrease in MFR in patients with cardiac amyloidosis, associating it with the presence of anginal symptoms. It has even been suggested that this alteration could be the first clinical manifestation of the disease. (16,18,24)

The emergence of different specific therapeutic options for CA, many of which are still in the research phase, poses new challenges in clinical practice. Identifying the patients who will benefit most from treatment, choosing the optimal time to start treatment, and selecting the most appropriate drug, or even the possibility of drug combination, given that they act on different pathophysiological mechanisms, are key issues that still require further definition. In this context, measuring MFR could be a useful tool, as it is a functional parameter that has been associated with prognosis and could help stratify patients and guide more personalized therapeutic decisions. (25-27)

A prospective multicenter study is currently underway to evaluate MFR using CZT cameras in patients with ATTR-CA diagnosis free from previous treatment, with baseline measurement and reassessment two years after initiation of tafamidis therapy. Although the results have not yet been published, this study is expected to provide relevant information to further investigate the pathophysiological mechanisms involved and the functional response to specific treatment, important aspects that remain poorly explored in this population. (28)

Our findings reinforce the presence of microvascular dysfunction in patients with ATTR-CA. The reduction in MFR observed in our population, associated with a homogeneous distribution of amyloid deposits and marked deterioration of GLS, suggests that functional compromise of the coronary tree may represent an early manifestation independent of the degree of structural infiltration. Although no correlation was found between MFR and amyloid burden, this observation raises new pathophysiological and methodological questions that deserve further exploration. The use of noninvasive tools, such as CZT cameras, in combination with more accurate tissue quantification techniques, could open new opportunities for risk stratification and therapeutic monitoring in this population.

CONCLUSION

Myocardial flow reserve is compromised in patients with ATTR-CA diagnosis and abnormal peak flow values, suggesting microvascular involvement due to interstitial amyloid protein deposition. However, it was not possible to associate MFR compromise with amyloid tissue burden in this population.

We found no correlation between MFR, cardiac amyloid distribution, and GLS.

Myocardial flow reserve assessment could become a tool for understanding disease progression and stratifying risk in patients with ATTR-CA.

Acknowledgments

Our sincere and heartfelt thanks go to the entire technical team, whose invaluable contribution and constant dedication have been fundamental for the completion of this work. Without their efforts, this project would not have been possible;

Limitations

The study population was small and in advanced stages of the disease.

Conflicts of interest

None declared.

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

REFERENCES

1. Bloom MW, Gorevic PD. Cardiac Amyloidosis. Ann Intern Med 2023;176:ITC33-ITC48. https://doi.org/10.7326/AITC202303210

2. Kourek C, Briasoulis A, Magouliotis DE, Georgoulias P, Giamouzis G, Triposkiadis F, et al. Recent advances in the diagnostic methods and therapeutic strategies of transthyretin cardiac amyloidosis. World J Cardiol 2024;16:370-9. https://doi.org/10.4330/wjc.v16.i7.370

3. Spaccavento A, Rodríguez MD, Meretta A, Elissamburu P, Carvelli V, Gobbo M, et al. Prevalence of transthyretin amyloid cardiomyopathy in patients admitted for acute heart failure. Curr Probl Cardiol 2024;49:102385. https://doi.org/10.1016/j.cpcardiol.2024.102385

4. Gobbo M, Meretta A, Carvelli MV, Elissamburu P, Spaccavento A, Costabel JP, et al. Transthyretin cardiac amyloidosis: development of a prediction model and scoring scale for diagnosis. Rev Argent Cardiol 2024;92:420-8. https://doi.org/10.7775/rac.es.v92.i6.20838

5. Alwan L, Benz DC, Cuddy SA, Dobner S, Shiri I, Caobelli F, et al. Current and evolving multimodality cardiac imaging in managing transthyretin amyloid- -cardiomyopathy. JACC Cardiovasc Imaging 2024;17:195-211. https://doi.org/10.1016/j.jcmg.2023.10.010

6. Taqueti V, Di Carli M. Coronary microvascular disease pathogenic mechanism and therapeutic options: JACC state-of the-Art Review. J Am Coll Cardiol 2018;72:2625-41. https://doi.org/10.1016/j.jacc.2018.09.042

7. Camici P, Mamati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and assessment. Nat Rev Cardiol 2015;12:48-62. https://doi.org/10.1038/nrcardio.2014.160

8. Agostini D, Roule V, Nganoa C, Roth N, Baavour R, Parienti J, et al. First validation of myocardial flow reserve assessed by dynamic 99mTc-sestamibi CZT-SPECT camera: head-to-head comparison with 15O-water PET and fractional flow reserve in patients with suspected coronary artery disease. The WATERDAY study. Eur J Nucl Med Mol Imaging 2018;45:1079-90. https://doi.org/10.1007/s00259-018-3958-7

9. Wells G, Marvin B. Measuring SPECT myocardial blood flow at the

University of Ottawa Heart Institute. J Nucl Cardiol. 2021;28:1298-303. https://doi.org/10.1007/s12350-020-02102-7
10. Acampa W, Zampella E, Assante R, Genova A, De Simini G, Mannarino T, et al. Quantification of myocardial perfusion reserve by CZT-SPECT: A head to head comparison with 82Rubidium PET imaging. J Nucl Cardiol 2021;28:2827-39. https://doi.org/10.1007/s12350-020-02129-w
11. Hanna M, Ruberg FL, Maurer MS, Dispenzieri A, Dorbala S, Falk RH, Hoffman J, Jaber W, Soman P, Witteles RM, Grogan M. Cardiac Scintigraphy With Technetium-99m-Labeled Bone-Seeking Tracers for Suspected Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jun 9;75(22):2851-2862. doi: 10.1016/j.jacc.2020.04.022
12. Van Tosh A, Nichols KJ. SPECT measurements of myocardial blood flow and flow reserve: from development to implementation. J Nucl Cardiol. 2023 Aug;30(4):1437-1442. doi: 10.1007/s12350-023-03273-9.
13. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019 Jan;32(1):1-64. doi: 10.1016/j.echo.2018.06.004.
14. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310 :2191–2194. doi:10.1001/jama.2013.281053)
15. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. JACC Cardiovasc Imaging 2016;9:126–38. https://doi.org/10.1016/j.jcmg.2015.05.014
16. Bravo PE, Di Carli MF, Dorbala S. Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies. Heart Fail Rev 2017;22:455-64. https://doi.org/10.1007/s10741-017-9628-1
17. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2021;42:1554-68. https://doi.org/10.1093/eurheartj/ehab072
18. Nam MC, Nel K, Senior R, Greaves K. Abnormal myocardial blood flow reserve observed in cardiac amyloidosis. J Cardiovasc Ultrasound 2016;24:64-7. https://doi.org/10.4250/jcu.2016.24.1.64
19. Clemmensen TS, Eiskjær H, Mølgaard H, Larsen AH, Soerensen J, Andersen NF, et al. Abnormal coronary flow velocity reserve and decreased myocardial contractile reserve are main factors in relation to physical exercise capacity in cardiac amyloidosis. J Am Soc Echocardiogr 2018;31:71-8. https://doi.org/10.1016/j.echo.2017.09.007
20. Dorbala S, Vangala D, Bruyere J Jr, Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. J Am Coll Cardiol 2014;2:358-67. https://doi.org/10.1016/j.jchf.2014.03.009
21. Neben-Wittich MA, Wittich CM, Mueller PS, Larson DR, Gertz MA, Edwards WD. Obstructive intramural coronary amyloidosis and myocardial ischemia are common in primary amyloidosis. Am J Med 2005;118:1287. https://doi.org/10.1016/j.amjmed.2005.06.017
22. De Gaspari M, Sinigiani G, De Michieli L, Della Barbera M, Rizzo S, Thiene G, et al. Relative apical sparing in cardiac amyloidosis is not always explained by an amyloid gradient. Eur Heart J Cardiovasc Imaging 2023;24:1258-68. https://doi.org/10.1093/ehjci/jead107
23. Bulut M, Keles N, Caliskan Z, Kostek O, Aksu F, Ozdil K, et al. Is the presence of AA amyloidosis associated with impaired coronary flow reserve? Atherosclerosis 2016;251:389-95. https://doi.org/10.1016/j.atherosclerosis.2016.05.041
24. Al Suwaidi J, Velianou JL, Gertz MA, Cannon RO 3rd, Higano ST, Holmes DR Jr, et al. Systemic amyloidosis presenting with angina pectoris. Ann Intern Med 1999;131:838–41. https://doi.org/10.7326/0003-4819-131-11-199912070-00007
25. Kelshiker MA, Seligman H, Howard JP, Rahman H, Foley M, Nowbar AN, et al. Coronary flow reserve and cardiovascular outcomes: a systematic review and meta- . Eur Heart J 2022;43:1582-93. https://doi.org/10.1093/eurheartj/ehab775
26. Gdowski MA, Murthy VL, Doering M, Monroy-Gonzalez AG, Slart R, Brown DL. Association of isolated coronary microvascular dysfunction with mortality and major adverse cardiac events: a systematic review and meta-analysis of aggregate data. J Am Heart Assoc 2020;9:e014954. https://doi.org/10.1161/JAHA.119.014954
27. Choi KH, Lee JM, Kim SR, Kim D, Choi JO, Kim SJ, et al. Prognostic value of the index of microcirculatory resistance over serum biomarkers in cardiac amyloidosis. J Am Coll Cardiol 2020;75:560-1. https://doi.org/10.1016/j.jacc.2019.11.045
28. Vançon B, Bisson A, Courtehoux M, Bernard A, Bailly M. A study protocol for an observational cohort investigating cardiac transthyretin amyloidosis flow reserve before and after Tafamidis treatment: The AMYTRE study. Front Med (Lausanne) 2022;9:978293. https://doi.org/10.3389/fmed.2022.978293

ORIGINAL ARTICLE

SONQO-CALCHAQUÍ Program, 4th Edition, 2024. Evaluation of Cardiovascular Variables in a High-Altitude Indigenous Community

Programa SONQO-CALCHAQUÍ Edición IV 2024. Evaluación de variables cardiovasculares en una comunidad originaria de alta montaña

RICARDO SEBASTIÁN GALDEANO [1, MTSAC], SERGIO OSCAR MAURO[1], DANIEL ABREGÚ[1], LAURA FLORES[1], GABRIELA SONIA ZEBALLOS[1], LUIS FISZMAN[1], GUILLERMINA ELLEIT[1], RODRIGO ALDERETE[1], RODRIGO OSCAR MARAÑON[1-3], CLAUDIO JOO TURONI[1-3, MTSAC]
ON BEHALF OF THE SONQO-CALCHAQUÍ IV PROGRAM*

ABSTRACT

Background: In Argentina, high-mountain indigenous communities have been scarcely studied due to a combination of factors, including difficult access, an isolated environment, and their closed nature. However, their habits are becoming increasingly westernized, which could affect their cardiovascular health. Through the IV Edition of the SONQO-CALCHAQUÍ Program, a cardiovascular check-up was carried out in the Coranzulí community (province of Jujuy, 4100 meters above sea level).
Objective: The aim of this study was to characterize the cardiovascular health status of the Coranzulí indigenous population.
Methods: This was a descriptive cross-sectional study. A comprehensive assessment was carried out on the residents (aged 18 years or older) who attended the IV Edition of the SONQO-CALCHAQUÍ Program (September 30 to October 4, 2024).
Results: A total of 241 residents (44.1±0.1 years old) were included in this study. They presented changes consistent with adaptation to life at high altitude: increased hematimetric values and low oxygen saturation. The diet preserves indigenous elements (e.g., llama meat and "anchi") associated with flours and processed foods. In general, they have good sleep quality, physical activity, and cardiovascular function. Grip strength was within the normal range in 80.3% of cases.
According to the body mass index, 0.4% were malnourished; 32.0% presented normal weight; 36.5% were overweight; 23.2% were obese; and 7.9% were morbidly obese. Waist circumference was elevated in 56.7% of the population. Systolic blood pressure was elevated in 8.8% and diastolic blood pressure in 12.6% of residents.
On the electrocardiogram, 13.3% had a right axis deviation and 7.1% had right bundle branch block. On the arterial Doppler echo, 90.0% had no atheromatous plaques.
Conclusions: Although the Coranzulí indigenous population maintains characteristics that can be considered cardioprotective, it is undergoing a westernizing process. The true role of this change in the general and cardiovascular health of this population remains to be evaluated, which requires the continuation of multisectoral studies, such as the SONQO-CALCHAQUÍ Program.

Keywords: Indigenous population - South America – High-mountain - Cardiovascular variables - Epidemiology

RESUMEN

Introducción: En Argentina, las comunidades originarias de alta montaña han sido escasamente estudiadas debido a una conjunción de características que incluyen un difícil acceso, un entorno aislado y su carácter cerrado. Sin embargo, se está observando una occidentalización de sus hábitos, que podría afectar su salud cardiovascular. Mediante el Programa SONQO-CALCHAQUÍ (Edición IV), se realizó un control cardiovascular en la comunidad de Coranzulí (provincia de Jujuy, 4100 metros sobre el nivel del mar).
Objetivo: Caracterizar el estado de salud cardiovascular en la población originaria de Coranzulí.
Material y métodos: Estudio descriptivo transversal. Se evaluó, en forma integral, a los pobladores (18 años o más) que asistieron al Programa SONQO-CALCHAQUÍ Edición IV (30 de setiembre al 4 de octubre del 2024).
Resultados: Fueron incluidos en el presente estudio 241 pobladores (44,1±0,1 años). Presentaron cambios compatibles con la adaptación a la vida en altura: aumento de los valores hematimétricos y baja saturación de oxígeno. Su dieta preserva elementos autóctonos (por ejemplo, carne de llama y “anchi”) asociados a harinas y alimentos procesados. En general tienen buena calidad de sueño, actividad física y función cardiovascular. La fuerza prensil estuvo dentro de rango normal en 80,3% de los casos.
Según el índice de masa corporal 0,4% presento desnutrición; 32,0% normopeso; 36,5% sobrepeso; 23,2% obesidad y 7,9% obesidad mórbida. El perímetro de cintura estuvo elevado en 56,7% de los pobladores. La presión arterial sistólica estuvo elevada en el 8,8% y la diastólica en el 12,6% de los pobladores.

Rev Argent Cardiol 2025;93:278-285. https://doi.org/10.7775/rac.v93.i4.20914

Received: 05/05/2025 – *Accepted:* 07/31/2025

Correspondence: Claudio Joo Turoni. Email: claudiojoo@fm.unt.edu.ar

[1] Argentine Society of Cardiology
[2] School of Medicine, Universidad Nacional de Tucumán, Tucumán, Argentina
[3] Higher Institute of Biological Research (INSIBIO), CONICET-UNT- Tucumán, Argentina
*.- Appendix I

En el electrocardiograma, 13,3% presentó el eje desviado a la derecha y 7,1% bloqueo de rama derecha. En el eco Doppler arterial 90,0% no presentaban placas ateromatosas.
Conclusiones: Si bien la población originaria de Coranzulí mantiene características autóctonas que pueden considerarse cardioprotectoras, está transitando un proceso de occidentalización. Queda como tarea evaluar el verdadero rol de este cambio en la salud general y cardiovascular de esta población, para lo cual es necesaria la continuación de estudios multisectoriales, tales como el Programa SONQO-CALCHAQUÍ.

Palabras clave: Población originaria - Sudamérica - Alta montaña - Variables cardiovasculares - Epidemiología

INTRODUCTION

Through the SONQO-CALCHAQUÍ Program (Editions I to III), a group of physicians from different parts of the country conducted cardiovascular checks on the inhabitants of the indigenous communities of the Calchaquí Valleys (provinces of Tucumán, Salta, and Catamarca) who live in mid- and high-mountain areas. The population presented a high rate of obesity, a prevalence of cardiovascular risk factors similar to that of urban centers, and a diet based on flour. These results show an adoption of cultural, economic, and/or social elements typical of Western culture, either voluntarily or imposed, in their lifestyles. (1-3) This westernization has already been described in other indigenous populations in Argentina. (4-6)

The adaptive challenges of performing activities (7) and living (8) at altitudes above 2500 m above sea level (high-mountain) are still being studied worldwide. In Argentina, high-mountain indigenous communities have been scarcely studied due to a combination of characteristics that include difficult access, an isolated environment, and their closed nature. However, a westernization of their nutritional habits is being observed, especially in younger populations. (9)

In the IV Edition of the SONQO-CALCHAQUÍ Program, the cardiovascular health study was extended to the residents of the Coranzulí community (Susques department, province of Jujuy).

The Coranzulí community is located 4100 meters above sea level in a rugged and dry environment. (10) The population of the Susques department in 2022 was 4098 inhabitants, (11) and that of Coranzulí in 2014, 339 inhabitants. (10) There is no more recent data, and the actual number of inhabitants in Coranzulí is difficult to estimate because most of them are semi-nomadic and have been herding American camelids since pre-Hispanic times. (10) This population presents itself as a closed and isolated indigenous community. However, the advance of the mining industry in the area poses multiple challenges that must be evaluated. (12)

The objective of this study was to characterize the cardiovascular health status of the indigenous population of Coranzulí.

METHODS

This was a descriptive cross-sectional study. Residents (aged 18 years or older) who voluntarily attended the IV Edition of the SONQO-CALCHAQUÍ Program (September 30 to October 4, 2024) were evaluated. In order to assess only the indigenous population, we worked in conjunction with the community delegate. Seven clinics were set up at Secondary School No. 18 (Coranzulí), where the following tests were carried out:

Clinic 1 (Laboratory): routine tests were performed. Glomerular filtration rate was calculated using the MDRD-4 formula. (13) Thyroid-stimulating hormone (TSH) and serology for Chagas disease were also measured.

Clinic 2 (Surveys):

- Targeted socioeconomic survey. (1)
- 24-hour dietary recall test. (14)
- Food consumption frequency test: semi-quantitative questionnaire indicating the frequency of consumption of 19 foods (daily, weekly, or monthly) in the last year. (2,3)
- SF-12 questionnaire: assesses self-perceived health status, with a score between 0 (none) and 48 (maximum). (15)
- Pittsburgh Sleep Quality Index. (16)

Clinic 3 (Anthropometry, blood pressure, and oximetry): body mass index (BMI) was calculated, and, expressed in kg/m2. Values ≥18.5 and <25 were considered normal. Waist circumference (normal ≤ 88 cm in women and ≤ 102 cm in men) and neck circumference (normal ≤43 cm) were measured.

Blood pressure (BP) was assessed with a digital sphygmomanometer (Omrom® 7120) according to the guidelines of the Argentine Consensus on Hypertension. (17)

Oxygen saturation (%) and heart rate (bpm) were measured with a digital oximeter (Contec® CMS50N).

Clinic 4 (Electrocardiogram, ECG): a 12-lead digital recording (Jotatec® TaurusTouch) was performed.

Clinic 5 (Echocardiography): recording of cardiac structure dimensions (mm) and areas (cm^2) (Esaote® MyLab 30 Gold) were made, with calculation of left ventricular ejection fraction (LVEF) using the Simpson biplane method. (18)

Clinic 6 (Peripheral arterial ultrasound): Doppler ultrasound technique was used on neck and iliofemoral arteries (Esaote® MyLab 30 Gold).

Clinic 7 (Physical capacity): exercise tolerance using the Ruffier-Dickson test. (19) The Ruffier index [(sum of baseline, intra-exercise, and post-exercise heart rates) – 200)/10] was calculated and the following scale was used: 0: very good; 0.1 to 5: good; 5.1 to 10: average; 10.1 to 15: insufficient; and 15.1 to 20: poor.

Maximum handgrip strength was measured using a hydraulic dynamometer (Jamar®) in the dominant hand, calculated as the average of three attempts. Values ≥ 27 kg in men and ≥ 16 kg in women were considered normal. (20)

Exclusion criteria included sensory, cognitive, or motor disabilities.

Statistical analysis

Results were expressed as frequency and percentage for qualitative variables and as mean ± standard error for quantitative variables. Qualitative variables were compared using the chi-square or Fisher's exact test, as appropriate, and quantitative variables using Student's t-test. Data were analyzed using Prism 5.0.2 software. Values with $p < 0.05$ were considered statistically significant.

Ethical considerations

The study was approved by the Provincial Health Ethics and Research Committee of the Ministry of Health of the Province of Jujuy (File No. 773-1251/2024). All participants gave their informed consent to participate.

RESULTS

A total of 404 persons were analyzed in the IV Edition of the SONQO-CALCHAQUÍ Program. Among them, 241 (average age 44.1±0.1 years) were included in this study: 139 women (57.7%) and 102 men (42.3%). All the communities where residents came from were located more than 2500 meters above sea level.

Clinic 1: Table 1 shows the results of the routine analysis. The calculated glomerular filtration rate was 107.4±1.7 mL/min, and TSH values were 5.8±1.8 mIU/L. Only one resident tested positive for Chagas disease serology.

Clinic 2:

Targeted socioeconomic survey:

a) Educational level: 5.0% were illiterate; 56.4% had completed primary school; 21.6% had completed secondary school; and 17.0% had completed tertiary education.
b) Occupation: 60.2% were active workers; 19.9% performed household tasks; 0.8% were students; 12.9% were retired; and 6.2% were unemployed.
c) Health coverage: 71.4% had social security; 0.8% had prepaid coverage, and 27.8% had no health coverage.

In 91.7% of cases, residents had a cell phone, with an average use of 3.9±0.2 hours/day.

Regarding cardiovascular risk factors, 13.7% had history of hypertension (HTN); 2.9% had diabetes, 16.2% had dyslipidemia, and 15.8% were smokers. The age of the residents was higher in the group with HTN (54.2±2.6 years vs. 42.4±1.0 years in those without HTN; p<0.001) or diabetes (57.0±3.3 years vs. 43.7±1.0 years in residents without diabetes; p= 0.032).

24-hour dietary recall test: breakfast consisted mainly of tea (43.2%) and mate (30.3%), usually accompanied by bread (40.2%). At mid-morning, 36.1% had a snack. At lunch, 78.4% ate meat (beef 58.9%, chicken 14.5%, and llama 5%), usually accompanied by flour or rice. Dessert was fruit (39.8%), cornmeal ("anchi"; 9.1%), or another dessert (7.5%). The afternoon snack was similar to breakfast, and dinner was similar to lunch.

Food consumption frequency test: during the previous year, residents consumed the following number of monthly portions: lean meat: 21.5±1.3 (mainly llama and lamb); white meat: 10.0±0.1; fish: 1.8±0.4; vegetables: 37.1±1.5; fruit: 28.0±1.6; nuts: 1.8±0.5, legumes: 3.8±0.5; fat: 22.8±1.3; refined cereals: 22.8±1.8; whole grains: 1.6±0.8; sugar: 17.6±1.6; dairy products: 9.2±0.7; and eggs: 11.9±0.9.

Almost half of the residents (48.9%) reported regular alcohol consumption.

SF-12 questionnaire: the average score was 26.7±0.3 points (63.7±0.6% of the total value). Figure 1 shows the answers to the questionnaire.

Pittsburgh Sleep Quality Index: bedtime was at 10:42 p.m.±00:05 a.m. and wake-up time was at 7:48 a.m.±00:02 a.m. (9.1±0.05 hours of sleep). During the last month, 38.8% of residents had no trouble falling asleep; 51.7% got up during the night to go to the bathroom; 16.3% reported feeling apnea; 38.3% snored;

Table 1. Routine test results (n=241)

Variable		Value
Hematocrit (%)		54.4±0.4
Hemoglobin (g/dL)		18.1±0.1
Red blood cells (million/dL)		6.2±0.0
White blood cells (thousand/dL)		6.8±0.1
Platelets (thousand/dL)		245.2±3.6
Erythrocyte sedimentation rate (mm)		7.5±0.3
Blood glucose (mg/dL)		76.6±0.7
Creatinine (mg/dL)		0.7±0.0
Urea (mg/dL)		20.6±0.4
GOT (IU/L)		7.2±0.2
GPT (IU/L)		6.9±0.2
Alkaline phosphatase (IU/L)		190.4±3.8
Bilirubin (mg/dL)	Total	0.4±0.0
	Indirect	0.3±0.0
	Direct	0.2±0.0
Cholesterol (mg/dL)	Total	169.1±2.8
	HDL-C	42.8±0.4
	LDL-C	101.5±2.7
Triglycerides (mg/dL)		122.0±2.0

GOT: Glutamic-oxaloacetic transaminase; GPT: Glutamic-pyruvic transaminase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.
Variables are presented as mean ± standard error.

and 30.4% had nightmares. Regarding sleep quality, 29.9% indicated that it was very good; 59.7% fairly good; 7.5% fairly poor; and 2.8% very poor; 96.7% did not take sleep medication.

Clinic 3: Table 2 shows the results of the parameters recorded. According to BMI, 0.4% were malnourished; 32.0% had normal weight; 36.5% were overweight; 23.2% were obese; and 7.9% were morbidly obese. Waist circumference was elevated in 56.7% and neck circumference in 8.0% of residents. Systolic BP was elevated in 8.8% of the population and diastolic BP in 12.6%. Average arterial O2 saturation was 88.3 ±0.4%.

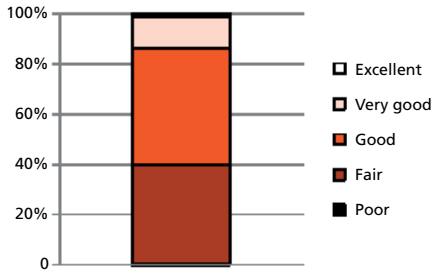
Clinic 4: Mean heart rate on the ECG was 68.8±0.7. The average QRS complex duration was 101.7±7.4 msec., and the QT interval 404.9±2.1 msec. The cardiac axis was 43.6±4.5°. In 32 residents (13.3%), the axis was deviated to the right, and 17 (7.1%) had right bundle branch block. One resident had atrial fibrillation.

Clinic 5: Table 3 shows the quantifiable findings of the echocardiogram. Thirteen residents had mitral regurgitation; 6 had tricuspid regurgitation; 3 had aortic stenosis; and 1 had pulmonary stenosis. Hypokinesia was found in 7 residents and abnormal septal motility in 1. In 5 residents, the right ventricle was dilated. Signs of pulmonary hypertension were found in 7 residents.

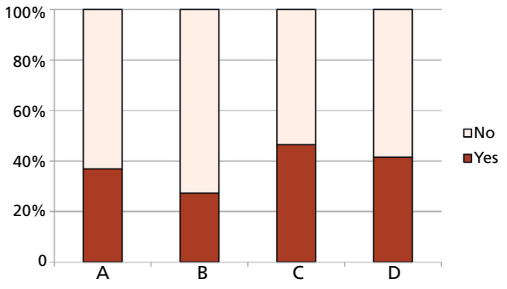
Clinic 6: No aneurysms, tumors, or malformations were found in any resident.

Fig. 1. Self-perceived health status: responses to the SF-12 Form (n=241)

A. How do you perceive your health?

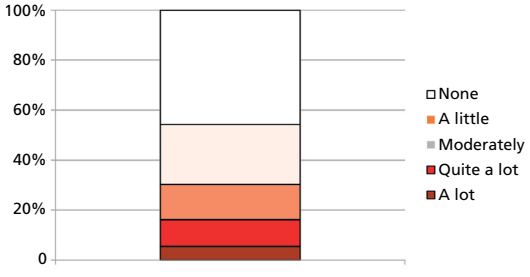


B. During the last 4 weeks:

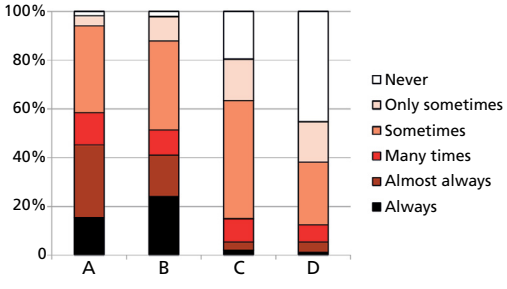


A: Did you do less than you would have liked because of your physical health?
B: Did you have to stop doing some tasks at work or in your daily activities because of your physical health?
C: Did you do less than you would have liked to do because of an emotional problem (such as feeling sad, depressed, or nervous)?
D: Did you not do your work or daily activities as carefully as usual because of an emotional problem?

C. During the last 4 weeks, to what extent has pain made your usual work difficult?



D. During the last 4 weeks:



A: How long did you feel calm and peaceful?
B: How long did you have a lot of energy?
C: How long did you feel discouraged and sad?
D: How often have physical health or emotional problems made it difficult for you to engage in social activities?

Neck arteries: Seven residents had myointimal thickening. Ten residents had thyroid nodules. There was no difference in TSH values between residents with and without nodules.

Iliofemoral arteries: Three residents had myointimal thickening and five had wall irregularities.

Presence of plaques: 23 residents had atheromatous plaques in the carotid bed; 8 in the iliofemoral bed and 2 in both beds. Ninety percent of residents had no plaques in any of the beds studied.

Residents with atheromatous plaques were older (56.1±2.7 years vs. 42.2±1.0 years in those without plaques, $p<0.001$).

Clinic 7:

Ruffier-Dickson test: Baseline HR was 70.7±0.8 beats/min; during exercise 96.0±1.3 beats/min (24.7±1.0% increase from baseline), and after exercise 72.6±1.0 beats/min (23.3±0.9% decrease from exercise). The Ruffier index was 4.1±0.3. It was considered very good in 15.6% of the population; good in 50.5%; average in 28.0%; insufficient in 4.1%; and poor in 1.8%.

Grip strength: The average value was 29.4±0.6 kg. In 80.3% of cases, it was within the normal range.

DISCUSSION

The population studied has an above-average self-perception of their health, (15) with good sleep quality and good cardiovascular function accompanied by adaptive changes to life at high altitude. On the other hand, a high prevalence of overweight/obesity with increased waist circumference was found. Added to this is high alcohol consumption.

The population was younger than that studied in previous editions of the SONQO- CALCHAQUÍ Program. (1-3) It should be clarified that this Program includes residents who attend voluntarily, which introduces a bias, since older residents have greater difficulty participating, thus selecting a younger population.

Unlike other editions of the SONQO-CALCHAQUÍ Program, O2 saturation values were below 90%. These values, which in other situations would be ground for hospitalization, (21) have been described as "normal" in high-altitude populations. (22) Increased hematimetric values, also described in other high-altitude populations, (23) would be compensatory to hypoxia. Although the hemodynamic cost of this adaptive process is still unclear, the fact that the echocardiogram and physical capacity were within normal limits indicates a cardiovascular physiology compensated for these conditions. This hypothesis is supported by the results of the Pittsburgh Index, with good sleep quality and low prevalence of apnea, as sleep quality has been shown to be altered by hypoxemia. (24) In addition, they presented an electrocardiographic tracing within normal limits, a fact already observed in other high-altitude populations, (25) and laboratory indices of renal and hepatic function within physiological ranges.

Elevated TSH values were found, and in some residents, thyroid nodules. Alterations in the hypothalamic-thyroid axis have been described in high-moun-

Table 2. Anthropometric and hemodynamic variables of the population (n=241)

	Variable (Unit)		Value
Anthropometric variables	Weight (kg)		69.5±0.9
	Height (cm)		158.4±0.5
	BMI		27.8±0.3
	Waist circumference (cm)		96.2±0.8
	Neck circumference (cm)		37.4±0.3
	Arm span (cm)		149.1±2.7
	Upper arm circumference (cm)	Right	28.8±0.3
		Left	29.1±1.1
	Calf circumference (cm)	Right	35.2±0.2
		Left	35.2±0.2
Hemodynamic variables	Blood pressure (mmHg)	Systolic	115.2±1.0
		Diastolic	75.9±0.7
		Differential	39.5±0.8
		Mean	88.9±0.7
	Oxygen saturation (%)		88.3±0.4
	Heart rate (bpm)		69.8±0.7

BMI: body mass index; bpm: beats per minute. Variables are presented as mean ± standard error

Table 3. Quantifiable echocardiographic findings. Measurements in the parasternal long axis. (n=241)

Variable	Value
LVEDD (mm)	41.7±0.5
LVESD (mm)	25.8±0.3
LVEF (%)	63.6±0.5
IVS thickness (mm)	9.5±0.2
PWT (mm)	9.5±0.4
LVOTd (mm)	18.5±0.2
Ao root(mm)	22.0±0.3
LAAPD (mm)	16.7±0.3

Ao root: aortic root diameter; IVS: interventricular septum; LAAP:Left atrial anteroposterior diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVOTd: left ventricular outflow tract diameter; PWT: posterior wall thickness
Variables are presented as mean ± standard error.

tain populations (26) so the real role of these findings in cardiovascular function, and whether a diet supplemented with iodine could be beneficial, should be evaluated in future studies.

With regard to the nutritional status, 67.6% of the population had an increased BMI (with 7.9% reaching morbid obesity) and 56.7% had increased waist circumference. These findings are similar to those observed in previous editions of the SONQO-CALCHAQUÍ Program in other indigenous populations in northwestern Argentina (1-3) and to those reported in other American indigenous communities. (27,28) Obesity, currently considered a pandemic, (29) is also affecting indigenous populations. (1-3, 27-31)

On the other hand, the Coranzulí population has a low prevalence of cardiovascular risk factors, and cholesterol and blood glucose levels within the normal range. These cardioprotective characteristics could explain the low prevalence of atheromatous plaques in the arteries studied, a phenotype shared with the indigenous populations of the Calchaquí valleys. (2,3) This cardioprotective phenotype is more evident in younger residents (who have a lower prevalence of cardiovascular risk factors and atherosclerotic plaques). Although the genetic and/or epigenetic factors involved remain to be elucidated, the nutritional regime could play a role in this regard, as the diet preserves indigenous elements (e.g., mate, llama meat, and "anchi"). Added to this is the physical activity that residents perform in daily tasks, which is reflected in their physical capacity. Further studies with similar populations may shed more light on this aspect. Another factor to study, which could have some implications, is the low daily use of cell phones. Excessive use has been shown to increase cardiovascular risk. (32)

The beneficial and harmful effects of westernization on the cardiovascular health of indigenous peoples are still being debated. Although associated with higher obesity rates, it also promotes access to resources and technology linked to longer life expectancy. (33) In Coranzulí, this ambivalence is exemplified by two facts: on the one hand, a high prevalence of overweight/obesity (already described in other indigenous communities) accompanied by high alcohol consumption, but on the other hand, a high rate of medical coverage and a low illiteracy rate.

CONCLUSIONS

The Coranzulí community presents itself as an indigenous population adapted to high- mountain life, which maintains indigenous elements with cardioprotective characteristics, notably nutritional habits and sleep quality. However, it is undergoing a westernization process. The task remains to evaluate the true role of these changes (including the massive influx of the Internet worldwide) on the general and cardiovascular health of this population, for which it is necessary to continue multisectoral studies, such as the SONQO-CALCHAQUÍ Program.

Acknowledgments

The authors would like to thank the following entities, without whose contribution this study would have been impossible. In alphabetical order:

- Argentine Society of Cardiology, represented by its President, Dr. Pablo Guillermo Stutzbach
- Government of the Province of Jujuy
- Coranzulí Secondary School No. 18
- Emergency Medical Assistance System of Jujuy
- La Chata Solidaria NGO
- Ministry of Culture and Tourism of Jujuy
- Ministry of Education of Jujuy
- Ministry of Health of Jujuy
- Municipal Commission of Coranzulí
- School of Medicine of Universidad Nacional de Tucumán, represented by its Dean, Dr. Demetrio Mateo Martínez

Limitations

The study population was small and in advanced stages of the disease.

Conflicts of interest

None declared.

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

REFERENCES

1. Galdeano R, Holownia D, Palavecino D, Abregú J, Rivas Jordan M, Frías SM, et al. Evaluation of cardiovascular variables in a Calchaquí population living in the mid- and high-altitude mountains of Tucumán. Rev Argent Cardiol 2021;89:20-6. https://doi.org/10.7775/rac.v89.i1.19095

2. Galdeano RS, Holownia D, Palavecino D, Abregú JD, Benger J, Alderete R, et al. SONQO-CALCHAQUÍ 2022 Program: Evaluation of cardiovascular variables in a Calchaquí population living in the

mid- and high-altitude mountains of Tucumán. Rev Argent Cardiol 2024;92:193-201. https://doi.org/10.7775/rac.es.v92.i3.20765
3. Galdeano RS, Vogelmann OA, Mauro SO, Scattini G, Alderete R, Pastore FA, et al. SONQO-CALCHAQUÍ III Program (2023 Edition): evaluation of cardiovascular variables in indigenous communities of the Calchaquí Valleys (Northwestern Argentina). Rev Argent Cardiol 2024;92:429-36. https://doi.org/10.7775/rac.v92.i6.20847
4. Lanza N, Valeggia C, Peláez E. The reproductive transition in an indigenous population of northern Argentina. Biodemography Soc Biol 2013;59:212-30. https://doi.org/10.1080/19485565.2013.833784
5. Couceiro de Cadena M, Valdiviezo de Rodríguez MS, Zimmer Sarmiento MC. Food intake and anthropometric assessment of an indigenous mission in the province of Salta. Argentine Republic. Aten Primaria 1997;20:421-4
6. Rosas Muñoz M, Delgado Floody P, Cea Leiva F, Alarcón Hormazábal M, Alvarez San Martín R, Quezada Gallego K. Comparison of risks in eating disorders and body image between Mapuche and non-Mapuche students. Nutr Hosp 2015;32:2926-31.
7. Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: pathophysiology, prevention, and treatment. Prog Cardiovasc Dis 2010;52:467-84. https://doi.org/10.1016/j.pcad.2010.02.003
8. Ucrós S, Castro-Guevara JA, Hill CM, Castro-Rodriguez JA. Breathing Patterns and Oxygenation Saturation During Sleep in Children Habitually Living at High Altitude in the Andes: A Systematic Review. Front Pediatr 2022;9:798310. https://doi.org/10.3389/fped.2021.798310
9. Romaguera D, Samman N, Rossi A, Miranda C, Pons A, Tur JA. Dietary patterns of the Andean population of Puna and Quebrada of Humahuaca, Jujuy, Argentina. Br J Nutr. 2008;99:390-7. https://doi.org/10.1017/S0007114507801061
10. Barada, J. A village is a place. The urban form of a shepherding village in the face of state logic. Coranzulí, Puna de Jujuy, Argentina, from 1900 to the present. Rev de geografía Norte Grande 2020;77:367-95. https://doi.org/10.4067/S0718-34022020000300367
11. INDEC. National Population, Household, and Housing Census 2022, https://censo.gob.ar/
12. Baspineiro CF, Franco J, Flexer V. Potential water recovery during lithium mining from high salinity brines. Sci Total Environ 2020;720:137523. https://doi.org/10.1016/j.scitotenv.2020.137523
13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70. https://doi.org/10.7326/0003-4819-130-6-199903160-00002
14. Ferrari, M. Estimation of intake by 24-hour recall. Diaeta 2013;31:20-5
15. Vera-Villarroel P, Silva J, Celis-Atenas K, Pavez P. Evaluation of the SF-12 questionnaire: verification of the usefulness of the mental health scale. Rev méd Chile 2014;142:1275-83. https://doi.org/10.4067/S0034-98872014001000007
16. Macías Fernandez J; Royuela Rico A. The Spanish version of the Pittsburgh Sleep Quality Index. Informaciones Psiquiátricas 1996;146:465-72.
17. Argentine Consensus on Arterial Hypertension; Rev Argent Cardiol 2018;86:4-53.
18. Aurigemma GP, Gottdiener JS, Arnold AM, Chinali M, Hill JC, Kitzman D. Left atrial volume and geometry in healthy aging: the Cardiovascular Health Study. Circ Cardiovasc Imaging 2009;2:282-9. https://doi.org/10.1161/CIRCIMAGING.108.826602
19. Rodríguez Cabrero M, García Aparicio A, García Pastor T, Salinero JJ, Pérez González B, Sánchez Fernández JJ, et al. Physical Activity and Leisure Habits and Relation with Ruffier Index in Adolescents. RIMCAFD. 2015;15:165-80. https://doi.org/10.15366/rimcafd2015.57.012
20. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: normative data from twelve British studies. PLoS One 2014;9:e113637. https://doi.org/10.1371/journal.pone.0113637
21. Ayinbuomwan SA, Mokogwu N, Akoria OA, Okwara BU, Omuemu CE, Obaseki DE. Arterial Oxygen Saturation and other Clinical Predictors of Survival in Patients with Covid-19: A Review of Cases in a Tertiary Care Hospital in Nigeria. West Afr J Med 2021;38:109-13
22. Idrose AM, Juliana N, Azmani S, Yazit NAA, Muslim MSA, Ismail M, Amir SN. Singing Improves Oxygen Saturation in Simulated High-Altitude Environment. J Voice. 2022;36:316-21. https://doi.org/10.1016/j.jvoice.2020.06.031
23. Siebenmann C, Robach P, Lundby C. Regulation of blood volume in lowlanders exposed to high altitude. J Appl Physiol (1985) 2017;123:957-66. https://doi.org/10.1152/japplphysiol.00118.2017
24. Grimm M, Seglias A, Ziegler L, Mademilov M, Isaeva E, Tynybekov K, Tilebalieva A, Osmonbaeva N, Furian M, Sooronbaev TM, Ulrich S, Bloch KE. Sleep apnea in school-age children living at high altitude. Pulmonology 2023;29:385-91. https://doi.org/10.1016/j.pulmoe.2023.02.008
25. Parodi JB, Ramchandani R, Zhou Z, Chango DX, Acunzo R, Liblik K, et al. ANDES (Altitude Non-specific Distributed ECG Screening) Project Investigators. A systematic review of electrocardiographic changes in healthy high-altitude populations. Trends Cardiovasc Med 2023;33:309-15. https://doi.org/10.1016/j.tcm.2022.01.013
26. von Wolff M, Nakas CT, Tobler M, Merz TM, Hilty MP, Veldhuis JD, et al. Adrenal, thyroid and gonadal axes are affected at high altitude. Endocr Connect 2018 1;7:1081-9. https://doi.org/10.1530/EC-18-0242
27. Batal M, Decelles S. A Scoping Review of Obesity among Indigenous Peoples in Canada. J Obes 2019;3:9741090. https://doi.org/10.1155/2019/9741090
28. Baldoni NR, Aquino JA, Alves GCS, Sartorelli DS, Franco LJ, Madeira SP, et al. Prevalence of overweight and obesity in the adult indigenous population in Brazil: A systematic review with meta-analysis. Diabetes Metab Syndr 2019;13:1705-15. https://doi.org/10.1016/j.dsx.2019.03.024
29. Frank JW. Controlling the obesity pandemic: Geoffrey Rose revisited. Can J Public Health 2022;113:736-42. https://doi.org/10.17269/s41997-022-00636-6
30. Arévalo Velásquez CL, Ocampo Cañas JA, Buitrago Echeverri MT. Social determination of alcohol consumption among Indigenous peoples in Colombia: a qualitative meta-synthesis. BMC Public Health 2023;23:478. https://doi.org/10.1186/s12889-023-15233-6
31. Vargas M P, Saavedra P S, Araya A MV, Loyola A K, Huerta G P, Silva A M, Araya C S, Saavedra A W, Portales P P, Saavedra P W. Prevalence of cardiovascular risk factors in a rural Aymara population from northern Chile Rev Med Chil 2016;144:1144-9. https://doi.org/10.4067/S0034-98872016000900007
32. Lissak G. Adverse physiological and psychological effects of screen time on children and adolescents: Literature review and case study. Environ Res 2018;164:149-57. https://doi.org/10.1016/j.envres.2018.01.015
33. Ali-Hassan H, Eloulabi R, Keethakumar A. Internet non-use among Canadian indigenous older adults: Aboriginal Peoples Survey (APS). BMC Public Health 2020;20:1554. https://doi.org/10.1186/s12889-020-09659-5

REFERENCES

* PARTICIPANTS OF THE SONQO-CALCHAQUI IV PROGRAM

(in alphabetical order):

Abbate Ana Silvina[1]; Abrahan Francisco[2]; Abregú Daniel[1]; Acevedo Costello Benjamín Nicolás[2]; Agüero María del Rosario[2]; Alauie María[2]; Alderete Rodrigo[1]; Álvarez Carlos Eduardo[1]; Amarillo María Valentina[2]; Bregazzi Josefina[2]; Cabana Faustino[4]; Cabrera Valentín[1]; Cagnone Lorena[1]; Chemes Jerónimo[6]; Delgado Florencia Anahí[2]; Elleit Guillermina[1,4]; Fernández Rocío[1]; Fernández Sily Lucia[2]; Ferreyra Solana[2]; Fiszman Luis[1]; Flores Laura[1,4]; Flores, María Gimena[2]; Galdeano, Ricardo Sebastián[1]; Galván Rey Tobías[2]; García Cárdenas Tomás Sergio2; García, Karina1; González, Mikaela[2]; Ibañez Federico[4]; Joo Turoni Claudio[1,2,3]; Jure Pablo Hernán[4]; Juárez Rodríguez Tomás[2]; Kotowicz Mijail[2]; Langa Franadel Nerlina[2]; López María Cecilia[1]; Malica Mariano[2]; Marañón Rodrigo Oscar[1,2,3]; Mateo Martínez Demetrio[2]; Mauro Sergio Oscar[1]; Montero Andrea[1]; Nieva Fabricio[2]; Nieva Lucas Luciano[2]; Páez Mateo Javier[2]; Pastore Francisco Alberto[1]; Perea Gabriel[1]; Pereyra Nazareno René[2]; Pillitteri Roberto Ignazio[2]; Ramos Olivera Milagros[2]; Rivadeo Eloy[5]; Robledo Rocío Guadalupe[2]; Saavedra Sofía[2]; Santos Juan Carlos[2]; Scattini Gabriel; Silva Barro Santiago Lionel[2]; Simón Sassi Juan Bautista[2]; Sosa Hugo[4]; Stutzbach Pablo Guillermo[1]; Tefaha Liliana Monica[2]; Tomas Sofía Carolina[2]; Tonello Lourdes Andrea[2]; Toraño Castro Maia[2]; Urpi Julieta[2]; Vargas Aignasse Gabriela[2]; Villa Graciela[1]; Viñuales Guadalupe[2]; Vogelmann Oscar Ariel[1]; Zeballos Gabriela Sonia[1,4]

1. Argentine Society of Cardiology
2. School of Medicine, Universidad Nacional de Tucumán, Tucumán, Argentina.
3. Higher Institute for Biological Research (INSIBIO), CONICET-UNT, Tucumán, Argentina
4. Ministry of Health of Jujuy, Jujuy, Argentina
5. Tucumán Provincial Health System, Tucumán, Argentina.
6. La Chata Solidaria NGO

ORIGINAL ARTICLE

Genotype-Phenotype Correlation in a Cohort of Patients with Hypertrophic Cardiomyopathy

Correlación genotipo-fenotipo en una cohorte de pacientes con miocardiopatía hipertrófica

JOSEFINA B PARODI[1], LUCILA CAROSELLA[1], FLORENCIA MANDO[1], MARTÍN MUNIN[1,MTSAC], MICHAEL SALAMÉ[1], JAVIER GUETTA[1,MTSAC], JORGE THIERER[1,MTSAC]

ABSTRACT

Background: Sarcomere protein mutations are commonly found in patients with hypertrophic cardiomyopathy (HCM). Identifying the genetic basis allows for cascade screening and provides prognostic information, although the yield of genetic testing (GT) is variable. It is recommended that patients be selected based on the likelihood of a high yield of GT, given its significant cost and limited accessibility.
Objective: The aim of this study was to describe the clinical characteristics and the results of diagnostic tests in a cohort of patients with HCM followed-up at a non-specialized center, and to analyze which variables are significantly associated with a positive GT.
Methods: We conducted a retrospective cohort study of patients diagnosed with HCM. The clinical data and the results of the electrocardiogram (ECG), ECG Holter monitoring, multi-modality imaging and GT were analyzed. Phenocopies were excluded.
Results: A total of 72 patients were included. Forty-one patients underwent GT, which was positive (G+) in 13 (31.7%). G+ patients were younger (mean age 38.4 vs. 50.8 years) and had higher prevalence of negative T waves in the ECG (92.3% vs. 42.9%) and of non-sustained ventricular tachycardia (NSVT) on ECG Holter monitoring (61.5% vs 10.5%). Reverse septal curvature pattern was more common in G+ patients (84.6% vs. 17.9%) and median wall thickness was greater (21 vs. 17 mm). All G+ patients exhibited fibrosis on cardiac magnetic resonance, vs. 69.6% in the rest of the patients. All these differences were statistically significant. Reverse septal curvature was the only independent predictor of a positive GT.
Conclusion: One-third of patients with HCM who underwent genotyping present sarcomere protein mutations. The presence of reverse septum appears to be the variable most strongly associated with G+. Given the limited availability of GT in our setting, knowing the variables that predict better performance is advisable for the appropriate selection of patients.

Keywords: Cardiomyopathies-Hypertrophic cardiomyopathy-Echocardiography- Genetic testing- Sarcomere mutations- Cardiac magnetic resonance- Sudden cardiac death

RESUMEN

Introducción: Las mutaciones habitualmente encontradas en pacientes con miocardiopatía hipertrófica (MCH) involucran proteínas del sarcómero. Identificar la base genética permite realizar estudios en cascada y aportar información pronóstica, aunque el rendimiento del estudio genético (EG) es variable. Por su alto costo y difícil acceso, seleccionar pacientes en los que el rendimiento del EG sea mayor es recomendable.
Objetivos: Describir las características clínicas y de estudios complementarios en pacientes con MCH en un centro no especializado, y analizar qué variables clínicas y paraclínicas se asocian significativamente con un EG positivo.
Material y métodos: Estudio de cohorte retrospectivo de pacientes con diagnóstico de MCH. Se analizaron los datos clínicos, del electrocardiograma (ECG) y Holter, de estudios multiimagen y el EG. Se excluyeron fenocopias.
Resultados: Se incluyeron 72 pacientes. En 41 de ellos se realizó EG, y 13 (31,7%) fueron positivos (G+). Los pacientes con G+ eran más jóvenes (media de edad de 38,4 vs. 50,8 años), presentaban más frecuentemente ondas T negativas en el ECG (92,3% vs. 42,9%) y taquicardia ventricular no sostenida (TVNS) en el ECG Holter (61,5% vs. 10,5%), más hipertrofia tipo septum reverso (84,6% vs. 17,9%) y mayor espesor parietal (medianas de 21 vs. 17 mm). El 100% de los G+ presentaron fibrosis en la resonancia cardíaca, vs. 69,6% en el resto. Todas las diferencias citadas fueron estadísticamente significativas. Solo el septum reverso se asoció de manera independiente con un estudio positivo.

Rev Argent Cardiol 2025;93:286-292. https://doi.org/10.7775/rac.v93.i4.20915

Received: 05/13/2025 – *Accepted:* 07/15/2025

Correspondence: Josefina Belén Parodi. E-mail: josefinab.parodi@gmail.com
Sources of funding: None

[1] Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" (CEMIC), Buenos Aires, Argentina

Conclusión: Un tercio de los pacientes con MCH evaluados genotípicamente presentan mutaciones sarcoméricas. La presencia de septum reverso parece ser la variable más fuertemente asociada a G+. Ante la escasa disponibilidad del EG en nuestro medio, conocer las variables que predicen mayor rendimiento resulta aconsejable para una selección adecuada de los pacientes.

Palabras clave: Cardiomiopatía - Miocardiopatía hipertrófica - Ecocardiografía - Estudio genético - Mutaciones sarcoméricas - Resonancia magnética cardíaca - Muerte súbita cardíaca

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with a prevalence of up to 1 in 500 people. (1) It is a complex and variable disease in terms of pathophysiology, clinical presentation, prognosis and survival, and is the leading cause of sudden cardiac death in young people and athletes. However, most patients are asymptomatic, which complicates the diagnostic process. Genetic HCM usually corresponds to a single gene disorder with an autosomal dominant pattern of inheritance. (2) Most variants or mutations detected are in genes encoding sarcomere proteins. (3) The percentage of positive genetic testing (GT) varies according to phenotype, but it can reach 70-80% in selected groups. (4) The identification of the genetic basis of HCM is not only a reason to perform cascade genetic screening in family members, but also provides valuable prognostic information. (5,6) Nevertheless, this tool is not yet routinely used due to its high cost and limited availability. Defining the group of patients in whom a positive GT is most likely to occur may be useful in addressing this issue.

OBJECTIVES

The aim of this study was to describe the clinical characteristics and the results of diagnostic tests in a cohort of patients with HCM who were being followed-up at a non-specialized center, and to analyze which variables are significantly associated with positive GT.

METHODS

A retrospective cohort study was conducted on patients evaluated at a non-specialized center from January 2022 to January 2025, with a diagnosis of HCM made by transthoracic color Doppler echocardiography (TTE) and defined by a left ventricular (LV) wall thickness ≥15 mm in at least one myocardial segment. The cohort also included relatives of patients with a diagnosis of HCM based on the presence of LV wall thickness ≥13 mm. In all cases, increased wall thickness could not be explained by the presence of hypertension, other heart disease, systemic disease, or congenital heart disease. (1) The clinical data, family history and the results of electrocardiogram (ECG), TTE, exercise stress test, ECG Holter monitoring, cardiac magnetic resonance (CMR) with gadolinium-based contrast agent and the results of GT (when available) were analyzed. Patients exhibiting phenocopies, including amyloidosis and Fabry disease, along with those with other causes of heart disease such as severe valvular heart disease were excluded from the study.

Genetic testing

GT was performed using next-generation sequencing (NGS) based on a panel of hypertrophic cardiomyopathies which should include, at least, a basic panel. This panel contains the core genes, i.e., those with sufficient clinical and functional evidence to be considered associated with the disease, as well as genes related to the main phenotypes of this condition. (1,7) The panels used encompassed the analysis of at least 10 sarcomeric genes (MYH7, MYBPC3, TNNT2, TPM1, MYL2, MYL3, TNNI3, TNNC1, TPM1, ACTC1, and CSRP3), four genes from other myocyte cell structures (PTPN11, PLN, JPH2, DES), and four genes associated with storage diseases (GLA, LAMP2, PRKAG2, TTR) to rule out phenocopies. Deoxyribonucleic acid (DNA) was extracted from whole blood spotted on filter paper or from saliva using an automated method. Single nucleotide variants (SNVs) and small insertions and deletions (indels) were identified with a minimum coverage of 20 fragments ≥ 98%. The variants were classified following the guidelines of the American College of Medical Genetics and Genomics 2015 (ACMG) (8) and were characterized as pathogenic, likely pathogenic (90% certainty of a variant being disease-causing), variants of uncertain significance (VUS), likely benign (90% certainty of a variant being benign), or benign.

Statistical analysis

Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's test, as appropriate. Continuous variables with normal distribution are expressed as mean ± standard deviation (SD) and those with non-normal distribution as median and interquartile range (IQR). Normality of distribution was assessed using graphical methods (histogram or plots) or the Shapiro Wilk test. Quantitative variables were compared using the Student's t test or the Wilcoxon rank sum test, as appropriate. The association of the evaluated variables with positive genetic test results was investigated through the analysis of a contingency table. All those variables with a p-value < 0.10 as well as those considered clinically relevant were included in a multivariate logistic regression model to define the variables independently associated with a positive GT result. A p-value < 0.05 was considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the institutional review board. The investigation was conducted following the recommendations of the Declaration of Helsinki. (9) All the patients gave their informed consent before participating in the study.

RESULTS

A total of 72 patients were included; mean age was 54 ± 16 years and 55 (76.4%) were men. Twenty-seven patients (37.5%) had a family history of HCM or sudden cardiac death. Twenty-nine patients (40.3%) had hypertension, which was mild in all cases and was being treated with a single drug. The presence of any symptoms was reported by 43 patients (59.7%), the

most common being dyspnea. Electrocardiographic changes occurred in 83.3% of patients (n=60), 41.7% presented criteria for left ventricular hypertrophy (LVH), and 61.1% had negative T waves. Twenty-eight patients (39.4%) had left ventricular outflow tract obstruction (LVOTO), and septal reduction therapy had been indicated in 4 (5.5%). A total of 9 patients (12.5%) had an implantable cardioverter-defibrillator (ICD) for the primary or secondary prevention of sudden cardiac death. The most common patterns of LVH on echocardiography were reverse septal curvature in 33 (45.8%), sigmoid septum in 29 (40.3%), and apical hypertrophy in 8 (11.1%). Mean maximal wall thickness measured by echocardiography was 18.5± 3.9 mm. Sixty-one patients underwent CMR, which revealed late gadolinium enhancement (LGE) in 49 cases (81.7%), predominantly mild (less than< 5% of myocardial mass). Only 16 patients exhibited extensive LGE (> 15% myocardial mass). The average sudden cardiac death risk score (HCM Risk-SCD score) recommended by the European Society of Cardiology(ESC) (10) was 2.7±1.9 (risk <4% at 5 years). The remaining parameters are described in Table 1.

Although GT was routinely indicated in all patients to avoid selection bias, it was eventually performed in 41 of the 72 patients (57%) due to issues related to lack of coverage, costs, or patient refusal. When these 41 patients were compared with the remaining 31, no significant differences were found in the most relevant clinical variables, nor in the findings on echocardiogram or CMR.

In 13 (31.7%) of the genetic panels performed, a positive result was obtained for a sarcomere protein mutation (G+ group): 5 in MYBPC3, 5 in MYH7, 2 in TNNT2, and 1 in FLNC. The remaining 28 cases (68.3%) were negative results or VUS in genes not phenotypically associated with HCM (G- group). G+ patients were younger at the time of diagnosis (mean age 38.4± 15.3 vs. 50.8± 11.7 years, p = 0.007). Gender and cardiovascular risk factors were similar in both groups. There were no differences in the presence of symptoms (dyspnea, angina, palpitations, or syncope). Regarding the ECG, negative T waves were more prevalent in G+ patients (92.3% vs. 42.9%, p = 0.003). These patients also exhibited a higher incidence of non-sustained ventricular tachycardia (NSVT) on ECG Holter monitoring (61.5% vs. 10.5%, p = 0.002). On imaging tests, the reverse septal curvature phenotype of LVH was more common in G+ patients (84.6% vs. 17.9%) while the sigmoid septum phenotype was more frequently observed in G- patients (67.9% vs. 7.7%). In both cases these differences were statistically significant. Median maximum wall thickness measured by transthoracic echocardiography was greater in G+ patients compared to G- patients (21 mm, IQR 17.7-22.5 vs. 17 mm, IQR 16-18.8, respectively; p = 0.016). Left atrial diameter was smaller in G+ patients (38.6 ± 5.8 mm vs. 44.5 ± 4.5 mm; p = 0.001). The information of CMR with gadolinium-based contrast agent was obtained in 37 of the 41 patients. LGE was observed in all G+ patients compared to 69.6% of the 28 G- patients (p = 0.027).

With regard to the risk of sudden cardiac death, median ESC HCM Risk-SCD score was higher in G+ patients (2.3, IQR 1.8-4.5 vs. 1.8, IQR 1.4-2.7; p = 0.038). Of the 13 G+ patients, 6 had an ICD implanted or received an ICD during follow-up, compared to 1 patient of the 28 G- patients (p = 0.0001). The results of the comparison between G+ and G- patients are shown in Table 2. Multivariate analysis revealed that the presence of reverse septal curvature was the only independent predictor of positive GT (OR 21.5, 95% CI 2.72-171.28, p = 0.004).

Table 1. Baseline characteristics of the population (n=72)

Variable	Value
Age, years	46.4 ±16.3
Male gender	55 (76.4)
Family history of HCM	27 (37.5)
High blood pressure	29 (40.3)
Atrial fibrillation	19 (26.4)
Implantable cardioverter-defibrillator	9 (12.5)
Symptoms	43 (59.7)
ECG	
Signs of LVH	30 (41.7)
Negative T waves	44 (61.1)
TTE	
Maximum septal thickness, mm	18.57 ±3.9
Reverse septal curvature	33 (45.8)
Sigmoid septum	29 (40.3)
Apical LVH	8 (11.1)
Dynamic LV obstruction	28 (39.4)
≥ mild mitral regurgitation	45 (61.4)
Mitral valve systolic anterior motion	29 (41.4)
LVEF, %	60 ± 11
Left atrial diameter, mm	42.5± 6.6
≥ Mild diastolic dysfunction	62 (85.7)
CMR	
Maximum thickness, mm	19.1 ± 5.3
Mitral valve abnormality	27 (45)
Apical displacement of papillary muscles	19 (33.3)
LGE	49 (81.7)
HCM Risk-SCD score	2.7 ± 1.9

CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; mm: millimeters; LGE: late gadolinium enhancement; TTE: transthoracic echocardiography
Qualitative variables are presented as frequency and percentage, and quantitative variables as mean ± standard deviation.

The most relevant findings of the analysis are summarized in Figure 1.

DISCUSSION

Genotype-phenotype correlation

HCM is a disorder with variable phenotypic expression, and the genotype-phenotype correlation is a significant area of ongoing research. In our study, we found that 31.7% of the population undergoing genotyping had a pathogenic (or like pathogenic) variant in sarcomere proteins. The two most common variants were found in the genes that encode the cardiac myosin binding protein C (MYBPC3) and the beta-myosin heavy chain (MYH7), as described in the literature. (1)

The reverse septal curvature pattern had the strongest association with positive GT. Since the initial descriptions of genotype-phenotype correlation, such as those by the Mayo Clinic group, this pattern has been demonstrated to be the strongest predictor of positive GT (79% in G+ patients vs. to 8% in patients with a sigmoid septum). (11) Our results were similar: 68.8% of patients with reverse septal curvature were G+ vs. only 5% of patients with sigmoid septum. In Bayesian analysis, the presence of reverse septal curvature increased the probability of positive GT from a pre-test value of 31.7% to 71%, corresponding to a positive likelihood ratio of 5.17. This finding serves to reinforce the notion that the potential yield of GT in selected patients can be remarkably high.

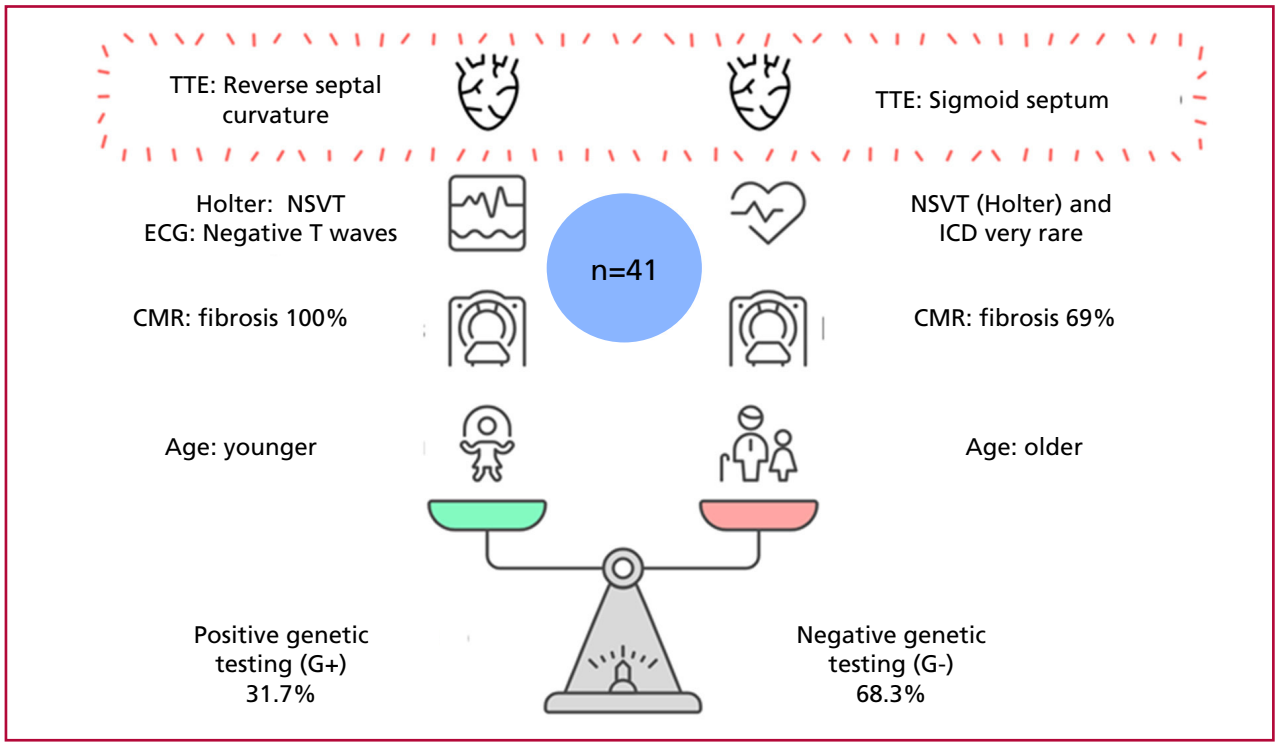
In the general cohort, the percentage of positive GT was similar to the 38% reported by the Mayo Clinic in an unselected population. The Mayo Clinic score is a prognostic tool used to predict the diagnostic yield

Table 2. Clinical findings and complementary tests according to the presence of positive (G+) or negative (G-) genetic testing

Variable	G+ (n = 13)	G- (n = 28)	p
Age, years	45.3 ±16.4	57.1 ±11.7	0.012
Age at diagnosis, years	38.4 ±15.3	50.8 ±11.7	0.007
Male	12 (92.3)	21 (75)	0.056
Family history of HCM/SCD	8 (61.5)	6 (21.4)	0.012
Hypertension	6 (46.2)	21 (75)	0.072
Symptoms	8 (61.5)	20 (71.4)	0.527
Implantable cardioverter defibrillator	6 (46.2)	1 (3.6)	0.001
ECG/Holter			
Negative T waves	12 (92.3)	12 (42.9)	0.003
Signs of LVH	7 (53.8)	9 (32.1)	0.185
NSVT	8 (61.5)	2 (10.5)	0.002
TTE			
Reverse septal curvature	11 (84.6)	5 (17.9)	0.001
Sigmoid septum	1 (7.7)	19 (67.9)	0.001
Maximum septal thickness, mm	21 (17.7-22.5)	17 (16-18.8)	0.016
LVEF, %	60 (56-66)	63 (51-65)	0.958
LA diameter, mm	38.6 ± 5.84	44.5 ± 4.52	0.001
Dynamic obstruction	3 (23.1)	11 (39.3)	0.308
≥ mild mitral regurgitation	7 (53.8)	16 (57.1)	0.467
Systolic anterior motion, mitral valve	5 (38.5)	9 (32.1)	0.750
≥ mild diastolic dysfunction	12 (92.3)	23 (82.1)	0.504
CMR			
LGE	13 (100)	16 (69.9)	0.027
Maximum septal thickness, mm	19.6 (17.8-22.8)	17.4 (14.7-20.1)	0.049
Apical displacement of papillary muscles	5 (41.7)	5 (23.8)	0.283
HCM Risk-SCD score	2.3 (1.8-4.5)	1.8 (1.4-2.7)	0.038

CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; LA: left atrial; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LGE: late gadolinium enhancement; mm: millimeters; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death; TTE: transthoracic echocardiography
Qualitative variables are presented as frequency and percentage, and quantitative variables as mean ± standard deviation or median and interquartile range.

Fig. 1. Variables associated with positive versus negative genetic testing



CMR: cardiac magnetic resonance ; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; NSVT: non-sustained ventricular tachycardia; TTE: transthoracic echocardiography;

of GT. It incorporates various clinical and echocardiographic parameters, including age at diagnosis < 45 years, maximum septal thickness ≥ 20 mm, family history of HCM or sudden cardiac death, and reverse septal curvature on echocardiogram (one point for each factor). The concomitant presence of hypertension is a negative predictor, with a score of -1 point. (12) This score has undergone multiple subsequent validations, exhibiting adequate specificity but variable sensitivity. (13,14) A recent study conducted in Argentina demonstrated a diagnostic yield of 80% in patients with a Mayo Clinic score ≥ 3. (15) As with the score, our study found that G+ patients not only had a higher prevalence of the reverse septal curvature phenotype; they were also younger at the time of diagnosis, had a higher burden of family history, and had greater maximum wall thickness compared to G- patients. However, these variables did not reach significance in the multivariate analysis, possibly due to the small number of patients.

Prognostic implications

G+ patients already had an ICD implanted or it was implanted during outpatient follow-up in 46.2% of cases, compared to only 3.6% of G- patients. The prevalence of NSVT on ECG Holter monitoring was higher in G+ patients, who also presented higher HCM Risk-SCD score, as reported in the literature. (16) Various studies have shown that positive GT represents an increased risk of death, ventricular dysfunction, heart failure, and need for transplantation. (17,18) There is even evidence of higher-risk variants such as mutations in MYH7, mainly in highly conserved regions such as the converter region. (19) However, after adjustment for other factors, the association between sarcomeric variants and sudden cardiac death loses significance. (20) Therefore, the guidelines do not yet consider the genotype an indication for ICD placement. (1,21)

Finally, the presence of fibrosis on CMR in our study was more prevalent in the G+ group. However, despite fibrosis is clearly associated with a worse prognosis, some degree of LGE is a common finding in HCM, (22) so this finding cannot be considered to identify patients at higher risk.

Clinical perspectives and real-world applicability

According to the 2023 and 2024 guidelines for the management of cardiomyopathies, GT in patients with HCM is a class I recommendation with a level of evidence B to confirm the diagnosis, assess prognosis, stratify treatment, and provide reproductive counseling. (1,21) Nevertheless, in Argentina access to GT is limited, (23) and patients often have to cover the cost of the test themselves. In this context, phenotypic predictors that increase pretest probability

of a positive GT result may provide justification for funders or insurers, with a direct impact on improving access.

Our study validates that some phenotypic patterns (such as reverse septal curvature) can significantly increase the yield of GT. Moreover, the present study was conducted in a center that does not specialize in familial heart diseases. This fact underscores the clinical applicability of the study in real-world settings, where the majority of patients are typically seen in general centers.

STUDY LIMITATIONS

The most relevant limitation of our study is that, although GT was indicated in all patients to avoid selection bias and that it represents a general cohort, the results could only be obtained in just 55% of cases, primarily due to the high cost of the test and the lack of coverage by the health system. A recently published multicenter registry from Argentina that included data from eight provinces reported an even lower percentage of GT performed (23), which highlights the real difficulty access nationwide. In most cases, the NGS panel performed was basic and included only core genes and main phenocopies. Although this practice is supported by the literature, the yield of GT could have been improved if an expanded gene panel had been analyzed. (1) Both limitations reflect the high cost of this tool and its difficult access. It is clear that the introduction of precision medicine and a genetics-based approach confer benefits for patients, but it is also true that we constantly face limitations due to the socioeconomic situation and restrictions imposed by the different health coverages. Finally, it should be noted that, although multivariate analysis showed a statistically significant association between reverse septal curvature pattern and positive GT, the extremely wide confidence interval reflects a high level of uncertainty in the estimation, clearly related to the sample size. For this reason, we decided not to report this finding as a conclusive associated factor, and its result should be interpreted with caution.

CONCLUSIONS

In a cohort of patients diagnosed with HCM, one-third of those who underwent GT exhibited sarcomere protein mutations. The presence of a reverse septal curvature seems to be the variable most strongly associated with a positive GT. Given the limitations in our setting for accessing the test in patients with cardiomyopathies, knowing the variables that could be associated with a greater diagnostic yield may help refine the selection of patients who are candidates for this tool.

Conflicts of interest

None declared.

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

REFERENCES

1. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, y cols. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J 2023;44:3503-626. https://doi.org/10.1093/eurheartj/cehad194.

2. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, et al. Hypertrophiccardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation 2003;107:2227–32. https://doi.org/10.1161/01.CIR.0000066323.15244.54

3. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-6. https://doi.org/10.1093/eurheartj/ehm342.

4. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF, et al. Distinct subgroups in hypertrophic cardiomyopathy in the NHLBI HCM registry. J Am Coll Cardiol 2019;74:2333-45. https://doi.org/10.1016/j.jacc.2019.08.1057

5. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation 2018;138:1387-98. https://doi.org/10.1161/CIRCULATIONAHA.117.033200.

6. Sedaghat-Hamedani F, Kayvanpour E, Tugrul OF, Lai A, Amr A, Haas J, y cols. Clinical outcomes associated with sarcomere mutations in hypertrophic cardiomyopathy: a meta-analysis on 7675 individuals. Clin Res Cardiol 2018;107:30-41. https://doi.org/10.1007/s00392-017-1155-5.

7. Wilde AA, Semsarian C, Márquez MF, Sepehri Shamloo A, Ackerman MJ, Ashley EA, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases. Heart Rhythm 2022;19:e1-e60. https://doi.org/10.1016/j.hrthm.2022.03.1225.

8. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;(5):405-24. https://doi.org/10.1038/gim.2015.30.

9. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA 2013;310:2191-4. https://doi.org/10.1001/jama.2013.281053

10. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-20. https://doi.org/10.1093/eurheartj/eht439.

11. Binder J, Ommen S, Gersh B, Van Driest S, Tajik A, Nishimura R, y cols. Echocardiography-guided genetic testing in hypertrophic cardiomyopathy: septal morphological features predict the presence of myofilament mutations. Mayo Clin Proc 2006;81:459-67. https://doi.org/10.4065/81.4.459.

12. Bos J, Will M, Gersh B, Kruisselbrink T, Ommen S, Ackerman MJ. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. Mayo Clin Proc 2014;89:727-37. https://doi.org/10.1016/j.mayocp.2014.01.025.

13. Bonaventura J, Norambuena P, Tomašov P, Jindrová D, Šedivá H, Macek M, y col. The utility of the Mayo Score for predicting the yield of genetic testing in patients with hypertrophic cardiomyopathy. Arch Med Sci 2019;15:641-9. https://doi.org/10.5114/aoms.2018.78767.

14. Murphy S, Anderson J, Kapplinger J, Kruisselbrink T, Gersh B, Ommen S, y cols. Evaluation of the Mayo Clinic Phenotype-Based Genotype Predictor Score in Patients with Clinically Diagnosed Hypertrophic Cardiomyopathy. J Cardiovasc Transl Res 2016;9:153-61. https://doi.org/10.1007/s12265-016-9681-5.

15. Streitenberger G, Reyes GR, Velazco MP, Pasquevich V, De Santos M, Granillo Fernández M, et al. A Preliminary Study of the

Phenotype-Genotype Correlation in Cardiomyopathies in Patients Referred to a Tertiary Healthcare Center in the Suburbs of Buenos Aires. Rev Argent Cardiol 2023;91:55-69. https://doi.org/10.7775/rac.v91.i1.20598

16. Ingles J, Burns C, Funke B. Pathogenicity of Hypertrophic Cardiomyopathy Variants: A Path Forward Together. Circ Cardiovasc Genet 2017;10:e001916. https://doi.org/10.1161/CIRCGENETICS.117.001916.

17. Ho C, Day S, Ashley E, Michels M, Pereira A, Jacoby D, et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation 2018;138:1387-98. https://doi.org/10.1161/CIRCULATIONAHA.117.033200

18. Olivotto I, Girolami F, Ackerman M, Nistri S, Bos J, Zachara E, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc 2008;83:630-8. https://doi.org/10.4065/83.6.630

19. Lopes L, Brito D, Belo A, Cardim N. Portuguese Registry of Hypertrophic Cardiomyopathy. Genetic characterization and genotype-phenotype associations in a large cohort of patients with hypertrophic cardiomyopathy - An ancillary study of the Portuguese registry of hypertrophic cardiomyopathy. Int J Cardiol 2019;278:173-9. https://doi.org/10.1016/j.ijcard.2018.12.012

20. Bonaventura J, Rowin E, Chan R, Chin MT, Puchnerova V, Polakova E, et al. Relationship Between Genotype Status and Clinical Outcome in Hypertrophic Cardiomyopathy. J Am Heart Assoc 2024;13:e033565. https://doi.org/10.1161/JAHA.123.033565

21. Ommen S, Ho C, Asif I, Balaji S, Burke M, Day S, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2024;83:2324-405. https://doi.org/10.1016/j.jacc.2024.02.014

22. Green J, Berger J, Kramer C, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;370-7. https://doi.org/10.1016/j.jcmg.2011.11.021.

23. Cáceres L, Canoli R, Correa Sadouet C, Mahl A, Streitenberger G, Mazo G, et al. Hypertrophic Cardiomyopathy Registry in Nonspecialized Centers of Argentina. Exploring Behind the Veils of Common Practice. Rev Argent Cardiol 2024;92:147-53. http://dx.doi.org/10.7775/rac.v92.i2.20751

OPINION ARTICLE

From Technique to Wholeness: A Systemic Approach to Aortic Valve Replacement with Traditional and Rapid-deployment Valves

De la técnica al todo: enfoque sistémico del reemplazo valvular aórtico con válvulas tradicionales y de rápido implante

GERMÁN A. FORTUNATO[1], JESSICA BAROCHINER[2]

ABSTRACT

In recent decades, the number of patients with aortic valve disease requiring aortic valve replacement (AVR) has increased due to longer life expectancy. Many of these patients, especially those who are elderly and have comorbidities, face high preoperative risk. The complexity of cardiovascular disease and the adaptation of these patients to the intervention require a comprehensive and holistic approach, considering biological, genetic, and psychosocial factors. This article addresses the importance of understanding AVR as part of a complex system, emphasizing the interaction between multiple elements of the cardiovascular system such as the myocardium, conduction system, and coronary circulation, which affect surgical outcomes. It also highlights how the selection of heart valve prosthesis and other unpredictable factors can influence postoperative mortality, which should not be viewed as a simple cause-and-effect phenomenon. The use of advanced technologies, such as artificial intelligence, can improve outcomes in the preoperative, intraoperative, and postoperative phases of treatment. In conclusion, to improve outcomes in patients undergoing surgical RVA, it is essential to adopt a systemic approach, within the framework of complexity theory, that integrates innovative technologies and considers the individual characteristics of each patient. This could contribute to reduce in-hospital mortality.

Key words: Heart valve surgery -Valve dysfunction - Complexity analysis

RESUMEN

En las últimas décadas, el aumento de la esperanza de vida ha incrementado el número de pacientes con enfermedad valvular aórtica que requieren un reemplazo valvular aórtico (RVA). Muchos de estos pacientes, especialmente los de edad avanzada y con comorbilidades, enfrentan un alto riesgo preoperatorio. La complejidad de la patología cardiovascular y la adaptación de estos pacientes a la intervención requieren un enfoque integral y holístico, considerando factores biológicos, genéticos y psicosociales. En este artículo, se aborda la importancia de comprender el RVA como parte de un sistema complejo. Destaca la interacción entre múltiples elementos del sistema cardiovascular, como el miocardio, el sistema de conducción y la circulación coronaria, que afectan los resultados quirúrgicos. Se destaca, además, cómo la elección de la prótesis y otros factores no predecibles pueden influir en la mortalidad postoperatoria, que no debe ser vista como un fenómeno simple de causa-efecto. El uso de tecnologías avanzadas, como la inteligencia artificial, puede mejorar los resultados en cada fase del tratamiento: preoperatoria, intraoperatoria y postoperatoria. En conclusión, para mejorar los resultados en pacientes sometidos a RVA quirúrgico, es esencial adoptar un enfoque sistémico, desde el marco de la teoría de la complejidad, que integre tecnologías innovadoras y considere las características individuales de cada paciente. Esto podría contribuir a una menor mortalidad intrahospitalaria.

Palabras clave: Cirugía cardíaca valvular - Disfunción valvular - Análisis de la complejidad

INTRODUCTION

In recent decades, the number of patients with aortic valve disease requiring aortic valve replacement (AVR) has increased due to longer life expectancy, with a higher incidence in older age groups. Most patients with severe aortic stenosis (SAS) are elderly patients with several comorbidities and, therefore, high surgical risk. (1,2) This risk is also related to the challenges older patients face in adapting to cardiovascular disease and recovering from surgery, which can be affected by a reduction in their physiological adaptive capacity. This reduction can be understood as a decrease in the entropy of the cardiovascular system. The development of new technologies and therapies

Rev Argent Cardiol 2025;93:293-296. https://doi.org/10.7775/rac.v93.i4.20908

Received: 05/21/2025 – *Accepted:* 07/02/2025

Correspondence: Germán A. Fortunato. E-mail: german.fortunato@hospitalitaliano.org.ar

[1] Department of Cardiovascular Surgery, Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina.
[2] Department of Internal Medicine, Hypertension Section, Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina.

has tried to solve this situation by reducing surgical risk. Patients with aortic valve disease, considered in their biological and social dimensions, are made up of multiple agents that interact and adapt to constant hemodynamic changes in the cardiovascular system. This interaction occurs at cellular, tissue, genetic, and environmental levels. (3)

IMPORTANCE OF AORTIC VALVE REPLACEMENT WITH A COMPLEX SYSTEM APPROACH

Our center has recently published the results obtained in intermediate-risk patients in terms of in-hospital mortality associated with the use of traditional valve prostheses versus novel rapid-deployment valves (RDV). These results indicate a trend toward lower mortality with RDV (5.7% vs. 0%, p = 0.057). (4) However, when taking into account patient's specific cardiovascular disease, the procedure performed, the type of heart valve prosthesis utilized, and the surgeon responsible for the procedure, as well as the interrelated and unpredictable factors that collectively form a complex entity, it becomes challenging to assert that mortality can be attributed exclusively to the use of a specific type of heart valve prosthesis. It is imperative for cardiovascular surgeons to conduct a thorough analysis of all these elements to comprehensively assess postoperative mortality and to avoid an evaluation of solely the type of prosthesis. This holistic view is crucial to contributing to the success or failure of the surgical outcome in intermediate-risk patients.

Characteristics of the complex system

Understanding the characteristics of a complex system in patients undergoing AVR with heart valve prostheses may offer a renewed approach to their management and potentially improve surgical outcomes. (5)

1. *Large number of elements:* The myocardium consists of billions of myocytes. These structures exhibit a high degree of similarity and act and respond together, maintaining synchrony during physiological situations. (6) In addition, the coronary circulation displays a fractal geometry from the left main coronary artery to the tiny septal arteries.
2. *Dynamism:* Patients with aortic valve stenosis experience remarkable dynamism, with hemodynamic and structural ventricular changes. The progression of valvular heart disease, which often includes pure aortic stenosis and, in some cases, aortic stenosis and regurgitation, directly affects the left ventricle, which develops hypertrophy as an adaptive mechanism. However, this mechanism may not be sufficient, leading to heart failure and progression of symptoms, culminating in the need for AVR and subsequent improvement in ventricular function and reverse ventricular remodeling.
3. *Penetrance:* The elements of the system interact simultaneously and across different dimensions. For instance, the use of heart valve prostheses with a smaller effective orifice area can result in prosthesis-patient mismatch in many patients. This can lead to increased transvalvular gradients without a simultaneous reduction in ventricular afterload. (7)
4. *Non-linearity:* The response to a surgical procedure is not always predictable using traditional methods. Proper placement of the suture in the aortic annulus is crucial when implanting heart valve prostheses. Similarly, preserving the conduction system in the interventricular septum is essential. If the suture is placed too deeply, it can block the atrioventricular conduction system. This may require the placement of a dual-chamber pacemaker, resulting in a reduced life expectancy compared to patients who maintain sinus rhythm. As illustrated by the concept of the "butterfly effect," this single stitch can have significant consequences; a minimal initial change or action can trigger a substantial outcome in the future. (8)
5. *Recursive interactions:* Hemodynamic function improves after replacing the affected and stenosed valve.
6. *Open:* The patient undergoing surgery requires continuous monitoring by cardiologists and surgeons during the postoperative recovery period. The surgical outcomes are influenced by fluid balance as managed by the attending physician, the use of vasopressors, the necessity for temporary pacemaker implantation and the expertise of the nursing staff.
7. *Imbalance:* A patient who has undergone AVR is not in a state of equilibrium. For example, in a patient with low preload, volume expansion will be necessary, while fluid overload will require the use of diuretics. This ensures a constant supply of energy to maintain optimal hemodynamic responses to changes. Thus, the patient is in a permanent "transition," similar to what occurs in the cardiovascular system and in other contexts, as described, for example, in the case of patients with hypertension. (9)
8. *History:* Complex systems have a history, and in this case, the patient improves over time. Initially, the patient presented symptoms due to a stenotic valve, but following the intervention, there was a notable improvement in hemodynamic regulation.
9. *Local information:* The myocardium, conduction system, intrinsic pulmonary pressure, heart valve prosthesis, and aortic valve apparatus operate under their own rules at the local level, but they also interact with other systems. The goal is to achieve a relatively "stable" state, maintaining a cardiac output of approximately 4.5-5 liters/minute.

POSTOPERATIVE MORTALITY AS AN EMERGING PHENOMENON

Postoperative mortality can be considered a complex phenomenon in patients undergoing surgery and

should not be approached with a simplistic cause-and-effect model. Despite the attempts we made (4) to identify an intermediate-risk population using a universally accepted scoring system, such as STS-PROM, (10) it is imperative to acknowledge that each patient is unique. The possibility of death is determined by the interaction of various factors in the patient's system. Surgeons have the responsibility to understand and analyze these interactions, including patient's history of cardiovascular disease, physiology, and context, without limiting themselves to the idea that the selection of heart valve prosthesis will determine survival.

We observed that patients undergoing surgery for functional class I and II heart failure had better outcomes than those with more advanced heart failure, as well as those with moderate to severe ventricular dysfunction. If we could intervene in these patients earlier, they would probably achieve better outcomes. In the clinic, clinical cardiologists may assume that patients do not need surgery until they experience dyspnea on exertion, even if they present elevated gradients on transthoracic echocardiography. This linear approach fails to consider the complexity of unanticipated factors that influence each patient, as well as variations in the perception of dyspnea. Furthermore, it is imperative to assess the patient's psychosocial status, as those with preoperative depression, are more prone to adverse postoperative outcomes.

As surgeons, we can improve postoperative outcomes by understanding perioperative mortality as an emerging phenomenon, allowing us to design a comprehensive strategic plan for the preoperative, intraoperative, and postoperative phases.

Tools for addressing the complexity of patient mortality

A strategic plan for cardiovascular surgery can be approached at three key levels: preoperative, intraoperative, and postoperative. Each level has specific tools that seek to reduce mortality and improve outcomes in patients undergoing surgery.

In the **preoperative** phase, it is imperative to utilize tools that facilitate a multifactorial approach to decision-making. This includes a thorough analysis of patients' psychological status, assessment of their symptoms and their expectations regarding the procedure, among other factors. In addition, the incorporation of data science is imperative, as it facilitates the determination of the optimal heart valve prosthesis based on the available information. The use of international and national registries, hospital databases, meta-analyses, randomized trials and long-term results facilitates the selection of the most appropriate option for each patient. Current guidelines on valvular heart disease and indications for surgery offer a conventional and simplistic approach and do not take into account genetic, epigenetic, or environmental factors that could influence the patient's response. (11) In this regard, the Department of Cardiovascular Surgery at Hospital Italiano de Buenos Aires is launching a project that integrates artificial intelligence (AI) and machine learning techniques to analyze this data and offer more accurate projections when selecting heart valve prostheses during the phase of patient care at the clinic. This approach is consistent with the concept of "precision medicine," which aims to enhance patient survival and outcomes through individualized treatment.

During the **intraoperative** phase, the use of AI-based tools and real-time analysis constitutes a pivotal element for improving the outcomes. Decision-making processes, including the selection of procedures in conjunction with valve replacement (e.g., coronary artery bypass grafting, double valve surgery, or aortic root replacement), or the placement of prophylactic pacemakers, among others, should be based on an accurate and updated evaluation of the patient at the time of surgery. However, it is important to acknowledge that advanced technological solutions may not always be uniformly applicable across all centers. Variables such as costs and economic disparities between services may impede their extensive implementation.

During the **postoperative** phase, one of the most significant advances is the incorporation of AI-driven tools for monitoring in operating rooms and coronary care units. This tools, which allow for real-time feedback, provide continuous monitoring of vital signs, cardiac output, central venous pressure, pulmonary pressure, and vascular resistance, as well as remote and continuous electrocardiographic monitoring. This system enables immediate access to crucial data for surgeons and cardiologists participating in the procedure, thereby enhancing their capacity to respond to any changes in the patient's condition. This technology has only been implemented at a limited number of centers worldwide, and no definitive findings have been published regarding its impact on postoperative outcomes. Nonetheless, it is anticipated that, in the long term, this type of system will become the standard of quality for cardiac surgery centers.

CONCLUSIONS

Postoperative mortality in patients undergoing surgery should not be understood as an isolated or simplistic phenomenon. Rather, it is the result of the complex interaction of multiple factors, both biological and social, that affect each patient in a unique way. These factors range from the patient's specific cardiovascular disease to their genetic, epigenetic, and psychosocial profile, all of which can significantly influence surgical outcomes. The approach to cardiovascular surgery must be holistic and multidisciplinary, considering not only the type of heart valve prosthesis used but also the patient's individual context, the expertise of the surgical team, and the variables that interact throughout the process and are not directly predictable. The key to success lies in the integration of personalized approaches, the use of innovative technologies, and collaboration between the different

actors in the process. This will optimize patient care and offer them a better quality of life after the procedure.

Conflicts of interest

None declared.

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

REFERENCES

1. Holzhey D, Mohr FW, Walther T, Möllmann H, Beckmann A, Kötting J, et al. Current Results of Surgical Aortic Valve Replacement: Insights From the German Aortic Valve Registry. Ann Thorac Surg 2016;101:658-66. https://doi.org/10.1016/j.athoracsur.2015.07.090

2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607. https://doi.org/10.1056/NEJMoa1008232

3. Khan MI, Zahir RS, Dominguez AC, Romeo FJ. Role of Lipoprotein (A) in aortic valve stenosis: Novel disease mechanisms and emerging pharmacotherapeutic approaches. Int J Cardiol Heart Vasc 2024;55:101543. https://doi.org/10.1016/j.ijcha.2024.101543

4. Fortunato GA, D'Angelo T, Busnelli G, Tamara CA, Sultano N, Theaux J, y cols. Válvulas de rápido implante versus válvulas tradicionales en reemplazo valvular aórtico en pacientes de riesgo intermedio. Rev Argent Cardiol 2024;92:202–8. https://doi.org/10.7775/rac.es.v92.i3.20784

5. Levin SA. Ecosystems and the biosphere as complex adaptive systems. Ecosystems 1998;1:431-6. https://doi.org/10.1007/s100219900037

6. Corazza GR, Formagnana P, Lenti MV. Bringing complexity into clinical practice: An internistic approach. Eur J Intern Med 2019;61:9-14. https://doi.org/10.1016/j.ejim.2018.11.009

7. Tabata M, Shibayama K, Watanabe H, Sato Y, Fukui T, Takanashi S. Simple interrupted suturing increases valve performance after aortic valve replacement with a small supra-annular bioprosthesis. J Thorac Cardiovasc Surg 2014;147:321-5. https://doi.org/10.1016/j.jtcvs.2012.11.020

8. Higgins JP. Nonlinear systems in medicine. Yale J Biol Med 2002;75:247-60.

9. Barochiner J. Teoría de la Complejidad y el paciente hipertenso [Complexity theory and the hypertensive patient]. Semergen 2021;47:404-10. https://doi.org/10.1016/j.semerg.2020.12.008

10. Puskas JD, Kilgo PD, Thourani VH, Lattouf OM, Chen E, Vega JD, et al. The society of thoracic surgeons 30-day predicted risk of mortality score also predicts long-term survival. Ann Thorac Surg 2012;93:26-33; discussion 33-5. https://doi.org/10.1016/j.athoracsur.2011.07.086

11. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91. https://doi.org/10.1093/eurheartj/ehx391

SPECIAL ARTICLE

Nature, Heart, and Conscience: a Tear in Time

Naturaleza, corazón y conciencia: un desgarro en el tiempo

JORGE TRAININI[1, 2, MTSAC], MARIO BERAUDO[3] , ALEJANDRO TRAININI[1],JORGE LOWENSTEIN[4, MTSAC],MARIO WERNICKE[3], RICARDO ARANOVICH[5], OSCAR FARIÑA[2]

ABSTRACT

The knowledge gained in recent years on heart functioning, not only through basic research but also through technology, has unraveled essential questions. A thorough analysis reveals that the answers date back some 200 years to the Industrial Revolution, when man developed mechanical knowledge analogous to aspects of cardiac function that date back to the emergence of mammals in the Triassic and were demonstrated in the last decade. In other words, human consciousness surprisingly employed the same strategy in its evolution of knowledge that biological development used to construct the heart 200 million years ago, which, obviously, was unknown to man.

Keywords: Nature - Evolution - Heart - Consciousness

RESUMEN

El conocimiento del funcionamiento del corazón que se consiguió en estos últimos años, no solo con la investigación básica sino también con la tecnología, ha desentrañado preguntas esenciales. Las respuestas provienen desde hace unos 200 años con la Revolución Industrial, cuando el hombre desarrolló conocimientos mecánicos que son análogos a aspectos de la función cardíaca que datan de la aparición de los mamíferos en el Triásico y que fueron demostrados en esta última década. Es decir que la conciencia humana empleó de manera sorprendente la misma estrategia en su evolución del conocimiento que la que utilizó el desarrollo biológico para construir el corazón hace 200 millones de años, y que obviamente, el hombre desconocía.

Palabras clave: Naturaleza - Evolución - Corazón- Conciencia

INTRODUCTION

Mammals appeared in evolution about 200 million years ago. Since the Triassic period, the heart has been structurally consolidated. Some aspects of its recently studied functional organization are striking because they were imitated by human cultural evolution after the Industrial Revolution during the 18th and 19th centuries. This analogy exists between an organ formed millions of years ago and the current intellect of humans, who had no prior knowledge of its mechanisms.

When life and social composition reached a high level of complexity, the brain of *Homo sapiens* appeared. This happened about 250 000 years ago, a mere blink of an eye in relation to the appearance of matter, which occurred about fifteen to twenty billion years ago, while the first signs of life appeared only about 3500 million years ago. The human brain, as we know it, is the most recent of the remarkable patterns of evolution. This evolution, although staggered, left almost all of creation behind. It was woven together on a track where randomness and necessity complemented each other to continue a path of self-organization, with only the slogan that "order is change." It is currently believed that the vast majority of biological species are extinct. As for our class *Mammalia*, of the 32 orders, 14 have become extinct, leaving only 18 alive today.

Rev Argent Cardiol 2025;93:297-301. http://dx.doi.org/10.7775/rac.v93.i4.20907

Received: 06/03/2025 – *Accepted:* 07/05/2025

Correspondence: Jorge Carlos Trainini. Email: jctrainini@hotmail.com

[1] Hospital Presidente Perón, Avellaneda, Argentina
[2] National University of Avellaneda, Argentina.
[3] Clínica Güemes, Luján, Argentina
[4] Investigaciones Médicas, Autonomous City of Buenos Aires, Argentina
[5] Acta Foundation Mental Health Fund, Argentina

Let us not forget that the brain started out as primitive ganglia and eventually acquired a significant neocortex, a situation that *homo sapiens* has only been able to capitalize on in the last 30 000 years, while the evolution of the species dates back to about two million years.

In other words, biological evolution and human culture arrive to the same solutions, in this case mechanical ones, by different paths and without humans having any prior knowledge of them, since only recently has an understanding of cardiac function been achieved, while certain mechanisms invented by humans date back to the Industrial Revolution. We will discuss some of these findings.

Bearing

The first patent for a ball bearing was granted in 1794 to Philip Vaughan, and in 1898 Henry Timken patented the tapered roller bearing. This mechanism has different rotations between its inner and outer rings with an intermediate system, called a ball cage, which acts as an anti-friction device.

Recent technological advances have revealed that the left ventricle has different rotations in systole between the descending and ascending segments (inner and outer muscle rings), which are reversed in the protodiastolic phase. (1-4) This rotational mechanism is a fundamental determinant in the ejection and suction of the heart (Figure 1). (5-8) In this analysis, we found a correspondence between cardiac structure-function and the bearing mechanism.

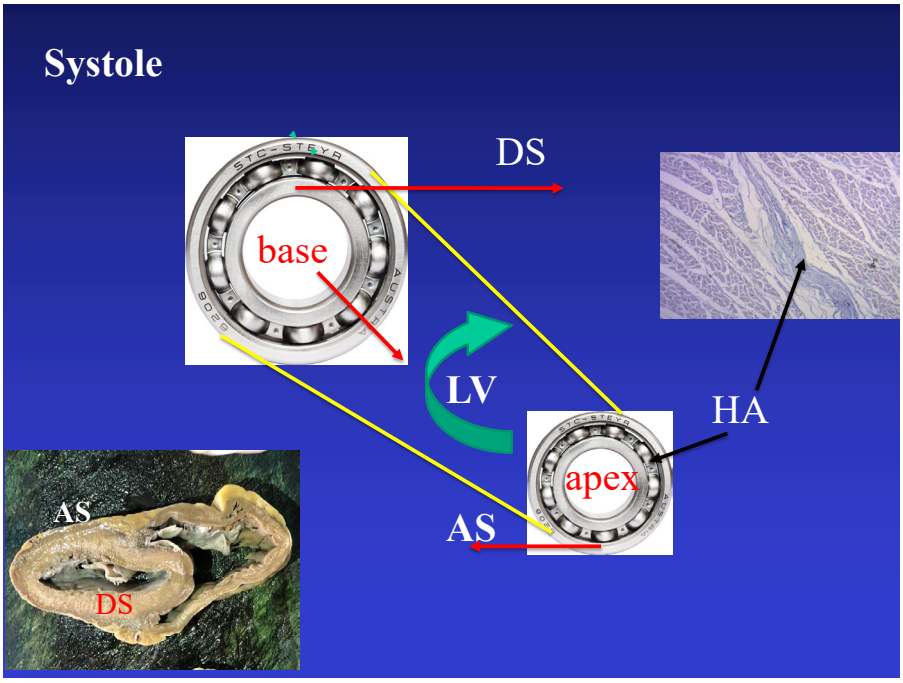
The existence of torsion (basal and apical rotations in opposite directions) is expressed in echocardiography as a rotational gradient with a positive value that is the sum of the basal and apical rotation angles. In our experience, in normal subjects it is around 19 ± 9º, with the rotation of the tip always predominating. (9)

Anti-friction mechanism

The bearing function has an anti-friction mechanism between its rings (ball bearing), which allows it to roll without generating energy loss.

In the heart, the sliding between the internal and external segments of the myocardium takes opposite directions in its movements during the systolic and suction phases of the heart, generating friction. From a physical point of view, friction between the segments also implies an opposition to movement. As expressed by Newton's first law, friction limits the temporal con-

Fig. 1. The movement of the base and apex of the heart can be seen, similar to the rolling of a ball bearing. The red arrows indicate the direction taken by the descending and ascending segments of the heart during systole. During suction (protodiastolic phase), they are reversed. It can also be seen that both between the outer and inner rings of the bearing and in the concentric cardiac muscle segments (descending and ascending segments) there is an anti-friction mechanism, called ball bearing in a bearing, and hyaluronic acid in the heart. The inset shows a human heart with the aforementioned segments.



HA: hyaluronic acid; AS: ascending segment; DS: descending segment. LV: left ventricle.

tinuity of movement (Figure 1).

In this regard, in all the hearts investigated, we found hyaluronic acid in the cleavage planes between the myocardial bundles. Our recent research has clarified this aspect of myocardial lubrication, which counteracts surface friction by exerting an anti-friction mechanism. Hyaluronic acid, with its lubricating capacity, facilitates sliding between the bundles. (10)

Fig. 2. Both in the anatomical heart and in the photo of a suspension bridge, we can see the analogy between the solutions found by biological evolution (nature) and human intellectual consciousness, without prior knowledge in the latter of the cardiac arrangement, which has only been understood in recent years.

MV: mitral valve

Fig. 3. Attachment of the tendinous cords of the mitral valve after the valve has been replaced.

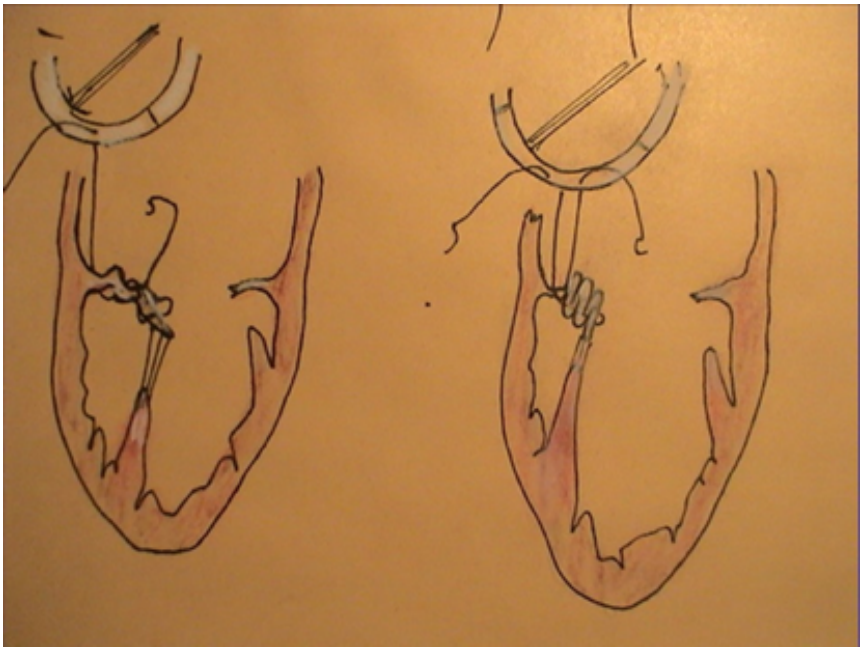
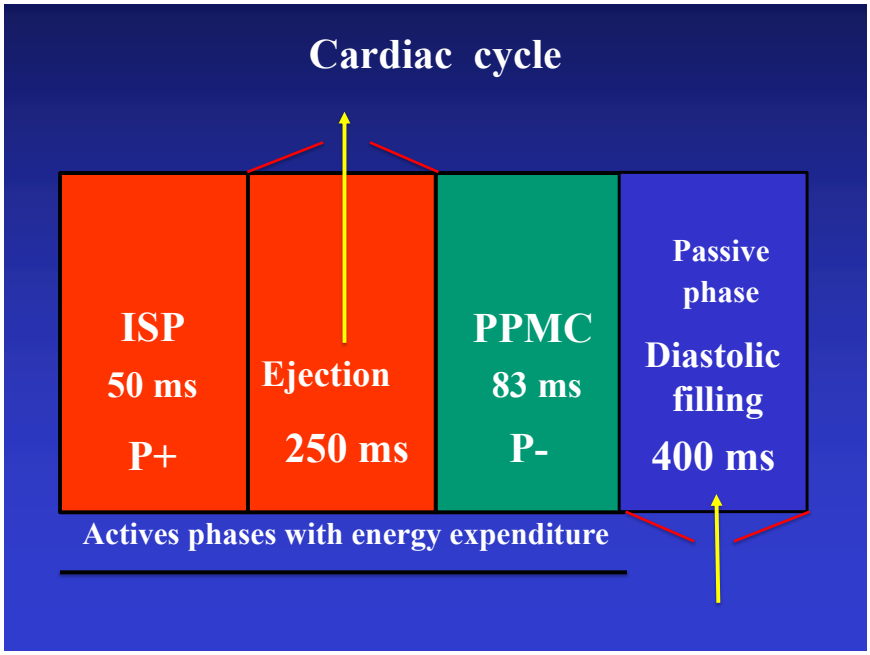


Fig. 4. Ejection and suction phases of the left ventricle



ISP: isovolumetric systolic phase; PPMC: protodiastolic phase of myocardial contraction; P+: positive pressure; P-: negative pressure.

Suspension bridge

We have found that the heart maintains its helical spatial arrangement through supports called papillary muscles strategically located at the beginning of the descending and ascending segments, the rings of the left ventricle (Figure 2). It can be assumed that they act as tensors of the left ventricular myocardium being attached by their cords to the mitral valve. They are the pillars that support the myocardium and also open and close the valve. In fact, in mitral valve replacement, removing the chordae tendineae can cause ventricular dysfunction.(11) This has led to the chordae of the papillary muscles not being sacrificed but rather tied to the prosthetic mitral annulus in order to preserve the tensors of the descending and ascending cardiac segments (Figure 3). This concept implies that the papillary muscles, with their chords and attachment to the mitral valve leaflets, not only act for valve functioning but also as a support for the myocardium, analogous to the recent construction of suspension bridges.

It is worth noting that the first important modern suspension bridge was the Menai Bridge, built in 1826. This bridge was designed by engineer Thomas Telford with a span of 125 meters, which allowed sailing ships to pass under it.

Engine

An engine is a machine that converts one type of energy into mechanical energy, usually to produce movement. This is exactly what the heart has been doing for 200 million years. Remember that the first engines appeared in the 19th century (Figure 4). (12-14)

Comments

Is there a correlation between biological evolution and the evolution of human consciousness, in light of the emergence of thought, knowledge, and learning? It would be reasonable to think that there is no way to deny this coherence. Sociocultural evolution could not have occurred without biological evolution. (15,16)

This advance, like all transformations involving flow of matter and energy in the universe, has also followed a journey in thought, in which the reductionist, mechanistic, or atomistic model has been vigorously debated in the face of the new model of self-organization and systems. Systemic thought has currently taken hold. Massive connectivity provides information to thought, which shapes it into ideas in a self-organizing process. Analogous to the homeostasis of organisms, thought is subjected to a process of self-organization. They are feedback loops characteristic of living beings (nonlinear network).

Thought is a network. Between the universe and each consciousness there is a limitless network. There are only consciousnesses as nodes controlling networks, within networks subjected to flows of matter and energy. Organizing relationships can belong to organisms, to society, and to thought. There are interactions between the parts, which are lost when dissected (properties of the whole). Biology has this organizational character.

Erwin Schrödinger (1887-1961) ascribed to a vast and unified consciousness, interrelated with individual consciousnesses. He reflected on a unified universal consciousness. (15) It is not understood that the vision of consciousness on the internal and external world has its own specific nature. We must accept that space-time is a representation of our consciousness. However, once we have achieved this representation, it becomes assimilated into our consciousness with an absolutely objective nature. The perception that consciousness establishes of a phenomenon depends on:

a) The prevailing ideas that occupy the intellectual space and misinterpret new ones.
b) The ability to delve deeper than the level reached with the new vision. This was the case with the work of Erwin Schrödinger, in which the phenomena described were considered too microscopic to be observed. This vision allows for spatial ordering in its entirety.

This analogy between the mechanisms of nature's construction of the heart, which began with mammals 200 million years ago, and the mechanical knowledge that humans have acquired over the last 30 000 years remains a mystery. But what is most surprising is that knowledge of these biological cardiac mechanisms is recent, subsequent to the development of bearing , the anti-friction mechanism, the engine, and suspension bridges. In fact, the same creative resource was used by human consciousness without knowing that this procedure had already been used by nature in hearts 200 million years ago, at the beginning of mammals.

The fact that human knowledge, faced with mechanical problems that have arisen in the last two centuries, has produced results analogous to those used by the biological evolution of the heart in prehistoric times, without any knowledge of them, is surprising and raises disturbing questions: Is there a point where the mind can enter a higher order? Is there a common plan for biological evolution and human consciousness? Can human consciousness be connected to a metaphysical plan? In this analogy between physis (nature) and human consciousness, is there a coincidence that occurred 200 million years ago, or is it the consequence of an unknown connection between humans and that higher order? Or could it be that we belong to a single consciousness?

Beyond these questions and their possible answers, perhaps we should understand that this development opens the much-needed path of complementarity between reason and faith, since science is a communion of both.

The art of medicine has always considered the heart to be taboo (vis pulsiva), despite being explored in its most intimate nooks. It has even been replaced. Despite the knowledge gained, its magic is unmatched and imperishable, an alchemy of anguish and movement. In it lies the fantasy of genesis and flickering infinites.

Acknowledgments

The authors would like to thank Prof. Dr. Ana Rita Jachimowicz for her valuable advice.

Conflicts of interest

None declared.

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

REFERENCES

1. Trainini J, Lowenstein J, Beraudo M, Trainini A, Mora Llabata V, Carreras Costa F, et al. Cardiac Helical Function. Fulcrum and Torsion. J Cardio Res & Rep 2023;7(1):OJCRR.MS.ID.000653. https://doi.org/10.33552/OJCRR.2023.06.000653.

2. Trainini JC, Lowenstein J, Beraudo M, Wernicke M, Trainini A, Llabata MV, et al. Myocardial torsion and cardiac fulcrum (Torsion myocardique et pivot cardiaque). Morphologie 2021;105:15-23. https://doi.org/10.1016/j.morpho.2020.06.010

3. Trainini JC, Herreros J, Elencwajg B, Trainini A, Lago N, López Cabanillas N, et al. Myocardial dissection. Rev Argent Cardiol 2017;85:44-50.

4. Torrent Guasp F. The macroscopic structure of the ventricular myocardium. Rev Esp Cardiol 1980;33:265-87.

5. Kocica MJ, Corno AF, Carreras-Costa F, Ballester-Rodes M, Moghbel MC, Cueva CN, et al. The helical ventricular myocardial band: global, three-dimensional, functional architecture of the ventricular myocardium. Eur J Cardiothorac Surg 2006; 29:Suppl-I:S21-40 https://doi.org/10.1016/j.ejcts.2006.03.011

6. Bagnoli P, Malagutti N, Gastaldi, Marcelli E, Lui E, Cercenelli L, et al. Computational finite element model of cardiac torsion. Int J Artif Organs 2011;34:44-53. https://doi.org/10.5301/IJAO.2011.6313

7. Nakatani S. Left ventricular rotation and twist: why should we learn? J Cardiovasc Ultrasound 2011;19:1-6. https://doi.org/10.4250/jcu.2011.19.1.1

8. Nayak KS, Nielsen JF, Bernstein MA, Markl M, D Gatehouse P, M Botnar R, et al. Cardiovascular magnetic resonance phase contrast imaging. J Cardiovasc Magn Reson 2015;17:71. https://doi.org/10.1186/s12968-015-0172-7

9. Mora Llabata V, Roldán Torresa I, Saurí Ortiza A, Fernández Galera R, Monteagudo Viana M, Romero Dorta E, et al. Correspondence of myocardial strain with Torrent-Guasp's theory. Contributions of new echocardiographic parameters. Rev Argent Cardiol 2016;84:541-9.

10. Trainini J, Beraudo M, Wernicke M, Carreras Costa F, Trainini A, Mora Llabata V, et al. The hyaluronic acid in intramyocardial sliding. REC: CardioClinics 2023;58(2):106-11. https://doi.org710.1016/j.rccl.2022.07.008

11. Agustín J, Pérez de Isla, Núñez-Gil Vivas D, Manzano M, Marcos-Alberca P, Fernández-Golfín C, et al. Study of myocardial deformation: predictor of medium-term ventricular dysfunction after surgery in patients with chronic mitral regurgitation. Rev Esp Cardiol 2010;63:544-53. https://10.1016/S0300-8932(10)70116-0

12. Trainini J, Beraudo M, Wernicke M, Trainini A, Lowenstein J, Valle Cabezas J, et al. Fundamental Conclusions on Research into the Anatomy and Organization of the Helical Heart. Am J Biomed Sci & Res. 2024; 23(5):AJBSR.MS.ID.003125. https://doi.org/10.34297/AJBSR.2024.23.003125

13. Trainini J, Beraudo M, Wernicke M, Trainini A, Lowenstein J, Bastarrica M E, et al. Cardiac Fulcrum. Cardiovasc Surg Int 2021;2:CSI-02-1011.

14. Sosa Olavarría A, Martí Peña A, Martínez A, Zambrana Camacho J, Ulloa Virgen J, Zurita Peralta J, et al. Trainini's cardiac fulcrum in the fetal heart. Rev Peru Ginecol Obstet 2023;69(4) 1-8. https://doi.org/10.31403/rpgo.v69i2579

15. Trainini JC. The medical commitment to the human factor. Ed. Biblos, Buenos Aires, Argentina, 2024.

16. Sinnott EW. The biology of the spirit. Fondo de Cultura Económica, Mexico, 1970.

LETTER TO THE EDITOR

Decalogue of the Position Paper on frailty and Comprehensive Assessment in Cardiology

Decálogo del documento de posición de fragilidad y valoración integral en Cardiología

MARÍA SOLEDAD PALACIO[1], PATRICIA BLANCO[1, MTSAC], GUILLERMO SUÁREZ[1]

In March of this year, the first position paper on frailty and comprehensive assessment in cardiology was published (1), developed during 2024 and presented at the 50th Argentine Congress of Cardiology. During a recent council meeting attended by leaders from across Ibero-America, the spirit of the document was summarized in ten key points. The objective of this decalogue is the dissemination of these key concepts and their incorporation into daily clinical practice.

1. Emphasize biological age over chronological age and eliminate the term "special population": While we recognize the influence of chronological age, the ageist concept is only a biased and partial viewpoint in decision-making due to the significant heterogeneity within the population. The impact of multimorbidity, polypharmacy, socioeconomic conditions, among other factors, and the different models of vascular aging mark the discordance between them. In turn, the term "special populations," coined years ago to refer to older people, is obsolete and imprecise, as this is usually the most significant population group in the epidemiology of cardiovascular diseases. (1,2)

2. Prioritize person-centered care with a multidisciplinary approach: We prioritize the individual over the disease in decision-making and acknowledge the role of the social environment and a multidisciplinary team in patient care. (1,3)

3. Conduct a comprehensive assessment based on five domains: We incorporate nutrition into the classic domains of geriatrics (clinical, functional, mental, and social) due to its impact on different cardiovascular diseases and vice versa. A comprehensive assessment allows us to identify specific vulnerabilities and guide personalized interventions, prioritizing those domains that affect prognosis and quality of life. (1)

4. Emphasize the concept of multimorbidity over comorbidity: Multimorbidity, an expanded concept of comorbidity, stands out as a geriatric syndrome in geriatric cardiology due to its high association with adverse cardiovascular events. It refers to the presence of several chronic diseases, clinical and non-clinical conditions in the same person, transversally, without dominance or interrelation of one over the other. (1,4)

5. Promote appropriate prescribing: In the field of cardiology, it is not uncommon to encounter patients who are taking multiple medications due to the high prevalence of multimorbidity. Polypharmacy, a global issue, refers to the use of five or more medications, irrespective of whether they are prescribed. It is imperative to distinguish between appropriate and inappropriate polypharmacy, and in the latter case, to promote deprescribing. As a response to this problem, our working group is developing a document on Appropriate Medication in Cardiovascular Therapy (MATE, acronym of the name in Spanish Medicación Adecuada en TErapéutica Cardiovascular). (1,3,5,6)

6. Acknowledge the bidirectional relationship between frailty and cardiovascular disease: Multiple reviews have evaluated and documented the relationship between frailty and adverse cardiovascular events. It has been demonstrated that both entities share risk factors and that there is a negative feedback between them. Consequently, intervention measures on either one have a direct impact on the other. (1,7)

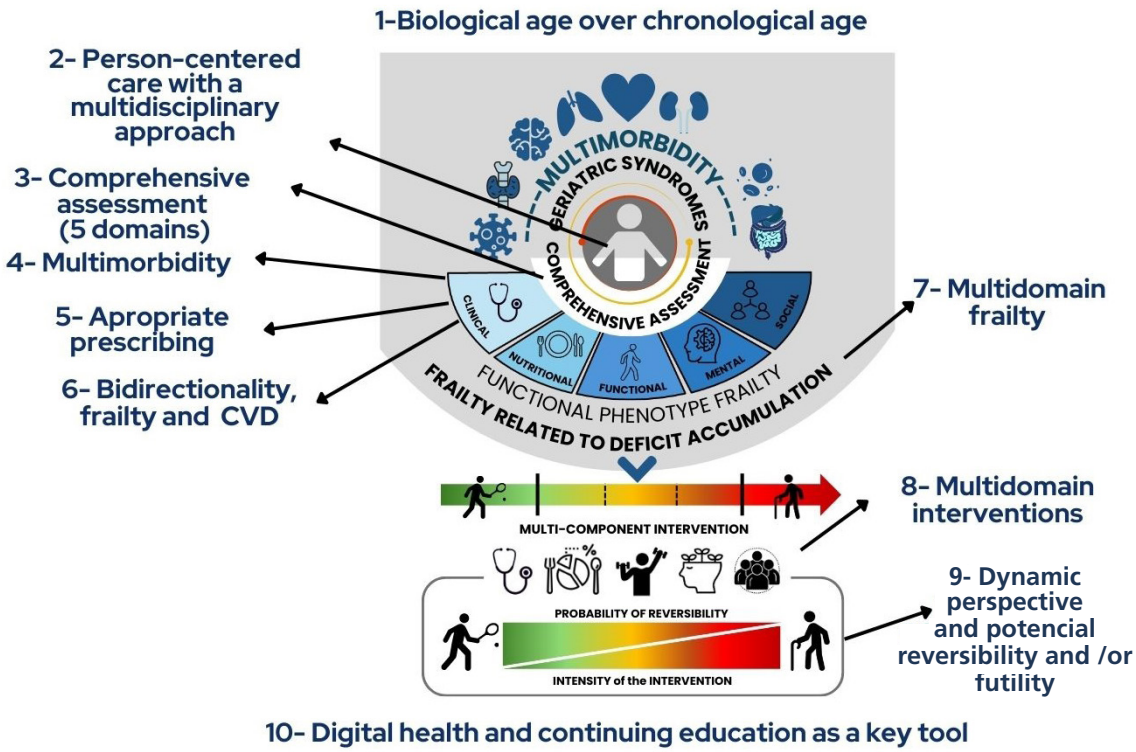
7. Assessment of frailty in relation to deficit accumulation (multidomain): Our guideline supports a comprehensive assessment because, although frailty has an impact on functionality, it provides a partial view of the problem. However, we emphasize

Rev Argent Cardiol 2025;93:302-304. http://doi.org/10.7775/rac.v93.i4.20917

Received: 04/22/2025 – *Accepted:* 06/02/2025

[1] Unidade Local de Saúde do Alto Ave, Guimarães, Portugal

Central illustration. Decalogue of the position paper and comprehensive assessment in cardiology



CVD: cardiovascular disease

the role of the functional domain as one of the pillars of the comprehensive assessment and evaluation of frailty in relation to the accumulation of deficits. (1,7,8)

8. Promote multidomain interventions: Once the comprehensive assessment has been carried out, the interventions should target the different domains. We emphasize the significance of paying close attention to clinical conditions, polypharmacy, vaccinations, the adaptation of nutritional plans, multicomponent exercise, and psychosocial interventions. (1,4,6)

The acronym "VIDA" (Vaccination, drug Interaction, Diet, physical Activity) is the starting point for the design of a new position paper on prevention and tools for a better quality of life.

9. Dynamic perspective and potential reversibility and/or futility: We emphasize the need to address the concept of "frailty" from a dynamic perspective that considers different situations: pre-frailty, mild, moderate, and severe frailty. Each one offers potential interventions for reversibility, since early and timely detection can make a difference in quality of life.

It is imperative to identify and avoid futile interventions, incorporate palliative care and comfort when appropriate, promote person-centered medicine through therapeutic adaptation based on patient values and preferences and their social and family environment, and implement preventive measures. All these principles constitute the pillars of person-centered medicine. (1,7,8)

10- Digital health and continuing education as key tools: New digital health technology tools must be applied and adapted for the assessment and treatment of older adults in order to provide care and quality of life.

Finally, none of the aforementioned changes will be possible unless geriatric cardiologists are included in the training of cardiologists and other related specialties. (1,9)

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Acknowledgments

The authors express their gratitude to the Clinical Practice Standards and Consensus Statements Area of the Argentine Society of Cardiology, and to Daniel Piñeiro (World Heart Federation), Robinson Cuadros (Latin American Committee of the International Association of Gerontology and Geriatrics), Pablo Stutzbach, Mario Spennato, and Jorge Trongé (Argentine Society of Cardiology), José Ángel Pérez Rivera

(Spanish Society of Cardiology), Alberto Barón and Jerson Quitián (Colombian Society of Cardiology), Yalile Nahúm (Chilean Society of Cardiology), Alexandra Castillo (Dominican Society of Geriatrics), Amir Gómez León Mandujano (Mexican Society of Cardiology), Adriana López (Chilean Society of Geriatrics and Gerontology), and Matías Manzotti (Argentine Society of Gerontology and Geriatrics), for their valuable and selfless contributions.

REFERENCES

1. Palacio MS, Blanco P, Suárez G, Villalba Nuñez M, Schygiel P, Tavella MJ, y cols. Documento de posición sobre fragilidad y valoración integral en Cardiología. Rev Argent Cardiol 2025;93 (Suplemento 1): 1-87. https://doi.org/10.7775/rac.es.v93.s1

2. Damluji AA, Nanna MG, Rymer J, Kochar A, Lowenstern A, Baron SJ, et al. Chronological vs Biological Age in Interventional Cardiology: A Comprehensive Approach to Care for Older Adults: JACC Family Series. JACC Cardiovasc Interv 2024;17:961-78. https://doi.org/10.1016/j.jcin.2024.01.284.

3. Birtcher KK, Allen LA, Anderson JL, Bonaca MP, Gluckman TJ, Hussain A, et al. 2022 ACC Expert Consensus Decision Pathway for Integrating Atherosclerotic Cardiovascular Disease and Multimorbidity Treatment: A Framework for Pragmatic, Patient-Centered Care: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023;81:292-317. https://doi.org/10.1016/j.jacc.2022.08.754.

4. Forman DE, Maurer MS, Boyd C, Brindis R, Salive ME, Horne FM, et al. Multimorbidity in Older Adults With Cardiovascular Disease. J Am Coll Cardiol 2018;71:2149-61. https://doi.org/10.1016/j.jacc.2018.03.022

5. Delara M, Murray L, Jafari B, Bahji A, Goodarzi Z, Kirkham J, et al. Prevalence and factors associated with polypharmacy: a systematic review and Meta-analysis. BMC Geriatr. 2022;22:601. https://doi.org/10.1186/s12877-022-03279-x. Erratum in: BMC Geriatr 2022;22:742. https://doi.org/10.1186/s12877-022-03388-7

6. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. Eur Geriatr Med 2021;12:443-52. https://doi.org/10.1007/s41999-021-00479-3.

7. James K, Jamil Y, Kumar M, Kwak MJ, Nanna MG, Qazi S, et al. Frailty and Cardiovascular Health. J Am Heart Assoc 2024;13:e031736. https://doi.org/10.1161/JAHA.123.031736

8. Kim DH, Rockwood K. Frailty in Older Adults. N Engl J Med 2024;391:538-48. https://doi.org/10.1056/NEJMra2301292

9. Linn N, Goetzinger C, Regnaux JP, Schmitz S, Dessenne C, Fagherazzi G, et al. Digital Health Interventions among People Living with Frailty: A Scoping Review. J Am Med Dir Assoc 2021;22:1802-12.e21. https://doi.org/10.1016/j.jamda.2021.04.012.

SCIENTIFIC LETTER

Fibrinolysis After Failed Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: A Case Report

Fibrinolisis post angioplastia fallida en infarto agudo de miocardio con elevación del segmento ST: reporte de un caso

LUCILA MARÍA CAROSELLA[1], PAUL CARAGUAY SALINAS[1], MIRZA RIVERO[1, MTSAC]

We report the case of a 62-year-old obese patient with untreated dyslipidemia and a smoking history of 30 pack-years, with no other relevant medical history. He presented to the Emergency Department at 7 p.m. with precordial pain at rest, radiating to his upper limbs, rated 8/10 in intensity, lasting 1 hour. Physical examination revealed no relevant findings. The electrocardiogram (ECG) showed ST-segment elevation in the anterior leads and reciprocal ST-segment depression in the inferior leads. The clinical condition was interpreted as anterior ST-segment elevation myocardial infarction (STEMI), Killip and Kimball class A. He received 300 mg of acetylsalicylic acid and 300 mg of clopidogrel. The center did not have an emergency catheterization laboratory, so the patient was transferred to our institution.

He was admitted at 10 p.m. with persistent precordial pain and an ECG showing the previously described changes (Figure 1). Coronary angiography was performed via left radial artery access, with a door-to-needle time of 10 minutes (Figure 2 A). It revealed occlusion of the left anterior descending (LAD) artery at its origin, and faint opacification of the distal bed through homocoronary and heterocoronary collateral circulation. The lateroventricular branch of the circumflex artery showed an 80% stenosis in the proximal third. The right coronary artery was occluded in the middle third, and its distal bed was opacified through homocoronary collateral circulation.

Attempts were made to cross the ostial occlusion of the left anterior descending artery using guidewires of different stiffness, but this was unsuccessful. Thromboaspiration was also unsuccessful, so the procedure was concluded at 12:30 a.m. without complications.

The patient was admitted to the Coronary Care Unit after the procedure, with precordial pain rated 6/10. He was alert and had good peripheral perfusion, heart rate 95 bpm, and blood pressure 120/60 mmHg. Heart sounds were normal, with no murmurs; respiratory mechanics was preserved, with no signs of heart failure, and no requirement for supplemental oxygen.

Intravenous nitroglycerin infusion was initiated, without improvement in precordial pain. The ECG showed persistent ST-segment elevation.

A bedside echocardiogram showed severe global hypokinesis of the left ventricle, predominantly in the apical segments, without evidence of low cardiac output and with adequate filling pressures.

The team discussed possible strategies for achieving effective reperfusion and, given the patient's low bleeding risk, a therapy with fibrin-specific fibrinolytics was initiated. Recombinant tissue plasminogen activator (rTPA) was administered at a weight-adjusted dose according to the local protocol: 15 mg over 2 minutes, followed by 50 mg over 30 minutes, and then 35 mg over 60 minutes (total infused dose: 100 mg).

Serial ECGs showed improvement in ST-segment elevation after 30 minutes.

Monitoring from 35 minutes onwards showed frequent ventricular ectopic beats, accelerated idioventricular rhythm (AIVR), and non-sustained monomorphic ventricular tachycardia.

After completion of the rTPA infusion, precordial pain decreased, now rated 2/10, and intravenous nitroglycerin was continued.

At that time, reperfusion criteria were met: decreased ST-segment elevation in V2, (the lead with the greatest elevation), ventricular arrhythmia, and pain relief.

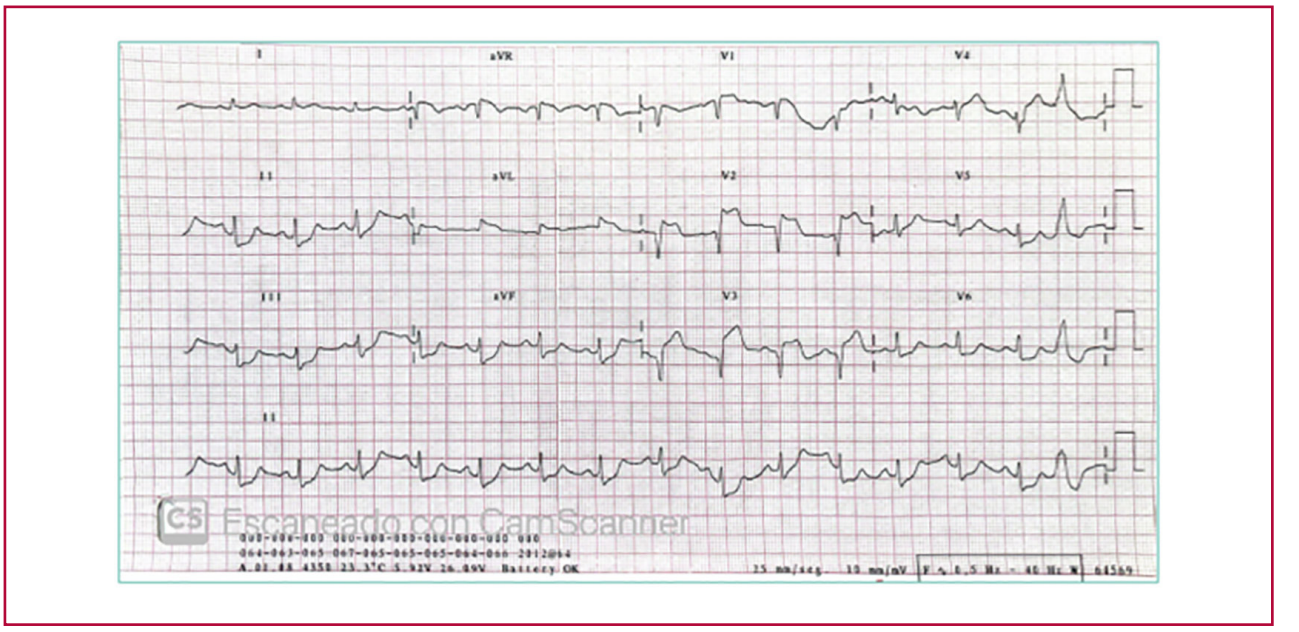
On day 1 of hospitalization, the echocardiogram revealed moderate deterioration of left ventricular function, with a left ventricular ejection fraction (LVEF)

Rev Argent Cardiol 2025;93:305-308. http://doi.org/10.7775/rac.v93.i4.20918

Correspondence: Lucía M. Carosella. E-mail: lucila.carosella@gmail.com

[1] Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno (CEMIC), Ciudad Autónoma de Buenos Aires, Argentina

Fig. 1. Electrocardiogram prior to the first coronary angiography showing ST-segment elevation in the anterior leads and ST-segment depression in the inferior leads.



estimated at 40% by the Simpson method, akinesia of the mid-septal, mid-anterior, and all apical segments, mild diastolic dysfunction, and a dilated inferior vena cava with minimal collapse.

Twenty-four hours after admission, a new coronary angiography showed an ulcerated lesion in the left main coronary artery and a patent left anterior descending artery, with an extensive severe lesion from its origin to the middle third, showing TIMI II flow (Figure 2 B). The rest of the arteries showed no changes compared to the previous catheterization. During this procedure, PCI was performed on the left anterior descending artery with placement of two drug-eluting stents, on the left main coronary artery with one drug-eluting stent, and on the circumflex artery with two drug-eluting stents.

The procedure was performed via radial access without complications (Figure 2 C and D).

He was readmitted to the Coronary Care Unit, where he developed acute heart failure (Stevenson class B) on day 3 of hospitalization, with a good response to subsequent medical therapy.

After a favorable course without further complications, he was discharged on optimized therapy for coronary artery disease and heart failure. Figure 3 shows the discharge ECG.

DISCUSSION

The treatment of choice for STEMI is invasive, consisting of urgent primary percutaneous coronary intervention (PCI) performed as early as possible. Primary PCI is the recommended reperfusion strategy within the first 120 minutes after the ECG and is superior to fibrinolysis in reducing mortality, non-fatal reinfarction, and stroke. (1)

Fibrinolysis with fibrin-specific drugs is indicated within the first 12 hours of symptom onset, as the start of the pharmacoinvasive strategy, and should be used when PCI is not feasible within the first 120 minutes. (1)

In rare cases, primary PCI may fail. This outcome is associated with higher Killip and Kimball class on admission, multivessel disease, clinical history of acute myocardial infarction (AMI), longer duration of infarction, and TIMI 0-1 flow on admission. (2)

Exceptionally, the culprit vessel cannot be identified. This occurs in the case of ostial lesions, or when the occlusion does not clearly show the stump. (3)

We should consider urgent coronary artery bypass grafting (CABG) for patients with a significant area of myocardium at risk, anatomy unsuitable for PCI, with a patent artery or cardiogenic shock. (1)

The benefits of urgent CABG in patients with PCI failure or acute occlusion not amenable to PCI are uncertain. Therefore, it is not a routine indication, given the high surgical risk of these patients and the low likelihood of improving prognosis. (1)

Primary PCI failure is associated with high morbidity and mortality.

In this setting, the exceptional use of intracoronary fibrinolytics, such as the "marinade technique" has been described, which has few systemic effects, thereby reducing bleeding risk and allowing high drug concentrations at the thrombus site. It has been reported that the use of intracoronary fibrinolytics immediately after PCI could improve coronary perfusion

Fig. 2. Coronary angiography (CAG). A. CAG on admission. B. CAG 24 h after treatment with fibrinolytics. C. PCI of the culprit lesion, guidewire in the left anterior descending artery. D. Final angiographic result after stent placement.

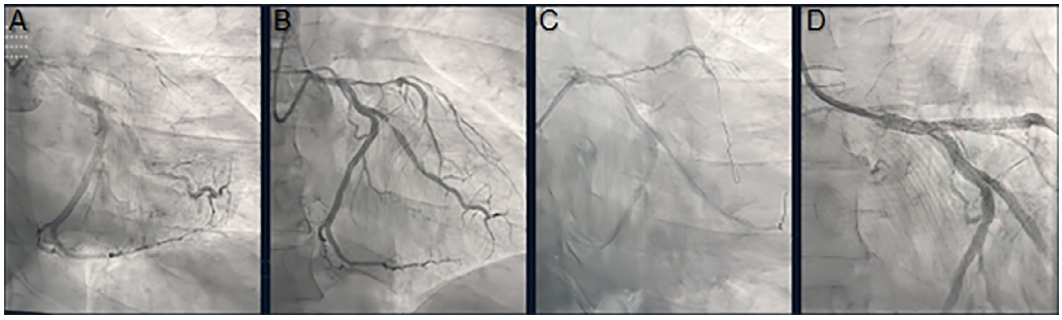
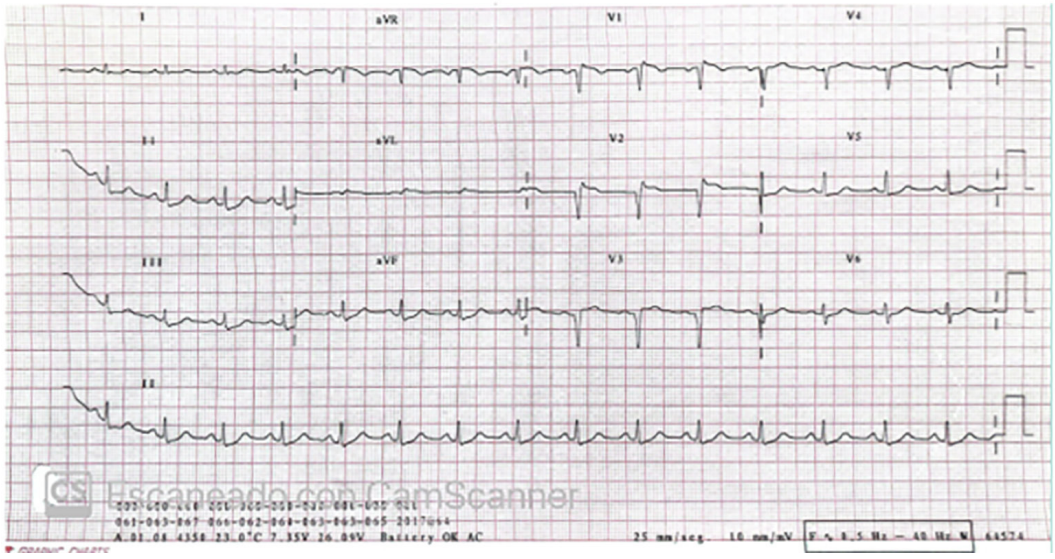


Fig. 3. Electrocardiogram after successful PCI, prior to hospital discharge



in the first few days after STEMI, improving the area of ischemia and preventing ventricular dysfunction. (4,5)

There is no scientific evidence for "rescue systemic fibrinolysis" (use of systemic fibrinolytics after failed PCI). In our literature search, we found one case in which it was performed in a patient with inferior STEMI. The patient had moderate left ventricular dysfunction. After failed PCI, alteplase was infused achieving reperfusion criteria; then, a PCI of the right coronary artery was successfully performed. (3)

In the case we present, the patient continued to experience pain, with persistent ST-segment elevation, a bedside echocardiogram with a poor prognosis, and an ostial lesion of the left anterior descending artery. As this was a patient with a low risk of bleeding, an off-label drug strategy was chosen to improve the patient's prognosis and eventually reevaluate the coronary arteries with a new angiography.

This clinical case reminds us of the importance of using fibrinolytic treatment according to international guidelines, which is easily accessible and usable in emergency departments that lack emergency primary PCI. It also highlights the current delays in the treatment of STEMI and emphasizes the need for improvements in hospital networks for the management of patients with AMI.

We are used to thinking of rescue PCI in the event of failed fibrinolytic therapy. Although there is no evidence on the reverse procedure—the use of systemic fibrin-specific thrombolytics after failed PCI—, we believe this case has clinical and pathophysiological relevance for exceptional real-world patients with AMI and primary PCI failure.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

REFERENCES

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720–826. https://doi.org/10.1093/eurheartj/ehad191

2. Levi A, Kornowski R, Vaduganathan M, Eisen A, Vaknin-Assa H, Abu-Foul S, et al. Incidence, predictors, and outcomes of failed primary percutaneous coronary intervention: a 10-year contemporary experience. Coron Artery Dis 2014;25:145-51. https://doi.org/10.1097/MCA.0000000000000065

3. Alvarado Casas T, Diego Nieto G, Rojas González AM, Antuña Álvarez P, Rivero Crespo F, Alfonso F. "Rescue fibrinolysis" after failed primary angioplasty. Med Intens 2021;45:187-9. https://doi.org/10.1016/j.medin.2019.04.005

4. Unzué L. Intracoronary fibrinolysis as a rescue strategy in the event of a massive thrombotic catastrophe. How would you do it? REC, interventional cardiology. https://doi.org/10.24875/recic.m22000300

5. Unzué L, García E, Del Río MR, Osende J, Teijeiro-Mestre R, Fernandez-Friera, L. Local intracoronary fibrinolysis with distal occlusion: A series of cases using marinade technique. Cardiovasc Rev Med 2023;53S:S239–S244. https://doi.org/10.1016/j.carrev.2023.05.004

SCIENTIFIC LETTER

Type 2 Acute Myocardial Infarction Secondary to Carbon Monoxide Poisoning: Case Report

Infarto agudo de miocardio tipo 2 secundario a intoxicación por monóxido de carbono: reporte de un caso

LEANDRO PARRILLA[1], EZEQUIEL NUDELMAN[1], IGNACIO N. DE URQUIZA[1], FERNANDO GARCÍA LODIFE[1], DANIEL O. GAUNA[1]

Carbon monoxide (CO) poisoning is a medical emergency of global importance, with a spectrum of clinical presentations ranging from mild and nonspecific symptoms to severe multiorgan involvement and death. Cardiovascular complications are one of the leading causes of morbidity and mortality in patients with CO poisoning and can occur both in the acute phase and in the long term.

We present the case of a 40-year-old male patient with a history of smoking and dyslipidemia who was admitted to our service on January 18, 2025, with loss of consciousness on the previous day secondary to carbon monoxide poisoning, evidenced by a carboxyhemoglobin (COHb) level of 55% on admission.

The admission electrocardiogram (ECG) showed atrial fibrillation rhythm with rapid ventricular response, with ST-segment depression in DI, DII, DIII, aVF, and V3 to V6, and ST-segment elevation in aVR. Ultrasensitive troponin (UST) levels were 593.6/1459/1173 ng/L. The admission echocardiogram showed a left ventricular ejection fraction (LVEF) of 40% with generalized hypokinesia. The condition was interpreted as type 2 acute myocardial infarction (AMI) secondary to CO poisoning, and the patient was admitted to the Coronary Care Unit for monitoring and treatment with oxygen therapy.

A brain and chest computed tomography scan showed no abnormalities, and oxygen therapy with a hyperbaric chamber was administered. The patient was admitted to the intensive care unit in a hemodynamically stable condition, asymptomatic for angina and dyspnea, with no signs of fluid overload or low cardiac output. After hyperbaric chamber therapy, an ECG was performed on the same day, showing sinus rhythm at 75 beats/minute, with no signs of acute or sequelae ischemia, and decreased COHb to 1.2%.

On January 20, 2025, a Doppler echocardiogram revealed a left ventricle with slightly increased wall thickness, no motility disorders, and preserved LVEF (68%). Subsequently, an invasive coronary angiography was performed via the right radial artery, which did not disclose any significant lesions. Laboratory tests during hospitalization included a complete blood count with hematocrit 48.7, hemoglobin 16.4 g/dL, platelets 225 000/mm^3 and leukocytes 8530/mm^3. The lipid profile showed HDL cholesterol 44 mg/dL, LDL cholesterol 130 mg/dL, total cholesterol 195 mg/dL, and triglycerides 180 mg/dL. Glycated hemoglobin (HbA1c) was 5.9%. Serology tests for hepatitis B, hepatitis C, and HIV were nonreactive. Given the patient's favorable clinical course and the absence of criteria for hospitalization, it was decided to discharge him from hospital on January 21, 2025.

Carbon monoxide poisoning can cause a variety of acute and chronic cardiovascular complications, even in patients with no history of heart disease. It exerts its toxicity mainly through tissue hypoxia, mitochondrial dysfunction, and oxidative damage, significantly affecting the myocardium and the vascular system. (1,2)

Acute myocardial injury is observed in approximately 37% to 53% of patients with acute CO poisoning, evidenced by elevated cardiac biomarkers (troponin, CK-MB) and electrocardiographic abnormalities, such as ischemic changes in the ST-segment and T wave. Myocardial injury can occur even in young, previously healthy individuals. (3,4) In the case here presented, elevated troponin and initial electrocardiographic abnormalities are consistent with this finding.

Left ventricular dysfunction may manifest as decreased LVEF or alterations in global longitudinal strain, detectable by echocardiography and cardiac

Rev Argent Cardiol 2025;93:309-310. http://doi.org/10.7775/rac.v93.i4.20912

Correspondence: Ignacio N. de Urquiza. E-mail: ignaciodeurquiza@gmail.com

[1] Coronary Care Unit, Hospital General Carlos G Durand. Autonomous City of Buenos Aires, Argentina.

magnetic resonance imaging. (4,5) In our patient, left ventricular function was preserved at the time of the echocardiogram.

Carbon monoxide can induce supraventricular and ventricular arrhythmias, including tachycardia, bradycardia, and, in severe cases, ventricular fibrillation. (1,2) The rapid ventricular response to atrial fibrillation initially observed in our patient is an example of this complication.

Cases of AMI secondary to CO poisoning have been documented, attributable to both hypoxia and endothelial dysfunction, and coronary vasospasm. (2,5). The present case is a clear example of type 2 AMI induced by poisoning. The absence of significant coronary lesions on coronary angiography supports this classification.

Cohort studies have shown that patients with a history of CO poisoning have a significantly increased risk of major cardiovascular events, including AMI, heart failure, and stroke, compared with the general population (adjusted HR ≈ 2). (6)

The risk of mortality from cardiovascular causes remains high after poisoning, even after normalization of biomarkers and initial cardiac function. Cardiac magnetic resonance imaging can detect persistent myocardial fibrosis several months after poisoning, which is associated with subclinical dysfunction and potential risk of future heart failure. (5)

In severe cases, poisoning can cause cardiovascular collapse, severe hypotension, and cardiac arrest, especially with massive or prolonged exposure. (1,2)

In conclusion, CO poisoning is a clinical entity that requires high suspicion and comprehensive management, given its potential serious cardiovascular complications. The case presented here illustrates the manifestation of a type 2 AMI in the context of CO poisoning, highlighting the importance of cardiac monitoring and complementary studies for proper diagnosis and treatment. Long-term follow-up of these patients is essential due to the increased risk of cardiovascular events and mortality.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

REFERENCES

1. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Carbon Monoxide Poisoning: Wolf SJ, Maloney GE, Shih RD, Shy BD, Brown MD. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Carbon Monoxide Poisoning. Ann Emerg Med 2017;69:98-107.e6. https://doi.org/10.1016/j.annemergmed.2016.11.003.

2. Rose JJ, Wang L, Xu Q, McTiernan CF, Shiva S, Tejero J, et al. Carbon Monoxide Poisoning: Pathogenesis, Management, and Future Directions of Therapy. Am J Respir Crit Care Med 2017;195:596-606. https://doi.org/10.1164/rccm.201606-1275CI.

3. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Carbon Monoxide Poisoning; Wolf SJ, Maloney GE, Shih RD, Shy BD, Brown MD. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Carbon Monoxide Poisoning. Ann Emerg Med 2017;69:98-107.e6. https://doi.org/10.1016/j.annemergmed.2016.11.003.

4. Szponar J, Goliszek S, Kujawa A, Tchórz M, Sutkowska A, Radoniewicz-Tchórz A, et al. Echocardiographic and clinical patterns in patients with acute carbon monoxide poisoning without cardiovascular and other chronic diseases. Clin Toxicol (Phila) 2025;63:246-52. https://doi.org/10.1080/15563650.2025.2456689.

5. Cho DH, Ko SM, Son JW, Park EJ, Cha YS. Myocardial Injury and Fibrosis From Acute Carbon Monoxide Poisoning: A Prospective Observational Study. JACC Cardiovasc Imaging 2021;14:1758-70. https://doi.org/10.1016/j.jcmg.2021.02.020.

6. Ahn GJ, Lee S, Heo YW, Cha YS. Mortality Risks and Causes in Previous Carbon Monoxide Poisoning: A Nationwide Population-Based Cohort Study. Crit Care Med 2024;52:1866-76. https://doi.org/10.1097/CCM.0000000000006414.

SCIENTIFIC LETTER

Peripartum cardiomyopathy: when pregnancy unmasks genetic dilated cardiomyopathy

Miocardiopatía periparto: cuando el embarazo revela una miocardiopatía dilatada genética

MARGARIDA MARTINS CASTRO[1], LUÍSA PINHEIRO[1], OLGA AZEVEDO[1], FILIPA ALMEIDA[1], JOÃO PORTUGUÊS[1], ANTÓNIO LOURENÇO[1]

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening condition that presents as heart failure (HF) during the peripartum period and may progress to cardiogenic shock. (1) Recent genetic studies indicate that up to 20% of PPCM patients carry mutations in genes associated with dilated cardiomyopathy (DCM), such as the TTN gene, which encodes titin, emphasizing the value of genetic testing in this population. (2) We describe a challenging case of PPCM with a severe clinical course and a novel truncating TTN variant, focusing on diagnostic complexity and management, particularly regarding implantable cardioverter-defibrillator (ICD) timing.

A 33-year-old Caucasian woman with no relevant medical history presented to the emergency department five days postpartum with sudden dyspnea, orthopnea, and chest discomfort. She had one previous uneventful full-term pregnancy and a miscarriage. Family history was negative for cardiac disease.

On admission, she was tachycardic, tachypneic, and hypotensive. Auscultation revealed an irregular rhythm, apical systolic murmur, and bilateral basal crackles. Laboratory testing showed elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide, 4400 pg./mL, normal value <450 pg./mL) and D-dimers (6000 ng/mL, normal value <500 ng/mL). In the computed tomography pulmonary angiography identified small bilateral pleural effusions. Electrocardiogram showed sinus tachycardia (140 bpm) with frequent ventricular bigeminy; QT interval was normal (Figure 1).

Echocardiography revealed a severely dilated and dysfunctional left ventricle (LV) with left ventricular ejection fraction (LVEF) 20%, borderline right ventricular (RV) function, and severe secondary mitral regurgitation (Figure 2).

She was admitted to the cardiac intensive care unit for clinical stabilization.

Within 24 hours, she deteriorated to cardiogenic shock and required levosimendan and norepinephrine. Lactation was suppressed using bromocriptine following shared decision-making with the patient. Anticipating need for mechanical support, she was transferred to a tertiary care center, where she responded to inotropic therapy with dobutamine without requiring circulatory assistance.

Disease-modifying drugs for heart failure were gradually introduced, though limited by her hemodynamic profile.

On day 23, cardiac magnetic resonance imaging (MRI) confirmed severe LV dilation and dysfunction (LVEF 28%) and mild RV dysfunction, without inflammation, fibrosis, or myocardial infiltration. She was discharged on day 40 and referred for genetic evaluation.

Follow-up in HF clinic allowed gradual uptitration of disease-modifying therapy. Genetic testing identified a novel, likely pathogenic, truncating variant in TTN (c.98319dup p.(Asp32774*)). First-degree relatives showed no abnormalities on echocardiography.

After 6 months of optimized therapy, cardiac MRI still showed severe LV dysfunction and a subcutaneous ICD was implanted. She ultimately achieved complete recovery of LV function (LVEF 54%) eight months post-admission.

Recent advances have provided new insights regarding the genetic basis of PPCM showing that up to 20% of patients with PPCM carry mutations in genes known to be associated to DCM. (2)

This case supports emerging data on the genetic underpinnings of PPCM, particularly the role of TTN truncating variants, which are known to correlate

Rev Argent Cardiol 2025;93:311-313. http://doi.org/10.7775/rac.v93.i4.20911

Correspondence: Margarida Castro. Rua dos Cutileiros, Creixomil. 4835-044 Guimarães. E-mail: amargaridamcastro@gmail.com

FUNDING: No funding

[1] Unidade Local de Saúde do Alto Ave, Guimarães, Portugal

Fig. 1. Initial electrocardiogram showing sinus tachycardia and ventricular bigeminy

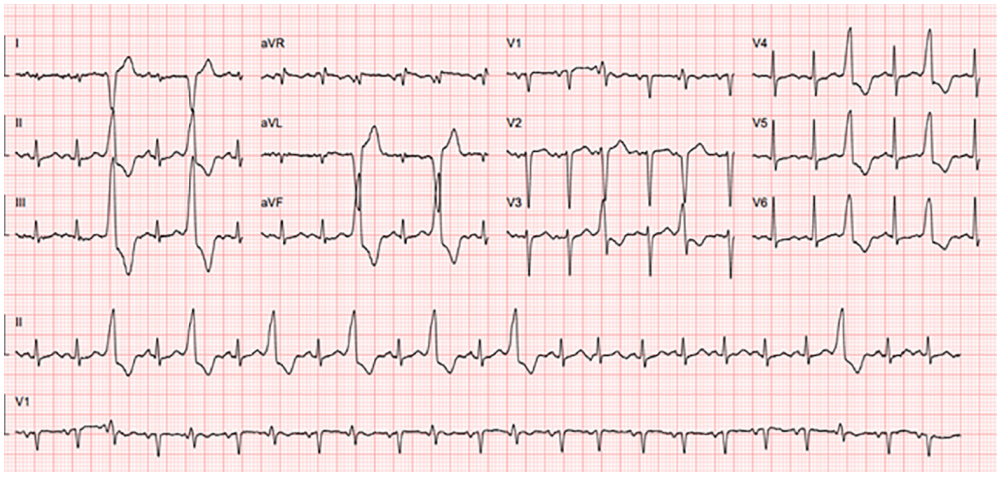
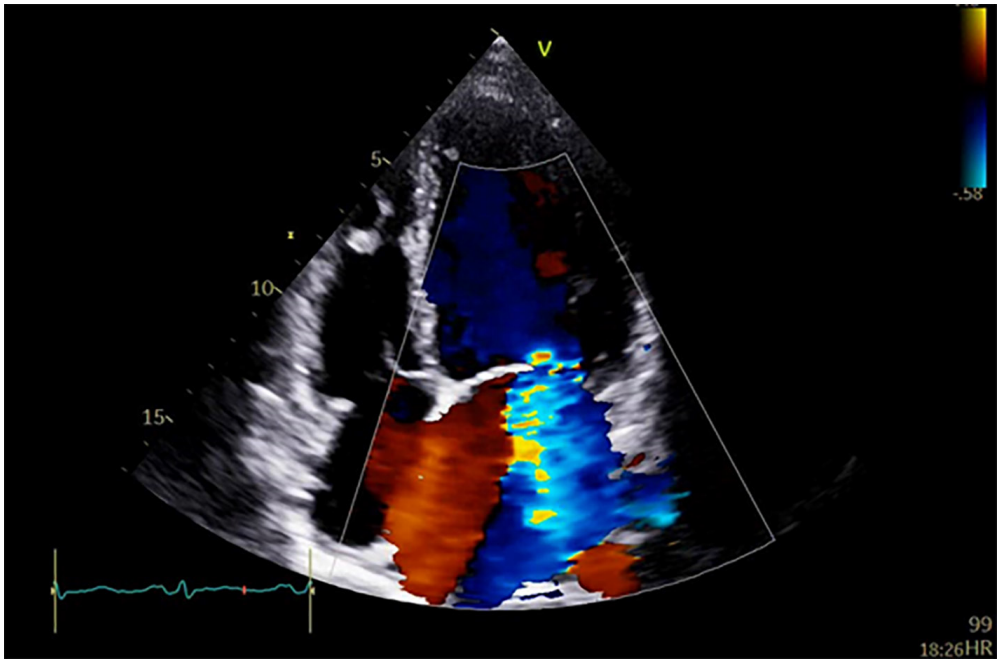


Fig. 2. Transthoracic echocardiogram showing severe dilated left ventricle and severe secondary mitral regurgitation



with adverse LV remodeling and reduced recovery. (2) The hypothesis of pregnancy as a physiological "second hit" that unmasks latent genetic DCM is reinforced. (3)

Data have shown that complete recovery of ventricular function occurs in a substantial proportion of women, and predictive factors include a baseline LVEF greater than 30%, as suggested by previous studies. (4) Although LVEF recovery can occur in up to 65% of patients by six months, (5) some recover only after a year or more. This variability complicates the timing of cardioverter-defibrillator implantation. Early permanent implantation may be premature, particularly in reversible cardiomyopathies, but data on ventricular arrhythmias in PPCM remain limited.

Some studies report high arrhythmic burden early in PPCM, with life-threatening ventricular arrhythmias observed in 12–43% of patients. (6) Wearable cardioverter-defibrillators (WCDs) have shown utility in this context. In one prospective series, 3 of 7 patients experienced ventricular fibrillation successfully terminated by the WCD. (6)

Although current guidelines are non-specific, WCDs may be a reasonable bridge strategy in patients with new-onset PPCM and severely reduced LVEF.

However, their limited availability in some countries may restrict routine use in clinical practice and complicate the decision of when to indicate an ICD

This case illustrates the complexity of managing severe PPCM in the presence of a pathogenic TTN variant. It highlights the importance of genetic testing, the need for shared decision-making regarding lactation suppression, and the dilemma of ICD timing—particularly when an underlying genetic variant is associated with poorer left ventricular reverse remodeling.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

REFERENCES

1. Bauersachs J, König T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. Eur J Heart Fail 2019;21:827-43. https://doi.org/10.1002/ejhf.1493

2. Goli R, Li J, Brandimarto J, Levine LD, Riis V, McAfee Q. Genetic and Phenotypic Landscape of Peripartum Cardiomyopathy. Circulation 2021;143:1852-62. https://doi.org/10.1161/CIRCULATIONAHA.120.052395

3. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005;80:1602-6. https://doi.org/10.4065/80.12.1602

4. McNamara D, Damp J, Elkayam U, Hsich E, Ewald G, Cooper L, et al. Myocardial recovery at six months in peripartum cardiomyopathy: results of the NHLBI Multi-center IPAC study. Circulation 2013; 128:A12898.

5. Modi KA, Illum S, Jariatul K, Caldito G, Reddy PC. Poor outcome of indigent patients with peripartum cardiomyopathy in the United States. Am J Obstet Gynecol 2009;201(2):171.e1-5. https://doi.org/10.1016/j.ajog.2009.04.037.

6. Duncker D, Westenfeld R, Konrad T, Pfeffer T, Correia de Freitas CA, Pfister R, et al. Risk for life-threatening arrhythmia in newly diagnosed peripartum cardiomyopathy with low ejection fraction: a German multi-centre analysis. Clin Res Cardiol 2017;106:582-9. https://doi.org/10.1007/s00392-017-1090-5.

Echocardiography, Subclinical Cardiac Damage and Indexing Method

Ecocardiografía, daño cardíaco subclínico y método de indexación

FRANK ALEXANDER BUSTAMANTE MAYURI[1]

I read with great interest the article published by Travetto and Argento entitled Detection of subclinical cardiac damage *by echocardiography in a hypertensive population with a high prevalence of obesity: discrepancies observed according to the indexing method used*, (1) which highlights the clinical relevance of using height-based allometric indices to detect target organ damage in hypertensive patients who are overweight or obese. The purpose of this letter is to point out certain limitations identified in the study, which could help improve future research of this kind.

The study's findings, which show a significant underestimation of left ventricular hypertrophy (LVH) and left atrial enlargement (LAE) when using body surface area-based indexing (BSAI), are particularly relevant in the context of a population where obesity is highly prevalent. The fact that up to 38% of patients were reclassified when using allometric height-based indexing (AHI) highlights the potential clinical impact of this methodological choice on cardiovascular risk assessment. However, despite the results obtained, the study has some important limitations.

As this is a single-center, cross-sectional study without long-term follow-up, it is not possible to establish causal relationships or evaluate the prognostic value of the different indexing methods. This contrasts with studies such as that by Chirinos et al., (2) where AHI not only improved LVH detection but also showed a greater predictive value for cardiovascular events over time. Similarly, De Simone et al. (3) identified that left ventricular mass indexed to height2.7 was associated with a higher population-attributable risk of events in the Strong Heart Study, which included a long-term follow-up.

Furthermore, the results were not validated in other populations or in different clinical contexts. This issue has been addressed by Liao et al., (4) who, in a large, diverse cohort, concluded that AHI offered greater diagnostic accuracy, particularly in overweight or obese women. Kuznetsova et al. (5), meanwhile, analyzed the discrepancies between BSAI and AHI according to the degree of obesity in a multinational cohort, and found results similar to those reported by Travetto et al., but with broader validation.

For all these reasons, I believe that future research should apply multicenter and longitudinal designs with external validation, evaluate the reproducibility of measurements, and incorporate technologies that allow for the automatic calculation of allometric formulas in echocardiographic equipments.

I congratulate the authors for rising awareness of this issue and agree that it is urgent to incorporate AHI as standard clinical practice in hypertensive patients who are overweight or obese.

Sincerely,

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

REFERENCES

1. Travetto CM, Argento L V. Detection of subclinical cardiac target organ damage by echocardiography in a population of hypertensive patients with a high prevalence of obesity: discrepancies observed depending on the indexing method used. Rev Argent Cardiol 2025;93:6-14. https://doi.org/10.7775/rac.es.v93.i1.20850

2. Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D, et al. Left ventricular mass: Allometric scaling, normative values, effect of obesity, and prognostic performance. Hypertension. 2010;56:91-8. https://doi.org/10.1161/HYPERTENSIONAHA.110.150250

3. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, et al. Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251-60. https://doi.org/10.1016/0735-1097(92)90385-Z

4. Liao Y, Cooper RS, Mcgee DL, Mensah GA, Ghali JK. The Relative Effects of Left Ventricular Hypertrophy, Coronary Artery Disease, and Ventricular Dysfunction on Survival Among Black Adults. JAMA: The Journal of the American Medical Association. 1995;273:1592-7. https://doi.org/10.1001/jama.1995.03520440046035

Rev Argent Cardiol 2025;93:314-315. https://doi.org/10.7775/rac.v93.i4.20919

Correspondence: Frank A. Bustamante Mayuri. E-mail: frank.bustamante@upsjb.edu.pe

[1] Medicine student at Universidad Privada San Juan Bautista, Ica, Perú , Ica, Peru

5. KKuznetsova T, Haddad F, Tikhonoff V, Kloch-Badelek M, Ryabikov A, Knez J, et al. Impact and pitfalls of scaling of left ventricular and atrial structure in population-based studies. J Hypertens 2016;34:1186-94. https://doi.org/10.1097/HJH.0000000000000922

AUTHORS' REPLY

We thank the reader for his interest in our study and acknowledge that it has certain limitations that should be considered when interpreting the results. However, we believe that the reported findings have fulfilled the objectives for which the study was proposed, raising awareness of this problem, which is of increasing interest and importance in clinical practice, not only in the field of Cardiology but also in other specialties, in which indexing structures to body surface area is not appropriate for addressing the phenomenon under study in overweight and obese subjects.

Sincerely,

Carolina Travetto, Laura Argento MTSAC

The Right Ventricle in Transthyretin Amyloidosis: Looking Beyond the Left Ventricle

El ventrículo derecho en la amiloidosis por transtiretina: mirar más allá del ventrículo izquierdo

GUILLERMO LINIADO[1], MTSAC,

The study by Elissamburu et al., recently published in Revista Argentina de Cardiología, provides relevant data on right ventricular (RV) function in patients with transthyretin cardiac amyloidosis (ATTR-CM). In a cohort of 154 patients, almost half presented with RV systolic dysfunction measured by TAPSE, which was independently associated with mortality, hospitalization for heart failure, and the onset of atrial fibrillation. (1)

This finding is important because care for cardiac amyloidosis has historically focused on the left ventricle, while the right ventricle has tended to be overlooked. However, in clinical practice, RV dysfunction has a decisive prognostic weight, not only in amyloidosis but also in most cases of heart failure, especially in those with preserved ejection fraction. (2,3) In this sense, the study reinforces a well-known concept: the evolution of patients with HF depends on both the right and left sides of the heart.

The practical relevance of this study lies in highlighting that a simple, accessible, and reproducible parameter such as TAPSE can be useful in risk stratification. Given the complexity of amyloidosis, which often requires sophisticated studies for diagnosis, the possibility of having a simple echocardiographic index available in any laboratory is a significant contribution. Systematically incorporating TAPSE measurement in patients with suspected or confirmed ATTR-CM can help identify higher-risk subgroups and guide specific decisions.

For example, a patient with reduced TAPSE could benefit from closer monitoring, a lower threshold for initiating anticoagulation upon the onset of atrial fibrillation, or earlier evaluation for specific therapies. In a clinical setting where access to disease-modifying drugs such as tafamidis remains limited, having parameters that allow for better selection of who to prioritize becomes particularly useful in real-world practice.

At the same time, we must not lose sight of a general consideration: when a new prognostic marker is proposed, its true value lies in demonstrating increased capacity over what we already know. If RV dysfunction appears almost inevitably in patients with advanced heart failure or in those with elevated NT-proBNP and troponin, it is worth asking how much TAPSE adds beyond confirming an already evident risk. The study by Elissamburu et al. shows statistical independence, but future studies should demonstrate added value over models that integrate biomarkers and clinical variables.

In short, this work invites us to look at the right

Rev Argent Cardiol 2025;93:315-316. https://doi.org/10.7775/rac.v93.i4.20923

Correspondence: Guillermo Liniado. Email: guillermoliniado@yahoo.com.ar

[1] Head of Heart Failure, Hospital General de Agudos Dr. Cosme Argerich, Autonomous City of Buenos Aires, Argentina

ventricle with the importance it deserves. It is not a secondary player, but a key piece in the evolution of ATTR-CM. But the message is broader: in all heart failure conditions, and particularly in those with preserved ejection fraction, RV function is a major determinant of outcome. Incorporating its routine assessment not only enriches our understanding of the disease, but can also translate into more timely and beneficial decisions for our patients. (4)

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

REFERENCES

1. Elissamburu P, Spaccavento A, Ballari F, Burgos L, Conde D, Vivas M et al. Right ventricular function and prognosis in patients with transthyretin amyloid cardiomyopathy. Rev Argent Cardiol 2025;93:186-91. https://doi.org/10.7775/rac.v93.i3.20896
2. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2016;18:1472–87. https://doi.org/10.1002/ejhf.630
3. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 2014;35:3452–62. https://doi.org/10.1093/eurheartj/ehu193
4. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol. 2023;9;81:1810-34. https://doi.org/10.1016/j.jacc.2023.01.049

AUTHORS' REPLY

We thank Dr. Guillermo Liniado for his valuable comments on our recently published work. We fully agree on the importance of systematically evaluating right ventricular function in transthyretin amyloid cardiomyopathy.

Our study showed that decreased TAPSE is independently associated with mortality, hospitalization for heart failure, and the onset of atrial fibrillation, even after adjusting for NT-proBNP and troponin. This independence suggests that TAPSE provides complementary prognostic information, which we consider a relevant finding for clinical practice.

We recognize, as Dr. Liniado rightly points out, the need to validate its incremental value in multivariable models that include biomarkers and other clinical variables. We also agree that its simplicity and reproducibility make it an accessible tool for risk stratification and guiding therapeutic decisions.

We reiterate our gratitude for your observations, which enrich the debate and promote comprehensive evaluation of the right ventricle in this complex disease.

The authors

How Helpful Is a Risk Score Actually?

¿Cuánto nos ayuda realmente un score de riesgo?

PAULA PÉREZ TERNS[1, MTSAC]

The article by Lobo et al. in the last issue of the Argentine Journal of Cardiology (1) presents an uncomfortable truth: in patients with type 2 diabetes, cardiovascular risk scores are not always consistent and do not provide equivalent information. In this cohort of patients in primary prevention, the authors observed different results after using various calculators. Depending on the model, between 10% and 70% of patients were considered to be at high risk. What do clinicians do with that information?

The discordance between tools is more than a statistical problem. This is a practical issue: which patients should receive more intensive treatment? In which patients should I be more aggressive in managing their lipids or in choosing antidiabetic drugs with cardiovascular benefits? This study shows that, although there is good correlation between scores, the actual concordance (defined as the agreement in the final classification) is low. This leaves us, once again, relying on clinical judgment as our compass.

Diabetes is not a uniform condition, but rather one with different phenotypes and clinical courses. Most

Rev Argent Cardiol 2025;93:316-317. https://doi.org/10.7775/rac.v93.i4.20922

Correspondence: Paula Perez Terns. Email: paulaperezterns@gmail.com

[1] Department of Cardiology, Sanatorio Anchorena, Autonomous City of Buenos Aires, Argentina

importantly, the cardiovascular risk associated with diabetes varies from person to person. For years, it was assumed that type 2 diabetes mellitus was a heart disease equivalent. Today we know that this is a dangerous simplification. However, we have moved to the opposite extreme, where scores have become increasingly complex, incorporating dozens of variables... and yet there is still a lack of consensus. (3)

In this context, the search for subclinical disease, such as carotid atheromatosis, which was evaluated in this study, makes sense again. Finding a plaque in an "intermediate" risk patient may justify more aggressive interventions. (4) Conversely, if a patient has no other risk factors and shows no signs of vascular damage, we can be more cautious.

The message is clear: scores help, but they do not decide for us. In the meantime, while we await a simple, locally calibrated, and pragmatic model, we go on doing our best: listening to patients, reviewing their medical records, interpreting their exams, and making decisions collaboratively. Sometimes, this can be more valuable than any algorithm. (5)

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

REFERENCES

1. Lobo LM, Masson W, Molinero GB, Giunta G, Lavalle Cobo A, Masiello C, et al. Cardiovascular Risk Assessment in Primary Prevention in Patients with Type 2 Diabetes: Comparison of Multiple Scores and Detection of Subclinical Atheromatosis. Rev Argent Cardiol 2025;93:202-12. https://doi.org/10.7775/rac.es.v93.i3.20899

2. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med 2009;26:142-8. https://doi.org 10.1111/j.1464-5491.2008.02640.x.

3. Dziopa K, Asselbergs FW, Gratton J, Chaturvedi N, Schmidt AF. Cardiovascular risk prediction in type 2 diabetes: a comparison of 22 risk scores in primary care settings. Diabetologia. 2022;65:644-56. https://doi.org/10.1007/s00125-021-05640-y.

4. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010;55:1600-7. https://doi.org/10.1016/j.jacc.2009.11.075.

5. Liu J, Tang W, Chen G, Lu Y, Feng C, Tu XM. Correlation and agreement: overview and clarification of competing concepts and measures. Shanghai Arch Psychiatry. 2016;28:115-20. https://doi.org/10.11919/j.issn.1002-0829.216045

AUTHORS' REPLY

We greatly appreciate your thorough review and valuable feedback on our work. We fully agree that the heterogeneity of cardiovascular risk scores in patients with type 2 diabetes poses a challenge not only in terms of methodology, but also for decision-making in clinical practice. It is noteworthy to mention that risk scores depend on the population in which they were developed, which may affect their applicability and accuracy in different contexts. The variability of the same risk score across different populations is not a new issue. Brindle et al. addressed this problem by comparing the Framingham risk score among 71 727 patients in 27 studies. This reflects the difficulty of applying a risk score to a population other than the one in which it was developed. (Brindle P., Beswick A., Fahey T., Ebrahim S. Heart 2006;92:1752-1759).

As previously mentioned, the differences between the various tools require physicians to integrate evidence with clinical judgment, the patient's individual history, and, to a growing extent, the search for markers of subclinical damage. We believe this is a key point: cardiovascular risk scores are a useful tool for coordinating the use of resources, but they do not replace comprehensive assessment or shared decision-making. Rather, they complement these processes.

We also agree with the observation on how the paradigm has evolved, starting from the idea that all type 2 diabetes cases are a heart disease equivalent (NCEP ATP III, JAMA, 2001; 285: 2486–2497; SAC Consensus on Cardiovascular Prevention, Rev. Argent. Cardiol. 2020;88:9–3), to the current situation in which the complexity of the models does not always translate into clear utility in clinical practice. In this scenario, the identification of carotid plaques or other indicators of subclinical vascular disease may provide additional clinically relevant criteria for personalizing treatment intensity.

As the recent consensus statements of the Argentine Society of Cardiology have recommended, risk stratification should consider not only available scores but also the assessment of markers of subclinical vascular damage, particularly in patients with type 2 diabetes in primary prevention. (SAC Consensus Statement on Cardiovascular Prevention. Rev Argent Cardiol. 2020;88:9-3; Rev Argent Cardiol. 2024;92:F-19). Both documents underscore the need to move toward simpler models that are calibrated to our population and useful for daily clinical practice, in line with the considerations outlined in the letter.

In short, the discussion raised in your letter enriches the debate and reinforces the need to move towards simpler prediction models that are better calibrated to local populations and, most importantly, can be effectively implemented in daily practice. Meanwhile, and as is well emphasized, the combination of science, clinical experience, and dialog with the patient remains our most robust tool.

Yours sincerely,

The authors

The Need for a Strategic Plan at SAC for the Coming Years

La necesidad de un plan estratégico en SAC para los próximos años

Reviewing the history of our Society and its evolution ignites our understanding of why we exist and what our mission and vision are. Since its origin, the SAC has been able to adapt to the times, merging research, teaching, and clinical care to serve the cardiovascular health of the country. This journey reminds us that our strength lies not only in who we are today, but in the path we have built to face the challenges of tomorrow.

As an inspiration and model, we remember the Royal Society, established in 1660, the oldest scientific society in the world. Its motto, "Nullius in verba" — on no one's word— sums up a philosophy that guided researchers to seek the truth through experimentation and evidence, not authority or tradition. That attitude of well-understood skepticism and constant verification is what we want to embody at the SAC: a commitment to truth, transparency, and continuous improvement that serves the cardiovascular health of our population.

Since its inception, the SAC has evolved from a journal to a scientific society linked to universities and public hospitals in Buenos Aires, Córdoba, and Rosario. Throughout Argentine history, we have been able to adapt to contexts of great social upheaval, maintaining cooperation between public and private health care, and often advancing practices and ideas in the region. This legacy requires us to review our actions for the coming years in light of the current paradigm shifts in science and society.

At the 2025 ESC Congress in Madrid, the SAC was recognized as the first scientific society affiliated with the European Society of Cardiology in 2005, a decision made by Dr. Daniel Piñeiro. This recognition is not simply a badge of honor: it is tangible proof that our increasingly ambitious and coordinated strategic decisions have had an impact over time. It invites us to look ahead with the same conviction: to turn evidence, experience, and innovation into actions that improve the cardiovascular health of all Argentineans.

With this in mind and with this vocation, in recent months, after multiple meetings with SAC strategic leaders at the national level, we have identified global and local scenarios that require robust planning: population aging, acceleration of diagnostic and therapeutic innovations, and the emergence of artificial intelligence in clinical practice, teaching, and research. In Argentina, the arrival of new technologies coexists with structural challenges: insufficient infrastructure, inequities in access, and a heterogeneous, fragmented, and underfunded healthcare system. These realities require a strategic vision to guide decisions, prioritize investments, and strengthen the impact of our work.

Our mission and vision—to be a non-profit public welfare association committed to improving cardiovascular health in the country; and to be a leader in cardiovascular health training and information, promoting good practices, constant updating, and the integration of technological advances with emphasis on equity and sustainability in the health system — compel us to go beyond clinical cardiology. We want to participate in improving the organization, financing, and rational use of health system resources, focusing on health priorities.

The strategic plan (SP) we are developing, which we will present at the 51st SAC Congress in October, has a horizon of three government terms. It is a guiding framework for decisions, actions, and investments. It is not a detailed document that limits each member; it is a consensus framework to improve decision-making, organizational efficiency, and the SAC's contribution to the country's cardiovascular health.

We are adopting a participatory approach: developed by the Presidency, with the collaboration of the Board of Directors and leaders from different functions and regions, through workshops and working meetings. We seek coherence and consistency, aligning actions across three administrations, and we place ethics and equity at the center of all lines of action.

Our commitment is articulated in three areas that guide each step: Education, Research, and SAC Membership. In Education, we want to create and strengthen the Institute of Continuing Medical Education, a precursor to the SAC University Institute; generate and transmit knowledge in medical sciences and cardiology, prioritize professional development and education focused on patient benefit, and continue to position the SAC as a benchmark in training, knowledge generation, and technological development

Rev Argent Cardiol 2025;93:318-319. http://dx.doi.org/10.7775/rac.v93.i4.20925

at national and international levels.

In Research, we aim at developing scientific knowledge that improves clinical practice and human resources training; to generate national data and statistics on cardiovascular health; to consolidate a methodology that represents the reality of our country; and to continue promoting multicenter registries and the participation of research centers throughout the territory on an ongoing basis.

In the SAC Members Area, we propose a training program for leading cardiologists to professionalize leadership and management, preparing them for the advancement of new technologies, globalization, and new challenges.

The strategic plan is not a luxury: it is an indispensable tool for guiding efforts, optimizing resources, and raising the quality of cardiovascular health in Argentina. With a clear framework, committed leadership, and a culture of continuous improvement, we can face the challenges and take advantage of the opportunities offered by scientific and technological progress.

Pablo Stutzbach MTSAC,
President of the Argentine Society of Cardiology