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Summary

EDITORIAL

Delirium in Cardiac Surgery: The Brain, That Organ We Must Not Overlook

Delirio en cirugía cardíaca: el cerebro, ese órgano que no debemos olvidar

JULIO GIORGINI[1]

Delirium is a common condition, particularly in elderly patients admitted to intensive care units. In addition to age, loss of sleep-wake rhythms, prolonged exposure to artificial light, spending days in a monotonous and depersonalized environment, and the use of sedative drugs—both for procedures and for the treatment of anxiety—are well-recognized predisposing factors. In many cases, these interventions could be avoided or mitigated through more active communication with patients or more open models of care that encourage family contact. All these factors are so well known and common, that those who work in critical care units can often predict, upon admission to the area, which patients are likely to become disoriented during their hospitalization.

If we add cardiac surgery to this context, in which sedation, extracorporeal circulation, alterations in the internal milieu, anemia, fluid overload, systemic inflammation, and mechanical ventilation converge, the onset of delirium is no longer a remote possibility. The problem is that delirium is not a simple disorder of consciousness: it is the clinical expression of a vulnerable brain exposed to systemic aggression, and its onset marks a prognostic turning point, with a proven impact on mortality, persistent cognitive impairment, and use of healthcare resources. (1–3)

In cardiac surgery, this vulnerability is further enhanced. Extracorporeal circulation, systemic inflammatory response, hemodynamic fluctuations, deep sedation, and advanced age create a particularly fertile ground for acute brain dysfunction. (4,5) However, despite this accumulated knowledge, delirium remains a paradoxical entity: it is clinically relevant, extensively studied, and at the same time underdiagnosed and often poorly treated.

In this issue of the Argentine Journal of Cardiology, Crippa et al. present the results of the multicenter ARGEN-CCV registry, which analyzes the incidence and predictors of delirium in more than 1500 patients undergoing cardiovascular surgery in our country. (6) The study reports an overall incidence of 9.1% and identifies coronary artery disease, postoperative sepsis, postoperative atrial fibrillation, and prolonged mechanical ventilation as independent predictors, with a risk model of adequate discriminatory power. This is a local, multicenter evidence with a sample size unprecedented for our region.

The international literature on cardiac surgery describes incidences that can reach 30%, with extremely wide ranges depending on the type of surgery, the population age, and, fundamentally, the diagnostic method used. (7,8) This variability is not a minor methodological detail, but rather highlights that delirium is an entity that is deeply dependent on how it is sought.

When we look beyond cardiac surgery, the discrepancy becomes even more evident. In common intensive care units, delirium affects the majority of patients on mechanical ventilation, with incidences exceeding 60–70% when systematic detection tools are used. (1,2) Even in non-ventilated patients, the figures rarely fall below 20–30%. In coronary or cardiac critical care units, contemporary studies describe incidence rates of delirium in the range of 14–20%, even in populations with a lower surgical burden than cardiac surgery. (9,10)

Non-cardiac surgery, major abdominal procedures, orthopedic surgery, and, in particular, hip fractures show incidences ranging from 10% to 37%, depending on age and the diagnostic methodology used. (8, 11–13) From this perspective, the 9.1% reported by the ARGEN-CCV registry is clearly at the lower end of what has been published.

This discrepancy should not be interpreted as a difference attributable to the type of patient or pro-

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cedure performed, but rather, as the authors themselves point out, as a methodological problem. In the ARGEN-CCV registry, the diagnosis of delirium was based on clinical identification by the treating teams, without the systematic application of validated tools such as CAM-ICU or ICDSC. (6) The accumulated experience in critical care is compelling: delirium that is not actively investigated may not be detected, (1,3) especially in its hypoactive forms, which are frequent and clinically relevant.

The risk factors identified by Crippa et al. show clear pathophysiological consistency. Postoperative sepsis, prolonged mechanical ventilation, and postoperative atrial fibrillation emerge as robust markers. (6–8) Sepsis represents the paradigm of inflammatory encephalopathy, where endothelial dysfunction, microvascular alterations, and neuroinflammation converge to compromise brain function. (14) Prolonged mechanical ventilation condenses deep sedation, sleep deprivation and immobility, all recognized triggers of delirium. (1,2) Postoperative atrial fibrillation, often interpreted as an electrical complication, can also be read as a marker of systemic inflammation and hemodynamic instability, an association confirmed in recent meta-analyses. (7)

Thus, delirium does not appear as an isolated event, but as the clinical result of a cascade of metabolic and organic dysfunction. Although frailty did not reach full statistical significance in Crippa's work, it summarizes neurological vulnerability and lower physiological reserve and has been consistently associated with an increased risk of postoperative delirium. (15)

The main merit of the ARGEN-CCV registry lies not only in the figures reported, but also in the discussion it enables. Incorporating systematic detection of delirium as part of standard care would allow for more accurate estimation of its actual incidence, evaluation of preventive strategies, optimization of sedative use, and improvement of cognitive outcomes. (1,3,16)

Delirium is not just background noise in the postoperative period, but a clinical sign where there is still ample room for improvement. Optimizing the hospital environment, preserving the sleep-wake cycle, minimizing unnecessary stimuli during the night, encouraging family contact, taking an adequate psychiatric history, using validated diagnostic tools, and forming interdisciplinary teams dedicated to the neurocognitive care of cardiovascular patients (16) are necessary steps if the incidence of delirium in the postoperative period of cardiac surgery is to be reduced.

Conflicts of interest

None declared

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EDITORIAL

Prognostic Stratification in Chagas Cardiomyopathy: Precision Medicine Adapted to the Local Real-World Setting

Estratificación pronóstica en cardiopatía chagásica: hacia una medicina de precisión adaptada a la propia realidad

LUIS EDUARDO ECHEVERRÍA[1,2]

> *"..... The world was so recent that many things lacked names, and to mention them, it was necessary to point at them with a finger."*
> **One Hundred Years of Solitude.**
> **Gabriel García Márquez**

Until Carlos Chagas identified it just over a century ago, the disease caused by the flagellate protozoan *Trypanosoma cruzi* had no name. Although anthropological evidence documents the presence of Chagas disease (CD) in the Americas for more than nine millennia, (1) the first documented clinical case in Argentina was recorded only 100 years ago. (2) Renowned local scientists, such as Salvador Mazza and Cecilio Romaña, made fundamental contributions to the global epidemiological understanding of the infection. (3) The subsequent description of the chronic cardiac form of the CD consolidated its public health impact. (4) Today, barely a century later, Argentina remains one of the major global epicenters of the disease and, according to most estimates, ranks as the country with the second highest number of cases worldwide. (5)

CD represents one of the most complex and persistent challenges in cardiology in Argentina and the rest of Latin America, and its most feared complication, chronic Chagas cardiomyopathy (CCC), is associated with higher mortality than that observed in other causes of heart failure, (6) which places a considerable burden on health systems, particularly in resource-limited settings. (7) This excess mortality is driven by complex pathophysiological mechanisms, including persistent myocardial inflammation, extensive fibrosis, autonomic dysfunction, and malignant ventricular arrhythmias. (8) In this context, appropriate risk stratification is not merely an academic exercise, but rather a central tool for defining the intensity of follow-up, prioritizing interventions, and optimizing resource allocation.

Establishing the prognosis of CCC has historically been challenging. The indeterminate phase may last for years, and the transition to clinical disease occurs with marked variability in structural, arrhythmic, and functional phenotypes. In this context, although prognostic models are available, their performance tends to decline when applied to populations different from those in which they were developed, particularly in terms of calibration and clinical utility. A paradigmatic example is the Rassi score, derived from a Brazilian cohort, which was published more than two decades ago and remains the most widely used model in clinical practice, demonstrating adequate discriminatory capacity in certain populations. (9) Despite this, it has relevant limitations that constrain its current applicability. It was developed in a historical context in which both the therapeutic arsenal and the availability of devices were considerably more limited; therefore, it does not incorporate the impact of contemporary management strategies. Furthermore, it relies on tools currently considered suboptimal for cardiovascular assessment, such as chest radiography for the evaluation of cardiomegaly. Finally, and perhaps most importantly, its application in other countries and healthcare systems across the region cannot be assumed to be universal or automatic but rather requires rigorous external validation before widespread adoption. In this scenario, validation of the model in the rest of Latin America or the development of a region-specific score emerge as a necessary alternative.

In this issue of the Argentine Journal of Cardiology, María Carvelli and colleagues opt for the latter

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approach and present a prognostic stratification tool developed specifically for the local context: the Argen-CHAG score. (10) This model was derived and validated in a contemporary cohort of 603 adults with serological tests positive for CD treated within the public health system of the City of Buenos Aires, of whom 422 comprised the derivation cohort and 181 the validation cohort. During a median follow-up of 6.6 years, the score demonstrated robust predictive capacity for all-cause mortality over the medium and long term. The score was constructed using three independent predictors: age, left ventricular ejection fraction, and history of implantable cardioverter-defibrillator (ICD) placement, identified through multivariate analysis and weighted according to their prognostic contribution. The selection of these variables is not based solely on statistical criteria but rather coherently reflects the main pathophysiological determinants of CCC, integrating the impact of cumulative structural myocardial damage, the temporal progression of the disease, and the presence of a malignant arrhythmic substrate associated with a high risk of fatal outcomes.

Despite its remarkable simplicity, the Argen-CHAG score demonstrated high and consistent discriminatory capacity in both the derivation and validation cohorts, with areas under the curve greater than 0.8 for the prediction of 5- and 8-year mortality. Stratification into three risk categories allowed the identification of clearly differentiated mortality gradients, ranging from a favorable prognosis in low-risk patients to extremely high mortality in those classified as high risk. This robust and reproducible performance reinforces the clinical value of the model and its potential usefulness in routine clinical practice.

However, several weaknesses should be acknowledged. The score was derived from a single-center retrospective study within the public healthcare system, which entails an inherent risk of residual confounding, selection bias, and limitations related to historical data. Although the cohort is representative of real-world clinical practice, this limits its immediate generalizability to other settings. Furthermore, although the model has robust internal validation, it has not yet been evaluated in external cohorts, particularly from other national centers, making a subsequent multicenter validation phase desirable before widespread adoption. Finally, the inclusion of a history of ICD placement should be interpreted with caution, as it likely reflects the underlying severity of the disease and the presence of a malignant arrhythmic substrate rather than an independent causal effect on mortality.

Despite these considerations, the Argen-CHAG score marks a milestone in Chagas cardiomyopathy research and stands as a benchmark for the region. In this way, unlike the protagonists of García Márquez's masterpiece, populations historically condemned to a hundred years of solitude and oblivion now have a new tool for risk stratification and, perhaps, a second chance on Earth.

Conflicts of interest

None declared

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ORIGINAL ARTICLE

Postoperative Delirium in Cardiovascular Surgery: Analysis of Predictive Factors Based on the ARGEN-CCV National Registry

Delirium postoperatorio en cirugía cardiovascular: análisis de factores predictores a partir del registro nacional ARGEN-CCV

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ABSTRACT

Background: Delirium is a common and potentially preventable complication in the postoperative period following cardiovascular surgery (CVS). Its onset is associated with poorer clinical outcomes, such as longer hospital length of stay and higher mortality. Internationally, delirium in the postoperative context of cardiovascular surgery has been extensively studied in multicenter cohorts and observational studies, with varying prevalences. In Argentina, we have previous registries of CVS, but despite this, this complication has not been explored in depth.
Objective: The aim of this study was to analyze the incidence of postoperative delirium following CVS and to identify predictors that contribute to its development.
Methods: We conducted an analysis of the Argentine National Registry of Cardiovascular Surgery (ARGEN-CCV), a cross-sectional, multicenter study spanning 13 months from July 2021 to August 2022. Patients were recruited from 48 public and private centers. Data from consecutive patients aged 18 years or older admitted for central CVS were analyzed. Surgeries for congenital heart defects and peripheral vascular surgery were excluded from the registry. The diagnosis of delirium was based on clinical assessment. Univariate and multivariate analyses were performed to define independent predictors of delirium onset.
Results: A total of 1515 patients were included in the analysis with an incidence of delirium of 9.1%. Patients with delirium were older (68 vs. 64 years, p<0.001) and had a higher prevalence of chronic obstructive pulmonary disease (COPD), alcoholism, and frailty, as well as a higher incidence of postoperative atrial fibrillation (AF). On multivariate analysis, coronary artery disease (OR 1.64; 95% CI: 1.02–2.64; p=0.041), postoperative sepsis (OR 3.13; 95% CI: 1.65–5.96; p<0.001), postoperative AF (OR 2.07; 95% CI: 1.29–3.32; p=0.003), and prolonged mechanical ventilation (OR 2.86; 95% CI 1.68–4.86; p<0.001), were identified as independent predictors of delirium, while frailty showed a trend (OR 2.16; p=0.068). A predictive model was constructed using these variables, which demonstrated good discrimination, with an area under the curve (AUC) of 0.76 (95% CI: 0.71–0.80) and excellent calibration (Hosmer-Lemeshow test with p value = 0.999).
Conclusions: Postoperative delirium occurs in 9.1% of patients undergoing cardiovascular surgery in our series. Coronary artery disease, postoperative AF, and prolonged MV were identified as predictors for the development of delirium.

Keywords: Delirium - Cardiovascular surgery - Atrial fibrillation - Sepsis - Mechanical ventilation - Risk factors

RESUMEN

Introducción: El delirium es una complicación frecuente y potencialmente prevenible en el postoperatorio de la cirugía cardiovascular (CCV). Su aparición se asocia a peores resultados clínicos como mayor estadía hospitalaria y mayor mortalidad. A nivel internacional, el delirium en el contexto posquirúrgico de CCV ha sido ampliamente estudiado en cohortes multicéntricas y estudios observacionales, con prevalencias variables. En Argentina contamos con registros previos de CCV, pero a pesar de ello esta complicación no fue explorada en profundidad.
Objetivo: Investigar la incidencia de delirium en el postoperatorio de CCV y explorar variables predictoras de su aparición.

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Material y métodos: Se realizó un subanálisis del Registro Nacional de Cirugía Cardiovascular en Argentina (ARGEN-CCV), un estudio multicéntrico, prospectivo, de corte transversal, de 13 meses de duración, entre julio de 2021 y agosto de 2022, donde participaron 48 centros públicos y privados de Argentina. Se analizaron datos de pacientes consecutivos mayores de 18 años, internados para llevar a cabo una CCV central. Se excluyeron procedimientos periféricos y cirugías de cardiopatías congénitas. El diagnóstico de delirium fue clínico. Se realizaron análisis uni y multivariado mediante regresión logística, para definir predictores independientes de la aparición de delirium.
Resultados: Se incluyeron en el análisis 1515 pacientes; la incidencia de delirium fue de 9,1%. Los pacientes con delirium fueron mayores (68 vs 64 años, p<0,001) y presentaron mayor prevalencia de EPOC (enfermedad pulmonar obstructiva crónica), alcoholismo y fragilidad, y mayor incidencia de FA (fibrilación auricular) postoperatoria. En el análisis multivariado, se identificaron como predictores independientes de delirium la enfermedad coronaria (OR 1,64; IC95%: 1,02–2,64; p=0,041), la sepsis postoperatoria (OR 3,13; IC95%: 1,65–5,96; p<0,001), la FA postoperatoria (OR 2,07; IC95%: 1,29–3,32; p=0,003) y la ARM (asistencia respiratoria mecánica) prolongada (OR 2,86; IC95% 1,68–4,86; p<0,001), con tendencia para la fragilidad (OR 2,16; p=0,068). Con estas variables se construyó un modelo predictivo que mostró buena discriminación (área bajo la curva, ABC, 0,76; IC95%: 0,71–0,80) y excelente calibración (Hosmer-Lemeshow p = 0,999).
Conclusión: El delirium postoperatorio afecta al 9,1% de los pacientes sometidos a cirugía cardiovascular en nuestra serie. Las variables que fueron identificadas como predictores para el desarrollo de delirium fueron la enfermedad coronaria, la FA postoperatoria y la ARM prolongada.

Palabras clave: Delirium - Cirugía cardiovascular - Fibrilación auricular – Sepsis - Asistencia respiratoria mecánica - Factores de riesgo.

INTRODUCTION

Delirium is a common and potentially preventable complication in the postoperative period of cardiovascular surgery (CVS). Postoperative delirium is defined as an acute disorder characterized by changes in attention, cognition and consciousness that occur during the postoperative recovery period. Its occurrence is associated with worse clinical outcomes, as longer length of hospital stay and higher mortality. It is a common but often underestimated clinical challenge in this context. (1) Despite advances in medical and surgical care, the incidence of delirium remains high, (2) which results in adverse clinical consequences for patients and economic consequences for the healthcare system. (3)

Delirium after cardiovascular surgery has been the subject of extensive international research. Multicenter cohorts and observational studies have reported prevalences ranging from 11.3% to 51.6%, depending on the population, type of surgery, and diagnostic method used. (4) According to the initial reports, several factors were identified as contributing to the development of delirium, including advanced age, baseline cognitive impairment, duration of surgery, cardiopulmonary bypass, and complications such as atrial fibrillation (AF) and sepsis. (5-8) These investigations have prompted the development of specific risk scales, such as the PRE-DELIRIC (PREdiction of DELIRium in ICU patients) model, which has been validated in intensive care patients and after CVS, (9) and recommended by international societies, such as the guidelines of the European Society of Anesthesiology, (10) which promote systematic detection and multimodal preventive strategies to mitigate its impact.

Although we have prior registries on CVS in Argentina, this complication has not been thoroughly explored. (11-13)

OBJECTIVE

The aim of this study was to analyze the incidence, risk factors, and outcomes associated with delirium in patients undergoing CVS.

METHODS

We conducted an analysis of the Argentine National Registry of Cardiovascular Surgery (ARGEN-CCV) (14), a cross-sectional, multicenter study spanning 13 months from July 2021 to August 2022. Patients were recruited from 48 public and private centers. The inclusion criteria were patients > 18 years admitted on an elective, urgent, or emergency basis for central CVS. Surgeries for congenital heart defects and peripheral vascular surgery were excluded from the registry. Preoperative, operative, and postoperative data were recorded during the hospitalization period and collected on the REDCap platform. This project was carried out by the Argentine Society of Cardiology, in conjunction with the Argentine College of Cardiovascular Surgeons. The study was registered in ClinicalTrials.gov (NCT0519916).

Diverse studies have examined the predictive variables associated with delirium included in internationally validated risk scores in critical care patients after CVS. (4) These predictors were age, cognitive impairment, the APACHE II (Acute Physiology and Chronic Health Assessment II) score, infection, emergency surgery, type of surgery, preoperative plasma creatinine levels, postoperative urea concentration, use of sedatives or analgesics, history of cerebrovascular disease, EuroSCORE (European System for Cardiac Operating Risk Evaluation), preoperative depression, blood transfusion, metabolic acidosis, alcohol abuse, insomnia, and coma. (9, 15-23)

The ARGEN-CCV database includes the following variables: age, history of cerebrovascular disease, creatinine levels, emergency surgery, type of surgery, alcohol abuse, EuroSCORE, APACHE II score, postoperative urea concentration, transfusions, and postoperative infection.

Ethical considerations

The study was approved by the ethics committee of the Argentine Society of Cardiology.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation, and those with non-Gaussian distribution as median and interquartile range

(IQR) 25%-75%. Qualitative variables were expressed as frequencies and percentages. Comparisons between groups were performed using Student's t-test or Wilcoxon test according to the distribution for continuous data, and 2x2 tables were used, as well as the chi-square test with Yates's correction for continuity for categorical variables. Univariate and multivariate analyses were performed to define independent predictors of delirium with the corresponding odds ratio (OR) and 95% confidence interval (95% CI). Different multivariate models were explored to develop a predictive model for postoperative delirium. Those variables with a p-value < 0.10 in the univariate analysis were included so as not to limit the variables potentially useful in the diagnosis. The Hosmer-Lemeshow test was employed to evaluate the adequacy of the model, and a ROC curve was constructed with the variables obtained to assess diagnostic performance, selecting the one with the optimal discrimination. A p value < 0.05 was considered statistically significant. The analysis was performed in R.

RESULTS

Of the 1515 patients evaluated, the incidence of delirium as a postoperative complication was 9.1% (137 patients). Patients who developed delirium were older (67.5 ± 11 versus 63.6 ± 11.3 years; p<0.001).

The clinical history of patients with and without postoperative delirium is summarized in Table 1. The prevalence of hypertension, smoking habits, peripheral vascular disease, chronic obstructive pulmonary disease, alcohol abuse, recent use of illicit drugs, and frailty was higher in patients with delirium.

The following variables were significantly associated with the development of postoperative delirium: coronary artery disease, combined surgery and median ArgenSCORE values (Table 2). There was no difference in baseline laboratory data. Regarding the intraoperative and postoperative variables, we highlight differences in transfusion requirements, longer cardiopulmonary bypass (CPB) time (105 min. vs. 98 min., p < 0.001), prolonged mechanical ventilation (MV), development of low cardiac output syndrome (LCOS), atrial fibrillation (AF), kidney failure, stroke, sepsis, and total length of hospital stay (medians of 9 vs. 6 days, p < 0.001). All patients who developed delirium received antipsychotic treatment during hospitalization. Seventy-two percent received monotherapy, while 24% were treated with two antipsychotic agents and 4% with three. The most used drugs were quetiapine (55 patients; 40%), haloperidol (54 patients; 39%), and risperidone (20 patients; 15%). In 53 cases (39%), other therapeutic alternatives were used, primarily benzodiazepines (Table 3).

Table 4 presents the univariate logistic regression analysis for the prediction of postoperative delirium, with the variables considered, their OR, 95% CI, and p-values. All variables with a p-value < 0.15 were considered in the multivariate analysis for the construction of different predictive models of postoperative delirium. The following model was found to have adequate predictive performance: postoperative AF (OR 2.07; 95% CI 1.29-3.32; p = 0.0026), prolonged MV (OR, 2.86; 95% CI, 1.68-4.86; p < 0.001), coronary artery disease (OR 1.64; 95% CI 1.02-2.64; p = 0.040), and sepsis (OR 3.13; 95% CI 1.65-5.96; p<0.001) (Table 5).

Although preoperative frailty did not reach statistical significance on multivariate analysis (OR, 2.16; 95% CI 0.94-4.98; p=0.068), we decided to incorporate it into the final model due to its theoretical weight and reproducibility as a predictor of delirium in other models.

The area under the curve for this model was 0.76 (95% CI 0.71-0.80) (Figure 1). The p-value for calibration of the model with Hosmer-Lemeshow test was 0.999.

DISCUSSION

This subanalysis of the ARGEN-CCV registry evaluated the incidence and factors associated with postoperative delirium in patients undergoing CVS in Argentina. Given that this common complication has prognostic impact that is often underestimated, this study attempts to provide evidence on the factors associated with its development. The observed incidence of delirium (9.1%) was close to the lower limit of the 10-51% range reported in international studies. (4)

Through multivariate analysis, risk factors that had already been validated in previous studies were identified, such as previous coronary artery disease and postoperative sepsis. Both factors reflect clinical conditions that can influence patients' inflammatory and hemodynamic status. These elements are considered essential in the pathophysiology of delirium and have been described in previous studies, including those conducted by Sugimura et al. (1) and Smulter et al. (3)

However, two traditionally less prominent variables also emerged as significant predictors on univariate analysis: AF and the need for prolonged MV, which were confirmed as independent predictors through multivariate analysis. These findings could theoretically play a relevant role in the onset of delirium due to their level of association, with OR of 2.07 and 2.86 for AF and prolonged MV, respectively. Should this assertion be consistently confirmed, their inclusion in future predictive scores could improve the sensitivity for detecting patients at risk. Brown et al. (6) have reported similar findings when they reported an association between AF and increased risk of postoperative neurological impairment. Nevertheless, we believe it is prudent to interpret these findings with caution. On the one hand, patients with prolonged MV are more prone to develop infections, kidney injury, and to be exposed to drugs such as opioids and benzodiazepines, and all these situations are associated with the risk of delirium. The association between postoperative AF and delirium through intensified inflammatory mechanisms in the context of surgical trauma is plausible, reinforcing the need to evaluate these factors together rather than in isolation. (24)

Table 1. Baseline clinical characteristics (n = 1515)

	Total		Delirium -		Delirium +		
	N	%	N	%	N	%	p
Patients	1515	100	1368	90.9	137	9.1	
Age, years, mean (SD)	64 (11)		63.6 (11.3)		67.5 (11)		<.001
Male	1122	74.1	1122	74.1	1122	74.1	0.007
Hypertension	1159	76.5	1159	76.5	1159	76.5	0.010
Diabetes Mellitus	436	28.8	436	28.8	436	28.8	0.150
Dyslipidemia	814	53.7	814	53.7	814	53.7	0.280
Active smoking	234	15.4	234	15.4	234	15.4	0.001
Reduced LVEF	243	16.0	243	16.0	243	16.0	0.280
Heart failure	225	14.9	225	14.9	225	14.9	0.260
AMI ≤30 days	157	10.4	157	10.4	157	10.4	0.200
AMI >30 days	190	12.5	190	12.5	190	12.5	0.200
CABG	69	4.6	69	4.6	69	4.6	0.170
Heart valve surgery	83	5.5	83	5.5	83	5.5	0.097
PCI	181	12.0	181	12.0	181	12.0	0.160
Immunosuppression	18	1.2	18	1.2	18	1.2	0.010
Chronic AF	109	7.2	109	7.2	109	7.2	0.260
Family history of CAD	159	10.5	159	10.5	159	10.5	0.010
Peripheral vascular disease	141	9.3	141	9.3	141	9.3	0.009
Pulmonary hypertension	96	6.3	96	6.3	96	6.3	0.060
Cerebrovascular disease	72	4.8	72	4.8	72	4.8	0.080
OSAHS	56	3.7	56	3.7	56	3.7	0.040
Moderate/severe COPD	106	7.0	106	7.0	106	7.0	<0.001
Recent use of illicit drugs	12	0.8	12	0.8	12	0.8	0.008
Alcohol abuse	226	14.9	226	14.9	226	14.9	0.020
Frailty	90	5.9	90	5.9	90	5.9	<0.001
Acetylsalicylic acid	796	52.6	796	52.6	796	52.6	0.120
P2Y12 inhibitor	194	12.8	194	12.8	194	12.8	0.020
Statins	875	57.8	875	57.8	875	57.8	0.330
Beta blockers	878	58.8	878	58.8	878	58.8	0.090
ACEI	436	28.8	436	28.8	436	28.8	0.450
ARB	492	32.5	492	32.5	492	32.5	0.110
Furosemide	207	13.7	207	13.7	207	13.7	0.060
Thiazides	97	6.4	97	6.4	97	6.4	0.450
Spironolactone	108	7.1	108	7.1	108	7.1	0.220
Insulin	94	6.2	94	6.2	94	6.2	0.280
Oral hypoglycemic agents	307	20.3	307	20.3	307	20.3	0.400
Oral anticoagulants	111	7.3	111	7.3	111	7.3	0.360

ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; AMI: acute myocardial infarction; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; OSAHS: obstructive sleep apnea-hypopnea syndrome; PCI: percutaneous coronary intervention; P2Y12 inhibitor: P2Y12 receptor platelet inhibitor

A notable finding is the role of preoperative frailty, which has been strongly linked to adverse events in multiple settings. While the present analysis did not demonstrate a significant association between frailty and postoperative delirium, its systematic evaluation in the context of CVS should be considered, not only due to its growing interest and theoretical basis, but also because it is part of comprehensive patient care,

Table 2. Main preoperative variables

	Total		Delirium -		Delirium +		
	N	%	N	%	N	%	p
Patients	1515	100	1368	90.9	137	9.1	
HF	53	3.5	49	3.6	4	2.9	0.600
Endocarditis	48	3.2	45	3.3	3	2.2	0.600
Acute aortic syndrome	27	1.8	22	1.6	5	2.6	0.650
Valvular heart disease	599	39.6	546	39.6	53	38.7	0.680
Coronary artery disease	933	61.6	834	61.1	99	72.3	0.004
Combined surgery	247	16.3	217	15.9	30	21.9	0.030
Type of procedure							
Elective	1195	78.9	1094	80.0	101	73.7	0.340
Urgency	280	18.5	249	18.2	31	22.6	0.400
Emergency	26	1.7	23	1.7	3	2.2	0.480
Scores							
EuroSCORE, median (IQR)	1.52 (0.93-2.94)		1.46 (0.88-2.83)		1.83 (1.25-3.44)		0.301
ArgenSCORE, median (IQR)	2.33 (1.12-4.78)		2.23 (1.08 - 4.74)		3.34 (1.86-7.31)		0.004

HF: heart failure; IQR: interquartile range

as proposed by Inouye et al., (25) who suggested including frailty as a key element in preventive strategies for delirium.

It is important to note that, although kidney failure did not reach statistical significance on the multivariate model, it has been consistently described as a predictor of delirium in multiple previous studies and should be assessed. (15,18)

In our cohort, all patients who developed delirium received treatment with antipsychotics, predominantly as monotherapy, though a considerable proportion required the administration of two drugs or greater. This finding reflects both the clinical burden of delirium and the complexity of its pharmacological management in the postoperative context of CVS. Although antipsychotics are commonly used to manage symptoms such as agitation or hallucinations, the evidence of their efficacy in delirium is inconclusive. Thus, their use must be balanced against the risk of adverse effects, especially in elderly patients or those with cardiovascular comorbidities. (26) The high frequency of haloperidol and quetiapine use in this series is consistent with standard practices reported in other critical care settings. However, it is necessary to move toward more standardized management strategies focused on non-pharmacological interventions whenever possible. (27)

We did not specifically evaluate the impact of monotherapy vs. the use of more than one drug on delirium duration or length of hospital stay. We consider that this analysis could provide valuable information for future research, given that the profile and combination of drugs could influence clinical evolution and functional recovery.

From a statistical point of view, the model constructed demonstrated good discrimination, with an area under the curve (AUC) of 0.76 (95% CI: 0.71–0.80) and adequate calibration as assessed by the Hosmer-Lemeshow test ($p = 0.999$). These parameters indicate that the model not only discriminates well between patients with and without risk but also predicts events with acceptable accuracy across the entire population analyzed.

Regarding clinical implications, our findings underscore the need for implementing systematic measures to early detect delirium at the local level, as well as multimodal management protocols that integrate AF monitoring, ventilation, and sepsis diagnosis. Furthermore, incorporating variables such as frailty and intercurrent events into future predictive models should be contemplated, as it has the potential to result in more comprehensive and dynamic tools for risk stratification.

Future lines of research should consider prospective models using validated scales, as the CAM-ICU, and explore the impact of preventive interventions in high-risk groups. Furthermore, it would be beneficial to examine the incremental value of incorporating biomarkers of inflammation, as IL-6 (interleukin-6), CRP (C-reactive protein), and NLR (neutrophil-to-lymphocyte ratio) or nervous system function in predictive models of delirium in CVS. (28)

Study limitations

Firstly, it should be noted that the observational and cross-sectional design of the study prevents us from establishing definitive causal relationships between the analyzed factors and the occurrence of delirium.

Table 3. Main intraoperative and postoperative variables

	Total		Delirium -		Delirium +		
	N	%	N	%	N	%	p
Patients	1515	100	1368	90.9	137	9.1	
Intraoperative							
Transfusions	500	33.0	439	32.1	61	44.5	0.002
CPB	1126	74.3	1016	74.3	110	80.3	0.059
CPB time (min), median (IQR)	100 (75-123)		98 (75-122)		105 (85-134.3)		0.007
ACC time (min), median (IQR)	71(50-94)		70 (50-93)		77.5 (60-94)		0.024
Bleeding	100	6.6	86	6.3	4	2.9	0.047
Cardiac arrest	38	2.5	33	2.4	5	3.6	0.190
Return to CPB	28	1.8	22	1.6	6	4.4	0.020
Postoperative							
IABP	24	1.6	20	1.5	4	2.9	0.110
Pulmonary artery catheter	29	1.9	24	1.8	5	3.6	0.070
Inotropic agents	30	2.0	27	2.0	3	2.2	0.400
Prolonged MV	140	9.2	104	7.6	36	26.3	<0.001
Days in MV, median (IQR)	4.5 (2-10)		4 (2-8.3)		7 (3-17)		0.030
Bleeding	159	10.5	140	10.2	19	13.9	0.090
Transfusions	141	9.3	126	9.2	15	10.9	0.090
Right ventricular failure	40	2.6	34	2.5	6	4.4	0.100
Low cardiac output syndrome	235	15.5	194	14.2	41	29.9	<0.001
Perioperative AMI	50	3.3	45	3.3	5	3.6	0.390
Postoperative AF	361	23.8	303	22.1	58	42.2	<0.001
Atrioventricular block	108	7.1	95	6.9	13	9.5	0.130
Ventricular arrhythmia	43	2.8	38	2.8	5	3.6	0.260
Temporary PM	370	24.4	344	25.1	26	19.0	0.053
Permanent PM	42	2.8	35	2.6	7	5.1	0.056
Kidney failure	201	13.3	155	11.3	46	33.6	<0.001
Hemodialysis	61	4	50	3.7	11	8.0	0.140
Stroke	50	3.3	39	2.9	11	8.0	0.002
Fever	131	8.6	102	7.5	29	21.2	<0.001
Sepsis	89	5.9	62	4.5	27	19.7	<0.001
Total length of hospital stay (days) Median (IQR)	6 (5-9)		6(5-8)		9 (6-15.8)		<0.001

AF: atrial fibrillation; AMI: acute myocardial infarction; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump; IQR: interquartile range; MV: mechanical ventilation; PM: pacemaker

Secondly, the diagnosis of delirium was based on the clinical assessment of the treating team, without the systematic use of validated scales such as the CAM-ICU. Therefore, the introduction of classification biases may be possible, and thus explain why the incidence of delirium is lower in this study than that observed in the literature. In addition, the database did not include certain relevant predictors, such as prior cognitive impairment or detailed use of sedatives, which could have introduced confounding variables that were not addressed in the analysis. Finally, although the study included multiple centers nationwide, no adjustments were made for center, and the impact of institutional variability on the detection or treatment of delirium was not explored.

CONCLUSION

Postoperative delirium was found to be a common and relevant complication in patients enrolled in the ARGEN-CCV registry. The proposed model of coronary

Table 4. Univariate logistic regression model

Predictors of delirium	OR	95% CI	p
Hypertension	1.65	0.83-3.25	0.150
Frailty	2.23	0.93-5.31	0.070
Prior coronary artery disease	1.45	0.84-2.53	0.180
Postoperative AF	1.83	1.09-3.09	0.020
Prolonged MV	2.63	1.41-4.75	0.002
Stroke	2.14	0.89-5.03	0.085
Postoperative sepsis	2.82	1.35-5.89	0.006
Peripheral vascular disease	1.67	0.83-3.34	0.150
Kidney failure	1.23	0.65-2.35	0.520

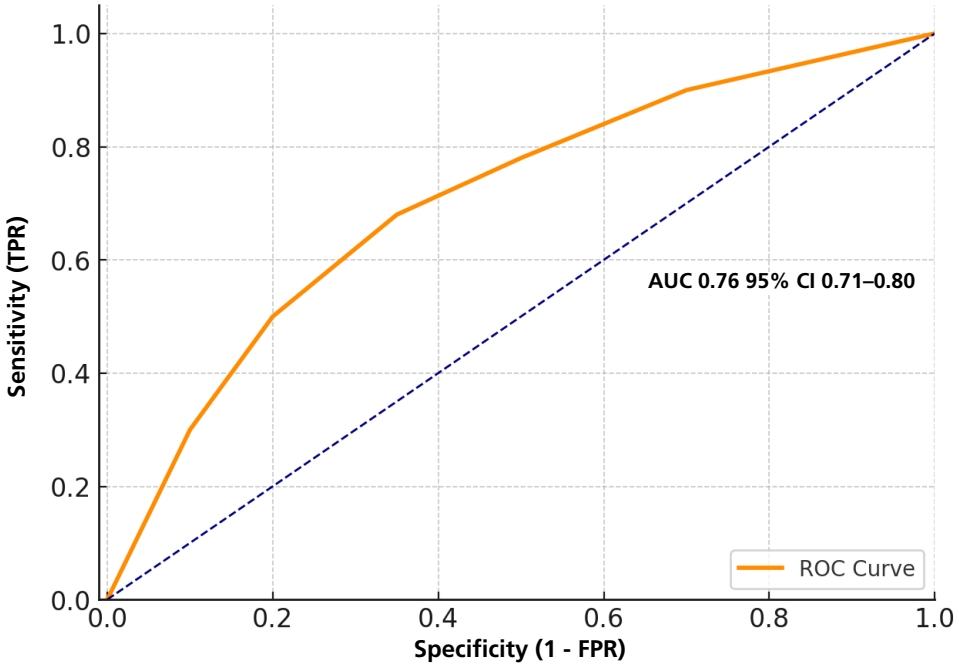
AF: atrial fibrillation; CI: confidence interval; MV: mechanical ventilation; OR: odds ratio

Table 5. Multivariate logistic regression model

Predictors of delirium	OR	95% CI	p
Prior coronary disease	1.64	1.02 – 2.6	0.04
Postoperative sepsis	3.13	1.65 – 5.96	<0.001
Postoperative AF	2.07	1.29–3.32	<0.001
Prolonged MV	2.86	1.68–4.86	<0.001
Frailty	2.16	0.94 – 4.98	0.068

AF: atrial fibrillation; CI: confidence interval; MV: mechanical ventilation; OR: odds ratio

Figure 1. ROC curve showing the discrimination ability of the model to predict postoperative delirium after cardiovascular surgery



AUC: 0.76;95% CI 0.71–0.80; AUC: area ander curve; FPR: false positive rate; TPR: true positive rate

artery disease, sepsis, AF, MV, and frailty as predictors of postoperative delirium showed adequate diagnostic performance. While not significant, frailty warrants particular consideration due to its potential clinical implications. These findings could guide early detection and preventive intervention strategies in high-risk surgical populations.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Development of a Prediction Model for Mortality in Patients with Positive Serology for Chagas Disease: Argen-CHAG Score

Desarrollo de un modelo de predicción para mortalidad en pacientes con serología positiva para Chagas: score Argen-CHAG

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ABSTRACT

Background: Infection with *Trypanosoma cruzi*, the etiological agent of Chagas disease, is endemic in 21 countries in the Americas and affects more than 7 million people. With an annual incidence of 30 000 cases and 12 000 deaths, it remains a critical public health challenge. Despite its impact, prognosis remains difficult to establish, and the predictive tools available are limited and poorly validated. Although Rassi et al. developed a mortality prediction model in Brazil, there are significant differences in cardiac involvement between Brazil and Argentina, so there are no validated models for the Argentine population.
Objectives: This study aimed to evaluate predictors of long-term mortality in the population infected with *Trypanosoma cruzi* who attend a public hospital in the city of Buenos Aires, and to develop a prognostic score for this population.
Methods: It included patients aged over 18 years with positive serology for Chagas disease who were evaluated at the Cardiology Division Chagas Program of a public hospital in Buenos Aires. Participants underwent clinical evaluation, ECG, echocardiography, and 24.h Holter monitoring. Follow-up data were obtained by reviewing the Unified Medical Records of the City of Buenos Aires and through telephone interviews with patients or relatives.
A derivation group was established assessing prognostic clinical, electrocardiographic and echocardiographic variables related with time to death using a Cox proportional hazards model. Independent predictors of mortality were identified and a score was generated which was subsequently applied to a validation group. The model's predictive capacity for 5- and 8-year mortality was evaluated using ROC curves.
Results: Among a total of 603 patients, 422 were assigned to the derivation group and 181 to the validation group. During a median follow-up of 6.6 years, 63 deaths in the derivation group and 20 in the validation group were observed. Three independent predictors were found: age, left ventricular ejection fraction (these two variables were rescaled into several categories), and history of implantable cardioverter-defibrillator. Each was assigned a score proportional to the hazard ratio.
A risk score was calculated for each patient and divided into three categories: 1) low risk: score 0-4 points, 2) moderate risk: score 5-12 points, and 3) high risk: score ≥ 13 points.
Survival was 12.5% at 6.3 years in the high-risk group, 67% at 8.75 years in the moderate-risk group, and 92% at 8.7 years in the low-risk group. The area under the curve for predicting death was 0.89 and 0.85 at 5 and 8 years, respectively.
Conclusion: The risk score proved highly effective, as it presented high prognostic accuracy based on only three predictors, which are easily accessible in clinical practice. This tool could contribute significantly to risk stratification and decision-making in resource-limited settings, especially in regions where the disease is endemic and existing models do not adequately reflect the local characteristics of the population.

Key words: Chagas - mortality - score - prognosis

RESUMEN

Introducción: La infección por *Trypanosoma cruzi*, agente causal de la enfermedad de Chagas, es endémica en 21 países de América y afecta a más de 7 millones de personas. Con una incidencia anual de 30 000 casos y 12 000 muertes, representa un problema de salud global. A pesar de su impacto, el pronóstico sigue siendo difícil de establecer y las herramientas predictivas disponibles son limitadas y poco validadas. Aunque Rassi et al. desarrollaron un modelo de predicción de mortalidad en Brasil, existen diferencias significativas en la afectación cardíaca entre Brasil y Argentina, por lo que no hay modelos validados para población argentina.

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Objetivos: Evaluar predictores de mortalidad a largo plazo en población infectada por *Trypanosoma cruzi* que concurre al hospital público en la Ciudad de Buenos Aires, y desarrollar un score pronóstico para esta población
Material y métodos: Se incluyeron todos los pacientes mayores de 18 años con serología positiva para Chagas que consultaron al Programa de Chagas del Servicio de Cardiología de un Hospital Público de la Ciudad de Buenos Aires. Se les realizó evaluación clínica, ECG, ecocardiograma y Holter. El seguimiento se efectuó mediante la revisión de la historia clínica unificada del Gobierno de la Ciudad de Buenos Aires y contacto telefónico con los pacientes o sus allegados. Se recolectaron datos de mortalidad.
Se generó un grupo de derivación en el que se evaluó el valor pronóstico de variables clínicas, electrocardiográficas y ecocardiográficas en relación con el tiempo a la muerte mediante el modelo de riesgos proporcionales de Cox. Se generó un score con los predictores independientes, que se aplicó en un grupo de validación. La capacidad predictiva del modelo en relación con la mortalidad a 5 y 8 años se evaluó mediante la curva ROC
Resultados: Se evaluaron 603 pacientes, de los cuales 422 fueron asignados al grupo de derivación y 181 al de validación. Durante una mediana de 6,6 años de seguimiento, se observaron 63 muertes en el grupo derivación y 20 muertes en el grupo validación. Entre los predictores estudiados, se encontraron tres predictores independientes: la edad, la fracción de eyección del ventrículo izquierdo (estas dos variables fueron reescaladas en varias categorías) y el antecedente de portar un cardiodesfibrilador implantable. Se asignó a cada uno un puntaje proporcional al Hazard ratio.
Se calculó el puntaje de riesgo para cada paciente y se dividió al mismo en tres categorías: 1) bajo riesgo: puntaje de 0 a 4, 2) moderado riesgo: puntaje 5 a 12, y 3) alto riesgo: puntaje igual a o mayor de 13 puntos.
Se observó una sobrevida de 12,5 % a 6,3 años en el grupo de alto riesgo, de 67 % a 8,75 años en el de moderado riesgo y de 92 % a 8,7 años en el grupo de bajo riesgo. El área bajo la curva para la predicción de muerte fue de 0,89 y 0,85 a 5 y 8 años respectivamente.
Conclusión: El puntaje de riesgo identificado mostró una gran eficacia, ya que presentó una alta certeza pronóstica basada en solo tres predictores, fácilmente accesibles en la práctica clínica. Esta herramienta podría contribuir significativamente a la estratificación del riesgo y a la toma de decisiones en contextos con recursos limitados, especialmente en regiones donde la enfermedad es endémica y los modelos existentes no reflejan adecuadamente las características locales de la población.

Palabras clave: Chagas - mortalidad - score - pronóstico

INTRODUCTION

Chronic infection with Trypanosoma cruzi, the etiological agent of Chagas disease, remains a critical public health challenge in Latin America. Current estimates suggest that over 7 million people are infected across 21 countries, with an annual incidence of approximately 30 000 new cases, 9000 of which result from vertical transmission. The disease accounts for roughly 12 000 deaths annually and has evolved into a global health threat due to increased migratory patterns. (1-4)

Although the chronic phase can remain asymptomatic for decades, up to 30% of patients eventually develop progressive cardiac complications, including complex arrhythmias, heart failure, dilated cardiomyopathy, and sudden cardiac death. (5-8)

Despite its significant clinical and socioeconomic burden, the prognosis for Chagas disease remains difficult to determine. Existing tools are limited and often lack adaptability to diverse clinical contexts. The Rassi score, developed in Brazil, is the most widely utilized model; however, its applicability outside Brazil is constrained by significant phenotypic and epidemiological variations across endemic regions. (9)

In Argentina, where Chagas remains a leading cause of cardiomyopathy and premature cardiovascular mortality in young adults, a locally calibrated risk model has yet to be established.

OBJECTIVE

The study aimed to identify long-term mortality predictors in a cohort of patients with chronic Trypanosoma cruzi infection at a public hospital in Buenos Aires and to develop a specific prognostic score for this population.

METHODS

This was a retrospective, single-center study. It consecutively included patients ≥18 years of age with confirmed positive serology for Chagas disease who attended the Cardiology Division Chagas Program at a public hospital in Buenos Aires. Each participant underwent a comprehensive evaluation, including clinical history, electrocardiogram (ECG), Doppler echocardiography, and 24-hour Holter monitoring.

Follow-up was performed by reviewing the unified electronic medical records of the Government of the City of Buenos Aires and through telephone contact with patients or their relatives. The primary endpoint was all-cause mortality.

Statistical analysis

Clinical and electrocardiographic variables, as well as echocardiographic left ventricular ejection fraction, were evaluated

To develop the score, patients were randomly divided into two groups a “Derivation” group, from which predictors were identified and selected to build the score, comprising 70% of the subjects, and a “Validation” group that assessed score performance.

Numerical variables are expressed as mean and standard deviation, using Student’s t-test to compare between groups. Categorical variables are expressed as number of cases and the corresponding percentage, using the chi-square test to compare between groups. Time to all-cause death was identified as outcome.

The different variables were evaluated in the derivation group, initially using the univariate Cox regression model, with time to all-cause as outcome and each of the clinical variables, ECG, Holter monitoring and echocardiogram as predictors. All predictors with $p < 0.\ 0.05$ were then used for the joint evaluation of their effect using a multivariate Cox regression model with backward selection strategy in the stepwise regression method. Subsequently, the predictors that in this analysis had an associated $p < 0.05$ were selected to build the score. To optimize score assignment numerical predictors were categorized into discrete groups.

Each independent predictor was assigned a weight proportional to its estimated hazard ratio. The score developed was then stratified into risk categories by estimating survival within the validation group using the Kaplan-Meier method. Finally, the model's predictive performance was assessed through the Area Under the ROC Curve (AUC) for 5- and 8-year mortality

The analyses were performed using the survival (3.8-3 version), survminer (0.5.0 version), and survival ROC (1.0.3.1 version) packages of the R software (4.5.0 version, R Development Core Team/R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki (10) and approved by the institutional Teaching and Research Committee.

RESULTS

Among a total of 603 patients enrolled, 422 were assigned to the derivation group and 181 to the validation group. Mean age was 58 ± 12 years, 63% were female, and mean left ventricular ejection fraction (LVEF) was 56%. Baseline characteristics were comparable across both groups, except for a slightly older age in the validation group (Table 1).

Quantitative variables are presented as mean ± standard deviation, and qualitative variables as n (%)

AF: atrial fibrillation; AVB: atrioventricular block; G: grade; ICD: implantable cardioverter-defibrillator; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LPFB: left posterior fascicular block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

Over a median follow-up of 6.6 years, 63 deaths occurred in the derivation group and 20 deaths in the validation group.

In the derivation group univariate Cox regression analysis, 9 predictors among all the variables

Table 1. Baseline population characteristics

	GROUPS		
	Derivation (n=422)	Validation (n=181)	p
Female	274 (64.9)	114 (62.9)	0.716
Age	59.04 ± 12.30	56.52 ± 12.71	0 .023
NYHA FC			0 .954
1	367 (87.0)	156 (86.2)	
2	44 (10.4)	21 (11.6)	
3	9 (2.1)	3 (1.7)	
4	2 (0.5)	1 (0.6)	
Hypertension	133 (31.5)	49 (27.1)	0.321
Diabetes	49 (11.6)	16 (8.8)	0.388
Smoking	15 (3.6)	2 (1.1)	0.162
Dyslipidemia	37 (8.8)	16 (8.8)	1
Coronary heart disease	0 (0.0)	0 (0.2)	1
LVEF	56.06 ± 13.26	56.94 ± 12.87	0.455
AF	48 (11.4)	13(7.2)	0.156
LBBB	32 (7.6)	7 (3.9)	0.129
RBBB	59 (14.0)	29 (16.0)	0-656
LAFB	70 (16.6)	35 (19.3)	0.485
LPFB	4 (0.9)	1 (0.6)	0.999
AVB 1G	10 (2.4)	6 (3.3)	0.734
AVB 2G Mobitz I	1 (0.2)	0 (0.0)	1
AVB 2G Mobitz II	1 (0.2)	0 (0.0)	1
AVB 3G	2 (0.5)	3 (1.7)	0.328
ICD	27 (6.4)	8 (4.4)	0.446

Quantitative variables are presented as mean ± standard deviation, and qualitative variables as n (%)
AF: atrial fibrillation; AVB: atrioventricular block; G: grade; ICD: implantable cardioverter-defibrillator; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LPFB: left posterior fascicular block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

analyzed were significantly associated with mortality rate. functional class, history of implantable cardioverter-defibrillator (ICD), presence of atrial fibrillation, left bundle branch block, right bundle branch block, ventricular arrhythmias and age were related with increased mortality, while LVEF was inversely proportional to mortality (Table 2).

These variables were included in a multivariate Cox regression model, in which three remained as independent predictors of mortality: age (HR 1.07; 95% CI 1.05–1.09; p<0.001), LVEF (HR 0.94; 95% CI 0.92–0.96; p<0.001) and history of ICD (HR 7.8; 95% CI 1.01–60.2; p=0.049). (Table 3)

Next, the relationship between the continuous predictors LVEF and age was explored in order to divide them into categories that would simplify the construction of the score without affecting its predictive accuracy.

Table 2. Univariate Cox regression analysis u

Predictor	HR	95% CI	p
LVEF	0.93	0.91-0.94	< 0.001
Age	1.08	1.05-1.11	<0.001
NYHA FC	2.19	1.61-2.96	<0.001
ICD	7.78	4.40-13.80	<0.001
AF	3.77	2.17-6.52	<0.001
LBBB	5.55	3.09-9.96	<0.001
RBBB	2.01	1.13-3.59	0.018
Coronary heart disease	6.27	0.87-45.36	0.069
Ventricular arrhythmia	3.14	1.80-5.47	0.001
Supraventricular arrhythmia	0.37	0.13-1.01	0.052
Hypertension	1.22	0.73-2.04	0.441
Diabetes	1.73	0.90-3.31	0.099
Smoking	2.03	0.63-6.50	0.232
Dyslipidemia	1.22	0.52-2.80	0.664
Female gender	0.34	0.20-0.56	<0.001
LAFB	1.74	0.96-3.01	0.066
LPFB	1.42	0.20-10.28	0.726
AVB 1 G	2.21	0.69-7.03	0.183

AF: atrial fibrillation; AVB: atrioventricular block; CI : confidence interval; G: grade; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LPFB: left posterior fascicular block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

Table 3. Multivariate Cox regression analysis

Variable	HR	95% CI	p
LVEF	0.94	0.92–0.96	<0.001
Age	1.07	1.05–1.09	<0.001
NYHA FC	2.19	1.61-2.96	<0.001
1.02	0.64–1.64	0.923	<0.001
ICD	7.86	1.01–60.2	0.049
AF	1.31	0.72–2.38	0.372
LBBB	0.90	0.43-1.90	0.787
RBBB	1.72	0.92-3.24	0.090
Ventricular arrhythmia	0.20	0.03-1.52	0.120

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

Figure 1 shows the survival function in relation to LVEF (A), which appeared to be nonlinear, and age (B), which appeared to be adequately linear. Therefore, the most appropriate partitioning of the LVEF and age scales was designed.

Age was divided into five categories: I) age < 40 years, II) age ≥ 40 years and < 50 years, III) age ≥ 50 years and < 60 years, IV) age ≥ 60 years and < 70 years, and V) age >70 years. It was analyzed as an ordinal scale, that is, the coefficient expresses the effect of changing from one category to the next.

LVEF was divided into four categories based on clinical evidence regarding its behavior in relation to prognosis and response to different treatments: I) LVEF ≥ 53%, II) LVEF < 53% and ≥ 40%, III) LVEF < 40% and ≥ 30%, and IV) LVEF < 30%. It was analyzed as a multinomial scale, that is, the coefficient expresses the effect of each category I in relation to category I (baseline).

Table 4 shows Cox regression results with age and LVEF rescaled variables. Subsequently, the score variables are shown with their corresponding values (Table 5).

Figure 2 shows modeling of the relationship between survival function, time, and score values, where there is a marked difference in survival between the lowest values, with virtually zero mortality, and the highest values, with very high mortality.

The risk score for each patient was then calculated according to the values of each predictor, and the final score was divided into three categories: 1) low risk: score 0 to 4, 2) moderate risk: score 5 to 12, and 3) high risk: score ≥ 13 points. The survival function was calculated in the derivation group to evaluate its discriminatory capacity between risk groups, and in the validation group to evaluate the performance of the score in another similar group.

Figure 3 shows the Kaplan-Meier survival curves for each of the three risk categories defined by the score, both for the derivation group (Figure 3A) and for the validation group (Figure 3B), where the wide difference in survival between the categories and the similar behavior in both groups suggest adequate risk discrimination and reproducibility. In the validation group, consistent with the derivation group, mortality was 87.5% at 6.3 years in the high-risk group, 33% at 8.75 years in the moderate-risk group and only 8% at 8.7 years in the low-risk group (Figure 4)

Figure 5 shows the performance of the model evaluated using the area under the ROC curve (AUC) for all-cause mortality at 5 years. The AUC was 0.82 in the derivation group (Figure 5A) and 0.89 in the validation group (Figure 5B). At 8 years, the AUCs were 0.81 and 0.85, respectively.

DISCUSSION

Our study presents the Argen-CHAG score, developed in a large and representative cohort of patients with positive serology for *Trypanosoma cruzi* treated in the public health system of the City of Buenos Aires. The model was constructed based on three simple and accessible predictors—age, LVEF, and ICD history —and demonstrated excellent prognostic performance, with high and consistent discriminatory ability in both derivation and validation groups.

The score allows patients to be stratified into three clearly differentiated risk categories, with a net and clinically relevant mortality gradient. This classification can be very useful for identifying those who require closer follow-up, therapeutic intensification, or

Fig. 1. Survival probability as a function of LVEF (a) and age (B)

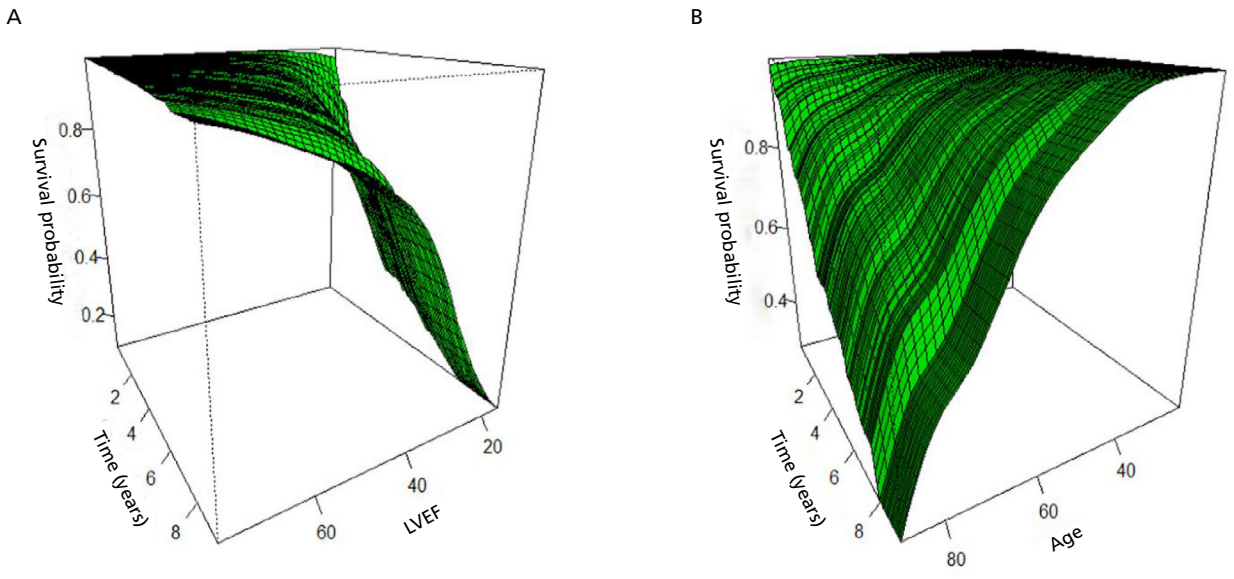


Table 4. Cox regression results with age and LVEF rescaled variables

Variable	HR	95% CI	p
Age (every 10 years from age 40 onwards)	2.28	1.70-3.06	<0.001
LVEF < 53-40	3.06	1.41-6.67	0.005
LVEF < 40-30	6.41	3.19-12.88	< 0.001
LVEF < 30	11.41	5.20-25.01	<0.001
ICD	1.84	0.89-3.80	0.099

CI: confidence interval; HR: hazard ratio; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction.

Table 5. Argen- CHAG variables with their corresponding scores

Variable	Category	Score
ICD	Present	2
	Absent	0
Age (years)	< 40	0
	40–49	2
	50–59	4
	60–69	6
	≥ 70	8
LVEF %	≥ 53	0
	40–52	3
	30–39	6
	<30	12

ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction;

Fig. 2. Modeling of the survival probability, time and score relationship

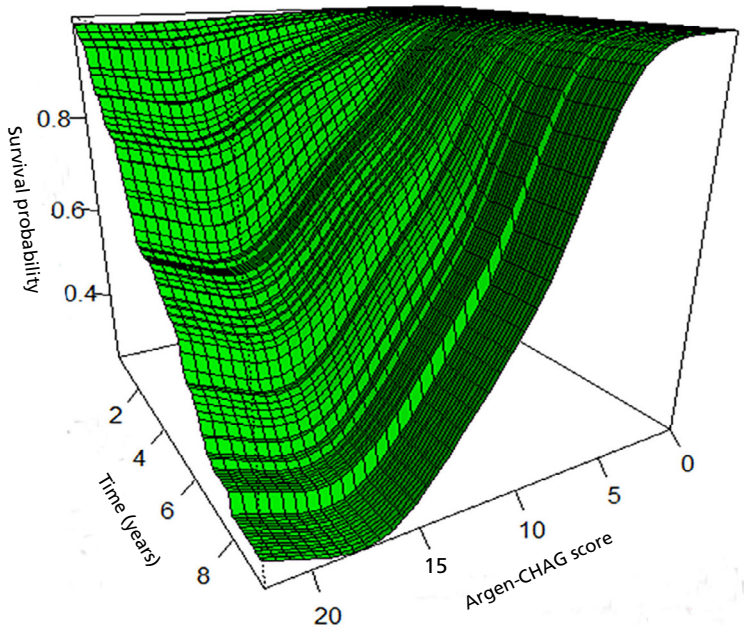


Fig. 3. Kaplan -Meier curves for each of the three score categories in both groups. A, Survival in the derivation group. B Survival in the validation group.

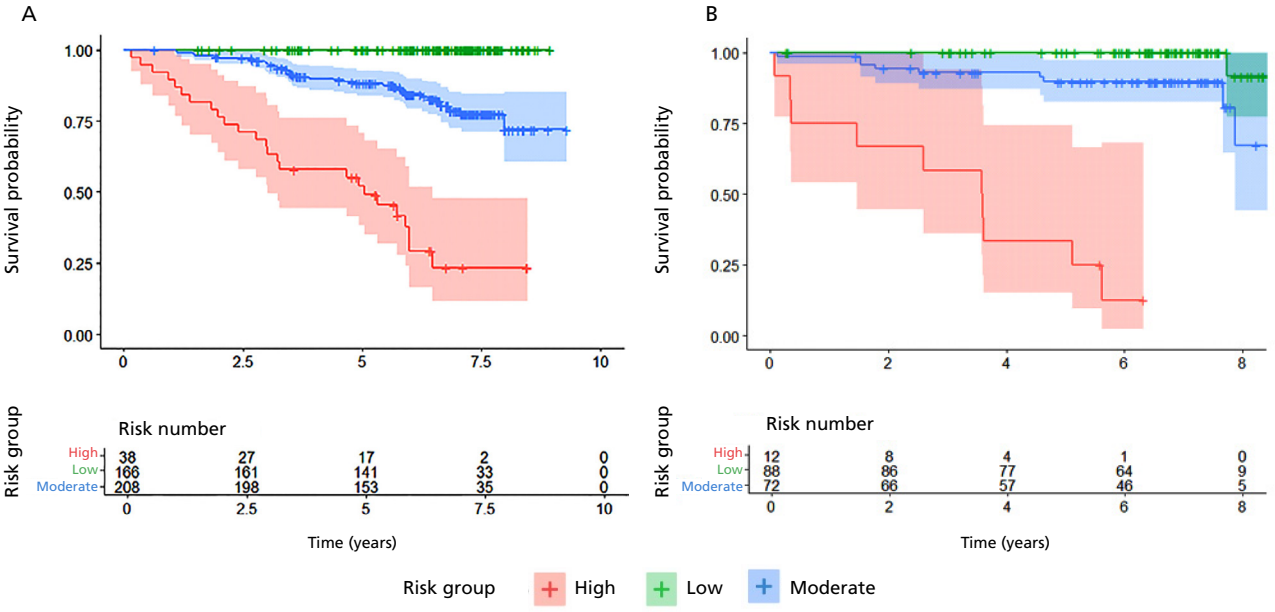
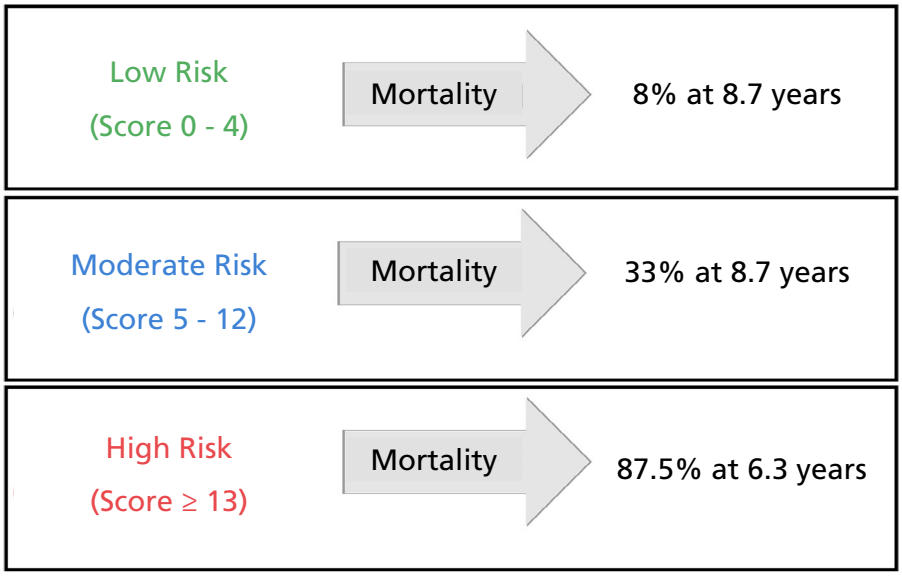


Fig. 4. Stratification of mortality risk according to the ARGEN-CHAG score, showing low, moderate and high-risk categories, together with mortality during follow-up.

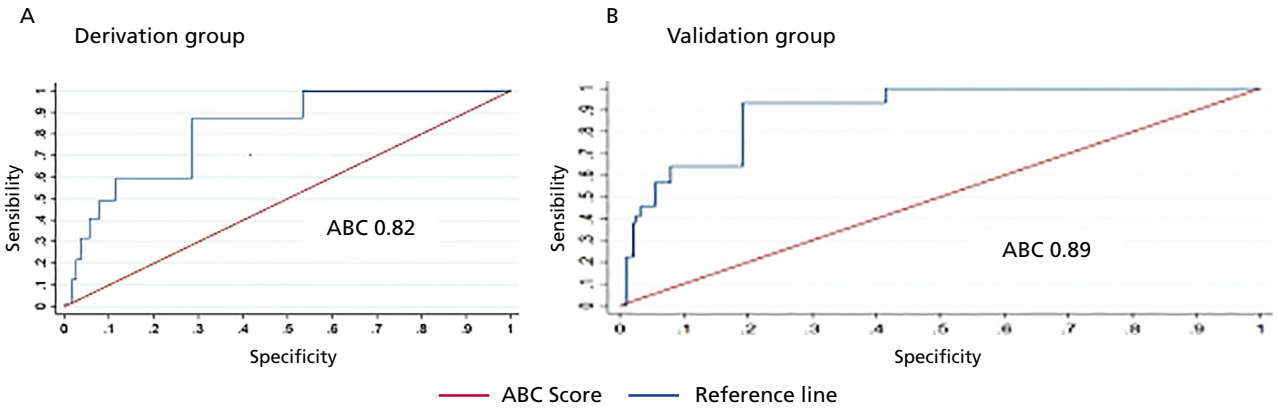


consideration of devices, while recognizing those at low risk, which avoids the overuse of resources. Thus, the model not only predicts but also offers a practical framework for clinical decision-making and resource optimization in contexts with high prevalence and structural limitations.

In Argentina, Chagas disease continues to be a significant cause of heart failure and sudden death. (11,12) Chronic Chagas cardiomyopathy (CCM) is associated with alarmingly high mortality, even higher than that observed in other forms of dilated cardiomyopathy. In a recent meta-analysis that included 37 studies and 17 949 patients, Gómez-Ochoa et al. demonstrated that patients with CCM have an almost twofold higher risk of mortality compared with those with non-ischemic and non-chagasic cardiomyopathies. (13)

The higher mortality rate of CCM can be explained

Fig. 5. Model performance: ROC curves to predict 5-year mortality for the Argen-CHAG score.



AUC: Area under the curve.

by its particular pathophysiology, characterized by persistent myocardial inflammation, diffuse transmural fibrosis, diffuse myocardial fibrosis, malignant ventricular arrhythmias, and a high thromboembolic burden. Added to this is the absence of randomized clinical trials demonstrating the advantage of specific therapies in this population, suggesting that the benefit of conventional treatments for heart failure may not be comparable to those observed in other etiologies. (13-15) In the recently published PARACHUTE-HF study, sacubitril valsartan, compared with enalapril, generated a greater reduction in natriuretic peptide values, without reducing cardiovascular mortality or the incidence of hospitalization for heart failure. (16)

Moreover, a systematic review and meta-analysis by Cucunubá et al. aimed to evaluate whether Chagas disease induces higher mortality compared with a control population with similar symptoms. This analysis included 25 studies with 10 638 patients and 53 346 person-years of follow-up, showing that *Trypanosoma cruzi* infection is associated with significantly higher mortality. The overall relative risk (RR) of death in patients with Chagas disease was 1.74 (95% CI 1.49–2.03) compared with uninfected individuals, with an annual mortality rate of 18% versus 10%, and an attributable risk of 42.5%. This excess mortality was observed in all clinical stages, although annual rates increased with severity (2% in asymptomatic patients, 16% in moderate-patients, and 43% in severe patients). However, a relevant limitation is the absence of studies conducted in Argentina. (17)

The Rassi score, published in 2006, represented a key progress in the prognostic stratification of Chagas disease. This model was developed from a Brazilian hospital cohort that initially included 424 patients, although the multivariate analysis was performed on 331 patients with complete data for all the variables evaluated. Patients were followed up for an average of 7.9 years to assess mortality. (9) However, its application has significant limitations outside the original context. First, the score was built with patients in advanced stages of the disease, which limits its extrapolation to populations with earlier or different clinical presentations. Furthermore, although the model performed well in Brazil, there are important differences in the manifestation and evolution of cardiac involvement between Brazil and Argentina, which reduces its validity for the Argentine population and highlights the need for locally validated prognostic tools.

Another notable limitation is the absence of variables derived from Doppler echocardiography in the original model. In recent years, this shortcoming has been one of the most questioned points, given that Doppler echocardiography is currently a fundamental tool, accessible in most health centers, with a consolidated prognostic value in the evaluation of cardiac function and structural heart diseases. (8,19) Finally, Rassi's model did not consider the inclusion of implantable devices, such as ICD, which are a current mainstay in the management of patients at high risk for ventricular arrhythmias and sudden death. (19-21)

Other recent studies have attempted to refine prognostic prediction in specific subgroups. Pereira et al. evaluated 117 CCM patients with ICD, observing a high incidence of appropriate therapies and a mortality rate of 6.2% person-years, predominantly due to refractory heart failure. In the multivariate analysis, secondary prevention, LVEF <30%, and intermediate Rassi score were associated with the occurrence of appropriate therapies, while functional class IV, LVEF <30%, and age >75 years were predictors of mortality. However, this was a single-center study, with a predominance of secondary prevention and a long inclusion period (2003-2021), which may have introduced heterogeneity in clinical management. (22)

Peixoto et al. developed and validated a specific prognostic score for CCM patients with pacemaker, a subgroup that was underrepresented in previous studies. They included 555 patients with an average

follow-up of 3.7 ± 1.5 years and a cumulative mortality rate of 18%. They identified six independent predictors of mortality (right ventricular dysfunction, functional class III-IV, chronic kidney disease, left ventricular end-systolic diameter >44 mm, atrial fibrillation, and radiographic cardiomegaly) and classified patients into risk categories with mortality rates of 8%, 20.4%, and 51%. Although its clinical applicability is high, the study was single-center, without external validation, and with a visual assessment of right ventricular function, which may limit its reproducibility. (23)

This evidence reinforces the need to develop specific and locally validated prognostic tools, especially in contexts such as Argentina, where epidemiological, clinical, and socioeconomic characteristics differ from those observed in the Brazilian cohorts predominant in the literature. In addition, the country under study may reflect a differential distribution of *T. cruzi* genotypes, which are believed to influence disease progression and, therefore, mortality. This biological heterogeneity, coupled with differences in access to and quality of healthcare systems, reinforces the notion that scores derived from other populations cannot be directly extrapolated to the Argentine context, justifying the development of specific prognostic models such as the one presented here. (24)

Limitations

The retrospective nature of the study does not allow us to rule out the presence of residual confounding factors inherent in a non-randomized observational design.

CONCLUSION

Chagas disease continues to be a significant cause of morbidity and mortality, and there is lack of prognostic tools adapted to the Argentine reality. In this scenario, the ARGEN-CHAG model emerges as a simple, accurate, and easy-to-apply prognostic tool, developed from a representative cohort of the Argentine public health system. Its high discriminatory power, based on only three easily assessed clinical predictors, positions it as a valuable resource for optimizing risk stratification, guiding therapeutic decisions, and improving the follow-up of patients with Chagas disease in our country.

Acknowledgments

Our deepest and most sincere thanks go to the patients with Chagas disease who participated in this study, as their contribution and that of their families was essential to perform this work. Therefore, we hope to continue generating evidence that will allow us to improve the follow-up and care of this group of patients.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Effects of Renin-Angiotensin System Blockade on the Renal Dopaminergic System in an Experimental Model of Chronic High-Fat Diet

Efectos del bloqueo del sistema renina angiotensina sobre el sistema dopaminérgico renal en un modelo experimental de dieta crónica alta en grasa

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ABSTRACT

Background: The renal dopaminergic system (RDS) exerts natriuretic and diuretic effects through D1 receptors and anti-inflammatory actions through D2 receptors. In contrast, angiotensin II, via AT1 receptors, generates opposite responses. Chronic consumption of high-fat diets (HFD) is associated with increased blood pressure and renal inflammation.
Objective: This study aimed to evaluate the impact of treatment with losartan, an AT1 receptor antagonist, on the RDS, blood pressure, and renal damage induced by a HFD.
Methods: Male Sprague–Dawley rats were studied for 8 weeks and randomly assigned to four experimental groups (n=4–6): control (C), high-fat diet (HFD), control + losartan (CL), and high-fat diet + losartan (HFDL). Systolic blood pressure (SBP), body, and plasmatic and urinary biochemical and metabolic parameters were assessed. Renal function, urinary excretion of L-dopa and dopamine (L-dopa/dopamine index), expression of receptors, dopamine transporters, and markers of inflammation, as well as renal structure and ultrastructure were also evaluated. Statistical analysis was performed using Student's t-test, one-way ANOVA with Tukey's post hoc test, Pearson's correlation, and linear regression. Results are expressed as mean ± standard error and $p<0.05$ was the level of significance.
Results: Losartan prevented the increase in SBP and the L-dopa/dopamine index (HFD vs. C, $p<0.01$; HFDL vs. HFD, $p<0.01$); the reduction in fractional and urinary sodium excretion and diuresis (HFD vs. C, $p<0.01$; HFDL vs. HFD, $p<0.05$); and decreased expression of the membrane transporter protein OCTN-1,2,3 (HFD vs. C, $p<0.01$; HFDL vs. HFD, $p<0.05$). It avoided overexpression of the dopamine D1 receptor (D1R) and Na^+K^+ATPase (HFD vs. C, $p<0.01$; HFDL vs. HFD, D1R $p<0.01$ and Na^+K^+ATPase $p<0.05$) and reduced the activation of nuclear factor kappa B, and transforming growth factor beta 1 (HFDL vs. HFD, $p<0.01$). It also mitigated structural alterations in the proximal tubules, increased interstitial fibrosis (HFD, $p<0.01$) and ultrastructural changes in the podocyte pedicels observed in HFD.
Conclusions: Under conditions of chronic consumption of a HFD, early administration of losartan favored RDS activity, prevented an increase in SBP, and attenuated interstitial fibrosis and renal inflammation, contributing to protection against target organ damage.

Keywords: Renal dopamine – High-fat diet – Blood pressure – Inflammation – Fibrosis – Losartan

RESUMEN

Introducción: El sistema dopaminérgico renal (SDR) ejerce efectos natriuréticos y diuréticos mediante receptores D1 y acciones antiinflamatorias mediante receptores D2. En contraste, la angiotensina II, vía receptores AT1, genera respuestas opuestas. El consumo crónico de dietas ricas en grasas se asocia con incremento de la presión arterial e inflamación renal.
Objetivo: Evaluar el impacto del tratamiento con losartán, antagonista de receptores AT1, sobre el SDR, la presión arterial y el daño renal inducido por una dieta rica en grasas.
Material y métodos: Ratas macho Sprague–Dawley fueron estudiadas durante 8 semanas y asignadas aleatoriamente a cuatro grupos experimentales (n=4–6): control (C), dieta grasa (DG), control + losartán (CL) y dieta grasa + losartán (DGL). Se determinaron presión arterial sistólica (PAS), parámetros corporales, bioquímicos, metabólicos plasmáticos y urinarios, función renal, excreción

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urinaria de L-dopa y dopamina (índice L-dopa/dopamina), expresión de receptores, transportadores de dopamina y marcadores de inflamación, así como estructura y ultraestructura renal. Análisis estadístico: prueba t+ de Student, ANOVA de una vía con post hoc de Tukey, correlación de Pearson y regresión lineal. Los resultados se expresaron como media ± error estándar; significancia $p<0,05$.
Resultados: El losartán previno el aumento de la PAS y del índice L-dopa/dopamina (DG vs. C, $p<0,01$; DGL vs. DG, $p<0,01$); la reducción de la excreción fraccional y urinaria de sodio y de la diuresis (DG vs. C, $p<0,01$; DGL vs. DG, $p<0,05$); y la disminución en la expresión de la proteína trasportadora de membrana OCTN-1,2,3 (DG vs. C, $p<0,01$; DGL vs. DG, $p<0,05$). Evitó la sobreexpresión del receptor dopaminérgico D1R y la Na^+K^+ATPasa (DG vs. C: $p<0,01$; DGL vs. DG: D1R $p<0,01$; Na^+K^+ATPasa $p<0,05$) y redujo la activación del factor nuclear kappa B, NF-κB, y el factor de crecimiento transformante beta 1 TGF-beta1 (DGL vs. DG, $p<0,01$). Mitigó las alteraciones estructurales de los túbulos proximales, el incremento de fibrosis intersticial (DGL vs. DG, $p<0,01$) y los cambios ultraestructurales en los pedicelos podocitarios observados en DG.
Conclusiones: En condiciones de consumo crónico de dieta rica en grasas, la administración temprana de losartán favoreció la actividad del SDR, previno el aumento de la PAS y atenuó la fibrosis intersticial y la inflamación renal, contribuyendo a la protección frente al daño de órgano blanco.

Palabras clave: Dopamina renal – Dieta rica en grasas – Presión arterial – Inflamación – Fibrosis – Losartán

INTRODUCTION

The worldwide consumption of diets rich in carbohydrates and fats is a key factor in the development of metabolic syndrome (MS), defined by the concurrence of at least three metabolic disorders—hyperglycemia, hypertriglyceridemia, insulin resistance, hypertension (HTN), systemic inflammation, or increased waist circumference — that damage various organs, particularly the kidneys, which are essential for electrolyte homeostasis and blood pressure control. (1,2) High-caloric diets induce structural and functional renal dysfunction and increase the risk of HTN, a chronic and asymptomatic disease responsible for approximately 50% of global cardiovascular mortality. (3,4) According to a 2021 World Health Organization population study published in The Lancet, including 104 million participants, the prevalence of HTN was 59% in women (aged 55–62) and 49% in men (aged 46–52), with only 47% and 38%, respectively, receiving treatment. (5) More recently, in 2023, the WHO report "Global Report on Hypertension: The Race Against a Silent Killer" noted a global prevalence of 34% in men and 32% in women, a difference that tends to disappear with advancing age. (6). In Argentina, the RENATA 2 study (2017) reported an incidence of 36.3% in adults aged 26–60 years, higher in men. (7)

The renal dopaminergic system (RDS) and the renin-angiotensin system (RAS) play a key role in the renal regulation of blood pressure. The RDS, located in the proximal convoluted tubule, promotes natriuresis, diuresis, and anti-inflammatory effects by acting on D1 and D2 receptors, counteracting the action of insulin and angiotensin II (Ang II). (8) Conversely, overactivation of the RAS stimulates tubular reabsorption of sodium and water and increases inflammation and oxidative stress. Both systems maintain functional antagonism, as angiotensin II inhibits dopaminergic synthesis and activity. (9) In this context, the L-dopa/dopamine ratio has been proposed as an early biomarker of renal damage in animal models of fructose-induced HTN. (10)

Pharmacological treatment of HTN includes AT1 receptor (AT1R) antagonists, including losartan (L), a potent and selective competitive blocker that specifically inhibits the effects of Ang II. (11) Although its antihypertensive efficacy is well known, its ability to modulate the RDS–RAS balance in MS induced by high-fat diets (HFD), as part of its nephroprotective action, has not been fully clarified. In this context, we proposed to evaluate whether a HFD alters this balance as a mechanism of HTN and whether early treatment with L prevents these alterations in an experimental model of MS induced by HFD for 8 weeks. The usefulness of the L-dopa/dopamine index as an early biomarker of renal dysfunction was also analyzed.

METHODS

A) Animals, experimental design, and diet.

Male Sprague-Dawley rats (6 weeks old, 180–200 g; Central Animal Facility, FFyB-UBA) were kept under controlled conditions (22±2°C, 50–70% humidity, 12 h light/dark) and studied for 8 weeks. The animals were divided into four groups (n=4–6):

- C: standard diet (SD) and water ad libitum (Asociación Cooperativas Argentinas; 20% protein, 3% fat, 2% fiber, 6% minerals, 69% starch, vitamins; 3.3 kcal/g);
- HFD: SD + 50% w/w fat and water ad libitum (Faty, Quick-food S.A., Argentina; 9 kcal/g, 99% total fat, 77% saturated, 19% trans);
- CL: C + losartan (L), 30 mg/kg/day, water. (Losartan potassium, 100% dry basis, Droguería Saporiti S.A.C.I.F.I.A, Buenos Aires, Argentina);
- HFDL: HFD + CL.

B) Body weight, food consumption, and calories.

Body weight was recorded daily. Food and drink intake was measured every 48 hours. Calculation included: I) food (g/day) = offered – remaining; II) drink (mL/day) = offered – remaining; III) calories: C and CL = SD (g) × 3.3 kcal/g; HFD and HFDL = SD (g) × 3.3 kcal/g + fat (g) × 9 kcal/g.

C) Systolic blood pressure (SBP).

This was measured at the start and before sacrifice using tail plethysmography with a photoelectric sphygmomanometer (Grass D.C. 7DAC) and oscilloscope (Grass D.C. 79D, Grass Instruments Co., USA).

D) Urine and blood collection.

Three days before sacrifice, the animals were housed in metabolic cages for 48 hours. Urine collection: I) the urinary fraction from the first 6 hours was recovered in an aqueous solution of hydrochloric acid with a 6N concentration (HCl 6N), aliquoted in HCl 1N and stored at −80°C for L-dopa

and dopamine assessed by high-performance liquid chromatography (HPLC); II) The urinary fraction from the following 18 hours was stored at −20°C for sodium, creatinine, and albumin assessment (Spectrum CCX, Abbott Diagnostics, USA). Diuresis was measured by total volume urinated in 24 h. On the sacrifice day, after 6-h fasting, blood was obtained by retro-orbital puncture under anesthesia (ketamine 80 mg/kg + xylazine 12 mg/kg, PRO-SER SA).

E) Tissue collection.

The animals were sacrificed under anesthesia in a CO2 chamber. The kidneys were decapsulated, weighed, and randomly distributed for histology, transmission electron microscopy (TEM), and Western blot.

F) Assessments.

F-1) Plasma metabolism: Blood glucose was assessed with Accu-Chek Performa Nano (Roche Diagnostics, Germany), triglyceridemia with TG Color GPO/PAP AA kit (Wiener Lab., Argentina) and insulin by ELISA test (Mercodia Rat Insulin ELISA, Sweden). The triglyceride-glucose product (TyG) (12) and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index were calculated. (13)

F-2) Renal function: Sodium and creatinine were measured in plasma and urine (Spectrum CCX), glomerular filtration rate (GFR) was estimated by creatinine clearance and tubular function was assessed by urinary sodium excretion (UNa+V) and fractional excretion of sodium (FENa).

F-3) Urinary catecholamines: L-dopa and dopamine were measured by reverse-phase HPLC (Zorbax RxC18 column; DuPont, USA; amperometric detection, ESA, USA). Internal standard: 3,4-dihydroxybenzylamine (Sigma-Aldrich, Cat. No. 858781). External standards were: L-dopa (Cat. No. 13248) and dopamine (Cat. No. 21992), both from Cayman Chemical. The detection limit was 20 pg/sample.

F-4) Albuminuria: It was measured with Cobas equipment (ALBT2 Tina-quant Albumin Gen.2; Roche Diagnostics, Switzerland); The urinary albumin/creatinine ratio was determined, considering microalbuminuria between 30–300 mg/g. (14)

F-5) Renal protein expression of the amino acid and thyroid hormone transporter LAT2, membrane transport proteins OCT2 and OCTN1,2,3, dopaminergic receptors D1R and D2R, Ang II receptor, sodium-potassium ATPase (Na^+K^+ATPase), transforming growth factor beta 1 (TGF-beta1), and nuclear factor kappa B1 (NFkB1) were assessed by Western blot. Beta-tubulin was used for load control and optical densitometry (ImageJ) for analysis. Because several of the antibodies have similar molecular weights, the membrane stripping technique with 5% acetic acid was used after the primary antibody was developed in order to mark the expression of the load control. (Table 1)

F-6) Renal histology: 8-micron thick sections were stained with hematoxylin-eosin and Sirius Red (15). Cortical fibrosis was quantified in 20 fields/animal (ImageJ) using a Nikon Type 104c microscope to obtain the images. Cortical fibrosis is expressed as: fibrosis percentage (%) = [Σ cortical interstitial collagen / (Total area – Σ vessels)] × 100.

F-7) Renal ultrastructure; 1 mm^3 renal cortical fragments were used for TEM and observed with a Zeiss EM 109T TEM with Gatan ES1000W digital camera.

Statistical analysis

InfoStat statistical package was used for Student's t-test, one-way ANOVA with Tukey post-hoc test, and Pearson and linear regression correlations. Results were expressed as mean ± standard error of the mean (SEM) and significance was $p<0.05$. GraphPad Prism v10.2.3 was used for graphs.

Ethical considerations

Procedures were approved by CICUAL-UBA (Res. CD No. 1881/1999, director Dr. M. R. Choi), in accordance with international ethical standards in animal experimentation.

RESULTS

Table 2 shows that HFD induced a significant increase in body weight compared with C, which was prevented by L in HFDL. Food intake decreased in HFD versus C, an effect reversed by L, while calorie intake increased in HFD with no differences between HFD and HFDL. Water intake did not vary between groups. Plasma parameters showed significant increases in HFD compared with C, with reductions in triglycerides and insulin in HFDL; Triglyceride-glucose product and HOMA-IR did not differ between groups.

Table 3 shows how HFD increased SBP and the urinary L-dopa/dopamine index compared with C, effects attenuated by L in HFDL. The CL group showed an additional reduction in SBP compared with C. No changes were observed in the urinary albumin/creatinine ratio or GFR. Diuresis, $FENa^+$, and UNa^+V decreased in HFD and were prevented by L in HFDL.

Hematoxylin-eosin staining showed cytoplasmic vacuoles in cortical tubular cells in HFD versus C, with no alterations in CL compared with C. Fewer vacuoles were present in HFDL than in HFD (Figure 1 A-D). The podocyte ultrastructure revealed shortening and fusion of pedicels in HFD, which was prevented by L in HFDL, and with no difference between CL and C (Figure 1 E to H).

HFD overexpressed AT1R and reduced the membrane transport protein OCTN1,2,3, compared with C, while L prevented this decrease. L also prevented the overexpression of the D1R dopaminergic receptor in HFDL compared with HFD and D2R, which was decreased in HFD and was not modified by L. LAT2 and OCT2 did not vary between groups. Na^+K^+ATPase was increased in HFD, but L returned it to normal values in HFDL compared with HFD (Figure 2).

The L-dopa/dopamine index correlated positively with SBP, insulinemia, and D1R, and inversely with UNa^+V and OCTN1,2,3. Losartan prevented these alterations in HFDL compared with HFD (Figure 3).

HFD significantly increased the expression of NFkB1 and TGF-beta1, effects that were prevented by L in HFDL. Interstitial fibrosis increased in HFD compared with C, and L significantly prevented this in HFDL compared with HFD, with residual foci and no changes in CL compared with C. Semi-quantitative analysis confirmed these findings (Figure 4).

DISCUSSION

High fat diet consumption significantly increased body weight compared with C, an effect that was prevented by L. Although food intake was lower in HFD, the caloric density of the diet resulted in 33% more calories consumed, which explains the increase in body weight, in agreement with findings reported by Pinhal et al. (16) Our results coincide with Smith et

Table 1. Primary antibodies used for Western blot.

Protein	Antibody	Dilution	Molecular weight	Supplier and catalog number
D1R	Rabbit polyclonal anti-D1R	1:1000	50 kDa	Proteintech, catalog number 17934-1-AP
D2R	Rabbit polyclonal anti-D2R	1:600	51 kDa	Proteintech, catalog number 55084-1-AP
OCTN 1,2,3	Rabbit polyclonal anti-OCTN 1,2,3	1:2000	90 kDa	Santa Cruz Biotechnology, Inc., catalog number sc-33534
OCT2	Goat polyclonal anti-OCT2	1:800	50 kDa	Santa Cruz Biotechnology, Inc., catalog number sc-19814
LAT2	Goat polyclonal anti-LAT2	1:800	50 KDA	Santa Cruz Biotechnology, Inc., catalog number sc-27581
AT1R	Rabbit polyclonal anti-AT1R	1:100	50 KDA	Proteintech, catalog number 25343-1-AP
Na+K+ATPase	Rabbit polyclonal anti-alpha-1 Na+ K+ ATPase	1:10,000	105 KDA	Abcam, catalog number ab74945
NFkB1	Rabbit polyclonal anti-NFkB1	1:1000	50 KDA AND 105 KDA	Proteintech, catalog number 14220-1-AP
TGF-beta1	Rabbit polyclonal anti-TGF-beta1	1:500	44 KDA	Proteintech, catalog number 21898-1-AP
Beta-tubulin	Rabbit polyclonal anti-beta-tubulin	1:3000	50 KDA	Abcam, catalog number ab6046

Table 2. Body weight, food, water, and calorie intake and plasma metabolic parameters.

Parameter	C	HFD	CL	HFDL
Body weight (g)	415.7±8.7	473.8±14.1*	389.7±3.8	359.13±7.93§
Food intake (g/24 hours)	20.9±3.6	13.8±1.3†	28.4±3.5	18.6±1.7‡
Water intake (mL/24 hours)	12.5±3.9	12.4±0.7	20.5±2.7	19.1±1.3
Calorie intake (kcal/24 hours)	60.5±10.8	103.6±11.5*	72.4±11.4	119.3±11.1
Triglycerides (mg/dL)	59.68±6.13	119.25±4.17†	53.20±4.41	82.97±6.93‡
Blood glucose (mg/dL)	117.5±7.5	152.2±4.6†	100.3±29.6	173.7±14.0‡
TyG index	8.0±0.2	10.5±0.1†	8.1±0.3	10.2±0.2
Insulin (ng/mL)	1.20±0.10	4.20±0.50†	1.3±0.2	2.8±0.4‡
HOMA-IR	0.7±0.1	3.3±0.5†	1.5±0.7	3.2±0.5

Results are expressed as mean ± SEM. Significance is considered as *p<0.05 C vs. HFD; †p<0.01 C vs. HFD; ‡p<0.05 HFDL vs. HFD; §p<0.01 HFDL vs. HFD.
C: standard diet and water ad libitum (SD); CL: C + losartan (L); HFD: SD + 50% w/w fat and ad libitum water; HFDL: HFD + CL; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; SEM: standard error of the mean; TyG: triglyceride-glucose product

al., (17) who described a reducing effect of L on body weight, suggesting a regulating role of AT1 antagonism in HFD-induced obesity. Moreover, Hosseini et al. (18) suggested that L may improve leptin resistance and modulate body weight in conditions of diet-induced obesity. Water intake did not differ between groups, and the previously validated L administration in drinking water (19) avoided the bias associated with chronic gavage (force-feeding).

The metabolic profile showed insulin resistance in HFD versus C, with increased triglycerides, blood glucose, insulin, TyG, and HOMA-IR, consistent with previous reports in HFD-induced MS models. (18) Losartan partially attenuated triglycerides and insulin without modifying blood glucose or indices, while CL did not differ from C. These findings are consistent with the literature regarding metabolic alterations caused by HFD and the beneficial effects of L, which could be due to the reduction of oxidative stress via the activation of superoxide dismutase (SOD), although the precise mechanism remains unclear. (17,20)

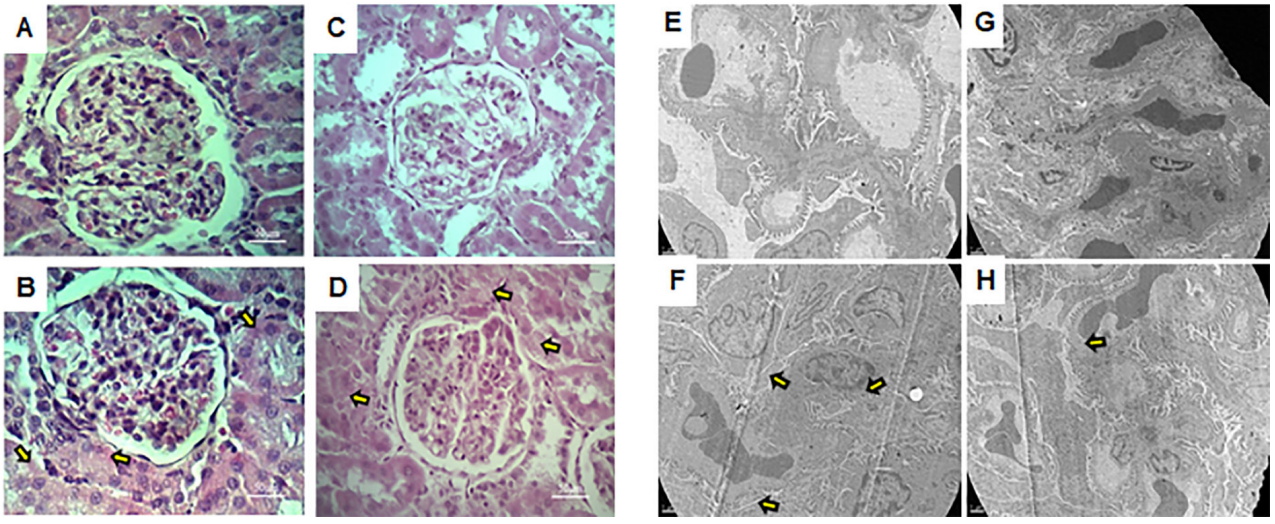
HFD significantly increased SBP compared with C, in agreement with findings of Jin et al. and Li et al. (21,22), who demonstrated that HFD induces obesity, insulin resistance, and hyperinsulinemia, accompanied by RAS activation, increased Ang II, aldosterone,

Table 3. Systolic blood pressure, urinary L-dopa/dopamine index and plasma and urinary parameters of renal function.

Parameter	C	DG	CL	DGL
SBP (mmHg)	120.7±2.3	134.8±2.3†	106.4±2.5 ¶	109.5±2.0§
L-dopa/dopamine index	1.1±0.1	2.9±0.2†	1.8±0.1	1.8±0.1§
Albumin/urinary creatinine (mg/g)	17.42±1.98	12.93±0.66	15.31±1.52	8.45±1.13
Diuresis (mL/24 hours)	16.4±2.2	3.5±0.3†	17.28±1.38	6.23±0.93‡
GFR (mL/min)	1.65±0.27	1.38±0.11	1.77±0.20	1.42±0.09
FENa (%)	0.50±0.06	0.16±0.02†	0.51±0.02	0.32±0.05‡
UNa^+V (mEq/24hours)	1.78±0.18	0.45±0.05†	1.95±0.01	0.78±0.10‡

Results are expressed as mean ± SEM (standard error of the mean). Significance is considered as: *p<0.05 C vs. HFD; †p<0.01 C vs. HFD; ‡p<0.05 HFDL vs. HFD; §p<0.01 HFDL vs. HFD; ¶p<0.01 CL vs. C; GFR: glomerular filtration rate; FENa: fractional excretion of sodium; SBP: systolic blood pressure; SEM: standard error of the mean; UNaV: urinary sodium excretion.

Figure 1. Structure and ultrastructure of the renal cortex



A, B, C, and D photos: Optical microscopy with hematoxylin and eosin staining, total magnification:400X E, F, G, and H photos: Transmission electron microscopy, total magnification: 7000X. Nomenclature: A-E: C group. B-F: HFD group. C-G: CL group. D-H: HFDL group. In A, B, C, and D, the yellow arrows point to the cytoplasmic vacuoles of the tubular cells. In E, F, G, and H, the yellow arrows point to the podocyte pedicels with altered morphology.

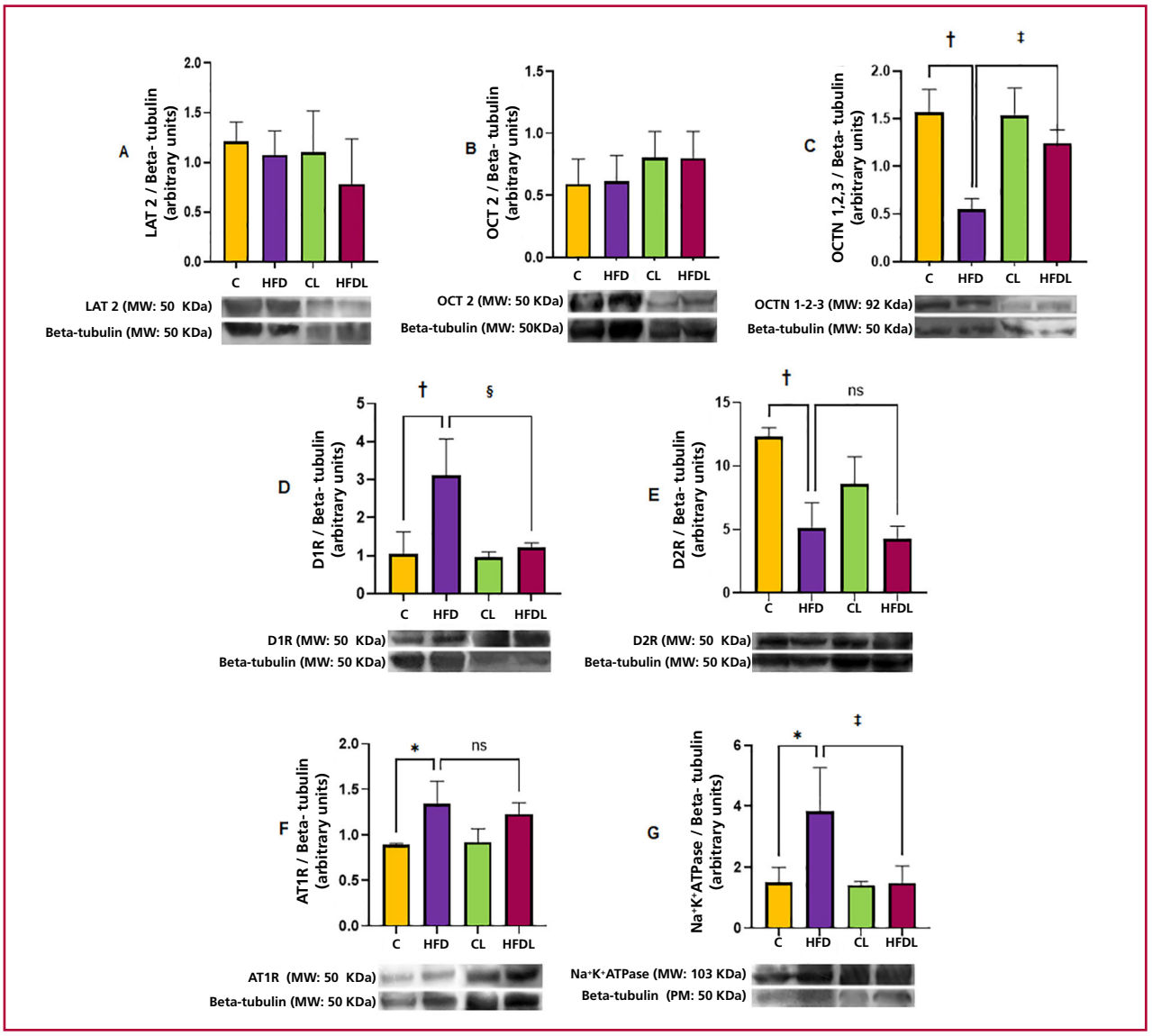
and AT1R expression, along with inflammation and renal fibrosis. In our model, concomitant administration of L prevented the increase in SBP in HFDL compared with HFD, an effect attributable to its antagonistic action on AT1R. (16) In addition, L significantly reduced SBP in normotensive controls (CL), in line with findings reported by Lee et al. (19) Li et al. (22) described an allosteric effect of L on AT1R, which potentiates D1R activity, contributing to its antihypertensive action.

Glomerular filtration rate showed no differences between groups. Similar results were reported by Roza et al. (23) in mice treated with HFD at 8 and 12 weeks. In addition, other groups reported increased levels associated with glomerular hyperfiltration in obese animals. (24,25) These findings suggest that the effect of HFD on GFR is variable. Treatment with L also did not modify this parameter between the groups evaluated.

The urinary albumin/creatinine ratio, which is more reliable than the absolute values of the metabolites separately, did not exceed 30 mg/g in any group, ruling out microalbuminuria. L did not modify this marker, suggesting that the alterations derive from the diet and not from the drug. In contrast, Sánchez-Navarro et al. (26) reported a significant increase of GFR under longer-term HFD, indicating that exposure time could be a determining factor.

HFD reduced diuresis versus C as reported by Sánchez-Navarro et al, (26) possibly due to lower RDS activity and higher RAS activity. (10) L prevented this reduction in HFDL, suggesting restitution of RDS function by AT1R blockade. (22) Similarly, $FENa^+$ and UNa^+V were reduced in HFD, partially prevented

Figure 2. RDS, RAS, and Na^+K^+ATPase protein expression in the renal cortex by Western blot



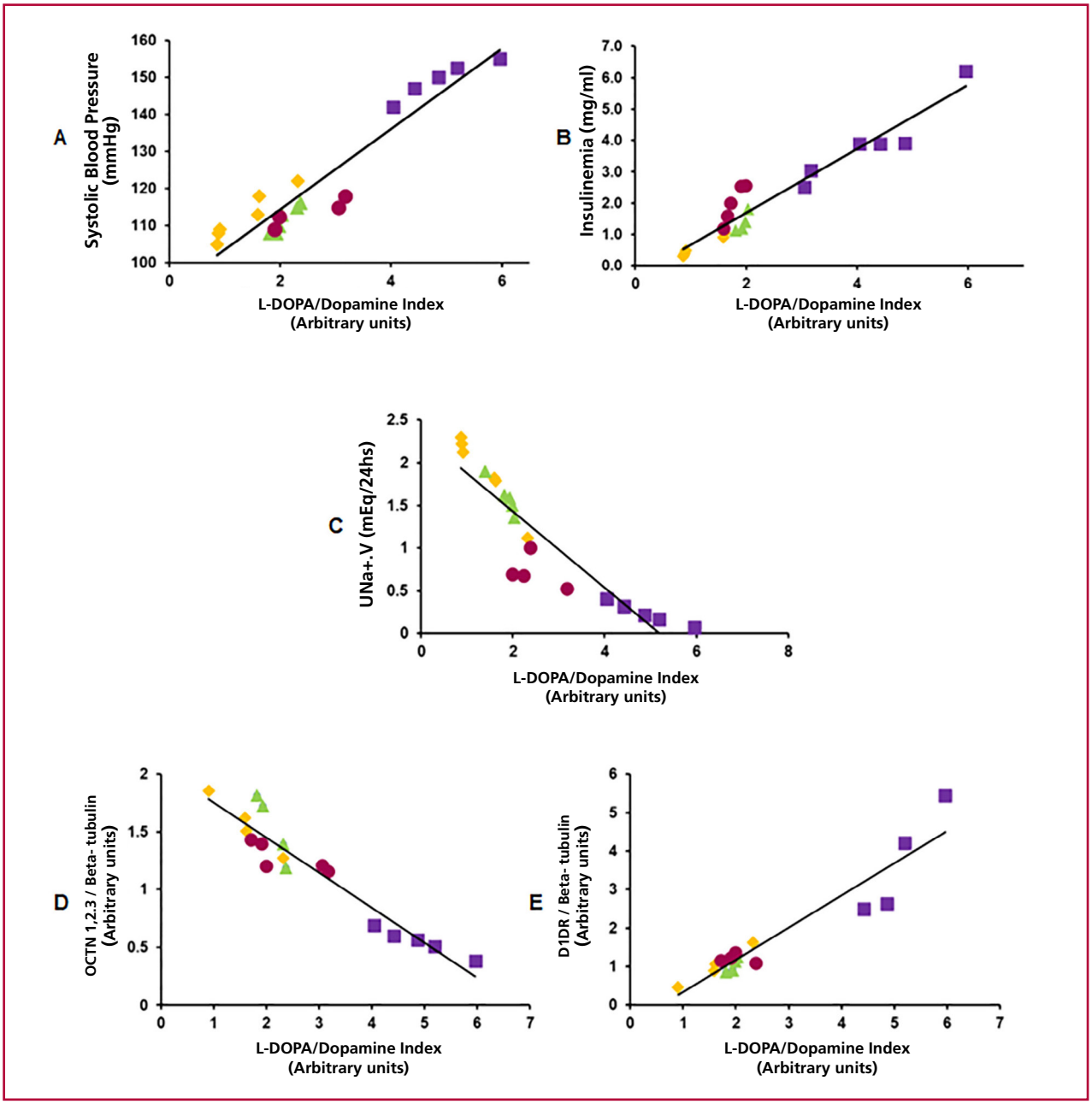
A: LAT2. B: OCT2. C: OCTN 1,2,3. D: D1R. E: D2R. F: AT1R. G: Na^+K^+ATPase. Results are expressed as mean ± SEM. Significance is considered as: *p<0.05 C vs. HFD; †p<0.01 C vs HFD; ‡p<0.05 HFDL vs HFD; §p<0.01 HFDL vs HFD.
C: standard diet and water ad libitum (SD); CL: C + losartan (L); HFD: SD + 50% w/w fat and ad libitum water; HFDL: HFD + CL; RAS: renin angiotensin system; RDS: renal dopaminergic system; SEM: standard error of the media. Remaining abbreviations in the text

by L in HFDL, although without reaching CL values, indicating the possible involvement of sodium reabsorption mechanisms independent of Na^+K^+ATPase, such as the Na^+/H^+ exchanger or the epithelial sodium channel (ENaC). (27,28) Previous results show disparity: Roza et al. (23) observed no changes, while Pinhal et al. (16) reported decreased FENav and UNa^+V in obesity or prolonged HFD. HFD is thus associated with the observed alterations, and L exerts a partial preventive effect.

Histologically, HFD induced cytoplasmic vacuoles in the proximal convoluted tubule (PCT), which was absent in C and partially prevented by L in HFDL, with no changes in CL. Although lipid stains were negative, the literature suggests that they could correspond to lipid vacuoles (4,29) or hydropic degeneration due to Na^+K^+ATPase dysfunction associated with lipotoxicity (30), and attenuated by L through reduction of inflammation and oxidative stress. (19) Ultrastructural analysis with TEM showed obliteration and interdigitation of pedicels and podocyte hypertrophy in HFD, which was partially prevented by L and is consistent with the nephroprotective role of dopamine (31) and the harmful effect of Ang II on AT1R. (32)

HFD-induced MS is associated with HTN through RAS activation, particularly through the action of Ang II on AT1R, which stimulates the Na^+K^+ATPase pump, promoting sodium retention and reducing its

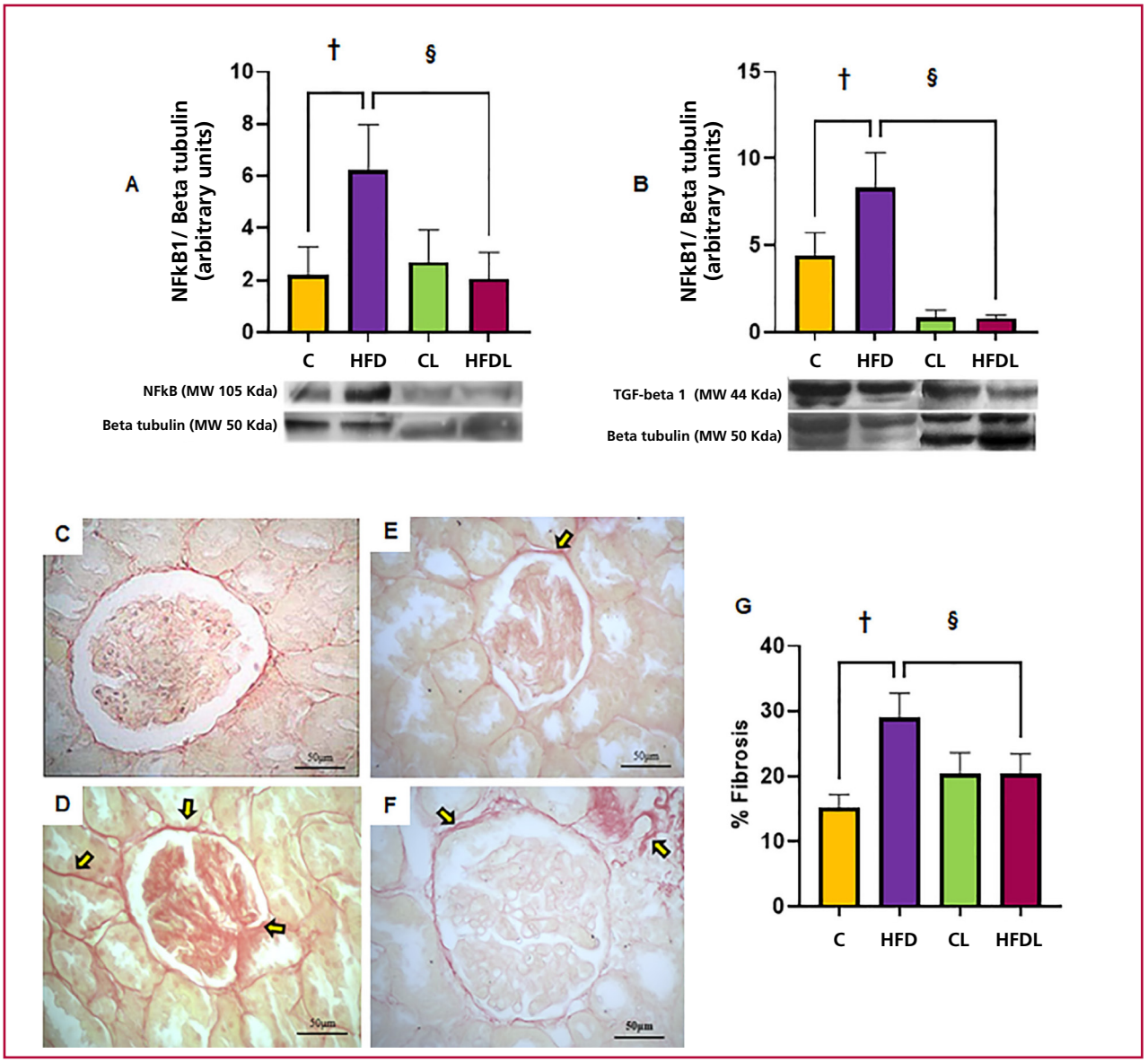
Figure 3. Functional correlations with the L-dopa/dopamine index



A: Linear regression SBP versus L-dopa/DA index; r = 0.95, R2 = 0.90, p<0.01; B: Linear regression of insulinemia versus L-dopa/DA index; r = 0.96, R2 = 0.91, p<0.01; C: Linear regression of UNa+V versus L-dopa/DA index; r = 0.91, R2 = 0.83, p<0.01; D: Linear regression of OCTN 1,2,3 versus L-dopa/dopamine index; r = 0.95, R2 = 0.91, *p<0.01 and E: Linear regression of D1R versus L-dopa/dopamine index; r = 0.95, R2= 0.89, *p<0.05. Group and color codes: C: Yellow. HFD: Violet. CL: Green. HFDL: Burgundy.

excretion. (1,22) Concomitantly, HFD inhibits RDS activity, enhancing the anti-natriuretic effect. There is negative reciprocity between AT1R and D1R in PCT cells, where activation of one induces internalization and abolition of signaling of the other, acting as a unit of opposites together with Na^+K^+ATPase as a common target. (33) In normotensive humans, a negative interaction between RDS and RAS has been demonstrated in the regulation of renal sodium transport, dependent on sodium intake. (34) HFD increased renal expression of AT1R compared with C, in accordance with models of MS and RAS activation. (21) L showed a tendency toward reduction in HFDL, suggesting that longer times may be necessary to demonstrate the effect. In contrast, L normalized the L-dopa/dopamine index, which was increased in HFD vs. C, (35) evidencing greater tubular dopamine availability and urinary excretion associated with res-

Figure 4. Evaluation of inflammation markers in the renal cortex by Western blot and fibrosis percentage by histology with Sirius red staining.



A: NFkB1. B: TGF-beta1. Photo C: C group. Photo D: HFD group. Photo E: CL group. Photo F: HFDL group. Graphic G: fibrosis percentage. The yellow arrows point to sites of increased interstitial fibrosis. Total magnification: 400X Results are expressed as mean ± SEM. Significance is expressed as: †p<0.01 C vs. HFD; §p<0.01 HFDL vs. HFD.

toration of OCTN1,2,3 transporters. LAT2 and OCT2 were not modified, in contrast to fructose overload. (35) HFD increased D1R, which was prevented by L, and reduced D2R, unchanged by L, reflecting renal dopaminergic alteration (36). HFD significantly increased cortical Na^+K^+ATPase compared with C, a finding consistent with Deji et al. (9,37). L prevented this increase in HFDL, without modifying baseline values (CL vs. C), an effect explained by its allosteric action on AT1R–D1R. (21)

The L-dopa/dopamine index correlated positively with SBP and insulin, and negatively with UNa^+V and OCTN1,2,3, which directly links RDS to blood pressure regulation and sodium balance, in interaction with insulin resistance. (38) L normalized these correlations by blocking AT1R and inhibiting Na^+K^+ATPase. Taken together, the results highlight the HFD-induced RDS-RAS imbalance and the potential of L to prevent associated renal and hemodynamic dysfunction.

In terms of inflammation, RDS exerts anti-inflammatory effects, while RAS potentiates them. (10,39) Renal dopamine, via D1R and D2R, attenuates the effects of Ang II by reducing inflammation and fibrosis (16). In contrast, HFD induced a proinflammatory environment with overexpression of NFkB1 and TGF-

beta1, increased interstitial fibrosis, and activation of oxidative pathways. (3,11,39) L prevented these changes by blocking Ang II and allowing the protective action of RDS to reduce fibrosis and oxidative stress. (40)

In conclusion, preventive and continuous treatment with L significantly attenuated RAS activity and reactivated RDS. AT1R inhibition by losartan reduced the action of Na^+K^+ATPase and normalized D1R expression, restoring OCTN1,2,3 transporter levels favoring dopamine access to the tubular lumen. Consequently, urinary dopamine excretion increased, the L-dopa/dopamine index normalized, and interaction with D1R was enhanced, promoting natriuresis and restoring RDS-RAS balance. In addition, L improved interstitial fibrosis, generated an anti-inflammatory renal environment, and preserved PCT structure and podocyte ultrastructure.

Limitations

One of the limitations of the present study was that the expression of the total Na^+K^+ATPase pump was assessed, without discriminating between the phosphorylated or active form and the non-phosphorylated or inactive one. Moreover, the activity of this transporter was not measured, based on the working group's own background showing in a fructose overload model with L that there were no variations between the different experimental groups.

Furthermore, it was not possible to perform immunohistochemistry on either the RDS transporters or receptors, which would have provided information about the cellular location of the different proteins, possibly directly related to the functionality of these proteins.

As a complement to TEM, it would have been suitable to determine the expression of nephrin and podocalyxine as structural markers of glomerular filtration barrier integrity, as well as to determine the expression of IL-6 as an acute marker of inflammation complementary to NFkB1.

These assessments are planned for the future in order to complete the corresponding profile..

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Cardiac Arrest as Presenting Symptom in ST-Segment Elevation Acute Coronary Syndrome. Data From The ARGEN-IAM-ST Registry

Paro cardiorrespiratorio como forma de presentación del síndrome coronario agudo con elevación del segmento ST. Datos del registro ARGEN-IAM-ST

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ABSTRACT

Background: Cardiac arrest (CA) in the context of acute coronary syndrome is a major cause of out-of-hospital and in-hospital death. Some patients present CA as the initial manifestation of the condition, and although almost half of them do not reach healthcare centers and die, others may be hospitalized.
Objectives: The aim of this study was to describe the prevalence of CA as a presenting symptom in ST-segment elevation myocardial infarction, and analyze the characteristics of these patients, treatment, and in-hospital mortality.
Methods: We conducted a retrospective analysis of patients included in the ARGEN-IAM-ST registry. Data regarding patients' characteristics, reperfusion strategies, and in-hospital outcomes were collected. The Redcap case record form has an item called "presenting symptoms" where physicians check the Killip and Kimball (KK) class on admission and the presence (yes box) or absence (no box) of CA. Cardiac arrest was defined as the sudden cessation of cardiac activity that can lead to death if resuscitation measures are not taken or if they are unsuccessful.
Results: A total of 7505 patients were included between March 2014 and April 2025. Cardiac arrest was the presenting symptom in 7.5% of cases (n = 564). Patients presenting with CA were older (median age 62 vs. 61 years) and had a higher prevalence of diabetes (32.8% vs. 26.8%), hypertension (61% vs. 53.5%), history of coronary artery disease (16.5% vs. 14.9%), chronic obstructive pulmonary disease (4.8% vs. 2.9%), and peripheral vascular disease (2.1% vs. 1.1%), with statistically significant differences in all cases. On coronary angiography, left main coronary artery disease (6.7% vs. 0.9%, p <0.001), left anterior descending coronary artery disease (48.6% vs. 47.6%, p <0.001), and multivessel disease (32.3% vs. 29.5%, p=0.004) were mostly common. Patients with CA as presenting symptom were less likely to receive reperfusion therapy (85.2% vs. 90.9%, p<0.001) and primary percutaneous coronary intervention (PCI) 67.9% vs. 75.2%, p=0.014). There were no differences in door-to-balloon time among those undergoing PCI. In patients with CA as the presenting symptom, 48.6% were in KK class D on admission. The use of mechanical ventilation (MV) was 50.4% vs. 5.1% (p<0.001). In patients with CA on admission, in-hospital mortality was 50.5% versus 4.6% (p<0.001). Mortality in patients with KK class D and CA on admission was 71%, and 36% in KK class D patients without CA (p <0.001). In multivariate analysis, diabetes and KK D were independent predictors of CA.
Conclusion: One out of 7 STEMI patients arrives at a healthcare center with CA as the presenting symptom. These patients exhibit an elevated risk profile, are less likely to receive reperfusion treatment and exhibit an increased incidence of heart failure, shock, and requirements of MV. Half of the patients presenting with CA die during hospitalization. This figure rises to 7 out of 10 if the patient also has cardiogenic shock on admission. Training staff in cardiopulmonary resuscitation (CPR) and post-cardiac arrest management is essential to reducing mortality.

Keywords: Myocardial infarction - Cardiac arrest - Registry

RESUMEN

Introducción: El paro cardiorrespiratorio (PCR) en el contexto de un síndrome coronario agudo es una causa importante de muerte, tanto extra como intrahospitalaria. Algunos pacientes presentan PCR como manifestación inicial del cuadro, y si bien casi la mitad de ellos no llegan a los centros asistenciales y fallecen, otros pueden ser ingresados.
Objetivos: 1) Describir la prevalencia de PCR como forma de presentación en el infarto agudo de miocardio con elevación del segmento ST. 2) Analizar las características de dichos pacientes, el tratamiento y la mortalidad intrahospitalaria.
Material y métodos: Se trata de un análisis retrospectivo de los pacientes incluidos en el registro ARGEN-IAM-ST. Se recabaron datos acerca de las características de los pacientes, estrategias de reperfusión y evolución intrahospitalaria. La ficha de registro en

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Redcap cuenta con un ítem llamado "forma de presentación" y allí los médicos consignan tanto el Killip y Kimball (K-K) de ingreso como si hubo PCR (casillas de si/no). Se definió PCR al brusco cese de la actividad cardíaca que puede conducir a la muerte si no se toman medidas de reanimación o si estas no son exitosas.

Resultados: Se incluyeron 7505 pacientes entre marzo de 2014 y abril de 2025. Un 7,5 % tuvo PCR como forma de presentación (n= 564). Los pacientes que se presentaron con PCR fueron más añosos (mediana de 62 vs. 61 años) y con mayor prevalencia de diabetes (32,8 % vs. 26,8 %), hipertensión arterial (61 % vs. 53,5 %), antecedentes coronarios (16,5 % vs. 14,9 %), enfermedad pulmonar obstructiva crónica, (4,8 % vs. 2,9 %,) y enfermedad vascular periférica (2,1 vs. 1,1 %), en todos los casos con diferencia estadísticamente significativa. En la cinecoronariografía presentaron más frecuentemente lesión de tronco de coronaria izquierda (6,7 % vs 0,9 %, p <0,001) descendente anterior (48,6 % vs. 47,6 %, p <0,001) y múltiples vasos (32,3 % vs 29,5%, p=0,004). Asimismo, fueron menos reperfundidos (85,2 % vs. 90,9 %, p<0,001) y recibieron menos angioplastia transluminal coronaria (ATC) primaria (67,9 % vs. 75,2 %, p=0,014). No hubo diferencias en el tiempo puerta balón entre los que recibieron ATC. El 48,6 % de los pacientes con PCR como forma de presentación tuvieron también Killip y Kimball (KK) D al ingreso. El uso de asistencia respiratoria mecánica (ARM) fue de 50,4 % vs 5,1 %, (p<0,001). La mortalidad intrahospitalaria de los pacientes con y sin paro cardiorrespiratorio (PCR) al ingreso fue del 50,5 % versus 4,6% respectivamente (p<0,001). La mortalidad de aquellos en K-K D con PCR de ingreso fue del 71 % y del 36 % en los K-K D que ingresaron sin dicha condición (p<0,001). En análisis multivariado la diabetes y el KK D fueron predictores independientes de PCR.

Conclusión: Uno de cada 7 pacientes con infarto con elevación del segmento ST que llega a los centros asistenciales se presenta con PCR. Los pacientes que ingresan con PCR tienen un perfil de riesgo más elevado, son menos reperfundidos y presentan más insuficiencia cardíaca, shock y uso de ARM que los que no lo presentan. La mitad de los pacientes con PCR como forma de presentación fallecen durante la internación, lo que se eleva a 7 de cada 10 pacientes si además se acompañan de KK D de ingreso. Es vital contar con personal entrenado tanto en la atención del PCR como en los cuidados post paro para intentar disminuir la mortalidad.

Palabras clave: Infarto - Paro Cardíaco - Registro

INTRODUCTION

The ARGEN-IAM-ST registry includes patients with ST-segment elevation acute myocardial infarction (STEMI) lasting less than 36 hours. Maintained continuously for over 10 years by the Research Area of the Argentine Society of Cardiology and the Argentine Federation of Cardiology, this registry allows the analysis of various aspects of myocardial infarction in our country. (1,2)

Cardiac arrest (CA) is the most frightening and serious event in patients with STE acute coronary syndrome (ACS), (3) and it is responsible for half of all STEMI patients' deaths before hospital admission. (4) The most common underlying cause is the development of ischemia-induced ventricular tachycardia/ventricular fibrillation (VT/VF), (5) a condition that can be reversed with the use of a defibrillator. This underscores the importance of having defibrillators available in places with high concentrations of people and emergency services, since ACS is the most common cause of out-of-hospital CA. (6)

The aim of this study was to define and analyze the prevalence, characteristics, and in-hospital course of patients with CA as presenting symptom of STEMI who are transferred to hospital.

METHODS

The database of patients included in the ARGEN-IAM-ST registry from March 2014 to March 2025 was analyzed.

Cardiac arrest was defined as the sudden cessation of cardiac activity that can lead to death if resuscitation measures are not taken or if they are unsuccessful. Cardiac arrest as presenting symptom of STEMI was considered when researchers checked the "presenting symptom" box in the presenting symptom section of the case record form. This form also documents the Killip and Kimball class on admission.

Cardiac arrest occurring after the first 24 hours of STEMI is recorded in the "in-hospital complications" section of the case record form and was not analyzed in this study.

Inclusion criteria: STEACS within 36 hours from the onset of symptoms.

Exclusion criteria: death before hospital admission, non-STEACS, CA resuscitated for a cause other than STEACS.

Statistical analysis

The variables of interest were included in a frequency table. Quantitative variables with normal distribution were expressed as mean and standard deviation, and those with non-normal distribution as median and interquartile range (IQR) 25%-75%, and were compared using the Student's t-test or the Wilcoxon, according to their distribution. Qualitative variables were expressed as percentages and were compared using the chi-square test or Fisher's exact test, as appropriate.

A multiple logistic regression analysis was performed on variables with statistical differences and a p-value ≤ 0.10 between patients with and without CA. To define the independent predictors of the outcome, the strength of association of each variable with the response variable was expressed by its odds ratio (OR) and 95% confidence interval. A two-tailed p-value < 0.05 was considered statistically significant.

Ethical considerations

The protocol design of the ARGEN-IAM-ST registry was evaluated and approved by the Committee on Bioethics of the Argentine Society of Cardiology, and was subjected to evaluations of the local committees, depending on the local regulations and institutional policies.

RESULTS

A total of 7690 STEMI patients were included between March 2014 and April 2025. Then, 185 patients were excluded from the analysis because the box "CA as presenting symptom" was not checked (yes/no). Of the 7505 patients, 564 had CA as presenting symptom

(7.5%). Table 1 compares the baseline characteristics according to the presence or absence of CA on presentation.

Patients with CA as presenting symptom were older (median age of 62 vs. 61 years) and had a higher prevalence of diabetes, hypertension, coronary artery disease, peripheral vascular disease, and chronic obstructive pulmonary disease. Only 31.2% of patients with CA as presenting symptom were in Killip and Kimball (KK) class A on admission, compared to 80.1% of those who did not present with CA ($p<0.001$). Half of the patients with CA presented with KK class D, compared to only 4% of those who did not present with CA.

On coronary angiography, lesions of the left main coronary artery, left anterior descending coronary artery and multivessel disease were more common in patients presenting with CA. Nevertheless, reperfusion therapy and primary percutaneous coronary interventions (PCI) were less common in these patients (85.2% vs. 90.9% and 67.9% vs. 75.2%, respectively). All these differences were statistically significant. There were no differences in infarct location and door-to-balloon time between those patients undergoing PCI with or without CA on admission. Almost 50% of patients with CA as presenting symptom also had KK class D on admission. The use of mechanical ventilation (MV) was 50.4% vs. 5.1% ($p<0.001$). In patients with CA on admission, in-hospital mortality was 50.5% compared to < 5% in the rest of the patients ($p<0.001$). Mortality in patients with KK class D and CA on admission was 71%, compared to 36% in KK class D patients without CA ($p <0.001$). Length of hospital stay was longer in patients who presented with CA.

Multivariate analysis using multiple logistic regression revealed that a history of diabetes (OR 1.32; 95% CI 1.051-1.668; $p=0.016$) and KK class D on admission (OR 21.593; 95% CI 17.052-27.343; $p <0.001$) were independently associated with CA as presenting symptom. (Table 2)

DISCUSSION

The prevalence of CA as presenting symptom was 7.5%in our population, similar to that described in other population-based registries. (7-11) As described in other studies, (12, 13) STEMI patients presenting with CA have a higher clinical risk profile, including higher prevalence of diabetes, history of coronary artery disease and heart failure, and left main and multivessel coronary artery disease. In our case, they were also older. There were no differences in infarct location, and both groups had a high rate of reperfusion therapy use, although it was lower among patients with CA. Most patients underwent primary PCI, in accordance with standard guidelines, (14) with similar times to those of patients without CA. However, in-hospital mortality in CA patients was significantly higher (50%), consistent with the 40%-60% mortality rate reported in other studies (15,16). This is in marked contrast to the 5% mortality rate observed in STEMI patients without CA, underscoring the critical role this event plays in infarction risk scores. (17) The high prevalence of cardiogenic shock (CS) on admission in the group of patients who presented with CA was a striking finding. It is important to note that CS can be due to different circumstances, including infarct size, a history of previous infarction, and myocardial dysfunction induced by the release of pro-inflammatory cytokines and catecholamine excess during CA, resuscitation, and return to spontaneous circulation. (18) This final possibility is supported by the observation that CS also develops in almost two-thirds of patients resuscitated from CA for any etiology, not just after AMI. (19-22) As in other studies, (23-25) the association of CA and CS resulted in higher mortality, which in our study reached 7 out of 10 patients in this situation. This further highlights the importance attributed to the presence of CA as a risk modulator in the SCAI classification of cardiogenic shock. (26) Factors associated with a worse prognosis in STEMI patients and CA include advanced age, delayed initiation of resuscitation maneuvers, the presence of asystole as initial rhythm, kidney injury, longer time to return to spontaneous circulation, and ventricular dysfunction on admission. The culprit vessel is also a relevant clinical determinant, since STEMI secondary to occlusion of the left anterior descending coronary artery is usually accompanied by worse outcomes due to the greater extent of myocardial damage. (27) Similarly, anterior wall infarction is recognized as an independent predictor of mortality in STEMI patients undergoing primary percutaneous coronary intervention. (28)

In our study, diabetes was an independent variable associated with CA on admission. While the evidence supporting this association is currently limited, the pathophysiological mechanisms involved include a greater extent of epicardial disease and microvascular coronary artery disease. This leads to a high incidence of non-reflux phenomenon and a lower rate of myocardial reperfusion, resulting in greater myocardial damage. (29)

Overall in-hospital mortality rate in our registry was 8%, and heart rhythm could be recorded in 97% of cases of CA. Our findings indicate that in 60% of these cases, CA was precipitated by VT/VF, a condition known to be associated with improved survival when accompanied by early defibrillation in both out-of-hospital and in-hospital cardiac arrests. This observation underscores the critical importance of continuous electrocardiographic monitoring of patients, as it directly impacts prognostic outcomes. (30-32)

Previously, it was thought that STEMI patients who experienced CA and survived the in-hospital stage had a similar prognosis to those without CA. (33) However, it is now known that these patients remain with a higher risk of death up to 30 and 90 days after the event. (34) Only after one year does this risk

Table 1. Baseline characteristics of the population according to the presence or absence of CA as presenting symptom.

	CA YES n = 564 7.5%	CA NO n = 6941 92.5%	p-value
Age	62 (56-71)	61 (53-69)	< 0.001
Male sex	433 (76.8)	5486 (79.0)	0.109
Diabetes	185 (32.8)	1858 (26.8)	0.001
Current smoking	197 (34.9)	2672 (38.5)	0.168
Dyslipidemia	224 (39.7)	2589 (37.3)	0.131
Hypertension	344 (61.0)	3712 (53.5)	<0.001
Obesity	105 (18.6)	1545 (22.3)	0.243
FH	67 (11.9)	1037 (14.9)	0.020
History of coronary artery disease	93 (16.5)	1037 (14.9)	0.021
History of heart failure	20 (3.5)	126 (1.8)	0.006
COPD	27 (4.8)	201 (2.9)	0.012
CKD	5 (0.9)	62 (0.9)	0.512
AF/AFL	3 (0.5)	26 (0.4)	0.332
Stroke	9 (1.6)	100 (1.4)	0.435
PVD	12 (2.1)	74 (1.1)	0.021
Anemia	5 (0.9)	22 (0.3)	0.047
Reperfusion	481 (85.2)	6312 (90.9)	<0.001
Anterior MI	230 (40.7)	2691 (38.8)	0.183
Primary PCI	383 (67.9)	5219 (75.2)	0.014
Fibrinolytic therapy	75 (13.3)	803 (11.6)	0.062
Both	48 (8.5)	522 (7.5)	0.124
Multivessel disease	182 (32.3)	2048 (29.5)	0.004
LAD culprit vessel	211 (37.4)	2783 (40.1)	<0.001
LMCA culprit vessel	29 (5.1)	53 (0.8)	<0.001
Door-to-balloon (min)	86 (44-148)	78 (45-135)	0.211
Door-to-needle (min)	28 (15-32)	30 (17-35)	0.585
KK A on admission	177 (31.24)	5563 (80.1)	<0.001
KK B on admission	85 (15.1)	964 (13.9)	<0.001
KK C on admission	13 (2.3)	98 (1.4)	<0.001
KK D on admission	274 (48.6)	274 (3.9)	<0.001
Requirements of MV	284 (50.4)	355 (5.1)	<0.001
KK D during hospitalization	284 (50.4)	432 (6.2)	<0.001
Length of hospital stay	4 (0-7)	4 (3-6)	<0.001
Death	285 (50.5)	319 (4.6)	<0.001

AF/AFL: atrial fibrillation/atrial flutter; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; FH: family history; KK: Killip and Kimball; LAD: left anterior descending coronary artery; LMCA: left main coronary artery; min: minutes; MV: mechanical ventilation; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease.
Qualitative variables are presented as frequency and percentage, and quantitative variables are expressed as median and interquartile range.

equalize with that of patients who did not experience CA. (35) It is imperative to consider this aspect when developing post-discharge follow-up and personalized treatment strategies for this subgroup of patients, taking into account their clinical risk.

Study limitations

The data reported are derived from STEMI patients included in the continuous ARGEN-IAM-ST registry, which means that the centers are affiliated with scientific societies (SAC/FAC), and therefore may not

Table 2. Multivariate analysis. Predictors of clinical presentation with cardiopulmonary arrest in STEMI patients

Variable	OR	95% CI	p-value
Age	0.99	0.99-1.00	0.689
Diabetes	1.32	1.05-1.69	0.016
History of coronary artery disease	1.24	0.92-1.68	0.155
Reperfusion	0.84	0.46-1.51	0.559
Multivessel disease	0.89	0.71-1.12	0.330
KK class D on admission	21.60	17.05-27.34	<0.001

95% CI: 95% confidence interval; KK: Killip and Kimball; OR: odds ratio; STEMI: ST-segment elevation myocardial infarction

represent the reality of all patients in the country. Additionally, there is a lack of specific data regarding certain characteristics of CA, including whether it occurred in in-hospital or out-of-hospital contexts, the duration of resuscitation maneuvers, and whether the patient was lucid or comatose post-CA.

CONCLUSION

One out of seven STEMI patients arriving at a healthcare center presents with a CA as the initial manifestation. These patients have an elevated risk profile, are less likely to receive reperfusion treatment and exhibit an increased incidence of heart failure, shock, and longer length of hospital stay. More than half of patients presenting with CA die during hospitalization. This figure rises to 7 out of 10 in the presence of cardiogenic shock on admission. It is imperative to ensure the availability of defibrillators from the early stages of care to minimize the time to treatment in this potentially fatal complication.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Percutaneous Pulmonary Valve Replacement in Native Right Ventricular Outflow Tract. One-Step Technique Using a Balloon-Expandable Valve: Initial Experience in Argentina

Reemplazo percutáneo de válvula pulmonar en tracto de salida nativo. Técnica de implante en "un paso" con válvula balón expandible: experiencia inicial en Argentina

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ABSTRACT

Background: The adverse impact of pulmonary valve incompetence (PVI) has been extensively studied in patients with tetralogy of Fallot (TOF) after surgical repair. Percutaneous pulmonary valve replacement (PPVR) with balloon-expandable and self-expanding valves is an alternative to surgical reintervention.
Objective: The aim of this study is to report on the initial experience of PPVR using a one-step implantation technique with a balloon-expandable heart valve in Argentina.
Methods: We conducted an observational and descriptive study of all consecutive patients treated with PPVR due to severe and/or free PVI with signs of right ventricular dilation/dysfunction who underwent transannular patch repair as part of the initial correction of their congenital heart disease. The one-step technique was defined as valve implantation in the native right ventricular outflow tract (RVOT) without prior stent placement to prepare the landing zone. A balloon-expandable Myval® valve (Meril LifeScience, India) was implanted in all cases.
Results: From July 2023 to April 2025, 10 patients (8 males) underwent PPVR. Three patients had previously required stenting of the left pulmonary artery branch. Median age and weight were 20 years (interquartile range, IQR, 12.5–34.3) and 61.3 kg (33.7–77.2), respectively. All patients were in functional class II. Valve implantation was successful in all cases. None of the patients exhibited significant RVOT gradient or PVI immediately after valve implantation. One patient presented mild paravalvular leak immediately after valve implantation and another increased the gradient 7 months after implantation.
After a median follow-up of 6.7 months (1.2-15.7), PVI remained grade 0 in all patients and mean peak systolic gradient across the valve, estimated by color Doppler, was 21.8 mm Hg (15-30.1). There were no cases of valve displacements and/or fractures, episodes of arrhythmias, infective endocarditis, need for valve explantation, or deaths during short- and mid-term follow-up.
Conclusions: Percutaneous pulmonary valve replacement in native RVOT using a one-step technique with a balloon-expandable valve is feasible, safe and efficient in this preliminary experience in Argentina. Inmediate restoration of pulmonary valve competence was observed after implantation.

Keywords: Tetralogy of Fallot, congenital heart disease, interventional cardiology, pulmonary valve, percutaneous valve replacement.

RESUMEN

Introducción: La incompetencia valvular pulmonar (IVP) ha sido ampliamente estudiada en pacientes con tetralogía de Fallot después de la reparación quirúrgica. El reemplazo percutáneo de válvula pulmonar (RPVP) con válvulas expandibles con balón y autoexpandibles es una alternativa a una reintervención quirúrgica.
Objetivo: Reportar la experiencia inicial de RPVP con técnica de implante en "un paso" con válvula balón expandible en Argentina
Material y métodos: Estudio observacional descriptivo. Se enrolaron todos los pacientes consecutivos tratados con RPVP debido a IVP grave y/o libre con signos de dilatación/disfunción ventricular derecha, a quienes se había colocado un parche transanular como parte de la corrección inicial de su cardiopatía congénita. Se consideró técnica de "un paso" el implante en tracto de salida nativo (TSN) sin preparación previa (pre dilatación y/o colocación de *stent* como "zona de anclaje"). Se utilizó la válvula balón expandible de pericardio bovino Myval® (Meril LifeScience, India).

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Resultados: Desde julio de 2023 hasta abril de 2025, 10 pacientes (8 varones) fueron intervenidos. Tres habían requerido colocación de *stent* en rama pulmonar izquierda previamente. La mediana de edad y peso fueron 20 años (rango intercuartílico, RIC, 12,5 - 34,3) y 61,3 kg (33,7 - 77,2) respectivamente. Todos los pacientes estaban en clase funcional II. El éxito de la implantación valvular se logró en todos los casos. Ninguno de los pacientes tuvo un gradiente significativo del tracto de salida del ventrículo derecho (TSVD) o IVP inmediatamente después del implante de la válvula. Un paciente presentó fuga paravalvular inmediata de grado leve, y otro, elevación del gradiente 7 meses posteriormente al implante.
En un seguimiento medio de 6,7 meses (1,2 - 15,7), la IVP permaneció en grado 0 en todos los pacientes y el gradiente pico sistólico medio por Doppler color a través de la válvula fue de 21,8 mm Hg (15 - 30,1). No se registraron desplazamientos y/o fracturas de las válvulas como tampoco episodios de arritmias, endocarditis infecciosa, necesidad de explante valvular ni fallecimientos durante el seguimiento.
Conclusiones: El RPVP en TSN con técnica de "un paso" utilizando una válvula balón expandible es posible, seguro y eficaz en esta experiencia preliminar en Argentina. Se observó restauración inmediata de la competencia valvular pulmonar post implante.

Palabras clave: Tetralogía de Fallot - Cardiopatías congénitas - Cateterismo intervencionista - Válvula pulmonar - Reemplazo valvular percutáneo

INTRODUCTION

Right ventricular outflow tract (RVOT) disorders are highly prevalent in children and adults with congenital heart disease. These disorders are often residual lesions that remain after previous surgery. (1) Improved survival in these patients has led to the identification of sequelae as arrhythmias and right heart failure resulting from right ventricular volume overload or pressure overload due to pulmonary valve dysfunction. (2) Historically, surgical pulmonary valve replacement has been the strategy of choice and is still performed nowadays with high levels of effectiveness. (3) In recent decades, the utilization of percutaneous pulmonary valve replacement (PPVR) has experienced exponential growth, to the point that treatment algorithms for RVOT dysfunction recommend it as the preferred strategy in patients with previous conduits, homografts, or bioprosthetic valves. (4,5) However, many patients have native or patched tracts (hereafter referred to as native RVOTs), in which the predominant lesion is pulmonary valve regurgitation (PVR). In such cases, percutaneous implantation is more complex due to the anatomy of the RVOT, its dynamic behavior, larger pulmonary valve annulus diameter, and the lack of an adequate landing zone for the valve. The differences in underlying congenital heart diseases, the type of previous surgical repair, and the anatomy of the pulmonary arteries result in RVOTs with variable morphology, posing significant challenges in planning and selecting patients. Recently, small studies have been published about the use of PPVR in native RVOTs, adapting heart valve prostheses to larger and more complex dimensions and anatomies. (6) In Argentina, most patients with tetralogy of Fallot (TOF) and its variants have undergone transannular patch repair, resulting in large RVOTs. This anatomy is challenging for the placement of balloon-expandable valves using a one-step technique (without previously preparing the landing zone for valve insertion).

We present the initial experience in our country with the balloon-expandable MyVal® (Meril Life Sciences, India) transcatheter heart valve (THV) for PPVR in native RVOTs using a one-step technique, along with a report on the immediate and mid-term results.

OBJECTIVE

The aim of this study is to report on the initial experience of PPVR using a one-step implantation technique with a balloon-expandable heart valve in Argentina.

METHODS

We conducted an observational and descriptive study of all consecutive patients treated with PPVR due to severe and/or free PVR with signs of right ventricular dilation/dysfunction who underwent transannular patch repair as part of the initial correction of their congenital heart disease. Cases were selected on an individual basis according to a pre-established study protocol. The one-step technique was defined as valve implantation in the native RVOT without previous dilation or stent placement for preparing the landing zone.

A balloon-expandable Myval® valve (Meril LifeScience, India) was implanted in all cases. This valve features a hybrid frame design, with a distal part consisting of hexagonal open cells and a proximal part featuring tightly packed hexagonal closed cells made of a nickel-cobalt alloy. The valve is made of bovine pericardium that has undergone anti-calcium treatment. It also has a proximal polyester polymer skirt to minimize the possibility of perivalvular leaks. A 14-Fr expandable sheath is used for implantation, and its maximal diameter reaches 34 mm. The valve is available in conventional (diameter 20, 23, 26, and 29 mm) and intermediate (diameter 21.5, 24.5, 27.5, 30.5 mm) sizes.

The variables analyzed included demographics and all data available before the procedure, during the procedure and at short and mid-term follow-up. After the procedure, all patients received aspirin 100 mg/day indefinitely.

Statistical analysis

Data collection and statistical analysis were performed in accordance with the guidelines for reporting mortality and morbidity after cardiac valve interventions. (7) Categorical variables are expressed as percentages. Continuous variables are expressed as median and interquartile range 25-75.

Ethical considerations

Percutaneous pulmonary valve replacement in native RVOT using a one-step technique with a balloon-expandable valve as an alternative to a new corrective surgery was approved by the institutional review board. Prior to undergoing the procedure, all adult patients or their parents or guardians

(in the case of minors), were required to sign a health information form. The study was conducted following the recommendations of the Declaration of Helsinki. (8).

RESULTS

From July 2023 to April 2025, 10 patients (8 males) underwent PPVR using the Myval® valve (Meril LifeScience, India) in native RVOTs with a one-step technique (Table 1). The primary diagnosis for the entire cohort was TOF; one patient had absent pulmonary valve variant, and another had acquired absence of the left pulmonary artery branch. Three patients had previously required stenting of the left pulmonary artery branch. All patients were in NYHA functional class II and had PVR after the initial transannular patch repair of their RVOTs. Median age was 20.2 years (IQR, 12.5–34.3) and median weight was 61.3 kg (IQR, 33.7–77.2). All patients were in NYHA functional class II and had PVR after the initial transannular patch repair of their RVOTs.

The median time since the last surgical repair was 13 years (8.7–19.5). Mean QRS duration was 143.4 ms (97.5–137.2). Pulmonary valve regurgitation, assessed by transthoracic color Doppler echocardiography, was grade 4 in all cases, with a median pulmonary annulus diameter of 24.5 mm (22.4–31). On cardiac magnetic resonance imaging, mean RV end-diastolic volume index was 151.4 mL/m^2 (137.7–189.7), RV end-systolic volume index was 81.6 ml/m2 (73–90.2), regurgitation fraction was 52.4% (41–63.4), and RV ejection fraction was 47% (40.3–54.6). In all cases, the RVOT was measured beforehand with a non-compliant balloon during cardiac catheterization to select the diameter of the pulmonary valve to be implanted. The potential for distortion and/or compression of the coronary arteries post-implantation was ruled out by performing a selective coronary angiography concomitant with inflation of the non-compliant balloon in the RVOT (Figure 1). All patients underwent temporary RV apical pacing during balloon inflation and valve implantation at heart rates between 180 and 200 beats per minute to prevent device migration and/or malposition.

Valve implantation was successful in all cases, with a mean fluoroscopy time of 26.5 min (23.7–39.4) (Figure 2). The diameters of the implanted valves were 24.5 mm (n = 1), 26 mm (n = 1), 27.5 mm (n = 2),

Table 1. Demographic data, anatomical diagnosis, types of surgery, valves used, and complications

Patient	Sex	Age (years)	Weight (kg)	Congenital heart defect	Type of repair	Valve and size (mm)	Final valve size implanted (mm)	Complications
#1	M	15	103	TOF	Transannular patch + LPAB stenting	Myval 24.5	25.4	Redilation 7 moths after implantation
#2	M	15	51	TOF	Transannular patch	Myval 32	30.5	No
#3	F	29	85	TOF	PV-sparing	Myval 30.5	31	No
#4	F	28	59	TOF	Transannular patch + LPAB stenting	Myval 26	24.5	No
#5	M	13	69	TOF	Transannular patch + LPAB stenting	Myval 27.5	26.8	No
#6	M	46	77	TOF	Transannular patch	Myval 30.5	28.4	No
#7	M	10	27	TOF Absent PV	Transannular patch	Myval 27.5	26.8	No
#8	M	13	27	TOF with absent LPAB	Transannular patch	Myval 32	29.7	No
#9	M	17	70	TOF	Transannular patch	Myval 32	30.4	Mild perivalvular leak
#10	M	16	45	TOF - Coronary artery anomaly	Transannular patch	Myval 30.5	28.7	No

LPAB : left pulmonary artery branch; PV: pulmonary valve; TOF: Tetralogy of Fallot

30.5 mm (n = 3), and 32 mm (n = 3). Mean pulmonary artery diastolic pressure increased from 11 mm Hg to 21.2 mm Hg. None of the patients exhibited significant RVOT gradient or PVR immediately after valve implantation, although one patient presented mild paravalvular leak immediately after valve implantation. The mean length of hospital stay was 36 hours (24-72). After a median follow-up of 6.7 months (1.2-15.7), PVR remained grade 0 in all patients, mean peak systolic gradient across the valve, estimated by color Doppler, was 21.8 mm Hg (15-30.1), and functional class improved to NYHA I in 9 patients. Only one patient increased the gradient 7 months after implantation and required high-pressure balloon dilation which reduced the gradient to 21 mm Hg. There were no cases of valve displacements and/or fractures, episodes of arrhythmias, infective endocarditis (IE), need for valve explantation, or deaths during short- and mid-term follow-up.

DISCUSSION

The adverse impact of PVR has been extensively studied in patients with TOF after surgical repair. (4) Percutaneous pulmonary valve repair using balloon-expandable valves is an established alternative to surgical reintervention and its use is limited to patients with dysfunctional conduits between the RV and pulmonary artery as well as on bioprosthetic valves. (4,5) Most TOF patients have undergone transannular patch repair, resulting in large RVOTs. (9) This anatomy is a challenge for the placement of balloon-expandable valves using a one-step technique.

Currently, two models of balloon-expandable valves are commercially available and approved for the treatment of dysfunctional bioprosthetic valves and conduits/homografts: the Melody® (Medtronic, United States) and Sapien® (model S3, Edwards Lifesciences, United States) bioprosthetic valves. Although they have not yet been authorized for implantation in native RVOTs, both have been used off-label in this setting. (10) The Melody heart valve prosthesis has a maximum diameter of 24 mm, while the Sapien S3 has a maximum diameter of 29 mm. To address the specific characteristics of native RVOTs, several models of self-expanding valves have been developed, such as the Venus-P® (Venus MedTech, China), PULSTA® (TaeWoong Medical, South Korea), and Harmony valves (Medtronic, United States) which have a maximum diameter of 34 mm according to the different models. The Alterra® device (Edwards Lifesciences, United States) has also been used. This valve serves as a self-expanding prestent onto which a SAPIEN S3 valve is later implanted.

In recent years, there has been a significant increase in the availability of data regarding the efficacy, safety, and durability of percutaneous valves implanted in the pulmonary position. The study with the largest number of cases is the IMPACT registry, conducted by the American College of Cardiology, which included 4513 patients who were treated with PPVR (57% with Melody valves and 43% with Sapien valves). Thirty-three percent of valve implants were into homograft conduits, another 33% into bioprosthetic valves, 25% were in native RVOTs, and 6% were into Contegra® conduits (Medtronic, United States). Success was achieved in 95% of patients (95.7% in homo-

Figure 1. (**A**) Angiography in right anterior oblique projection (45°) of the right ventricular outflow tract (RVOT). (**B**) Measurement of the RVOT with non-compliant balloon concomitant with right ventriculography to rule out peri-balloon leaks and estimate the correct diameter of the valve to be implanted. (**C**) Selective angiogram of the left coronary artery simultaneously with RVOT measurement with non-compliant balloon to rule out distortion and/or compression of the valve

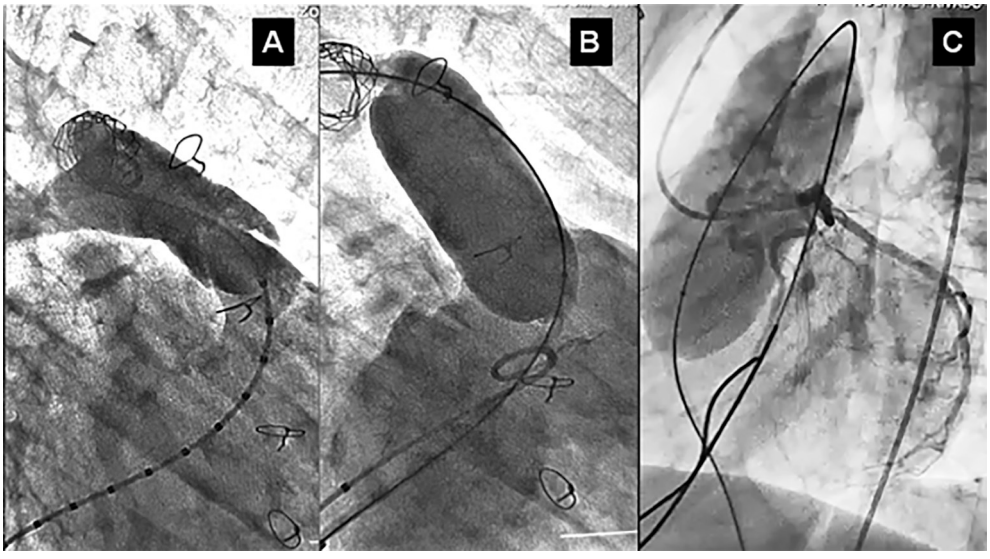
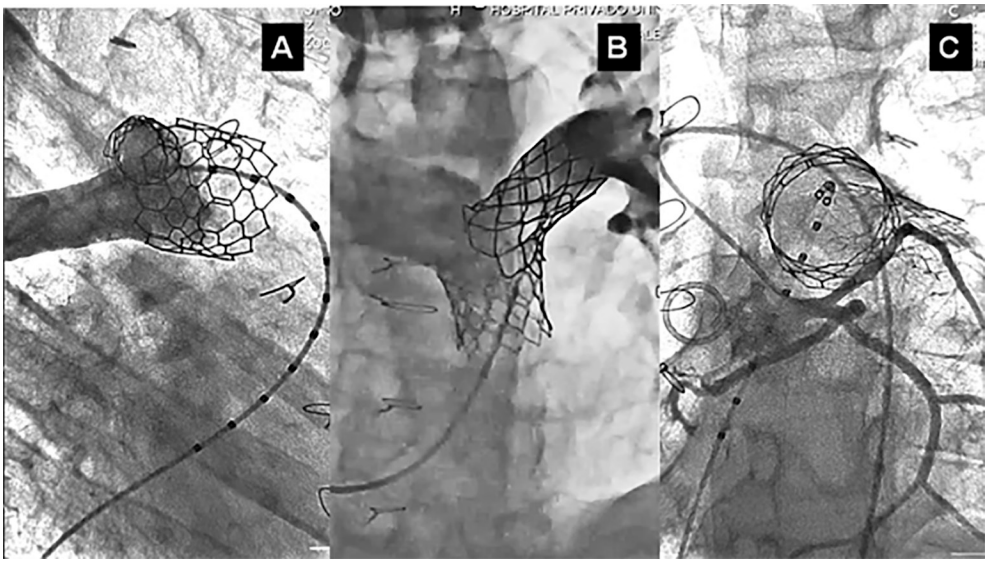


Figure 1. (**A**) Right ventricular outflow tract (RVOT) in right anterior oblique projection (45°) and (**B**) in left anterior oblique projection (30°) – cranial angulation (30°), with the valve in situ demonstrating the absence of residual valve regurgitation and perivalvular leaks. Its relationship to the stent previously placed in the left pulmonary artery branch is also observed. (**C**) Selective coronary angiography with valve in situ in the left anterior oblique projection (20°) - caudal angulation (30°), showing the integrity of the coronary arteries after valve implantation and the optimal circular expansion of the prosthetic valve, ruling out its underexpansion.



grafts, 96.2% in bioprosthetic valves, 94.2% in native RVOTs, and 95.4% in Contegra conduits). Adverse events occurred in 2.4% of patients, most commonly in homografts (2.9%) or native RVOTs (3.4%). (11)

Another multicenter registry, which included a significant number of patients, reported 2476 cases. The data indicate that 82% of the cases involved Melody valves, while 18% utilized SAPIEN valves, with 16% of these cases involving implants in native RVOTs. The 8-year survival rate following implantation was 91.1%, with a reintervention rate of 25.1%, which is consistent with the rates reported in other surgical series. (12,13)

Self-expanding valves were designed for large diameter RVOTs, adapting to the different and challenging anatomies of the outflow tracts with more stable fixation. The published data suggest a very high implant success rate with encouraging results during short- and mid-term follow-up, including a low complication rate. (14,15) Although the initial results of implanting these self-expanding valves were favorable, warnings have recently been published regarding their complications, including perforations of the main pulmonary artery and complex ventricular arrhythmias. (16-18) Regarding the latter, future access to the RVOT for an electrophysiology study with potential ablation of an arrhythmic substrate may be limited by the presence of the valve metal mesh in the anatomical site. (19)

The higher incidence of IE has been widely reported and associated with patient-related risk factors, as adult age, male sex, history of IE, discontinuation of aspirin, unprotected exposure to high-risk medical procedures. Procedure-related factors that increase the risk of IE include longer procedures, a higher number of stents placed as landing zones, higher residual gradients, the presence of homografts or bioprosthetic valves, and valves composed of bovine jugular tissue compared to those made from bovine pericardium. (20)

Considering the most common anatomical characteristics of dilated native RVOTs in our setting, the reported effectiveness and safety of balloon-expandable valve placement, the cost-benefit ratio of the intervention, the complications described in self-expanding valves and devices, the higher incidence of IE in cases where a safe landing zone is created with stents, and, in addition, the availability of a user-friendly, balloon-expandable valve requiring a small-diameter sheath (14F) that expand to a maximum diameter of 34 mm, such as Myval® (Meril LifeScience, India), we decided to begin implanting these valves in native RVOTs using a one-step technique.

Our initial data show that the implant has a high success rate and that the procedure is safe and effective. It should be noted that patient selection is crucial and must include an evaluation using advanced imaging methods and prior cardiac catheterization with accurate measurements of the native RVOT using non-compliant balloons. Concomitant compression and/or coronary distortion must also be ruled out. This strategy can reduce the incidence of the most common complications of this procedure, as valve migration/embolization (0–4.5%) in large native RVOTs without

a prior landing zone, paravalvular leaks, and coronary compression/distortion (3%). Additionally, the utilization of long (65 cm) sheaths (W.L. Gore, United States) has been shown to prevent another less frequently described complication, such as tricuspid valve injury (3–6%). (18) In patients with anatomies that present more challenges, such as those with stents in the pulmonary artery branches, we demonstrated favorable outcomes in three cases in the present series, thereby indicating that this is not a relative contraindication for this strategy. Transient RV apical pacing during valve inflation is strongly recommended in order to avoid malposition or migration of the bioprosthetic valve, particularly in dynamic RVOTs with large diameter variability at different times of the cardiac cycle. The occurrence of mild paravalvular leak in one case and the need for early valve redilation in another case in our series suggest that it will be necessary to include a larger number of patients with a longer follow-up period to confirm the initial results of our experience. Regarding valve durability, one year of follow-up data is currently available, confirming acceptable results. (21,22)

Finally, we believe that PPVR in native RVOTs using a single-step strategy, as presented in this experience, offers clear and significant advantages. These include simplifying the procedure, making it less invasive and less risky by avoiding the placement of stents as a landing zone and therefore potentially reducing the incidence of IE and complex ventricular arrhythmias. Additionally, and a key advantage in our context, it is highly cost-effective.

There are limitations to this study. The data were collected retrospectively and from a single center with expertise in percutaneous valve implants; therefore, the results presented may not be generally applicable. There may also be selection bias due to the inclusion of high-risk patients with RVOT with severe or free PVR. Finally, this is an initial and preliminary report of a novel procedure involving the use of valves approved for off-label use in RVOT, with a clear need for longer-term follow-up.

CONCLUSIONS

Percutaneous pulmonary valve replacement in native RVOT using a one-step technique with balloon-expandable Myval® valves (Meril LifeScience, India) is feasible, safe and efficient in this preliminary experience in Argentina. Immediate restoration of pulmonary valve competence was observed after implantation. The appropriate selection of patients and the size of the valve to be implanted are crucial variables for the success of the procedure.

Conflicts of interest

None declared.

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

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BRIEF ARTICLE

Multicenter Pilot Registry of Spontaneous Coronary Artery Dissection in Argentina

Registro piloto multicéntrico de disección coronaria espontánea en Argentina

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ABSTRACT

Background: Spontaneous coronary artery dissection (SCAD) is a major cause of acute myocardial infarction (AMI) in young adults, especially in women between the fourth and sixth decade of life who have no cardiovascular risk factors. Considering the low incidence of SCAD and the lack of data in our setting, we decided to create a multicenter registry of the clinical and evolutionary characteristics of a population with this disease.
Objectives: The aim of this study was to describe the clinical characteristics, treatment, and mid- and long-term outcomes of a population of patients with SCAD in our country, where the disease was previously poorly described.
Methods: This was an observational and prospective study conducted in four private medical centers and two university hospitals. During the two years of recruitment (January 2023-January 2025), 26 patients with SCAD defined by an angiographic study were registered. Various parameters were analyzed, including age, sex, cardiovascular risk factors, triggering factors, psychosocial and physical stressors, comorbidities, laboratory findings, angiographic characteristics, disease resolution, recurrence, and evolution up to one year after discharge.
Results: Twenty-six patients with SCAD were included and analyzed over a two-year period. Twenty-two (84.6%) were women, and median age was 47 years (interquartile range, IQR, 42–56.5). Hypertension was the most prevalent cardiovascular risk factor, present in 9 patients (34.6%). Fibromuscular dysplasia was sought in 15.4% of cases, with no positive results. There were no cases related to pregnancy or the postpartum period. Stress, whether physical or emotional, was the triggering factor in 61% of patients (19% and 41%, respectively). All patients presented with acute coronary syndrome: 57.7% corresponded to non- ST-segment elevation acute coronary syndrome, and the remaining to ST-segment elevation acute coronary syndrome. The most affected vessel was the left anterior descending artery (61.5%), with type 2A dissection as the most common pattern found in 14 patients (53.8 %) and multiple dissections in 2 cases. Intracoronary ultrasound was used in only one case. Fifteen patients (57.7%) were treated conservatively, with beta-blockers in 100% of cases and aspirin in 92%. Percutaneous angioplasty was performed in 12 patients (46.1%). During hospitalization, two patients developed clinical and dynamic changes in the electrocardiogram, and only one underwent emergency angioplasty. No deaths or re-infarctions occurred during one-year follow-up.
Conclusion: Spontaneous coronary artery dissection occurs in young women, mainly as non-ST-segment elevation myocardial infarction. Stress was identified as the triggering cause in most cases. In this first pilot registry in our country, the clinical characteristics and treatment designs observed are consistent with those reported in international cohorts.

Key words: Acute myocardial infarction in young people - Fibromuscular dysplasia -Acute coronary syndrome

RESUMEN

Introducción: La disección coronaria espontánea (DCE) es una causa importante de infarto agudo de miocardio (IAM) en adultos jóvenes, especialmente en mujeres entre la cuarta y sexta década de la vida que carecen de factores de riesgo cardiovascular. Considerando la baja incidencia de DCE y la ausencia de datos en nuestro medio, decidimos generar un registro multicéntrico de las características clínicas y evolutivas de una población con esta enfermedad.

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Objetivos: Describir las características clínicas, el tratamiento y los resultados a mediano y largo plazo de una población de pacientes con DCE en nuestro país, donde la enfermedad no había sido bien descrita previamente.
Material y métodos: Estudio observacional y prospectivo llevado a cabo en 4 centros médicos privados y dos hospitales universitarios. Durante los 2 años de reclutamiento (enero 2023-enero 2025) se registraron 26 pacientes con DCE definida por un estudio angiográfico. Se analizaron diversos parámetros, incluyendo edad, sexo, factores de riesgo cardiovascular, factores desencadenantes, estresores psicosociales y físicos, comorbilidades, hallazgos de laboratorio, características angiográficas, resolución de la enfermedad, recurrencia y evolución hasta el año del alta.
Resultados: Se incluyeron y analizaron veintiséis pacientes con DCE durante un período de dos años. Veintidós (84,6 %) eran mujeres, y la mediana de edad 47 años (rango intercuartílico, RIC, 42-56,5). La hipertensión fue el factor de riesgo cardiovascular más común, presente en 9 pacientes (34,6 %). Se buscó displasia fibromuscular en el 15,4 % de los casos, sin resultados positivos. No hubo casos relacionados con el embarazo o puerperio. El estrés, físico o emocional, fue el factor desencadenante en el 61 % de los pacientes (19 % y 41 % respectivamente). Todos los pacientes se presentaron como síndrome coronario agudo; un 57,7 % correspondió a síndrome coronario agudo sin elevación del segmento ST, y el resto a síndrome coronario agudo con elevación del segmento ST. La arteria más afectada fue la descendente anterior (61,5 %). La disección tipo 2A fue la más comúnmente encontrada, en 14 pacientes (53,8 %); en 2 casos se encontraron múltiples disecciones. Se utilizó ultrasonido intracoronario en solo un caso. Respecto del tratamiento, 15 pacientes (57,7 %) fueron tratados de forma conservadora, de ellos el 100 % recibió betabloqueantes y el 92 % aspirina. Se sometieron a angioplastia percutánea 12 pacientes (46,1 %). Durante la internación, 2 pacientes evolucionaron con cambios clínicos y dinámicos en el electrocardiograma y en uno solo se realizó angioplastia de urgencia. En el año de seguimiento no hubo muertes ni reinfartos.
Conclusión: La DCE se presenta en mujeres jóvenes, principalmente como infarto sin elevación del segmento ST. Se identificó el estrés como causa desencadenante en la mayoría de los casos. En este primer registro piloto de nuestro país, las características clínicas y los patrones de tratamiento observados se alinean con los informados en cohortes internacionales.

Palabras clave: Disección coronaria espontánea - Infarto agudo de miocardio en jóvenes - Displasia fibromuscular - Síndrome Coronario Agudo

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is increasingly recognized as a cause of acute coronary syndromes (ACS) not due to plaque rupture or erosion or coronary embolization, especially in young women. It represents between one-third and one-quarter of acute myocardial infarctions in women under 50 years of age in various international cohorts, and between 15% and 20% of infarctions in pregnant women and during the postpartum period. (1-5)

Spontaneous coronary artery dissection is a condition not fully understood, although the formation in the arterial wall of an intramural hematoma caused by a tear in the intima or spontaneous hemorrhage of the vasa vasorum, not related to atherosclerosis, iatrogenesis, or trauma, is the most widely accepted pathophysiology. (1-4) Timely diagnosis is a predictor of outcome and guides definitive treatment according to the type of dissection, and unlike atherosclerotic infarction, a conservative management takes precedence over interventional treatment in most cases, the latter being reserved only for cases of acute artery occlusion, or those in which there is hemodynamic instability. (5-8)

There are several registries from developed countries that reflect specific aspects of the development, approach, mortality, and SCAD recurrence. However, this is not the case in the Latin American population, especially in Argentina. (5-7)

This article presents the first multicenter SCAD experience in Argentina, including patients from both public and private healthcare systems from 2023 to 2025. The purpose of this first stage was to describe demographic data, clinical presentation, hospital outcomes, established treatment, and one-year clinical follow-up in order to understand the approaches to this pathology in our country and thus standardize diagnostic and therapeutic criteria.

METHODS

This was an observational, descriptive, retrospective, multicenter study conducted in two public hospitals and four private medical centers in the Autonomous City of Buenos Aires from January 2023 to January 2025, with the aim of obtaining local data on an underdiagnosed and increasingly prevalent disease. Participating centers had to meet physical and human standards to ensure definitive diagnosis of the disease. All patients were prospectively included since 2023 in two centers and retrospectively in the rest of the participating centers. The diagnosis and classification of SCAD was according to the Yip-Saw et al. classification and the modification proposed by a group of national researchers. (7,8) The definitive diagnosis was agreed upon by the heads of the interventional cardiology and coronary care units at each participating center. Patients with iatrogenic dissection or diagnostic doubts were excluded. Following established evidence, intravascular imaging was not used as a diagnostic method. (1-4) Due to the expected small sample size, a descriptive analysis was performed of the baseline demographic, clinical, and angiographic characteristics, as well as the therapy used during hospitalization and follow-up treatment. The presence of precipitating and predisposing factors was also analyzed. In addition, unexpected events such as death, reinfarction, unexpected revascularization, coronary dissection recurrence, chest pain during follow-up, and follow-up with noninvasive imaging (coronary computed tomography) were evaluated.

All patients included in the registry signed an informed consent form and agreed to participate in the analysis. Identifying data were anonymized at each center and were known only by the local investigators, responsible for telephone or in person follow-up of each patient. The analysis was conducted in accordance with the Declaration of Hel-

sinki and its amendments, (9) the guidelines for good clinical research practices, and the Personal Data Protection Act No. 25236. (10)

Excel software (Microsoft Windows, USA) was used to transfer the study variables and perform the descriptive analysis.

RESULTS

Twenty-six patients diagnosed with SCAD at two public hospitals and four private medical centers in the Autonomous City of Buenos Aires were included over a two-year period (Figure 1). Most patients were women (84.6%). Median age was 47 years (interquartile range, IQR, 42-56.5), and hypertension was the most common cardiovascular risk factor, present in nine patients (34.6%), followed by dyslipidemia in six (23.1 %) and type 2 diabetes mellitus in three (11.5%). The rest of the clinical characteristics, in addition to the predisposing and precipitating factors identified, are described in Table 1, which shows emotional stress as the main precipitating factor present in eleven patients (42.3%).

The presence of muscular fibrodysplasia was explored in three patients using non-invasive imaging, with no pathological findings. None of the patients with a history of pregnancy reported complications during pregnancy.

The clinical presentation was with typical chest pain in 100% of patients, and in seven cases (26.9%) it was accompanied by dyspnea. Non-ST-segment elevation acute coronary syndromes (NSTEACS) were the most frequent electrocardiographic presentation, in 57.7% (n=15) of cases. Table 2 shows the symptoms and baseline diagnosis on admission. The most commonly affected vessel was the left anterior descending artery (n= 16, 61.5%), and the most frequent type of dissection was type 2A in fourteen patients (53.8%), with multiple dissections identified in two cases. The rest of the angiographic characteristics are presented in Table 3, together with the motility and function characteristics of the baseline echocardiogram. Concentric, septal, and apical ventricular hypertrophy was detected in four patients (15.3%).

Fifteen patients (57.7 %) were initially treated conservatively. Beta-blockers were used in 100% of cases, and aspirin in 92%. Among this group, one patient underwent revascularization during hospitalization due to hemodynamic instability. A total of twelve patients (46.1 %), underwent revascularization, eleven at baseline and one during hospitalization, all by angioplasty, with 1.9 stents per patient.

Twenty-three patients (88.4%) received statins at discharge. Among patients who received conservative treatment without stent implantation, 35.7% were discharged with dual antiplatelet therapy, 92.8% with at least one antiplatelet agent, and one patient was anticoagulated.

Regarding events, there were no deaths and one emergency revascularizations during hospitalization.

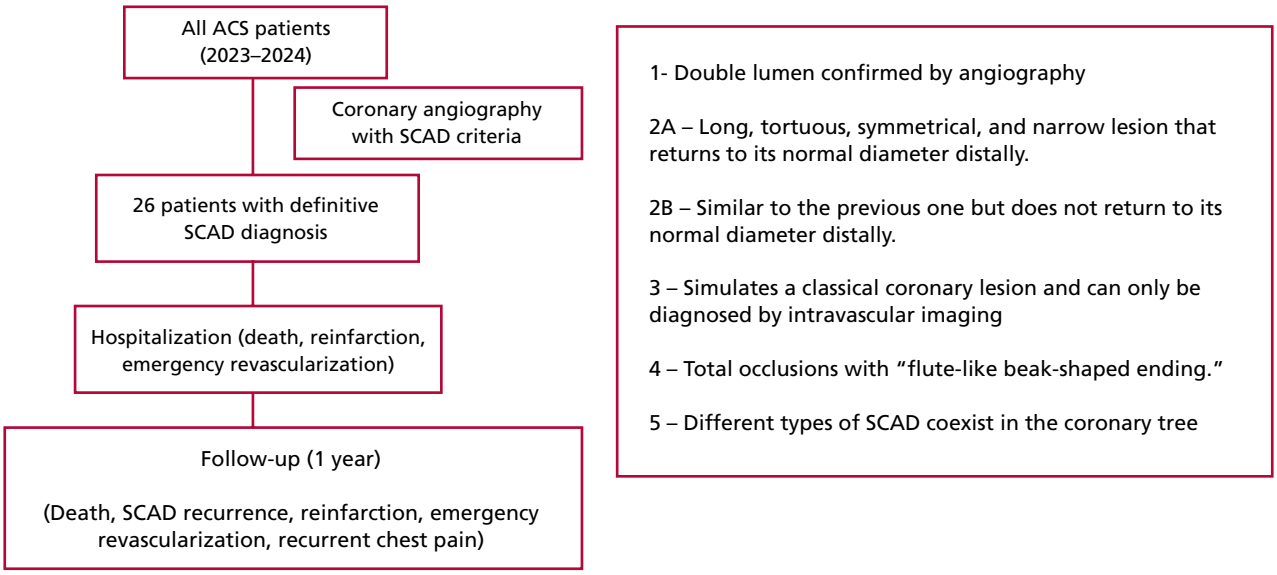
During follow-up, four patients (15.4 %) reported recurrent chest pain, and in three cases, anatomical evaluation was again performed, in two by coronary angiography and in one by computed tomography, without evidence of new dissections.

DISCUSSION

We present the first Argentine SCAD registry. Of note, a significant effort was made to recruit as many centers as possible and, hence patients with this rare disease.

Similarly, as in large global series, most cases were

Figure 1. Study design



ACS: acute coronary syndrome; SCAD: spontaneous coronary artery dissection

Table 1. Demographic, clinical, and angiographic characteristics.

Variable	
Female gender (%)	84.6
Age, years, mean (SD)	48.4 (10.3)
Cardiovascular risk factors (%)	
Smoking	23.1
Hypertension	34.6
Dyslipidemia	23.1
Diabetes	11.5
Family history of coronary heart disease, (%)	3.8
Weight, kg, mean (SD)	74.5 (15.6)
Height, cm, mean (SD)	155 (6.9)
Previous pregnancies, (%)	30.7
Predisposing factors (%)	
Current pregnancy	0
Postpartum period	0
Rheumatological diseases	11.5
Precipitating factors (%)	
Physical stress	19.2
Emotional stress	42.3
Toxic substances	7.7

SD: standard deviation

Table 2. Admission symptoms and electrocardiographic findings

Symptoms (%)	
Typical chest pain	10
Nausea/ vomiting	15.4
Dyspnea	26.9
Sudden death	3.8
Admission diagnosis (%) STEACS	42.3
NSTEACS	57.7

STEACS: ST-segment elevation acute coronary syndrome; NSTEACS: Non-ST-segment elevation acute coronary syndrome

perimenopausal women with high emotional stress. This could be explained by some genetic and conformational differences in the arterial walls of men and women, in addition to apparent hormonal modifications in coronary estrogen and progestogen receptors which trigger mechanisms that alter vascular architecture both in pregnancy and perimenopause and produce conformational changes predisposing to SCAD. (8, 11,12)

This disease accounts for 1 to 40 out of 1000 angiographies performed per center, and in turn explains 2 to 4% of all SCADs and up to one-third of AMIs in the perimenopausal female population. (13-16)

There are different genetic variants in collagen fibers that are associated with higher risk of developing the disease. (15-20) Although fibromuscular dysplasia is the arteriopathy and genetic condition most closely associated with SCAD development, (2,9) the search for this disease was very poor in our series and it was possible to perform angiotomography of intra-abdominal and cervical vessels only in 3 patients, without any positive results. Although pregnancy (especially in the third trimester and in the immediate postpartum) is associated with SCAD, it did not manifest in our series. (19)

In all the series presented, including ours, SCAD develops in populations with few or no cardiovascular risk factors. In the group analyzed, the most relevant cardiovascular risk factor was hypertension, analogous to classic coronary artery disease, and in line with other published series. (18-20)

When analyzing the presentation on admission, and comparable to large international series, more than half of the cases evidenced NSTEACS (5,6,11,18-20).

Also, similar to global reports, the most commonly involved artery was the left anterior descending artery, and, importantly, two patients presented with multiple types of dissection in different vascular territories. Despite the incidence of intravascular imaging in these patients is low, both in this registry and worldwide, there are recommendations that encourage its use in cases where there are diagnostic doubts. (1-3, 16)

There are some points worth highlighting in our registry. On the one hand, in our series, 1 in 5 patients continued to experience persistent pain after discharge, in line with other registries. (5,6,11,18-20) On the other hand, there was no evidence of consensus on antiplatelet therapy in patients treated conservatively, either in terms of selection (aspirin or clopidogrel), dosage (single or dual antiplatelet therapy), or duration.

Among the study limitations, the small sample size stands out. Nevertheless, different therapeutic

Table 3. Angiographic characteristics and modified Yip-Saw classification.

Affected artery (%)	
Right coronary artery	7.7
Left coronary trunk	0
Left anterior descending artery	61.5
Circumflex artery	38.4
Intravascular imaging (%)	7.7
Classification (%)	
Type I	11.5
Type 2	73.1
Type 2A	53.8
Type 2B	19.2
Type 3	11.5
Type 4	7.7
Type 5	7.7
Baseline echocardiogram (%)	
No wall motility disorders	19
Segmental hypokinesia	47.6
Akinesia	28.6
Ventricular hypertrophy	14.3
Preserved LVEF	76.2

LVEF: left ventricular ejection fraction.

approaches were evidenced, especially during follow-up, as well as the lack of screening for fibrodysplasia, which allows us to outline guidelines for possible position documents and recommendations from our Society.

CONCLUSION

Spontaneous coronary artery dissection occurs predominantly in women between the 4th and 5th decades of life without cardiovascular risk factors, generally as acute coronary syndrome and with emotional stress as the main triggering factor. Treatment was conservative except in cases of hemodynamic instability, and the results during hospitalization and at one year of follow-up were good. The lack of consensus on antithrombotic treatment in this group of patients should be noted.

Conflicts of interest

None declared.

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

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BRIEF ARTICLE

Prevalence of Infective Endocarditis in Patients Undergoing Transcatheter Aortic Valve Replacement at a Referral Center

Prevalencia de endocarditis infecciosa en pacientes con reemplazo valvular aórtico transcatéter en un centro de referencia

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ABSTRACT

Background: Infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR) is a rare but serious complication with a generally unfavorable outcome.
Objective: The aim of this study was to describe the incidence, characteristics, and in-hospital outcome of IE after TAVR.
Methods: We conducted a single-center, observational and retrospective study of patients > 18 years who underwent TAVR between March 2015 and May 2025. Infective endocarditis was classified as early (within one year following TAVR) or late (>1 year) according to the modified Duke criteria. Clinical, microbiological, and imaging characteristics were analyzed, as well as treatments received, indication for surgery and in-hospital mortality.
Results: 521 patients were included; median age was 84 years (interquartile range, IQR, 79–87) and 65% were women. The incidence of IE was 2.3% (n = 12); 42% of cases corresponded to early IE and 58% to late IE. The median age of the subgroup with IE was 83 years (IQR 78-86) and 75% were men. Enterococcus faecalis was the most common microorganism. Eight patients presented with fever as an initial symptom, nine had echocardiographic vegetations, and four presented embolisms. Four patients had indication for surgery but only one was operated on. In-hospital mortality was 16% (n=2); these two patients had indication for surgery, but the intervention was not carried out due to frailty. All the patients received antibiotic treatment guided by an antibiogram and one-third received suppressive treatment during follow-up.
Conclusions: In our cohort, the incidence of IE after TAVR was 2.3%. Its clinical progression, with high morbidity and mortality rates and limited surgical options, underscores the need for early diagnostic and therapeutic strategies to improve the outcome.

Key words: Infective endocarditis - Transcatheter aortic valve replacement - Severe aortic valve stenosis

RESUMEN

Introducción: La endocarditis infecciosa (EI) es una complicación poco frecuente pero grave tras el reemplazo valvular aórtico por vía transcatéter (TAVR), con una evolución generalmente adversa.
Objetivo: Describir la incidencia, características y evolución clínica intrahospitalaria de la EI post-TAVR.
Material y métodos: Estudio unicéntrico, observacional y retrospectivo que incluyó pacientes mayores de 18 años con TAVR entre marzo de 2015 y mayo de 2025. La EI se clasificó como precoz (≤1 año post-TAVR) o tardía (>1 año), según criterios de Duke modificados. Se analizaron datos clínicos, microbiológicos e imagenológicos, tratamiento recibido, indicación quirúrgica y mortalidad intrahospitalaria.
Resultados: Se incluyeron 521 pacientes con mediana de edad de 84 años (rango intercuartílico, RIC, 79-87); 65% mujeres. La incidencia de EI fue del 2,3% (n=12): 42% precoces y 58% tardías. La mediana de edad del subgrupo con EI fue 83 años (RIC 78-86), el 75% hombres. Enterococcus faecalis fue el patógeno más frecuente. Ocho pacientes presentaron fiebre como síntoma inicial, nueve vegetaciones ecocardiográficas, y cuatro fenómenos embólicos. Cuatro pacientes tuvieron indicación quirúrgica, pero solo uno fue operado. La mortalidad intrahospitalaria fue del 16% (n=2), asociada a indicación quirúrgica no llevada a cabo por fragilidad. Todos los pacientes recibieron antibiótico dirigido, y un tercio tratamiento supresivo en el seguimiento.
Conclusiones: La EI post-TAVR presentó una incidencia del 2,3% en nuestra cohorte. Su evolución clínica, con alta morbimortalidad y limitada posibilidad quirúrgica, subraya la necesidad de estrategias diagnósticas y terapéuticas tempranas para mejorar el pronóstico.

Palabras clave: Endocarditis infecciosa, reemplazo valvular aórtico transcatéter, estenosis aortica grave

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is the treatment of choice in patients > 75 years with aortic stenosis, those at high surgical risk, and those who are not candidates for surgery. In recent years, its indication has been progressively extended to include intermediate or low risk patients, resulting in an exponential growth in the number of TAVR procedures worldwide. (1–3)

Infective endocarditis (IE) is a rare but clinically significant complication after TAVR, characterized by a distinctive clinical and microbiological profile and a generally unfavorable outcome. (4) Despite its low prevalence, the number of patients at risk of developing this complication is expected to increase considerably in the coming years, as the number of procedures continues to rise and is extending to younger patients with longer life expectancy. (4,5)

Therefore, as IE after TAVR could represent an increasingly common and relevant clinical challenge, it is essential to have a thorough understanding of this condition and its potential complications in order to improve the clinical outcomes for this population. To date, there is little regional information available on its prevalence, characteristics, and clinical course during follow-up.

METHODS

We conducted a single-center, observational and retrospective cohort study. The cohort was made up of adult patients (>18 years) with a prosthetic aortic valve implanted via TAVR due to severe symptomatic aortic valve stenosis between March 2015 and May 2025.

The aim of the study was to describe the prevalence, characteristics, and in-hospital clinical course of IE in patients undergoing TAVR.

Clinical, microbiological, and imaging characteristics at the time of diagnosis were analyzed, as well as the treatments received and in-hospital clinical course. The diagnosis of IE was defined according to the modified Duke criteria, (6) and the disease was classified as "early" (within the first year following the TAVR procedure) or "late" (after the first year following the TAVR procedure). In addition, the surgical indications for IE were evaluated according to the criteria of the current clinical practice guidelines of the European Society of Cardiology. (6) Finally, in-hospital mortality for the entire cohort was recorded. Data were retrieved from the institutional electronic medical records.

Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as median with the corresponding interquartile ranges (IQR). All the statistical calculations were performed using SPSS 24.0 statistical package (SPSS; Chicago, IL, USA).

RESULTS

A total of 521 patients undergoing TAVR were included. Median age was 84 years (IQR 79-87) and 65% were female. Sixty-seven percent had hypertension, 16% had diabetes mellitus, and 14% had dyslipidemia. Most patients received a self-expanding aortic valve prosthesis (77%), primarily accessed via the femoral artery (72%), often via a surgical approach (69%). Median follow-up to evaluate the prevalence of IE was 620 days (IQR 142-1288).

In our cohort, the incidence of IE was 2.3% (n = 12). According to the modified Duke criteria, nine patients (75%) in this subgroup were classified as definite IE, and three (25%) were classified as probable IE. The median age of the subgroup with IE was 83 years (IQR 78-86) and 75% (n = 9) were men. All these patients had hypertension, while two-thirds of them had dyslipidemia and only one patient had diabetes. (Table 1).

The femoral access was used in 92% of cases with a surgical approach in 83%; and, unlike the global cohort, balloon-expandable prostheses were more commonly used (67%) (Table 1).

Of the total number of patients diagnosed with IE, five (42%) developed early EI and seven (58%) developed late EI (Table 1). Median time from TAVR to the diagnosis of early IE was 87 days (IQR 66-114) and 1142 days (IQR 722-1450) for late IE. Blood cultures were positive in 11 (92%) patients, with Enterococcus faecalis being the most common microorganism in both early (n = 2) and late (n = 3) IE cases. The remaining microorganisms were Staphylococcus epidermidis (n = 3), and Streptococcus hemolyticus, sanguinis, and viridans, with one case each.

Fever was the most common clinical presentation (67%). Vegetations were present on transesophageal echocardiography in 75% (n = 9) of the cases, 33% (n = 4) presented systemic embolism, and prosthetic valve dysfunction occurred in only one patient.

Four patients had indication for surgery: two due to cardiogenic shock refractory to standard measures, one due to a large vegetation (> 10 mm), and one due to persistent positive blood cultures despite antibiotic treatment guided by an antibiogram. However, only one patient ultimately underwent surgery, with favorable outcome. In-hospital mortality was 16% (n=2); although these two patients had indication for surgery, the intervention was not carried out due to frailty. All survivors received antibiotic treatment guided by an antibiogram for six weeks, and 33% (n = 4) subsequently received suppressive antibiotic treatment.

DISCUSSION

The main findings of this single-center study were: 1) the incidence of IE after TAVR in our cohort was 2.3%; 2) the microorganism most commonly isolated was Enterococcus faecalis; 3) antibiotic treatment guided by an antibiogram was the primary therapeutic strategy, with only one surgical intervention out of four patients with indication for surgery; and 4) in-hospital mortality was 16% (Figure 1).

First, the prevalence of IE in our cohort is similar to that reported in prior international studies, with an estimated annual incidence from 0.2 to 2%. (4,7) However, there is considerable variability in the prevalence and incidence of IE after TAVR, as most data

Table 1. Clinical and echocardiographic characteristics, clinical presentation, and outcome of patients with IE after TAVR

Variables	n = 12
Clinical characteristics	
Age, years	83 (78-86)
Male sex	9 (75%)
Body mass index	30 (25-33)
Diabetes mellitus	1 (8%)
Chronic kidney disease	5 (42%)
Previous coronary artery bypass graft surgery	2 (17%)
Echocardiographic characteristics	
Vegetation > 10 mm	3 (25%)
Prosthetic valve dysfunction	1 (8%)
Annular involvement	1 (8%)
LVEF > 55%	11 (92%)
Clinical presentation and laboratory test results on admission	
Positive blood cultures	11 (92%)
White blood count/mm3 on admission	8990 (6827-12 900)
Platelet count/mm3 on admission	153 850 (87 125-203 600)
C-reactive protein	64 (30-84)
In-hospital outcome	
Embolism	4 (33%)
Shock parameters	2 (17%)
Requirement of MV	2 (17%)
Redo surgery	1 (8%)
In-hospital mortality	2 (16%)

IQR: interquartile range; LVEF: left ventricular ejection fraction; MV: mechanical ventilation
Qualitative variables are presented as n (%) and quantitative variables as median (interquartile range)

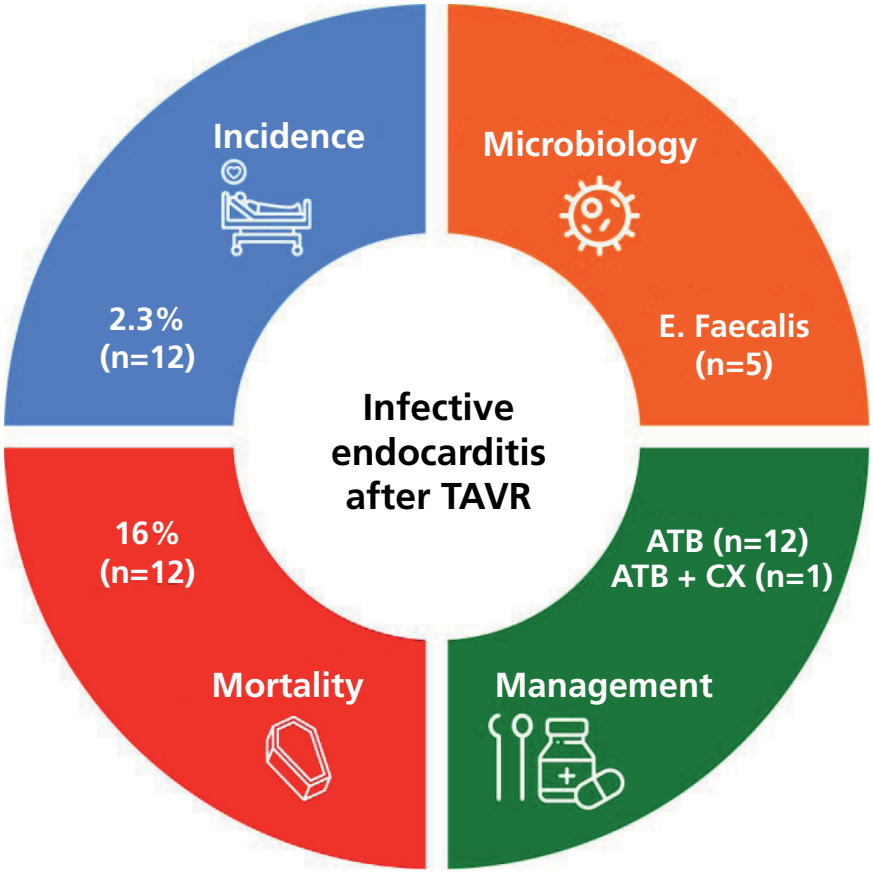
come from observational registries with highly heterogeneous populations. (4,8) Furthermore, few studies have compared the incidence of IE after TAVR versus IE after surgical aortic valve replacement (SAVR). So far, their incidence appears to be similar, as only two studies have shown a lower incidence associated with TAVR. (9,10)

Another issue to highlight is the onset of IE during follow-up. In our cohort, five patients—42% of cases—experienced the event during the first year after the procedure (early IE). Few studies have compared the incidence of early IE after TAVR with that after SAVR, and although the less invasive nature of TAVR could be associated with a lower incidence of early IE, the incidence is also similar with both techniques. (11-13) However, in recent years, there has been a global trend towards a minimalist TAVR approach. It seems reasonable to believe that this technique would reduce the incidence of IE after TAVR. However, to date only one study has analyzed this hypothesis, and although it showed a trend toward a lower incidence of IE, no statistically significant differences were found, with only a trend toward a lower proportion of early IE. (14, 15)

Regarding the microorganisms most commonly responsible for IE after TAVR, enterococci are the predominant agents in most series, including our cohort. (14,16,17) These microorganisms have a strong affinity for warm, moist habitats such as the groin region. (18) In this regard, the utilization of the transfemoral access as the preferred method for TAVR on a global scale may be associated with the isolation of this microorganism. In our series, 92% of cases that developed IE were treated using the transfemoral access.

The management of patients who develop IE following TAVR is challenging. To date, there are no randomized studies comparing different antibiotic regimens or therapeutic strategies in patients with IE after TAVR. Consequently, its treatment is extrapolated from data on IE in surgical prosthetic valves. (6) Since this is a type of IE involving prosthetic heart valves, treatment should be prolonged and last at least six weeks. (19) In our cohort, all of our patients received antibiotic treatment guided by an antibiogram during that period, and 33% also received subsequent suppressive treatment. Conservative treatment, defined as antibiotic therapy alone, is the most commonly used strategy in all series due to the fact that patients who undergo TAVR are currently considered to be at high surgical risk. This management could change in the coming years due to the increasing utilization of this technique among low- and intermediate-risk pa-

Figure 1. Graphical summary of the main findings of our single-center study



ATB: antibiotics, CX: surgery, TAVR: transcatheter aortic valve replacement

tients. In our cohort, only one of the five patients with indication for surgery was ultimately intervened, with favorable postoperative outcome.

There is a paucity of evidence comparing surgical intervention with conservative treatment in patients with indication for surgery. Notably, these studies have not demonstrated a clear benefit of surgery versus antibiotic treatment guided by an antibiogram. Surgery did not reduce in-hospital mortality, hospital readmissions, or one-year mortality. (20–22) We believe that this can be explained, once again, by the high surgical risk, which is at times prohibitive, of this group of patients. In the EXPLANT-TAVR registry, (23) patients undergoing transcatheter heart valve explant secondary to IE had higher 30-day and 1-year stroke rates and longer intensive care unit and hospital stays, compared to the subgroup of patients with other mechanisms of bioprosthetic valve dysfunction. Moreover, these patients had a higher 3-year mortality rate, which did not reach statistical significance given the relatively small sample size of this unique cohort and the reduced number of events. Despite the limited evidence, no specific surgical recommendations have been established for this population to date; indications are usually individualized according to each center's experience.

Finally, in our cohort. IE after TAVR was associated with high in-hospital mortality. According to the literature, in-hospital mortality rates have been reported to range from 16% to 64%. Once again, this wide range reflects the heterogeneity of the available data on this topic. However, and despite this variability, these figures are significantly higher than those reported for other types of prosthetic valve IE. (17,23–25)

In conclusion, IE after TAVR is a rare but clinically relevant complication with high in-hospital morbidity and mortality. Despite advances in minimally invasive techniques and antibiotic management guided by an antibiogram, significant diagnostic and therapeutic challenges persist, particularly given the lack of robust evidence and specific guidelines for this population. The high prevalence of Enterococci as etiological agents, particularly after transfemoral procedures, underscores the need for tailored preventive strategies. Given the limited efficacy of surgery in terms of

survival and the predominance of conservative treatment, it is essential to individualize the clinical approach and encourage prospective studies to establish clearer, evidence-based recommendations.

Conflicts of interest

None declared.

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

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LETTER TO THE EDITOR

Different Phenotypes of Left Ventricular Hypertrophy and Their Electrocardiographic Patterns

Diferentes fenotipos de hipertrofia ventricular izquierda y sus expresiones electrocardiográficas

SAMUEL SCLAROVSKY[1], HERALDO D'IMPERIO[2]

In this new communication, we continue to develop the concept of physiologic and pathologic ventricular hypertrophy, as referred to in previous publications. (1,2)

Ventricular hypertrophy can be revealed by a simple, low-cost complementary test, such as an electrocardiogram (ECG), which also has the advantage of correlating well with cardiac magnetic resonance imaging (CMR). (3,4). The ECG enables the detection of multiple affected segments and their association, which is of utmost importance because it provides relevant information about a patient's cardiovascular health.

Through the ECG, we can differentiate between two types of hypertrophy. Physiologic hypertrophy occurs in the early stages in response to systolic overload, where there is an increase in ventricular wall tension as the first response according to Laplace's law. Consequently, physiologic hypertrophy develops, accompanied by a reduction in diastolic and systolic volume. (5) In this instance, there is an increase in the number of sarcomeres in series, which increases myocyte size as a result of the stimulation of catecholamines on alpha 1 and alpha 2 adrenergic receptors. In turn, arrestin, a protein that controls beta receptors (by blocking beta 3 receptors), is stimulated (as part of what is known as the fetal gene program). (6-8). This phenomenon manifests as narrow, high-voltage QRS complexes, isoelectric ST segments, and positive T waves on an ECG. This electrocardiographic pattern can persist for many years or evolve into pathologic hypertrophy because the biological factors that maintain physiologic mechanisms are exhausted, as occurs in advanced age in response to persistent systolic overload. In addition to beta-adrenergic receptors, myocytes and fibroblasts have angiotensin-2 receptors and endothelin-1 receptors. These receptors stimulate the formation of parallel sarcomeres, which contribute to increased myocyte diameter and fibrosis secondary to collagen deposition. This, in turn, promotes changes in the ECG that manifest as a QRS >120 milliseconds. (9,10) Fibrosis induces diastolic dysfunction, which is evidenced by ST-segment depression with or without negative T waves (Figure 1). This phenomenon can be observed in sustained hypertension, aortic stenosis, aortic regurgitation, as well as in the context following an acute myocardial infarction and other clinical conditions, where the myocardium undergoes various morphological adaptations with their corresponding electrocardiographic patterns. (11-12)

In the Department of Interpretation and Electrocardiography at Assuta Medical Center in Tel Aviv, Israel, with 30 years of experience in analyzing ECGs from patients from various centers, we have identified different types of hypertrophy, especially in subjects who have suffered a myocardial infarction. In these patients, we have observed hypertrophy primarily in the segments opposite the areas of necrosis.

We have described five different patterns of hypertrophy, each with its corresponding electrocardiographic expression. The different ECG patterns depend on a random distribution and concentration of the beta-adrenergic receptors, which help to regulate wall tension, and are distributed heterogeneously in the endocardium of the left ventricle.

Basal hypertrophy: This pattern is characterized by an R wave in aVL > 10 mm and an S wave in LIII > 10 mm. This type of hypertrophy is not adequately detected by echocardiography. Basal hypertrophy is very common because it forms part of the left ventricular outflow tract and is directly affected by systolic overload pressure. It occurs only in adults

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with hypertension, when there is an acute angle between the left ventricle and the aorta of 120 degrees (the normal value is approximately 150 degrees). This can be seen on the ECG. The QRS is narrow, the ST-segment is not depressed, and the T waves are positive. When the compensatory mechanisms are exhausted, the QRS broadens, and the ST segment becomes depressed, indicating myocardial fibrosis and impaired diastolic function.

Apical hypertrophy: characterized by tall R waves in V4 (lower third of the anteroseptal septum), V5 (apex), and V6, which represents the lower third of the left lateral wall. These three segments are expressed together in almost all cardiac conditions because they originate from the same embryonic sac. Hypertrophy manifests as tall R waves in V4, V5, and V6, and giant T-wave inversion (>10 mm), present almost exclusively in this type of hypertrophy.

Posteroseptal hypertrophy: characterized by S waves in V2 and V3 and, in some cases, even V4. It is a common pattern in clinical practice. In pathological cases, it is accompanied by other hypertrophied segments. The short R wave that accompanies the deep S waves is due to depolarization of the anterior wall occurring prior to depolarization of the hypertrophied posterior wall. There is also right axis deviation on the frontal plane, suggesting a backward and downward direction of the vector. After an anteroseptal myocardial infarction, posteroseptal hypertrophic remodeling can be observed on the ECG, manifested as deep S waves > 20 mm.

Anteroseptal hypertrophy: the anterior septum may be affected in its upper, middle, or lower segment. It is characterized by tall R waves in V2, V2-V3, or V2-V4. We have observed that posterolateral myocardial infarctions are accompanied by anteroseptal hypertrophy, which is expressed by tall R waves in V1, V2, and V3.

Left lateral wall hypertrophy: This type of hypertrophy involves two segments:

-Mid-segment: characterized by tall R waves in LI, aVL (the R wave in LI is taller than in aVL), and S waves > 10 mm in aVR and V1.

- Basal segment: R waves in aVL > LI.

As one would expect, the combination of multiple segments with physiologic or pathologic hypertrophy as a compensatory response is the most prevalent finding, and it can be observed on the ECG. The combinations occur randomly because they depend on each patient's phenotype due to the non-homogeneous concentration of receptors within the myocardium, as previously mentioned.

The following examples are combinations of multiple segments with hypertrophy, when at least two segments are involved.

The first case shows tall R waves in V2, V3, and V4, as indicated by the arrows, which indicate anteroseptal hypertrophy in the upper, middle, and lower segments. The QRS complex is narrow, the ST segment is isoelectric, and the T waves are positive. These findings indicate physiologic hypertrophy in an 84-year-old male patient with hypertension and diabetes (Figure 1).

In the second case, the tall R waves in LI and deep S waves in aVR and V1 indicate hypertrophy of the left lateral wall of the left ventricle in its middle segment (narrow arrows). The tall R waves in V5 and V6 show apical hypertrophy (thick arrows) (Figure 2).

Fig. 1.

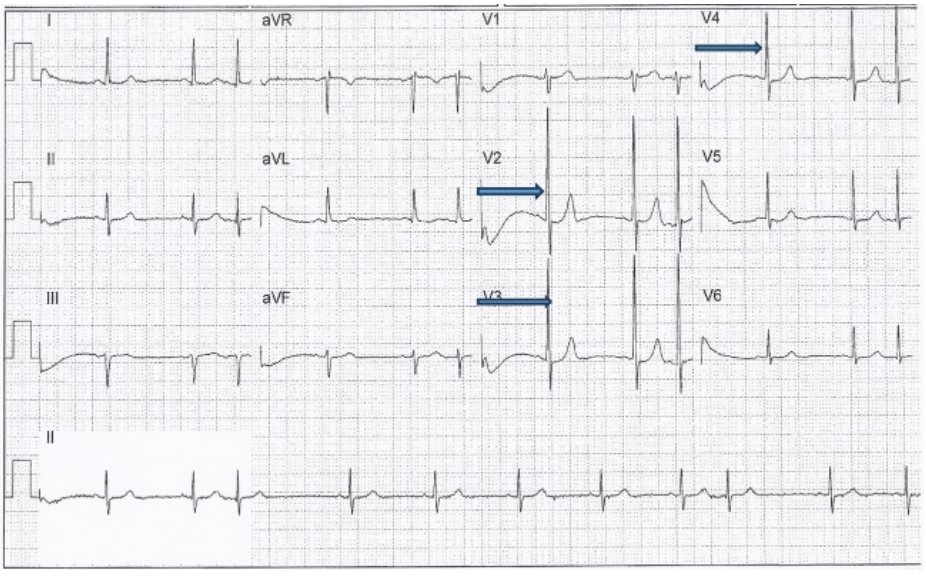


Fig. 2.

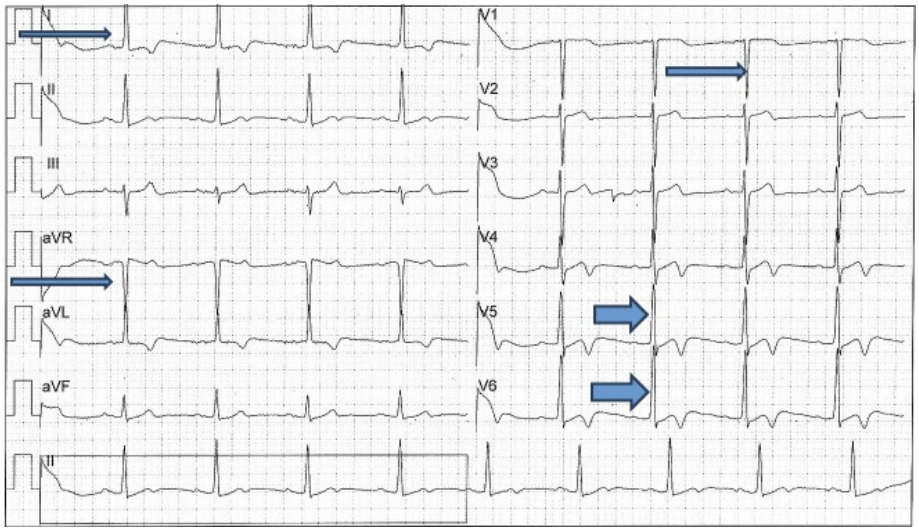
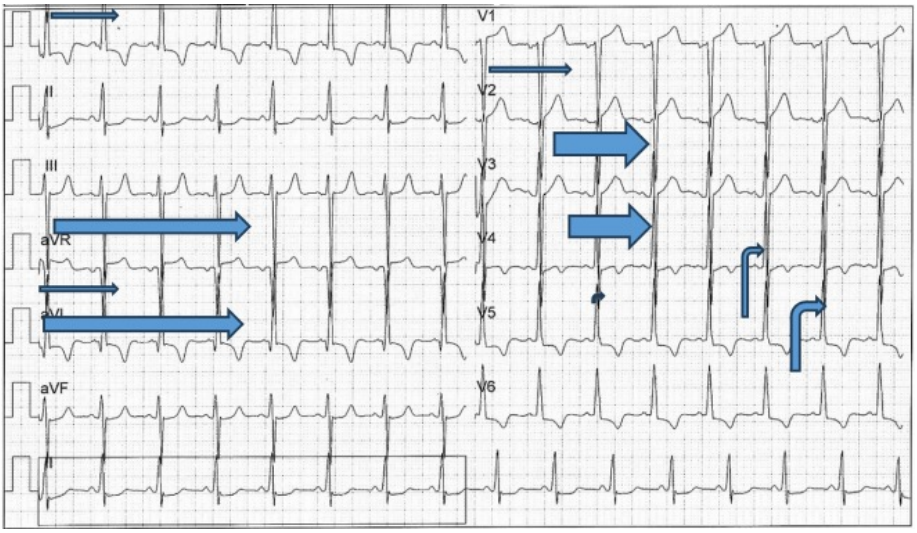


Fig. 3.



The third case shows hypertrophy of multiple segments. The tall R waves in LI and deep S waves in aVR and V1 indicate mid-lateral left ventricular hypertrophy (narrow arrows). The tall R waves in aVL and deep S waves in LIII suggest basal hypertrophy (long arrows). The deep S waves in V2 and V3 indicate posteroseptal hypertrophy (wide arrows). The tall R waves in V4 and V5 reveal apical hypertrophy (Figure 3)

CONCLUSIONS

The ECG reveals distinct patterns of left ventricular hypertrophy, indicating the affected segments. In general, the hypertrophy affects multiple segments. Understanding the electrical expression of these segments helps us to comprehend the different phenotypes that manifest in combination.

Conflicts of interest

None declared.

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

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Complex Systemic and Pulmonary Venous Anomalies: A Multimodality Imaging Case Report

Anomalías sistémicas y venosas pulmonares complejas: un caso clínico con imágenes multimodales

MARGARIDA CASTRO[1,2], RODRIGO ARANIBAR MARTINEZ[2,3*], ALBERTO BOUZAS MOSQUERA ALBERTO[3]

A 69-year-old male with a history of bicuspid aortic valve replacement presented with progressive right-sided heart failure. Transthoracic echocardiography revealed severe right heart enlargement and dysfunction with suspicion of an interatrial shunt (Fig. 1A-B). Transesophageal echocardiography (TEE) identified a superior sinus venosus atrial septal defect (SVASD), coronary sinus dilatation, and a persistent left superior vena cava (PLSVC), with absence of right superior pulmonary venous drainage into the left atrium.

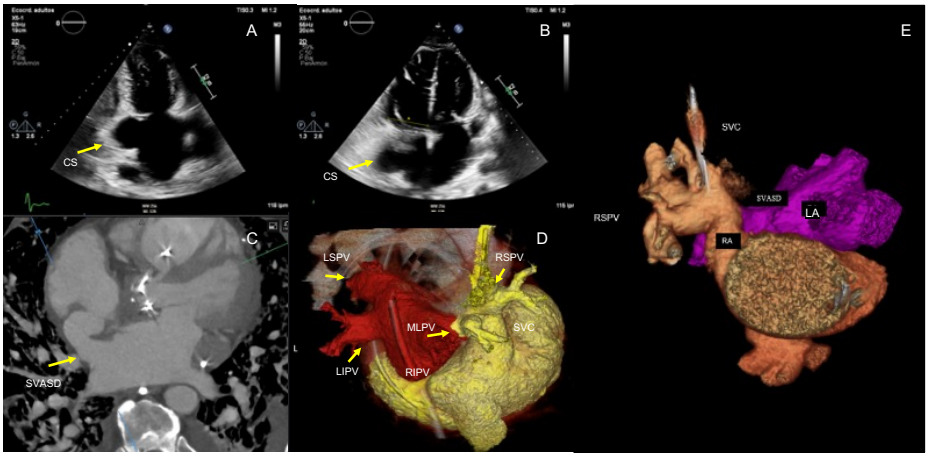
Cardiac computed tomography (CT) confirmed the SVASD and revealed a PLSVC draining into a dilated coronary sinus, with partial anomalous pulmonary venous drainage (PAPVD) of the right superior pulmonary vein and an accessory middle lobe vein draining into the superior vena cava (Fig. 1C-E). Dilatation of the pulmonary trunk was also noted, consistent with pulmonary hypertension.

The coexistence of SVASD, PAPVD, PLSVC, and bicuspid aortic valve is exceptionally rare, with no previous reports describing this combination. SVASD is frequently associated with venous anomalies such as PAPVD and PLSVC. (1,2). This unique constellation of congenital defects highlights how one anomaly often coexists with others and underscores the pivotal role of multimodality imaging in accurate diagnosis and preoperative planning. (3)

Ethical considerations

The authors obtained informed consent from the patient.

Fig. 1. Transthoracic echocardiogram showing a dilated coronary sinus (CS) (A) and marked right ventricular enlargement (RV) (B). Cardiac CT demonstrating a superior sinus venosus atrial septal defect (SVASD) (C). Three-dimensional cardiac CT reconstruction showing the left superior (LSPV), left inferior (LIPV), and right inferior (RIPV) pulmonary veins draining into the left atrium (LA), whereas the right superior pulmonary vein (RSPV) and the accessory middle lobe pulmonary vein (MLPV) drain anomalously into the superior vena cava (SVC) (D–E).



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Conflicts of interest

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

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SCIENTIFIC LETTER

Identity and heart: the cardiovascular challenge in gender transition

Identidad y corazón: el desafío cardiovascular en la transición de género

MARIELA KARINA HUERTAS[1], JUAN PABLO LESTARD[1], GIANFRANCO BOSQUE[1], NICOLAS MENICHINI[1], JUAN PABLO CAMPAGNA[1]

The cardiovascular health of transgender people is now an unavoidable clinical and scientific challenge. This historically invisible population group is beginning to emerge in everyday medical practice with specific needs and risks that have not yet been sufficiently explored. In Argentina, the 2022 National Census identified 196 956 people who do not identify with the sex recorded at birth, representing 0.4% of the population in private households. (1) Far from being a marginal number, this figure reflects a growing reality that directly challenges contemporary cardiovascular medicine.

Gender affirmation therapy—a pillar of comprehensive care for transgender people—involves a multidisciplinary approach, with hormone therapy playing a central role. In the case of transgender men, testosterone administration is the treatment of choice for inducing male secondary sexual characteristics, with the aim of aligning the body with the self-perceived gender identity. (2)

However, hormone therapy is not without risks. Recent studies have documented an increase in blood pressure, a higher prevalence of dyslipidemia, insulin resistance, and an increase in the incidence of major cardiovascular events, including acute myocardial infarction and ischemic stroke, in this population. There have also been reports of erythrocytosis, changes in blood viscosity, and potential acceleration of atherosclerosis, all of which are factors that increase cardiovascular vulnerability. (3)

This scenario raises a crucial question: how can we balance the psychosocial and mental health benefits of gender affirmation therapy with the emerging cardiovascular complications? The sustained increase in the visibility of and access to these treatments has brought to the forefront the need to understand their long-term effects on coronary heart disease, classic and nonclassic risk factors, and cardiovascular morbidity and mortality.

The case we present—a trans man suffering from acute myocardial infarction—not only highlights a clinical situation unprecedented in our daily practice, but also forces us to rethink the paradigms of prevention, diagnosis, and treatment in a population whose cardiovascular vulnerability is beginning to emerge with greater clarity and urgency.

The patient is a 24-year-old transgender man with a personal history of smoking, obesity, and borderline personality disorder, with a history of problematic substance use (marijuana and cocaine). He began hormone therapy for gender affirmation with intramuscular testosterone undecanoate on a quarterly basis in 2021. Surgical history of chest masculinization. COVID-19 vaccination schedule with two doses of the Sinopharm vaccine, administered in 2020.

Cardiovascular disease began approximately in March 2024 with episodes of short-lived oppressive precordial pain in emotional contexts. Subsequently, he had two new episodes, so he consulted a cardiologist at an outpatient clinic in May, where he underwent an ECG (Figure 1-A) and a transthoracic echocardiogram (TTE), which showed no abnormalities, as well as a TTE with insufficient stress to show myocardial ischemia. Laboratory tests revealed testosterone levels within the male range.

On June 25, he returns to the emergency room complaining of mild typical precordial pain during physical activity. Physical examination reveals hypertension (140/90 mmHg). The ECG shows a repolarization disorder in the anterolateral and inferior walls. Ultrasensitive troponin T within normal values. A new TTE shows preserved left ventricular ejection

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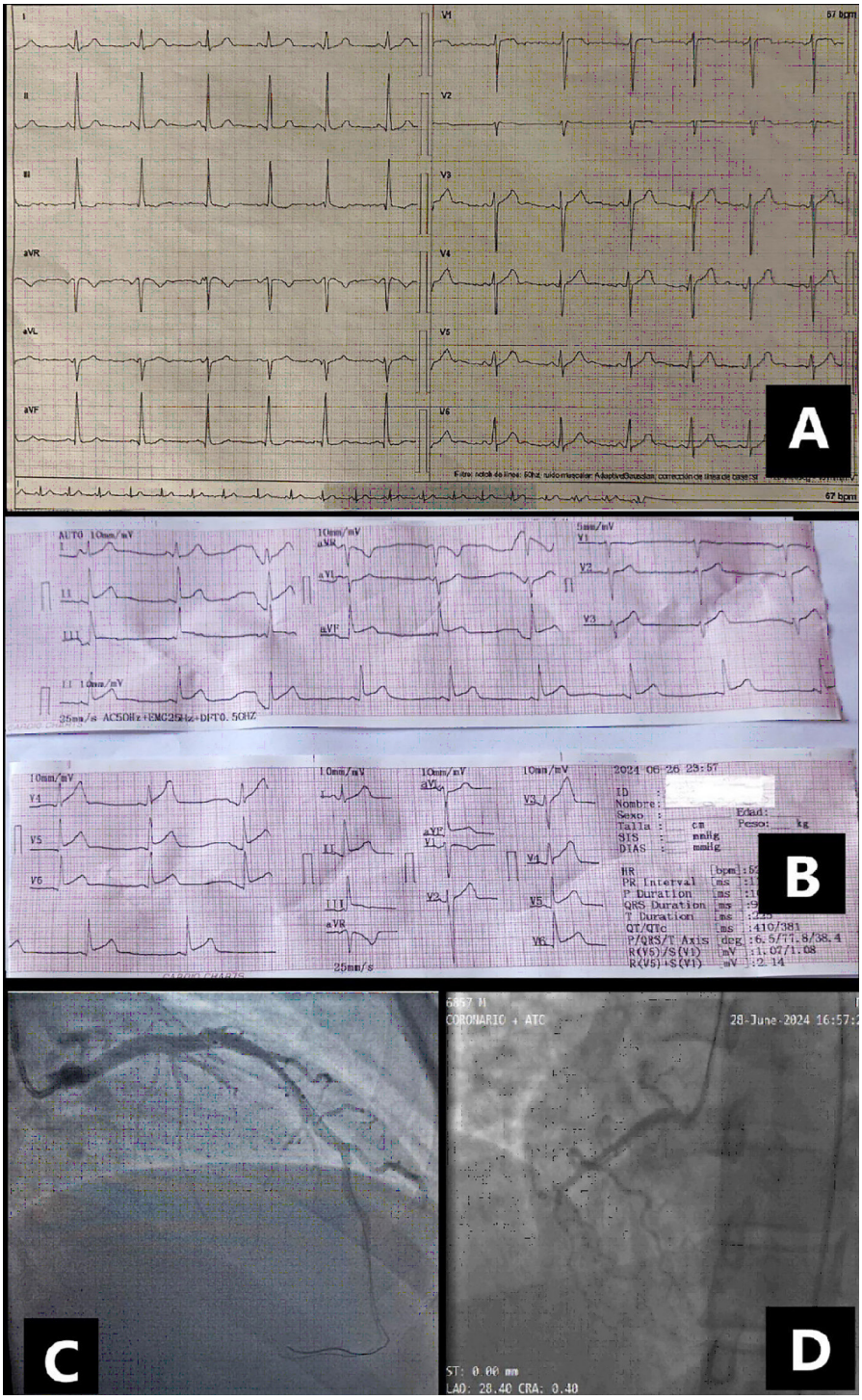
Fig. 1. A. Baseline ECG without abnormalities, **B.** Anterolateral and inferior subepicardial injury. **C.** Coronary angiography: left anterior descending artery with cord passage, proximal thrombus, and distal spasm. **D.** Dissection in the proximal segment of the right coronary artery.



fraction (LVEF) with no motility disorders. Admission to the pain unit is indicated, but the patient refuses. The following day, he presents with a new episode of oppressive precordial pain that begins during physical activity, lasts more than half an hour, is more intense (10/10), radiates to the jaw, and is accompanied by sweating, nausea, and belching. Physical examination reveals hypertension (160/100 mmHg) and good response to morphine analgesia. ECG unchanged from the previous day. During admission to the emergency room shock room, he presents another episode of pain with no changes in the ECG, with a lower response

to intravenous analgesia, and requiring intravenous nitrites; it is decided to transfer him to the intensive care unit.

There, subepicardial injury is observed on the anterolateral and inferior walls (Figure 1-B), and it is decided to transfer him urgently to the hemodynamics room. Coronary angiography shows proximal thrombotic subocclusion of the left anterior descending (LAD) artery and distal occlusion prior to the tip (Figure 1-C). A successful primary percutaneous coronary intervention (PCI) is performed with stent implantation in the proximal segment and balloon dilatation at the distal level, and intravenous infusion of IIb/IIIa inhibitor. TTE shows slightly depressed LVEF with apical hypokinesia.

The following day, he develops precordial pain and rising troponin levels, so it is decided to transfer him back to the catheterization lab. Anterograde dissection of the right coronary artery (RCA) is observed (Figure 1-D), requiring successful primary PCI with two stents, and confirmation of LAD artery with a permeable proximal stent without lesions and no changes at the distal level compared to the previous coronary angiography.

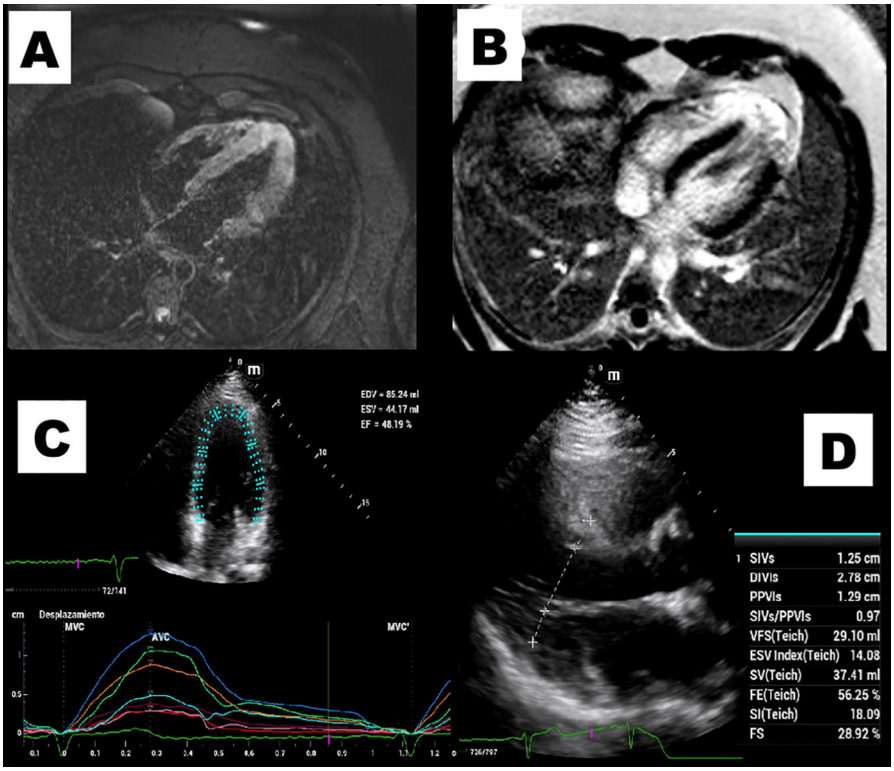
Cardiac magnetic resonance imaging (MRI) shows preserved LVEF and circumferential apical transmural necrotic sequelae with akinesia and apical septal thinning (less than 5 mm) and mild aneurysmal dilatation, without thrombi, and transmural sequelae of apical segments of the right ventricle (RV) (Figure 2-A and B).

After eight days of hospitalization, the patient is discharged with antihypertensive treatment, dual antiplatelet therapy, statins, and ezetimibe. Follow-up by outpatient consultation with hematology, endocrinology, and cardiology services was recommended. During the cardiology consultation, a TTE with strain determination is performed, showing LVEF 56% (Figure 2-C and D). Approximately 20 days after the acute event, a cardiac stress MRI is performed, which reported no changes from the previous study.

Finally, after one month, laboratory results were received that rules out antiphospholipid syndrome and thrombophilia. The patient is currently under close monitoring by a multidisciplinary team with a plan to provide the best possible therapeutic strategy.

It is essential to recognize that research on the effects of hormone therapy on the cardiovascular health of transgender people is still in its early stages. (4,5) Limitations in long-term follow-up and the youth of these patients at the start of hormone therapy create a significant gap in the available evidence. However, the growing identification of disparities in emerging cardiovascular risk factors within this community compels us, as cardiologists, to face new challenges. (6)

Fig. 2. A. Cardiac MRI. T2 sequence showing biventricular edema. **B.** MRI with late gadolinium enhancement showing transmural septal fibrosis, lateral apical and LV apex with thinning of the apical septal myocardial thickness and mild aneurysmal dilatation without evident thrombus. Transmural sequelae of RV apical segments.**C.** TTE with strain evidence of apical akinesia. **D.** LVEF (Teicholz) 56%.



It is crucial to emphasize the importance of cardiovascular risk stratification in this population at the start of therapy, which is not yet defined in the guidelines. Diagnostic studies such as calcium scoring, Lp(a), coronary angiotomography, arterial Doppler, etc. should be more rigorous in order to detect possible accelerated atherosclerosis at an early stage.

The impact of testosterone therapy as a cardiovascular risk factor, particularly in relation to thrombotic events and coronary artery dysfunction, requires a more rigorous approach. Its adverse effects have recently been documented, and the lack of consensus and solid evidence underscores the urgent need for further research and reports.

We must advance in this area with a multidisciplinary approach, collaborating with specialists in endocrinology, hematology, among others, to offer comprehensive and equitable medical care.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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SCIENTIFIC LETTER

Severe Mitral Regurgitation Due to Papillary Muscle Rupture Presenting as Alveolar Hemorrhage

Insuficiencia mitral grave por rotura del músculo papilar, manifiesta como hemorragia alveolar

BÁRBARA LAGE GARCIA[1], EMÍDIO MATA[1], LUCY CALVO[1], ANTÓNIO LOURENÇO[1]

Papillary muscle rupture (PMR) is a rare but life-threatening mechanical complication, typically after acute myocardial infarction (AMI) or infective endocarditis. (1) In the reperfusion era, it occurs in 1-5% of AMI patients, with up to 50% mortality within 24 hours of complete rupture. (1) It usually develops within the first week, particularly following an inferior AMI, causing abrupt, severe and acute mitral regurgitation (AMR), pulmonary edema or cardiogenic shock, if not promptly recognized. (2)

Although the classic presentation includes sudden hemodynamic collapse in a post-AMI patient, atypical features such as hemoptysis may obscure the diagnosis and delay definitive treatment, with potentially fatal consequences.

We present a challenging case of PMR with AMR complicating an AMI, initially presenting with pulmonary alveolar hemorrhage (PAH) and hypoxemic respiratory failure.

A 72-year-old male with hypertension and low-burden smoking presented with a one-week history of progressive dyspnea and fatigue. On the day of admission, he developed hemoptysis, prompting medical evaluation.

Chest computed tomography (CT) revealed diffuse bilateral ground-glass opacities and crazy-paving pattern, predominantly in the right lung, interpreted as either pneumonia or diffuse PAH (Figure 1A-B). He was initially admitted with suspected pneumonia and empirically started on antibiotics, but rapidly deteriorated with acute hypoxemic respiratory failure, requiring immediate intubation and invasive mechanical ventilation.

Laboratory testing showed markedly elevated high-sensitivity troponin I (17 062 ng/L) and ECG revealed sinus rhythm with new-onset Q waves in inferior leads, absent in prior tracings. Coagulation and liver function tests were within normal limits.

Transthoracic and transesophageal echocardiography (TEE) demonstrated preserved left ventricular systolic function with mid-basal inferoposterior hypokinesia, alongside severe, eccentric AMR, with pulmonary vein flow reversal, due to flail of the posterior mitral leaflet, involving P1-P2 scallops, consistent with probable posteromedial PMR (Figure 1C-F). A descending thoracic aortic atherosclerotic plaque with suspected mural thrombus was also noted, later confirmed with CT angiography, along with multiple splenic infarcts. (Fig.2).

These findings supported the diagnosis of inferior AMI, complicated by PMR with AMR, presenting as PAH and respiratory failure. Given the critical condition, cardiothoracic surgery team prioritized stabilization and hemorrhage control, before surgical intervention.

Within six hours, the patient developed acute ischemia of the right lower limb, with CT angiography confirming 56 mm right superficial femoral artery occlusion. Given the suspicion of systemic embolization, brain CT revealed a large right occipito-temporal infarct with mass effect and midline shift.

Due to hemorrhagic risk, anticoagulation was initially withheld. Following multidisciplinary reassessment, unfractionated heparin and acetylsalicylic acid were initiated, monitoring for hemoptysis or instability.

Following stabilization, the patient was transferred to a tertiary center for further multi-disciplinary evaluation. On arrival, revascularization was deemed non-beneficial due to irreversible cyanosis of all toes and surgical candidacy for mitral valve intervention depended on neurological evolution and prognosis.

Brain magnetic resonance imaging (MRI) confirmed extensive infarcts involving the entire left

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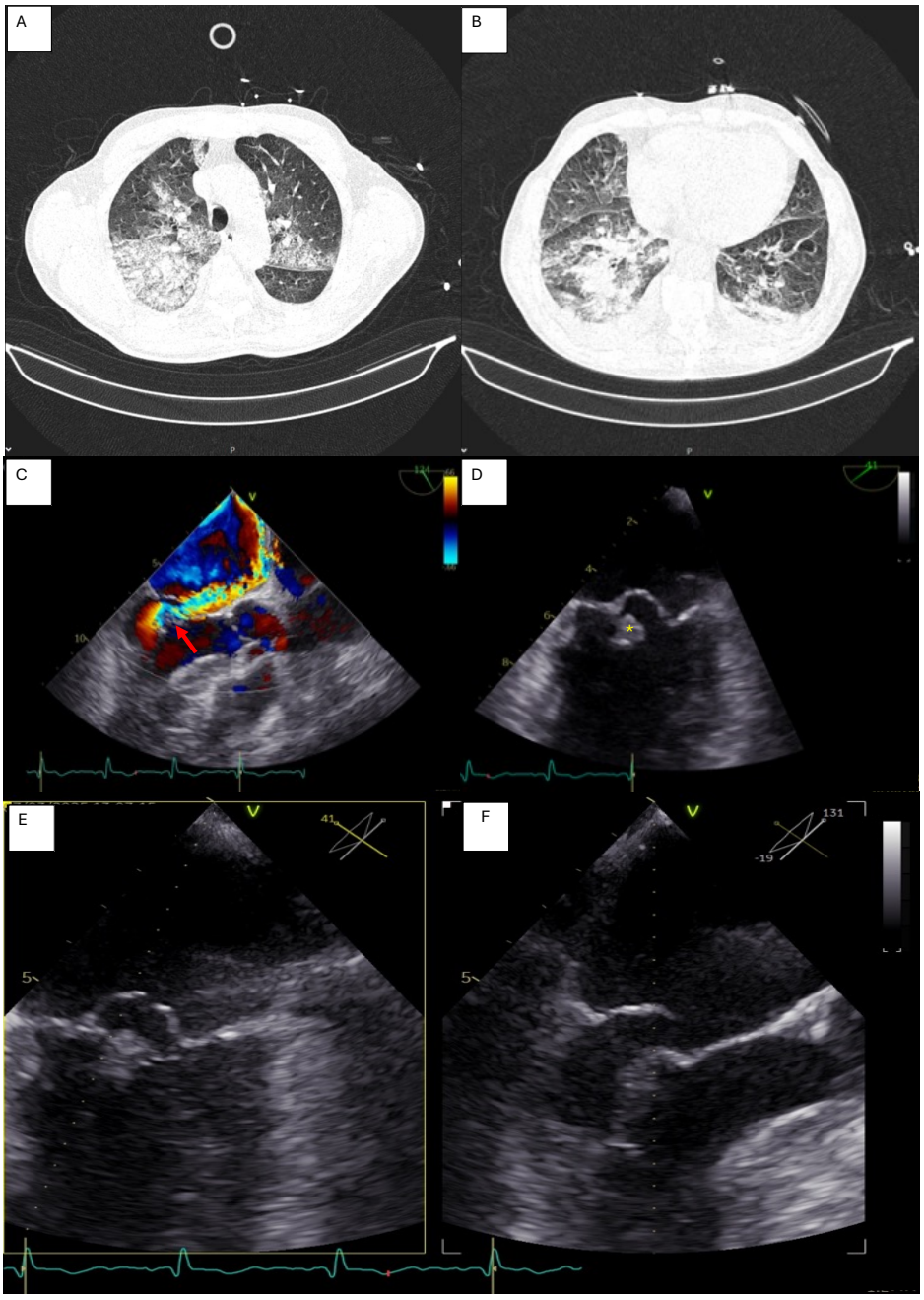
Fig. 1. Chest CT scan (**A-B**) showing diffuse bilateral ground-glass opacities and a crazy-paving pattern, consistent with pulmonary alveolar hemorrhage. Transesophageal echocardiography demonstrating severe eccentric mitral regurgitation (red arrow) through Color Doppler imaging (**C**) due to flail of the posterior mitral leaflet (P1–P2 scallops), consistent with posteromedial papillary muscle rupture (yellow asterix) (**D**). Multiplanar views of posterior mitral leaflet flail (**E-F**).



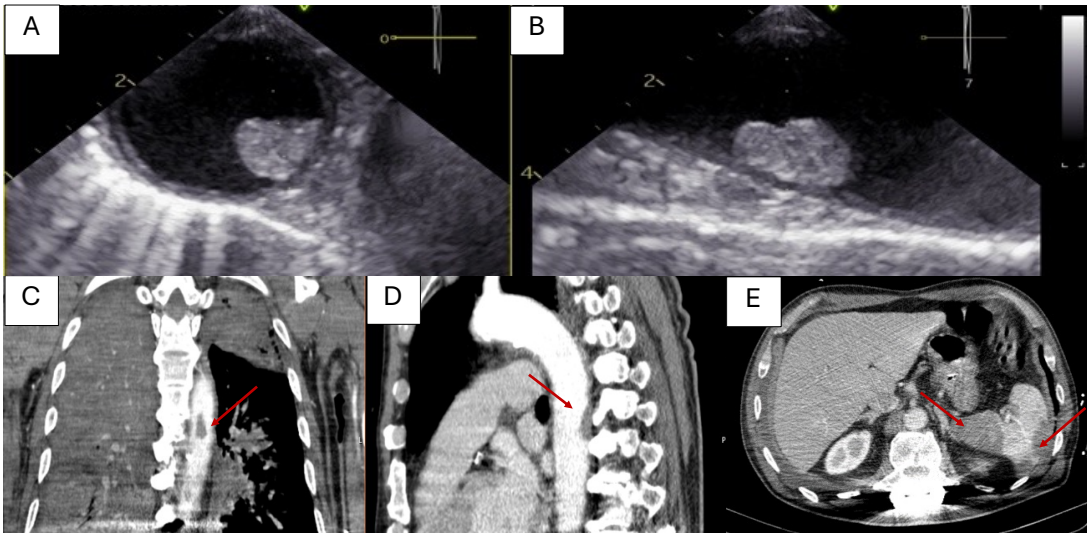
middle cerebral artery territory with thrombus in M1 segment, as well as infarcts in the right posterior cerebral artery territory, with thrombus in P1 segment.

Given the catastrophic neurological prognosis and persistent multisystem involvement, surgical intervention was deemed futile and the patient died shortly thereafter.

This case illustrates critical aspects of the clinical course and management of PMR, particularly when the presentation deviates from the classic pattern. The initial picture mimicked pneumonia with diffuse PAH, delaying recognition of a mechanical complication. The absence of prior cardiac symptoms and predominant respiratory presentation highlight that PMR may develop with progressive dyspnea, preceding hemoptysis, which became the dominant clinical feature, diverting attention from a cardiac cause.

PMR most commonly involves the posteromedial

Fig. 2. Transesophageal echocardiographic images of the descending thoracic aorta demonstrating an atherosclerotic plaque with suspected mural thrombus (**A**) short-axis view; (**B**) long-axis view. Contrast-enhanced chest CT scan in coronal (**C**) and sagittal (**D**) planes revealing an atherosclerotic plaque in the descending thoracic aorta with an adjacent non-enhancing area along the posterior wall, suggestive of a mural thrombus (arrows). Multiple splenic infarcts are also visible (**E**).



papillary muscle, due to its single blood supply from posterior descending artery (typically from the right coronary artery), (2) rendering it particularly vulnerable to ischemia.(1) In this patient, electrocardiographic findings and elevated troponin I confirmed an inferior AMI as the precipitating event. PMR often occurs in small infarcts (<25% of the ventricle) with poor collateral flow, where preserved ventricular function generates high shear stress on the ischemic muscle.(1)

In AMR, the left atrium is not compliant and cannot adapt to the sudden regurgitant volume, causing abrupt pressure rise, leading to pulmonary edema. (3) Although cases of PAH associated with AMR regurgitation have been reported,(4–6) massive hemoptysis is rarely described.

PAH is characterized by alveolar space bleeding, typically due to microvascular injury and commonly presents with bilateral lung involvement. (6) In AMR, unilateral right-sided pulmonary edema and hemorrhage may occur due to the posterosuperior and rightward orientation of the mitral valve, which directs the regurgitant jet toward the right pulmonary veins, (4,6) raising capillary pressure and leading to red blood cell leakage through the alveolar-pulmonary interface.

Early diagnosis of PMR is essential but challenging in the absence of classic signs. A new systolic murmur, often cited as a hallmark, may be soft or inaudible due to pressure equalization between left atria and ventricle. (3) Unilateral cases of PAH or edema can be mistaken for pneumonia, delaying diagnosis and treatment, (3) as initially suspected in this patient.

Echocardiography remains the gold standard for diagnosis, with TEE confirming leaflet flail and chordal rupture, with 92-100% sensitivity. (1,3) In this patient, TEE confirmed the diagnosis of severe AMR caused by flail of the posterior leaflet (P1–P2) secondary to PMR. The presence of inferoposterior wall hypokinesia further supported the association with inferior AMI.

Another striking feature was the occurrence of multiple systemic emboli, including splenic infarcts, limb ischemia, and extensive ischemic stroke, likely from descending aortic thrombus, further worsening prognosis. Management of thromboembolism in PAH created a therapeutic dilemma: anticoagulation was necessary but significantly increased bleeding risk.

Definite treatment requires urgent valve surgery and coronary revascularization, as medical management alone carries high mortality. (3) In this case, surgery was delayed by PAH, embolic events, and neurological injury, highlighting the challenge of balancing surgical timing, optimization of comorbid conditions, and mitigation of bleeding and thrombotic risks.

This case highlights the diagnostic and therapeutic challenges of PMR following AMI, particularly when presenting with misleading respiratory symptoms and PAH. Despite advances, mortality remains high, particularly when diagnosis is delayed or complicated by embolization, illustrating the devastating course of untreated mechanical complications.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

The authors declare that all procedures complied with institutional ethical standards and patient data confidentiality was ensured.

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OPINION ARTICLE

Cause and Effect: Unidirectional or Bidirectional?

Causa y consecuencia: ¿unidireccional o bidireccional?

MARIANO BERGIER, MARIA EUGENIA KNORRE, AGUSTÍN VIDAL, BIANCA AMBROSETTI, JUAN MARIA IROULART, ARTURO CAGIDE[2]

In cardiology, many clinical associations have a directionality that is difficult to define. Certain variables can be both cause and consequence, generating positive feedback loops that challenge classical causality analysis.

It is assumed that a presumed *cause* is associated with a probable *consequence* by demonstrating that this association is statistically significant or, if preferred, that there is less than a 5% probability that the link is random ($p<0.05$). From this perspective, it is possible to act on the cause to affect the consequence through an intervention.

In medicine in general, but in cardiology in particular, this principle supports decision-making: identifying the cause and then, through intervention, favorably modifying the consequence, improves quality of life, and reduces mortality.

Within this perspective, the association is unidirectional, from cause to effect.

But here a problem arises: statistical association does not imply direction, and although this distinction is usually irrelevant, it can be relevant under certain conditions.

"Laws of causality" have been described that, in principle, allow us to distinguish the direction from cause to effect. Although several criteria have been identified, three are of greater importance:

- temporality: the cause precedes the consequence
- biological plausibility: pathophysiological evidence supporting the direction
- intervention: removal of the cause affects the effect

However, although they seem unquestionable, these three principles are sometimes difficult to translate into clinical practice.

UNIDIRECTIONAL OR BIDIRECTIONAL?

If a patient with no history of hypertension experiences a myocardial infarction with a critical drop in ejection fraction (*cause*), the neurohormonal response (*consequence*) is mediated by the activation of circulatory receptors and by the kidney, which, by mistakenly interpreting the pump failure as hypovolemia, induces arterial vasoconstriction and sodium and water retention, aggravating circulatory failure. (1) This is clearly positive *feedback* or, if preferred, a bidirectional circuit that determines the progression of heart failure (HF) (Figure 1).

Figure 2 illustrates the effect of various pharmacological interventions on mortality in patients with HF. Neurohormonal blockade (renin-angiotensin-aldosterone and catecholamine inhibition) reduces mortality, calcium channel blockers are neutral, and direct vasodilators or inotropes have a negative effect. (2)

Thus, the benefit of neurohormonal blockade results from an intervention that acts on the consequence rather than the cause. In fact, the negative effect of direct vasodilators is a consequence of neurohormonal activation, which reinforces the above concept.

CLINICAL EXAMPLES AND BIDIRECTIONALITY

Perhaps some clinical examples will help to clarify the concept.

- In **arrhythmia-induced cardiomyopathy**, a high heart rate (HR) secondary to supraventricular arrhythmia (*cause*) leads to inotropic deterioration (*consequence*). The severity of contractile deterioration is directly related to HR and the time of evolution. Control of HR (intervention on the cause) is associated with recovery of function some time later. (3)

However, conversely, tachycardia is often the *consequence* of HF, a condition that acts as the *cause*. In this case, catecholamine activation increases HR and inotropism, which is a compensatory mechanism for

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Fig. 1. Diagram representing the positive feedback mechanism between HF and neurohormonal activation. HF promotes activation, which induces further myocardial damage, in a bidirectional circuit.

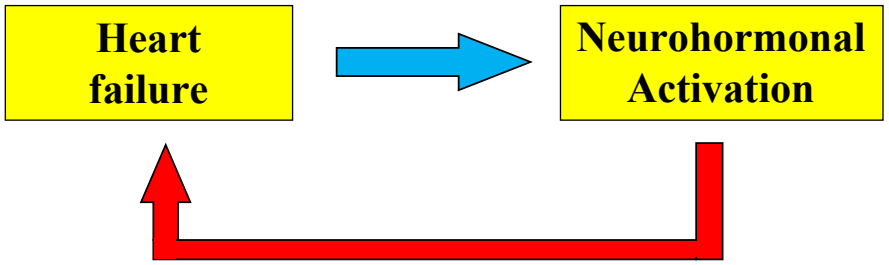
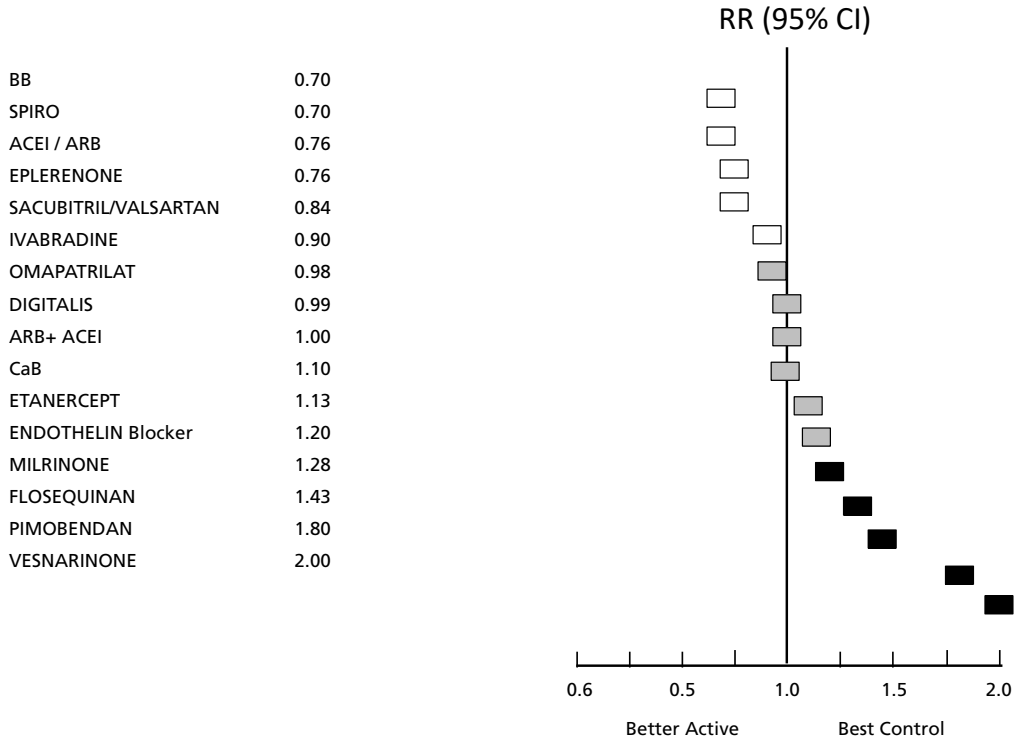


Fig. 2. Historical review of pharmacological interventions evaluated in controlled clinical trials (CCTs) for heart failure (HF) with reduced ejection fraction. Only neurohormonal blockade (renin-angiotensin-aldosterone blockade and beta-blockers) demonstrated a reduction in mortality. Calcium channel blockers, inotropic drugs, and direct vasodilators were ineffective or increased mortality. RR (CI 95%): relative risk, 95% confidence interval (personal communication, Arturo Cagide: Argentine Cardiology Congress 2010).



ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta blockers; CaB: calcium antagonists; Spiro: spironolactone

pump failure, so that the greater the circulatory deterioration, the greater the tachycardia. Clearly, in this case, the direction is opposite to that of arrhythmia-induced cardiomyopathy.

Therefore, control of HR or rhythm is one of the mechanisms associated with the benefit of beta-blockade in HF: the greater the decrease in the number of heartbeats, the greater the reduction in mortality (Figure 3). (4)

Ventricular extrasystoles are in the same scenario: they are usually, but not always, a *consequence* of ventricular remodeling (*cause*), but when they reach a certain number (>10%, >20 000/day), they are a cause for the progression of myocardial damage. (5)

- The close relationship between HF and **myocardial ischemia** does not warrant further analysis, as their interrelationship is a common considera-

tion in clinical practice. Delving into the pathophysiology is not the purpose of this paper, but it is clear that there is a close interrelationship and that treatment aimed at correcting both conditions has a definite impact on prognosis, regardless of which is the cause and which is the consequence.

- **Left bundle branch block** (LBBB) is a common complication of ventricular remodeling in cardiomyopathy. It has been found that the longer the QRS duration, the lower the survival rate, an unadjusted observational finding (Figure 4). (6) A controlled clinical trial (CCT) demonstrated that ventricular activation resynchronization improves survival by correcting the contractile dyssynchrony of LBBB (Figure 4). (7) In principle, it could be concluded that ventricular remodeling (*cause*) leads to LBBB (*consequence*), whose correction through intervention improves the progression of HF. However, it has also been demonstrated that in ventricles without functional impairment, LBBB (*cause*) is an independent predictor of ventricular dilation and remodeling (*consequence*).
- In **secondary mitral regurgitation** (SMR), left ventricular dilation displaces the papillary muscles laterally and apically, compromising the coaptation of both mitral valves.

Fig. 3. Relationship between the absolute reduction in heart rate (HR) due to beta-blockers and the clinical effect expressed as relative risk (RR) of mortality. When treating tachycardia resulting from HF, the greater the reduction in heart rate, the greater the reduction in mortality. This finding is indicative of the bidirectional relationship between tachycardia and contractile damage. Adapted from (4)

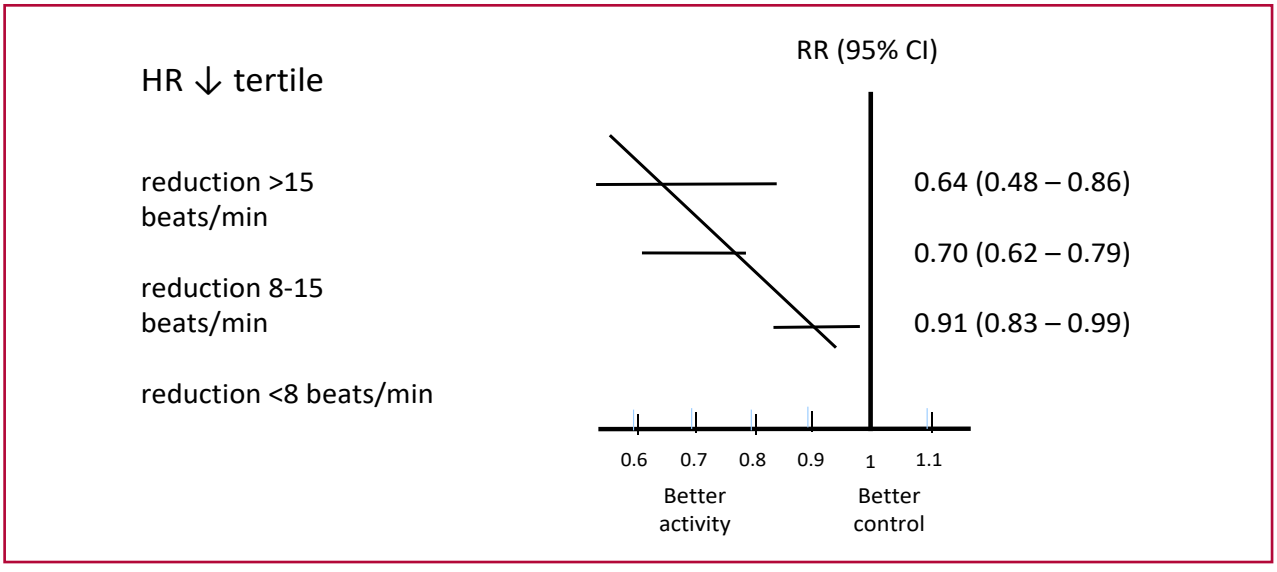
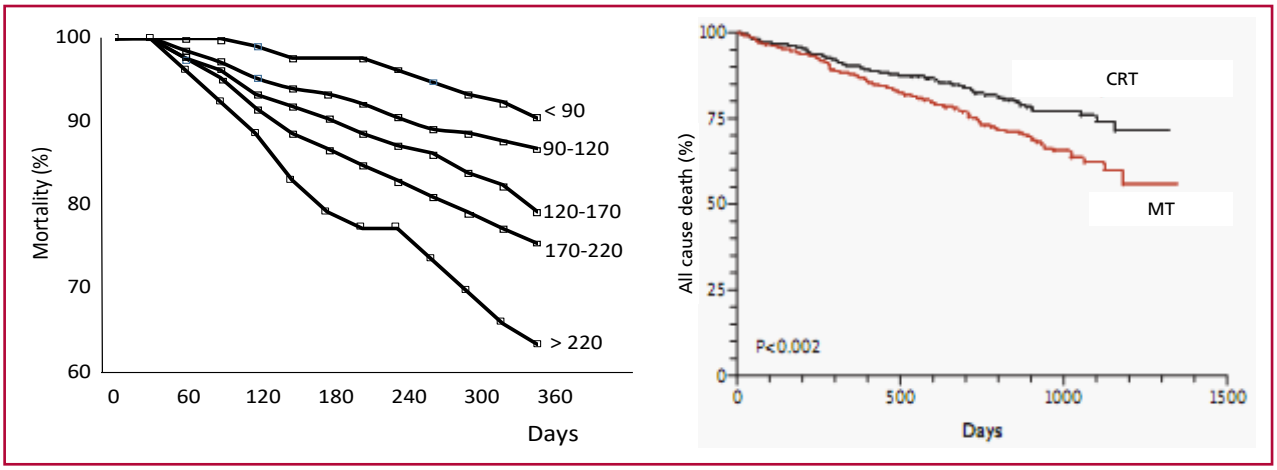


Fig. 4. The left panel shows the relationship between progressive degrees of QRS width in milliseconds, with left bundle branch block morphology and survival (unadjusted observational data). Adapted from (6) The right panel shows the CARE-HF results, demonstrating the effect of resynchronization on the evolution of HF with reduced ejection fraction, where correction of dyssynchrony due to LBBB, a consequence of myocardial damage, is associated with decreased mortality. Adapted from (7)



CRT: cardiac resynchronization therapy; MT: medical treatment

As suggested by its name, SMR is, as in the case of LBBB, a *consequence* of ventricular dilation and remodeling (*cause*) (Figure 5). A CCT (8) demonstrated that partial correction of mitral regurgitation through an intervention such as clipping improves SMR progression. Based on this and other studies, current valve disease guidelines recommend intervention for mitral regurgitation even when it is a *consequence* of ventricular failure. (9)

A second phenotype of SMR results from left atrial and atrioventricular annulus dilation, a condition frequently associated with AF (*cause*). In this case, the left ventricle is normal in morphology and function, with the defect being exclusively a consequence of atrial dilation (*cause*). Correction of SMR has been shown to be associated with improved clinical outcomes (Figure 5).

Certainly, SMR also extends to tricuspid regurgitation in the absence of valve damage.

- Finally, the concept of bidirectionality can be extended to three clinical syndromes: **diabetes** (with its associated entities, hypertension, obesity, and fatty liver), **heart failure, and kidney failure**.

Multiple epidemiological studies have demonstrated the bidirectional connection between HF and kidney failure and the unidirectional connection between diabetes and these entities. (10, 11)

However, the possibility that the association between diabetes and kidney and heart disease is a positive feedback loop has been argued by various authors for some time. The concept is currently gaining interest due to its clinical relevance (Figure 6).

Numerous CCT have demonstrated, regardless of the criteria for inclusion in the trial (diabetes, HF, or kidney failure), an overall and systematic effect of gliflozins and aldosterone blockade in significantly reducing cardiovascular mortality and readmissions for heart failure, as well as in the progression of kidney failure (Figure 6).

The mechanisms of action of these drugs can be interpreted from different perspectives: from the simple treatment and prevention of hypervolemia to the inactivation of various molecular mechanisms that interact in these clinical syndromes.

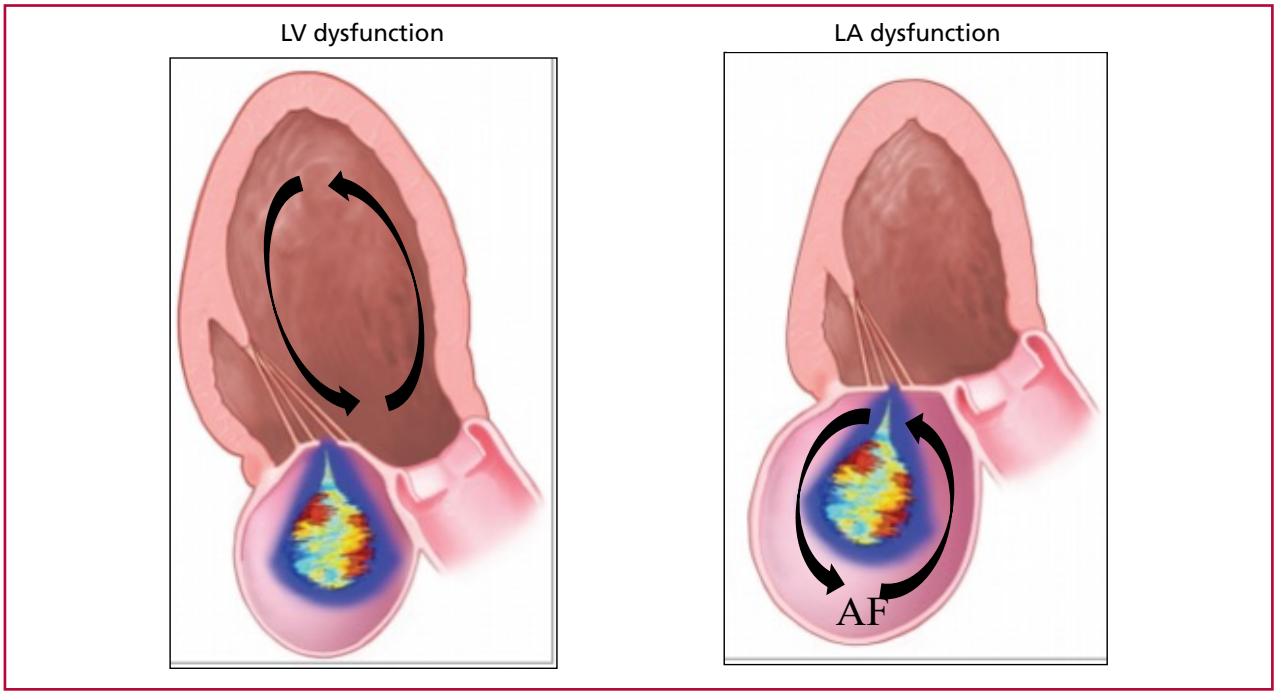
Moreover, it is clear that the renin-angiotensin system, inflammatory activation, insulin resistance, and oxidative stress, among others, play a central role.

The "overall effectiveness" of these drugs reinforces the concept of bidirectionality linking diabetes, HF, and kidney failure.

TEMPORALITY

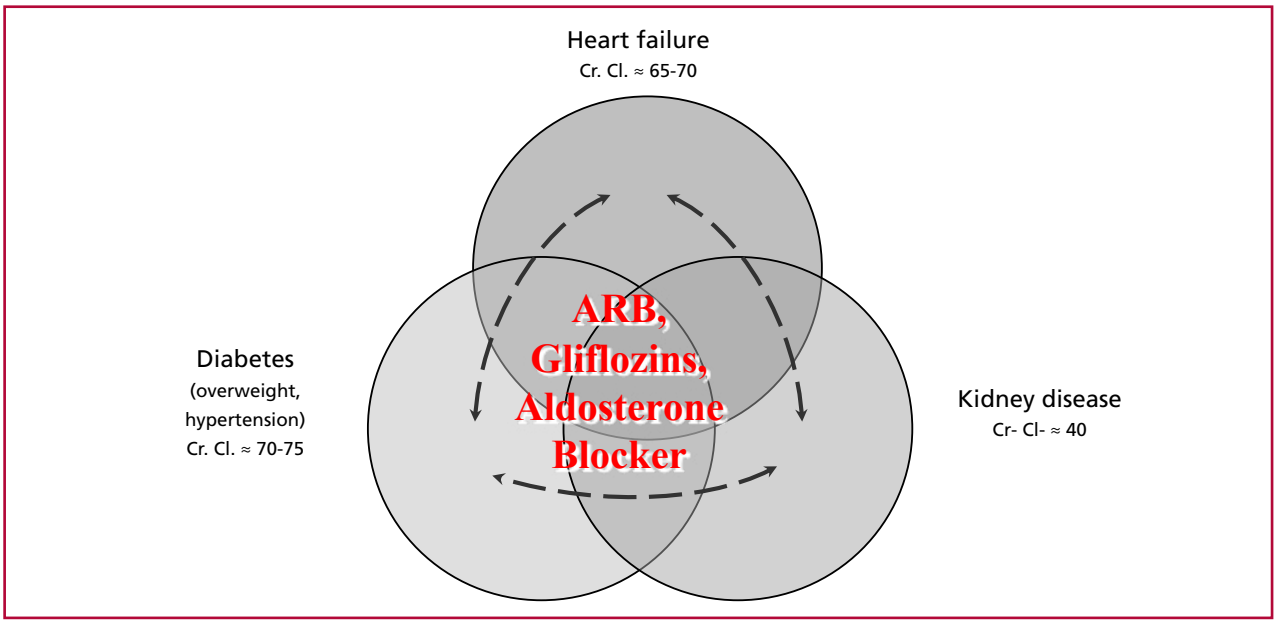
Figure 7 summarizes the mutual relationship between cause and consequence in some of the clinical entities

Fig. 5. The figure shows two conditions associated with secondary mitral regurgitation (SMR). On the left, SMR due to left ventricular dilation, with apical and lateral displacement of the papillary muscles (tethering) and, consequently, coaptation deficit of both valves. On the right, SMR due to atrial and atrioventricular annulus (mitral or tricuspid) dilation, usually associated with atrial fibrillation (AF) in the absence of ventricular involvement. The arrows indicate, in both conditions, the bidirectional mechanism underlying the progression of heart failure signs.



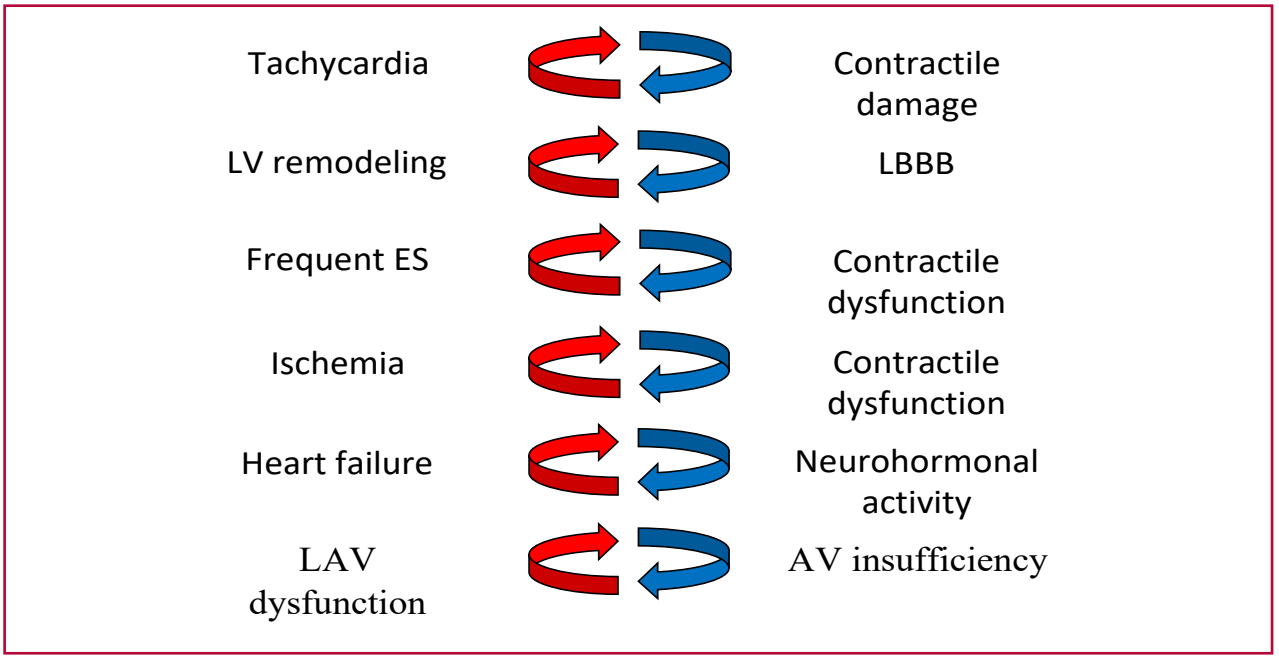
LA: left atrium; LV: left ventricle

Fig. 6. Three conditions, heart failure (HF), kidney disease (KD), and type 2 diabetes, the latter associated with hypertension and obesity, whose association has been demonstrated in epidemiological studies. Two interventions, gliflozins and aldosterone blockade demonstrated simultaneous benefit in the three clinical syndromes, suggesting a common pathophysiological substrate and bidirectional mechanisms as determinants of progression. Secondary analyses demonstrated the effect of angiotensin II blockade



ARB: angiotensin II blockade; Cr. Cl.: mean creatinine clearance.

Fig. 7. Various clinical conditions are summarized with their causes and consequences and the bidirectional substrate conditioning the positive feedback mechanism that determines clinical evolution.



AV insufficiency: atrioventricular valve insufficiency; ES: extrasystoles; LAV dysfunction: left atrioventricular dysfunction; LBBB: left bundle branch block; LV: left ventricle

supporting this presentation.

It is not only a matter of delving deeper into the blurred line between cause and consequence as a determinant of the choice of intervention, but also of advancing a concept that is sometimes difficult to transfer to clinical practice: the criterion of temporality. An example is the differential diagnosis between arrhythmia-induced cardiomyopathy and high-frequency arrhythmia secondary to HF.

CONCLUSION

The associations considered are much too complex to be summarized exclusively in terms of the link between cause and consequence and the probable positive feedback between them.

Left ventricular remodeling is only occasionally associated with LBBB or high-frequency ventricular extrasystoles, just as SMR does not occur systematically in ventricular chamber dilation. The involvement of other "individual" conditions determines the final phenotype that the clinical syndrome will adopt.

This presentation only aims to conclude that defining a variable as a consequence today does not imply its possible treatment in the immediate future. Ultimately, in the recent past, it was believed that SMR was not a treatable condition.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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Dynamic Coronary Roadmap in Real Practice

Dynamic Coronary Roadmap en la práctica real

JUAN M. PÉREZ ASOREY[1], JOAQUÍN PÉREZ ASOREY[2]

Contrast-induced nephropathy (CIN) remains a significant complication after percutaneous coronary intervention (PCI), particularly in elderly patients, diabetics, or those with preexisting chronic kidney disease. (1,2)

A significant body of evidence demonstrates a direct, dose-dependent association between the administered contrast volume and the risk of acute kidney injury. (1-3) In this context, total contrast volume is no longer a purely technical parameter but has become a relevant clinical variable that can be monitored and optimized during percutaneous procedures. (2,3)

In recent years, different strategies have been developed to reduce the contrast volume load during PCI. Low-contrast PCI, the systematic use of intravascular imaging, and the incorporation of software for navigation and planning have proven to be effective tools for reducing unnecessary injections and optimizing decision-making during the procedure. (4) Likewise, from an institutional perspective, excessive contrast media use increases direct costs for materials and indirect costs derived from renal complications, length of hospital stays, and use of complementary tests, with a negative impact on the efficiency of the healthcare system. (2,3)

In this context, Abud et al. evaluated the impact of the Dynamic Coronary Roadmap (DCR) as a tool to reduce the total contrast volume during PCI. This observational, retrospective, single-center study included 480 patients and compared DCR-guided procedures with conventional angiography. The authors demonstrated a significant reduction in the total contrast volume and in the volume used specifically during PCI, with no differences in radiation dose or serum creatinine levels between the two groups. (5)

The study provides relevant local evidence and underscores the concept that incorporating navigation tools can contribute to a more rational use of contrast media, primarily by reducing redundant injections and improving procedure planning. However, from a constructive perspective, it is important to contextualize these findings. Although the absolute reduction in contrast volume observed (20–30 mL) was statistically significant, it did not translate into measurable clinical changes, decreases in creatinine levels, or reduction of adverse kidney events. Furthermore, this is a single-center study with highly experienced operators, where baseline contrast volumes are already low, which could limit the magnitude of the incremental benefit of DCR.

In conclusion, DCR is presented as a useful tool within a comprehensive strategy to reduce contrast volume, particularly in high-risk patients. The study by Abud et al. represents a valuable contribution to this field and paves the way for future multicenter studies aimed at better defining its clinical impact in selected populations.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

Firstly, we would like to thank Dr. Pérez Asorey for his critical reading and constructive feedback on our work, as well as for the conceptual framework he provides on the clinical relevance of contrast-induced nephropathy and the need for strategies to optimize the total volume administered during percutaneous coronary interventions (PCIs).

We agree that the absolute magnitude of the reduction in the contrast agent used must be interpreted in context. In our cohort, the group guided by Dynamic Coronary Roadmap (DCR) showed a significant reduction in total contrast volume (median 120 mL vs. 140 mL). In turn, after adjusting for clinical and procedural variables, the estimated reduction was 37.3 mL per patient (95% CI: 24.3–50.5 mL). We acknowledge that a reduction of this magnitude may seem "incremental" in individual terms; however, we believe that its potential value is expressed in the context of (i) institutional strategies for continuous improvement (reduction of redundant injections, among others) and (ii) higher-risk subgroups, where every mL counts.

We understand that a key point for interpretation is that the DCR group included a significantly higher proportion of complex PCIs (39.6% vs. 17.6%). In other words, DCR was more commonly used in more demanding scenarios, where, in actual practice, contrast consumption is substantially higher. The fact that the reduction persists (and remains after multivariable adjustment) suggests a relevant signal of the tool's operational benefit in more complex anatomies and therapeutic strategies.

Regarding the absence of differences in renal function, we share this cautious interpretation. Although CIN was defined in the protocol as an increase in creatinine within 48–72 hours, the comparison presented was based on changes in creatinine levels measured prior to discharge. Moreover, the study was not powered to detect infrequent clinical outcomes. In this context, we consider it reasonable that a single-center observational study does not show "hard" clinical changes, even with a consistent reduction in contrast media, especially when baseline contrast volumes are already relatively low.

In conclusion, we interpret DCR as a valuable complementary tool within a comprehensive low-contrast PCI strategy, and we agree on the need for future multicenter studies (ideally prospective and regional) focused on populations at higher renal risk, with standardized creatinine measurement in the 48–72 h window and assessment of renal and economic outcomes.

Sincerely yours,

Marcelo A. Abud, Facundo Villa, Ignacio L. Paganini, Javier Cóggiola, Juan P. De Brahi
San Gerónimo Cardiovascular Institute
Endovascular Therapy Service

Argentine Registry of Cardiovascular Surgery

Registro Argentino de Cirugía Cardiovascular

GUILLERMO PARODI[1]

The study *Results of the ARGEN-CCV Argentine Registry of Cardiovascular Surgery* is a fundamental contribution to the evaluation of cardiac surgery in Argentina, presenting prospective and multicenter data on operative mortality and early outcomes. (1) The implementation of national registries is a key strategy for improving the quality of care and allows local results to be placed in the context of international standards, particularly those established by the *Society of Thoracic Surgeons* (STS) and the *European Association for Cardio-Thoracic Surgery* (EACTS).

The *STS Adult Cardiac Surgery Database* is currently one of the most robust clinical registries worldwide, with thousands of procedures included and a

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high degree of standardization in the definition of operative mortality and risk adjustment. Contemporary STS reports show that the observed mortality for isolated myocardial revascularization surgery remains around 1%, while isolated valve surgery has values close to 1-2%, with significant increases in combined or more complex procedures depending on the clinical characteristics of the patient undergoing surgery. (2) These data have been consolidated as international benchmarks for quality assessment.

Similarly, the EACTS has developed its *Adult Cardiac Database*, which allows surgical outcomes in multiple European countries to be analyzed and mortality rates between different centers to be compared. Publications derived from this database and using its risk score (EUROSCORE II) have reported mortality rates comparable to those of the STS for isolated procedures, with a progressive increase in multivalve or combined surgeries, reflecting the impact of surgical complexity and patient risk profile. (3)

In this context, the mortality rates reported by the ARGEN-CCV should be interpreted taking into account the heterogeneity of the participating centers and the characteristics of the Argentine health system and its patients. The marked socioeconomic inequality in Argentina has been linked to a significant increase in postoperative in-hospital mortality in cardiovascular surgery. Patients from lower-income households had lower health insurance coverage, a greater proportion of emergency surgeries, a higher burden of comorbidities, and more limited access to specialized care centers, which impact postoperative outcomes. (4) Therefore, the overall results of the registry are not within ranges comparable to those reported by the STS and EACTS for similar procedures, especially in isolated surgeries, suggesting that there is a lot of work ahead of us to align ourselves with international standards.

A relevant aspect highlighted by recent publications from both STS and EACTS is the need to look beyond in-hospital or 30-day mortality. Contemporary studies have shown that a significant proportion of deaths related to cardiac surgery occur after discharge, which may underestimate the real impact of the procedure if restrictive definitions are used. (5) In this regard, the ARGEN-CCV offers a platform with the potential to evolve towards longer follow-up models and even more robust comparisons, since patients are generally operated on and definitely discharged from the same institution.

In conclusion, the ARGEN-CCV represents a strategic initiative for Argentine cardiovascular surgery. It is essential to maintain databases in which all cardiovascular centers in the country participate. This will reinforce its value as a tool for quality assessment and future planning, and lay the foundation for continuous improvement based on reliable and internationally comparable data.

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

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AUTHORS' REPLY

We appreciate Dr. Parodi's letter and comments. We would like to point out that an attempt was made to follow up patients after hospitalization, but this was frustrated by the lack of adherence by many researchers to data collection, which is why the little information we had obtained was dismissed and only the follow-up during hospitalization remained.

On the other hand, it is worth clarifying that the registry was not designed to validate data with the most commonly used scores.

We fully agree with Dr. Parodi's comments about the need for larger registries with longer follow-up and covering as many centers as possible at the federal level. Permanent and updated registries will be necessary to take these results into account and eventually validate them with the scores currently in use.

Esteban Romeo
On behalf of the authors

Closing Speech of the 2025 SAC Academic Ceremony

Discurso de cierre de la ceremonia académica de la SAC 2025

Today, I am concluding a chapter in my career at the SAC. The presidency was an opportunity that I accepted with humility and responsibility, and it allowed me to try to give back some of what I received from this unique organization. Our society is moving forward, with a clear ethical commitment, to improving the cardiovascular health of the population. This final letter, as president, aims to establish an institutional record of our work and, at the same time, delineate a trajectory for those who will continue this task.

ABOUT THE SAC: MISSION AND PURPOSE

The SAC exists to promote excellence in cardiology in Argentina: to train competent professionals; to generate and adapt guidelines to the local context; and to advocates for health policies that facilitate access to quality care. Our mission is based on education, research, clinical quality, and the defense of cardiovascular health as a right for all Argentines. The vision that guides us is a health system that combines evidence, innovation, and regional solidarity to reduce the burden of heart disease.

The objective established for the present year was to adapt and professionalize our organization to ensure its sustainability and maximize the impact of its actions, avoiding personalism that could lead to mistakes that jeopardize that mission and vision, as well as its sustainability. To that end, we worked on agreements and strategic issues after several meetings with the leaders who will succeed me over the next three years. We developed a strategic plan that considered all organizational aspects within the current context.

Governance and ethics

- We have strengthened our transparency, accountability, and conflict of interest management practices with active committees and regular reports to our members.

Education and training

- We have developed the legal, organizational, and institutional foundations for the SAC University Institute, now called the SAC Continuing Education Institute and, in the future, the SAC University Institute.
- We have promoted the growth of regional and national conferences, synchronized the actions of the councils with districts nationwide, organized symposiums in different provinces and neighboring countries, and included doctors, nurses, and technicians.
- We have updated educational programs and clinical guidelines adapted to our local context and expanded continuing medical education with a practical, regional focus covering the entire spectrum of human resources in the health system.
- We have prioritized our beloved Argentine Journal of Cardiology, the foundation of our organization, for education and research, investing in consulting and trained human resources.

Research and data

- We have professionalized the research area nationwide and opened it up to generate registries that are representative of the national reality.
- We have provided counsel and promoted quality research among all SAC members.

Funding

Quality and standards

- We have promoted the implementation of evidence-based clinical practice tools, with efforts to standardize procedures and improve patient outcomes.

Collaborations and advocacy

- We have strengthened alliances with hospitals, universities, and other scientific societies, both nationally and internationally. These alliances have influenced health policies to benefit patients and communities. We developed a forum with 23 core and historical societies of Argentine medicine. This forum has become a valuable tool for assessing the healthcare system and its human resources, while also generating ideas and proposals to improve a system to which we all belong.

Representativeness and dversity

- We have incorporated a diverse range of voices from various regions, generations, and specialties within cardiology, with more open participation mechanisms.

Communication and institutional memory

- We have consolidated clear and accessible information channels and a memory of projects and lessons learned for future administrations.

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Communication and technological innovation

- We have initiated processes to improve digital platforms, data collection tools, and effective communication with partners and patients in the area of global communication.

Investment in infrastructure

- We carried out an enhancement of the central building while preserving its historical value, and initiated renovations to enable the establishment of the SAC University Institute and the SAC Museum, as well as the architectural integration with the Argentine Cardiology Foundation, as previously agreed with its authorities.

Succession and legacy

- We have prepared the next generation of leaders by providing mentoring, knowledge transfer, and strategic project continuity plans. To this end, we created the SAC Members Area, which offers training and leadership workshops.

CHALLENGES AND OUTLOOK FOR THE FUTURE

The Argentine healthcare system is undergoing one of the most critical periods in its history, facing significant challenges:

- Heterogeneity of the country: the geographical and cultural differences and fragmentation of the healthcare system, influence the implementation of guidelines and programs.
- Sustainability: ensuring resources for long-term projects, maintaining educational quality, and sustaining research initiatives in the face of fluctuating budgets.
- Implementation of innovations: adoption of new therapies, technologies, and tools necessitates investment of time, evidence, and training.
- Scope and equity: ensuring that the benefits of modern cardiology reach regions with less access and vulnerable populations.
- Impact measurement: defining clear success indicators and periodically evaluating them to demonstrate the value of initiatives.

My aspiration is for the SAC to continue being a responsible driver of innovation while maintaining scientific integrity and staying close to patients' needs. The strategic plan is a key tool for ensuring its continuity.

I would like to express my deepest gratitude to my colleagues who shared this journey with me, as well as to all SAC members from across the country and from the institution's various areas, councils, and districts.

I would also like to acknowledge the invaluable work of the SAC staff, who adapted to a very demanding work dynamic and new parameters for action.

Finally, the enormous commitment and team spirit of the Board of Directors were essential to achieving our goals. All decisions were made through responsible discussion and many hours of dedicated work.

I invite each member to continue participating with enthusiasm, rigor, and empathy. The SAC thrives on collective commitment: let us continue to promote quality research, continuing education, and the defense of cardiovascular health as a universal right.

Pablo Stutzbach MTSAC,
President of the Argentine Society of Cardiology