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EDITORIAL

Aortic Stenosis: Beyond the Aortic Valve...

Estenosis aórtica: más allá de la válvula ….

RODOLFO PIZARRO[1, MTSAC]

The left ventricle (LV), the aortic valve, and the aorta form a functional unit that is responsible for delivering blood flow to the organs. Any abnormality in one or more components of this unit hinders systemic perfusion and has an impact on morbidity and mortality. Aortic stenosis (AS) is the most common valvular heart disease as age increases, and it creates an imbalance in this functional unit. In patients with AS, the LV often faces a double load: a valvular load imposed by AS and an arterial load caused by a decrease in systemic arterial distensibility (or an increase in systemic vascular resistance) in the context of comorbidities (e.g., age, smoking, hypertension, diabetes). (1) In patients with AS, the LV hemodynamic load is not solely determined by the severity of the stenosis, but is also influenced by systemic vascular resistance, volume flow rate, and body size. Therefore, valvuloarterial impedance (Zva) represents the pressure cost in mm Hg for each systemic mL of blood indexed for body size pumped by the left ventricle during systole, considering the valvular load and the arterial load. Ventricular-arterial coupling (VAC) is calculated as the effective arterial elastance (Ea) to LV end-systolic elastance (Ees) ratio measured in the LV pressure-volume loop. (1) Effective arterial elastance is calculated as the mean LV systolic pressure to stroke volume ratio and is often considered a measure of the arterial hemodynamic load imposed on the LV. End-systolic elastance describes the maximum pressure that the ventricle can develop at any given LV volume and is an index of myocardial contractility, relatively insensitive to changes in preload, afterload, and heart rate. The Ea/Ees ratio is useful to assess the mechanical efficiency of the cardiovascular system and the interaction between cardiac performance and systemic vascular function. (1) Effective arterial elastance is calculated using LV end-systolic pressure and is therefore influenced by arterial load but does not consider valvular load.

In the study "Relationship Between Ventricular-arterial Coupling and Stage of Extravalvular Damage in Aortic Stenosis", Migliore et al. evaluated the relationship between VAC and the different stages of extravalvular damage in AS. (2)

The authors analyzed 205 patients. Mean age was 70 ± 11 years, 59 % had hypertension (HTN), 50 % were in FC III-IV and 40 % had a left ventricular ejection fraction (LVEF) < 60 % (mean LVEF 52± 19%). Baseline peak and mean aortic valve gradients were 70 mm Hg and 41 mm Hg, respectively. Baseline systolic pulmonary artery pressure was 46 ± 17 mm Hg. (2)

Patients were divided into five groups according to extravalvular cardiac damage: 0, no cardiac damage; 1, LV systolic or diastolic dysfunction or LVEF < 60%; 2, left atrial dilation, ≥ moderate mitral regurgitation or atrial fibrillation; 3, signs of pulmonary hypertension (≥ 60 mm Hg), ≥ moderate tricuspid regurgitation; and 4, right ventricular damage or stroke volume index < 30 mL/m^2. As the stage of myocardial damage progressed, VAC impairment increased. The authors concluded that the alteration of VAC that occurs from stage 2 to 4 is due to an increase in Ea without significant changes in the level of contractility (Ees). The progression of extravalvular myocardial damage appears to be associated not only with valvular disease but also with the characteristics of the arterial vasculature. (2)

Measurement of Zva showed differences in stage 4 versus the other stages as an expression of greater valvular heart disease progression.

Some considerations of the study arise from the study population and the above-mentioned results:

This population has long-standing severe AS,

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which is critical for a significant proportion of the population (as indicated by the fact that 107 patients, 52%, had an advanced stage). This assertion is supported by the authors, who note that there are no patients in stage 0, with elevated gradients and reduced left ventricular ejection fraction (LVEF), suggesting that they have an increased valvular load and reduced LV compliance (although their contractility, as measured by Ees, was not significantly different between the groups with structural damage) as the average E/e' ratio is 16.

In turn, 82% of stage 4 patients presented low aortic flow which is associated with higher Ea and Zva.

Hachica et al. analyzed Zva and observed that a cut-off value ≥ 3.5 mm Hg identified a population with excessive aortic impedance (hemodynamic load) that was associated with a more severe disease independently of the events. (3)

However, other studies have not identified Ea as a clinical predictor because it depends on aortic stiffness and heart rate (insensitive to pulsatile flow) and does not take into account valve flow or valve load. (4)

The Ea/Ees ratio was an independent predictor of mid-term outcomes after transcatheter aortic valve implantation (TAVI). (5)

Migliore et al. found increased Ea/Ees ratio in severe AS patients with symptoms or heart failure. (6)

Hypertension and stiffness may also alter VAC and thus accelerate the development of symptoms of AS. (7) In a series of 193 patients with AS, those with HTN developed symptoms earlier despite their valve areas were larger. (7)

Furthermore, in patients with low-flow, low-gradient AS, Zva was associated with lower mean aortic gradient. (8) Higher Zva is associated with impaired longitudinal LV systolic function, (9,10) and lower survival. (3,10) As it occurs with Ea, Zva has limitations because complex pulsatile afterload cannot be represented by a single parameter.

From a clinical perspective, adapting to these measurements would present a challenge and they would continue to be regarded as interesting physiological concepts. The measurement of blood pressure and keeping its values within normal limits are simple measures that can be taken to avoid further impairment of valvular afterload and ventricular function.

Does this limit the value of this work? If one considers that physiology is what allows us to understand biological phenomena in order to better understand diseases, it is always welcome to express pathophysiological bonds, and this is the merit of this research.

New methods (4D flow phase-contrast magnetic resonance imaging, algorithm-based P-V loops) are likely to give us a broader perspective on how to more accurately assess aortic stenosis beyond the valve. (11)

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

Ethical considerations
Not applicable.

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EDITORIAL

De novo Atrial Fibrillation in STEMI: A Clinical Red Flag

La fibrilación auricular de novo en el IAMCEST: una señal de alarma clínica

MIRZA RIVERO[1, MTSAC]

Atrial fibrillation (AF) is the most common arrhythmia encountered by cardiologists in a variety of clinical settings: in patients with heart failure, in the postoperative period following cardiac and non-cardiac surgery, in intensive care units, and, of course, in acute myocardial infarction (AMI). (1) It is estimated that approximately 10% of patients with acute coronary syndrome present with *de novo* AF on admission, (2,3) and this incidence may be even higher after intensive monitoring or the use of implantable devices. (4,5)

The risk factors for AF are well established: advanced age, obesity, hypertension, smoking, diabetes, and excessive alcohol consumption. (6,7) These factors largely overlap with those for myocardial infarction, which raises the question: why do some patients with AMI develop AF during the acute event? This question points, on the one hand, to the substrate (age, atrial fibrosis, structural heart disease) and, on the other hand, indicates that AF may be a marker of the severity of the clinical condition, likely triggered by an adrenergic discharge and the hemodynamic stress characteristic of acute heart failure. (2)

Attempting to predict which patients will develop AF in the context of AMI is an important step toward a more accurate risk stratification and better therapeutic guidance. In practice, patients with ST-segment elevation myocardial infarction (STEMI) and AF raise multiple questions: does AF necessarily indicate heart failure? Should rhythm or rate control be prioritized? Should anticoagulation be initiated immediately, even if AF reverts spontaneously? How should the balance between anticoagulation and antiplatelet therapy be managed?

In this issue of the Argentine Journal of Cardiology, Julia Janches Quiñones and colleagues address these questions through a retrospective analysis of the ARGEN-IAM-ST continuous registry, to assess the incidence, predictors, and prognostic value of *de novo* AF in STEMI. (8) In a cohort of over 7200 patients, they found a 4.3% incidence of *de novo* AF and, using the Boruta algorithm—a variable selection tool in machine learning environments—they identified age ≥70 years, Killip and Kimball classes B–D, tachycardia on admission, and ejection fraction <35% as clinical predictors.

In this analysis, *de novo* AF was associated with a higher incidence of ischemic stroke (2.5% vs. 0.8%), longer hospital stay, and a significantly higher in-hospital mortality rate (23.3% vs. 8.2%). However, after adjustment for confounding variables, *de novo* AF did not act as an independent predictor of mortality, suggesting that, rather than being a direct cause, it is more likely a marker of greater clinical severity and ventricular dysfunction, at least during hospitalization.

Although *de novo* AF was not shown to be an independent predictor of in-hospital death in this study, the role of AF in the long-term prognosis of these patients remains to be determined. Several similar studies suggest that the prognosis of *de novo* AF following AMI is similar to that of AF diagnosed prior to the ischemic event, with implications for increased thromboembolic risk, anticoagulation decisions, and higher bleeding risk. (9-11)

Unlike other prediction models developed in selected cohorts or clinical trials, this study offers a representative view of the real-world practice in Argentina. The use of the Boruta algorithm —a technique usually reserved for data science contexts to identify the most predictive variables— reflects a methodological advancement in national clinical registries. However, it is worth noting that the model did not include variables related to infarct size or location, atrial echocardiographic parameters, or post-hospitalization follow-up, which could enhance future developments.

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These findings complement and expand on observations made in other clinical settings. In a recent analysis of the SCACEST registry from the Buenos Aires I study, AF was also identified as a marker of higher clinical risk in patients with non-ST-segment elevation myocardial infarction, associated with older age, ventricular dysfunction, and heart failure, although without an independent impact on mortality. The comparison between the two registries —SCACEST and IAMCEST— reinforces the hypothesis that *de novo* AF in the context of acute coronary syndrome, rather than being an isolated entity, should be understood as an expression of the patient's hemodynamic severity and baseline frailty. (12)

This study represents a valuable local contribution that describes a frequent and challenging complication using national data, supported by a robust and continuous registry such as ARGEN-IAM. Although the predictive model does not, by itself, change therapeutic decision-making, it enables the clear identification of a clinical phenotype —elderly patients with hemodynamic deterioration and ventricular dysfunction— that justifies intensive monitoring, early assessment of complications, and a cautious approach to antithrombotic management.

Moreover, this work paves the way to further research into the long-term prognostic and therapeutic implications of novo AF following myocardial infarction, a field that remains largely unexplored in the region.

Conflicts of interest

None declared

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Ethical considerations

Not applicable.

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ORIGINAL ARTICLE

De novo Atrial Fibrillation in ST-Elevation Acute Myocardial Infarction. Analysis of the ARGEN-IAM-ST Registry

Fibrilación auricular de novo *en el infarto agudo de miocardio con elevación del segmento ST. Análisis del Registro ARGEN-IAM-ST*

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ABSTRACT

Background: Atrial fibrillation (AF) is the most frequent arrhythmic complication in patients with acute coronary syndrome (ACS), and its incidence ranges between 2.3% and 21%.
Objective: To determine the incidence and predictors of *de novo* AF in patients with ST-segment elevation myocardial infarction (STEMI).
Methods: The database of the ARGEN-IAM-ST continuous registry was analyzed. Conventional descriptive statistics were used. To reduce dimensionality and identify those variables associated with the outcome of interest, Machine Learning algorithms were used, and a multivariate logistic regression analysis was performed to identify those factors associated with *de novo* AF. These were included in a final ranking model which was assessed by using the receiver operating characteristic (ROC) curve. A p-value <0.05 was considered statistically significant.
Results: We included 7292 patients with STEMI. A total of 4.3% had *de novo* AF during hospitalization. This group was older (67 vs. 60 years, p <0.001), with higher heart rate and Killip and Kimbal score and lower left ventricular ejection fraction (LVEF) on admission. These patients had a higher incidence of stroke (2.5% vs. 0.8% p = 0.002) and in-hospital death (23.3% vs. 8.2%, p <0.001), but *de novo* AF was not an independent predictor of mortality. The following variables were independent predictors of in-hospital *de novo* AF after STEMI: stratified age (50 to 59 years: OR 2.16, 95% CI 1.11-2.73; 60 to 69 years: OR 1.77, 95% CI 1.07-2.96; 70 to 100 years: OR 3.98, 95% CI 2.60-6.26), Killip and Kimball score (B: OR 1.72 95% CI 1.19-2.46; C: OR 1.09, 95% CI 0.31-2.91, D: OR 2.48, 95% CI 1.60-3.78), tachycardia (OR 2.41, 95% CI 1.74-3.31) and LVEF <35% (OR 1.62, 95% CI 1.74-3.31). The area under the ROC curve (AUC ROC) of the model was 0.73; the sensitivity and specificity were 77% and 62%, respectively.
Conclusion: *De novo* AF was a relatively frequent complication. Factors such as age, heart rate, hemodynamic profile on admission and ventricular function were shown to be predictors of *de novo* AF after a myocardial infarction during hospitalization. However, *de novo* AF was not independently associated with in-hospital mortality.

Key words: Atrial fibrillation - ST-elevation myocardial infarction

RESUMEN

Introducción: La fibrilación auricular (FA) es la complicación arrítmica más frecuente en pacientes con síndrome coronario agudo (SCA), con una incidencia entre 2,3% y 21%.
Objetivos: Determinar la incidencia y predictores de FA *de novo* en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST).
Material y métodos: Se analizó la base de datos del registro continuo ARGEN-IAM-ST. La estadística descriptiva fue la convencional. Para reducir la dimensionalidad e identificar aquellas variables asociadas con el desenlace de interés, se utilizaron algoritmos de *Machine Learning* y se realizó un análisis multivariable de regresión logística para identificar aquellos factores asociados a la presencia de FA *de novo*. Los mismos fueron incluidos en un modelo de clasificación final que fue evaluado por medio de curva ROC. Se consideró un valor de p <0,05 como estadísticamente significativo.
Resultados: Se incluyeron 7292 pacientes con IAMCEST. El 4,3% presentó FA *de novo* durante la internación. Este grupo era más añoso (67 vs. 60 años, p <0,001). Al ingreso hospitalario, presentaba mayor frecuencia cardíaca, un score de Killip y Kimball mayor

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[3] Argentine Society of Cardiology

y una menor fracción de eyección del ventrículo izquierdo (FEVI). Estos Pacientes tuvieron mayor incidencia de accidente cerebrovascular (2,5% vs. 0,8% p = 0,002) y muerte intrahospitalaria (23,3% vs. 8,2%, p <0,001), pero la FA *de novo* no fue predictor independiente de mortalidad. La variable edad estratificada (50 a 59 años: OR 2,16, IC 95% 1,11-2,73; 60 a 69 años: OR 1,77, IC 95% 1,07-2,96; 70 a 100 años: OR 3,98, IC 95% 2,60-6,26); el score Killip y Kimball (B: OR 1,72 IC 95% 1,19-2,46; C: OR 1,09, IC 95% 0,31-2,91, D: OR 2,48, IC 95% 1,60-3,78) la presencia de taquicardia (OR 2,41, IC95% 1,74-3,31) y una FEVI <35 % (OR 1,62, IC95% 1,74-3,31) fueron predictores independientes de FA *de novo* intrahospitalaria posterior a un IAMCEST. El modelo presentó un área bajo la curva ROC (ABC ROC) de 0,73, con sensibilidad y especificidad de 77 y 62 %, respectivamente.
Conclusiones: la FA *de novo* fue una complicación relativamente frecuente. Factores como la edad, frecuencia cardíaca, el perfil hemodinámico al ingreso y la función ventricular mostraron ser predictores de FA *de novo* post infarto en la internación. Sin embargo, ésta no se asoció de manera independiente con la mortalidad intrahospitalaria.

Palabras clave: Fibrilación auricular - Infarto de miocardio con elevación del segmento ST

INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in adults, and its prevalence has been increasing over the past decades due to aging population and increased survival from other cardiovascular diseases. (1) It is associated with an increased risk of thromboembolic events, (2) cognitive impairment, (3) heart failure, hospitalizations, and death. (4)

In turn, it is the most frequent arrhythmic complication in patients with acute coronary syndrome (ACS), and its incidence ranges from 2.3% to 21%. (5) In Argentina, the incidence of *de novo* AF in this setting is 3.2%, as observed in the ARGEN-IAM-ST registry. (6) Over the last decades and with the advances in invasive and medical treatment, its incidence has decreased. (6) Several studies have evaluated the clinical characteristics of patients with *de novo* AF after ACS. The main predictors were advanced age, signs of heart failure, and tachycardia on hospital admission. These predictors have been maintained both in studies performed in the fibrinolytic era and in the present day, when percutaneous treatment is available. (7, 8)

In the general population and in patients with ACS, the presence of AF is associated with a worse prognosis. De novo AF in the setting of ACS is associated with increased morbidity and mortality. (9, 10) In turn, several observational studies have shown that patients with coexisting ACS and *de novo* AF are less likely to receive appropriate antithrombotic treatment. (11, 12) However, there is a lack of studies analyzing the predictors and prognosis of these patients in the setting of invasive and medical treatment, as recommended by the latest guidelines. This study aimed to evaluate the incidence of *de novo* AF during hospitalization for ST-elevation myocardial infarction (STEMI) and to determine the predictors associated with its development.

METHODS

Study design and population

This is an observational and retrospective study based on the analysis of the continuous registry of ST-segment elevation acute myocardial infarction (ARGEN-IAM-ST), which includes patients with STEMI from numerous centers in Argentina. Its protocol was previously published and has been active since 2015. (13,14) The protocol has been registered in ClinicalsTrials.gov under NCT 2458885. The cut-off date for the analysis of this work was May 2024.

Definitions and outcomes of interest

Our outcome of interest was *de novo* AF during hospitalization, defined as AF in patients who had an admission electrocardiogram (ECG) showing sinus rhythm and an episode of AF as a complication during their progress. This was modeled as a binary variable. We excluded from this definition those patients with a history of AF and atrial flutter.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to their type of distribution. The variables of age and heart rate were analyzed by strata. Qualitative variables are expressed as absolute and relative frequencies. Qualitative variables were compared using the chi-square test or Fisher's exact test, while continuous variables with parametric and nonparametric distribution were compared using Student's t test and the Mann Whitney U test, respectively.

To reduce dimensionality and identify those variables associated with our outcome of interest, the Boruta Machine Learning algorithm was used. (15) To ensure that variable selection was stable and reproducible, the algorithm performed up to 50 iterations which allowed a robust assessment of the importance of each predictor in *de novo* AF ranking. In addition, its performance was monitored during the process to verify consistency in feature selection. Multivariate analysis using logistic regression was performed with the most important variables to identify the factors independently associated with *de novo* AF. The models were trained and evaluated on two different databases randomly generated from the general database. The performance of the models and their discrimination ability was evaluated through the generation of receiver operating characteristic (ROC) curves. Since the aim of the model was to maximize sensitivity to identify the greatest number of cases of *de novo* AF, the optimal cut-off point was selected from the ROC curve with the highest possible sensitivity criterion, while maintaining clinically acceptable specificity. The Hosmer Lemeshow test was used to evaluate the goodness of fit of the model. The association between the predictors and the incidence of events was expressed as odds ratio (OR) with their 95% confidence intervals (CI). In addition, a multivariate model was performed to explore *de novo* AF as an independent predictor of mortality. All tests were two-tailed and statistical significance was set at a p-value <0.05.

The analysis was performed with R Studio, version 1.4.1106 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The ethics committee of the Argentine Society of Cardiology approved the protocol of the Argen IAM-ST registry.

RESULTS

Baseline characteristics of the population

We included a total of 7292 patients with STEMI and evidence of sinus rhythm on admission ECG , of which 79% were male, and had a median (IQR) age of 61 (53-69) years. Table 1 shows the baseline characteristics.

We identified that 4.3% of the sample patients had *de novo* AF during hospitalization. These patients were older than those with no *de novo* AF (median age 67 vs. 60 years; p <0.001). We found no differences between the groups related to body mass index (BMI), diabetes mellitus and dyslipidemia. However, 53.1% had arterial hypertension (HT), and the prevalence was higher in the group of patients who developed AF during hospitalization (65.7% vs. 52.5%; p <0.001). In turn, the history of coronary artery disease –which was present in 12.3% of the total sample– was also more frequent in the group with *de novo* AF (16% vs. 12.1%; p = 0.047).

Regarding reperfusion strategies in all patients, primary angioplasty was performed in 91%, a pharmacoinvasive strategy in 5%, rescue angioplasty in 2.8%, and elective angioplasty in 1.1%, with no significant differences between the study groups. However, multi-vessel angioplasty was performed in the initial procedure in a higher proportion of patients who developed AF during hospitalization. There were no significant differences in the treatment of the culprit vessel for AMI.

Regarding treatment with beta-blockers and angiotensin-converting enzyme inhibitors on admission, we found a lower use in patients with *de novo* AF, that is, 37.7% vs 50.5% (p = 0.001) and 40.6% vs.45.6% (p =0.090), respectively.

On hospital admission, those patients who developed AF had a higher heart rate (86 bpm vs. 80 bpm; p <0.001). Regarding laboratory tests, they had higher glycemia values, with a median (IQR) of 153 mg/dl (124-212) vs. 134 mg/dL (113-177), p <0.001, and higher creatinine values: 1.08 mg/dL (0.90-1.40) vs. 0.97 mg/dL (0.8-1.17), p <0.001.

This group of patients also had longer total ischemia time (medians 289 min vs. 252 min; p = 0.019), a more severe Killip and Kimball score (p <0.001) and lower left ventricular ejection fraction (LVEF) (p <0.001).

In-hospital events

The presence of *de novo* AF was associated with a higher incidence of ischemic stroke (2.5% vs. 0.8%; p = 0.002) and more days of hospitalization (medians 6 vs. 4 days; p <0.001). In-hospital all-cause death was also higher in the *de novo* AF group (23.3% vs. 8.2%; p <0.001) (Table 2).

Selection of important variables

Using the Boruta algorithm, an automated selection was performed to identify the variables with the greatest importance in the prediction of *de novo* AF. In the analysis, the Killip and Kimball, heart rate and LVEF variables were identified as the most important, followed by gender, age, dyslipidemia, and creatinine. Figure 1 shows the means of importance of each variable in the ranking. Subsequently, these variables were included in the multivariate logistic regression model to evaluate their association with the outcome.

Multivariate analysis: Independent predictors of *de novo* AF

The greatest weight variables associated with *de novo* AF were included in a multivariate logistic regression model. The stratified age (50 to 59 years, 60 to 69 years, and 70 to 100 years) was independently associated with the incidence of *de novo* AF (OR 1.72, 95% CI 1.11-2.73; OR 1.77, 95% CI 1.07-2.96; OR 3.98, 95% CI 2.60-6.25, respectively). Clinical presentation according to Killip and Kimball score (B: OR 1.72, 95% CI 1.19-2.46; C: OR 1.09, 95% CI 0.315-2.90; D: OR 2.48, 95% CI 1.60-3.78), tachycardia (OR 2.41, 95% CI 1.74-3.31) and impaired LVEF (<35%) (OR 1.62, 95% CI 1.04-2.50) were also independent predictors (Figure 2). To evaluate the performance of the model, a ROC curve was constructed and the area under the curve (AUC) was 0.733 (95% CI 0.698-0.769). The optimal cut-off point was determined at 0.10 to maximize sensitivity. According to this threshold, the model correctly identified 77% of patients with *de novo* AF (sensitivity) and 62% of patients without *de novo* AF (specificity). This cut-off point represents the threshold where the balance between sensitivity and specificity is clinically most appropriate for the detection of *de novo* AF (Figure 3). The goodness of fit of the model, assesed by the Hosmer-Lemeshow test, was good (χ^2 = 5.33, p = 0.618).

Multivariate analysis: *de novo* AF as an independent predictor of mortality

De novo AF was included with the main variables related to in-hospital mortality in a multivariate model. We observed that *de novo* AF did not behave as an independent predictor of in-hospital mortality (OR 0.79, 95% CI 0.41-1.50) (Figure 4).

DISCUSSION

We present data on the incidence of *de novo* AF during hospitalization for STEMI from the ARGEN-IAM-ST registry. On this occasion, cases with AF on admission ECG or with history of AF were excluded in order to evaluate the consequences of this event after AMI. The incidence of *de novo* AF was 4.3%, and the findings suggest an association with a greater number of in-hospital events and a longer hospital stay. In addi-

Table 1. Baseline clinical characteristics of participants with and without *de novo* AF

	Global	Without *de novo* AF	With de *novo* AF	p
n	7292	6974	7292	
Male gender, n (%)	5754 (79)	5512 (79)	5754 (79)	0.705
Age, years, median (IQR)	61 (53-69]	60 (53-68)	61 (53-69]	<0.001
BMI, kg/m^2, median (IQR)	27.65	27.68	27.65	0.041
	(25.47-30.61)	(25.51-30.76)	(25.47-30.61)	
DM, n (%)	1980 (27.2)	1900 (27.2)	1980 (27.2)	0.451
Smoking, n (%)	591 (8.1)	563 (8.1)	591 (8.1)	0.717
DLP, n (%)	2662 (36.5)	2553 (36.6)	2662 (36.5)	0.433
HT, n (%)	3870 (53.1)	3661 (52.5)	3870 (53.1)	<0.001
Previous coronary artery disease, n (%)	897 (12.3)	846 (12.1)	897 (12.3)	0.047
Beta-blockers , n (%)	3635 (50.0)	3519 (50.5)	3635 (50.0)	<0.001
ACEIs, n (%)	3301 (45.4)	3178 (45.6)	3301 (45.4)	0.090
Glycemia, mg/dL, median (IQR)	135 (113-179)	134 (113-177)	135 (113-179)	<0.001
Creatinine, mg/dL, median (IQR)	0.97 (0.80-1.18)	0.97 (0.80-1.17)	0.97 (0.80-1.18)	<0.001
Reason for PCI, n (%)				0.949
Primary	5003 (91.1)	4887 (70.1)	5003 (91.1)	
Pharmacoinvasive	273 (5.0)	646 (9.3)	273 (5.0)	
Rescue	154 (2.8)	976 (14.0)	154 (2.8)	
Elective	59 (1.1)	465 (6.7)	59 (1.1)	
SBP, mm Hg, mean (SD)	131 (29)	132 (29)	131 (29)	<0.001
HR, bpm, mean (SD)	80 (19)	80 (18)	80 (19)	<0.001
Killip and Kimball, n (%)				<0.001
A	5485 (77.0)	5456 (78.2)	5485 (77.0)	
B	1024 (14.4)	955 (13.7)	1024 (14.4)	
C	100 (1.4)	95 (1.4)	100 (1.4)	
D	516 (7.2)	468 (6.7)	516 (7.2)	
Door-to-balloon time, min, median (IQR)	84 (47-147]	91(50. 175]	84 (47-147]	0.439
Time window, min, median (IQR)	230 (135-440)	252.50 (146- 510)	230 (135-440)	0.019
Multi-vessel PCI in initial procedure, n (%)	351 (6.4)	360 (5.2)	351 (6.4)	0.026
LVSF, n (%)				<0.001
Normal	2397 (37.4)	2660 (38.1)	2397 (37.4)	
Mild impairment	1842 (28.7)	1994 (28.6)	1842 (28.7)	
Moderate impairment	1397 (21.8)	1466 (21.0)	1397 (21.8)	
Severe impairment	774 (12.1)	854 (12.2)	774 (12.1)	

ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; BMI: body mass index; bpm: beats per minute; DLP: dyslipidemia; DM: diabetes mellitus; HR: heart rate; HT: hypertension; IQR: interquartile range; LVSF: left ventricular systolic function; PCI: percutaneous coronary intervention;SBP: systolic blood pressure; SD: standard deviation

tion, certain factors such as age, heart failure assessed by the Killip and Kimball score, tachycardia, and impaired LVEF were shown to be independent predictors of *de novo* AF during hospitalization. These predictors were included in a ranking model to predict *de novo* AF, which showed an AUC of 0.733 (95% CI 0.698-0.769).

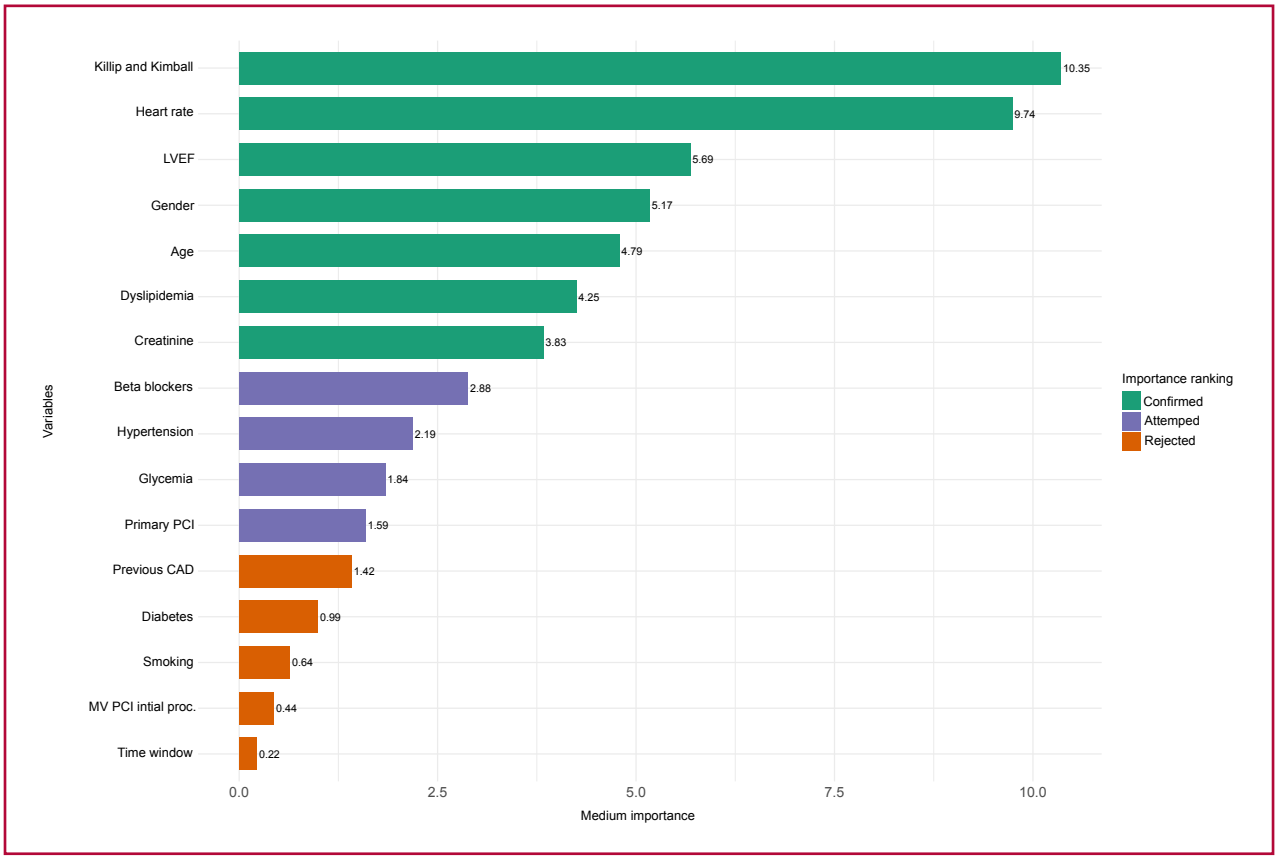
AF and ACS are two common heart diseases and, over the years, multiple studies have been performed to analyze the relationship between them. The risk of *de novo* AF increases by 60-77% in patients with AMI. (16) In the fibrinolytic era, the randomized GUSTO-I (1997) and GUSTO-III (2000) studies compared different fibrinolytic regimens in patients with STEMI, and highlighted a 7.9% and 6.5% incidence of *de novo* AF after ACS, respectively. (8, 17) In addition, OACIS,

Table 2. In-hospital events of participants with and without *de novo* AF

	Global	Without *de novo* AF	With de *novo* AF	p
n	7292	6974	318	
Reinfarction, n (%)	123 (1.7)	113 (1.6)	10 (3.1)	0.066
Stroke, n (%)	61 (0.8)	53 (0.8)	8 (2.5)	0.002
Cardiogenic shock, n (%)	682 (9.4)	576 (8.3)	106 (33.3)	<0.001
HF, n (%)	967 (13.3)	818 (11.7)	149 (46.9)	<0.001
In-hospital death, n (%)	591 (8.1)	563 (8.1)	28 (8.8)	0.717
LOS, days, median (IQR)	4 (3-6)	4 [3-6]	6 [4-11]	<0.001

AF, atrial fibrillation; HF, heart failure; IQR, interquartile range; LOS: length of stay

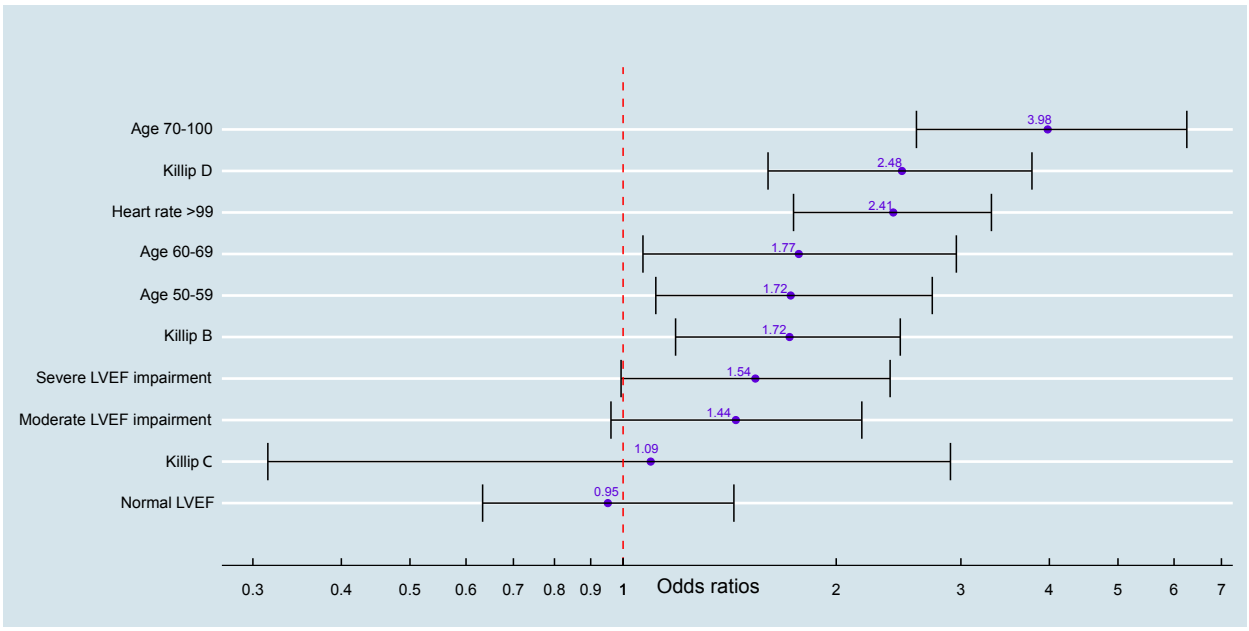
Fig. 1. Variables with the greatest importance in the prediction of *de novo* AF



AF: atrial fibrillation; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MV: multiple vessels; PCI: percutaneous coronary intervention; proc: procedure; time window: time in minutes from symptom onset to start of infusion in the case of fibrinolytics or to balloon inflation in the case of PCI

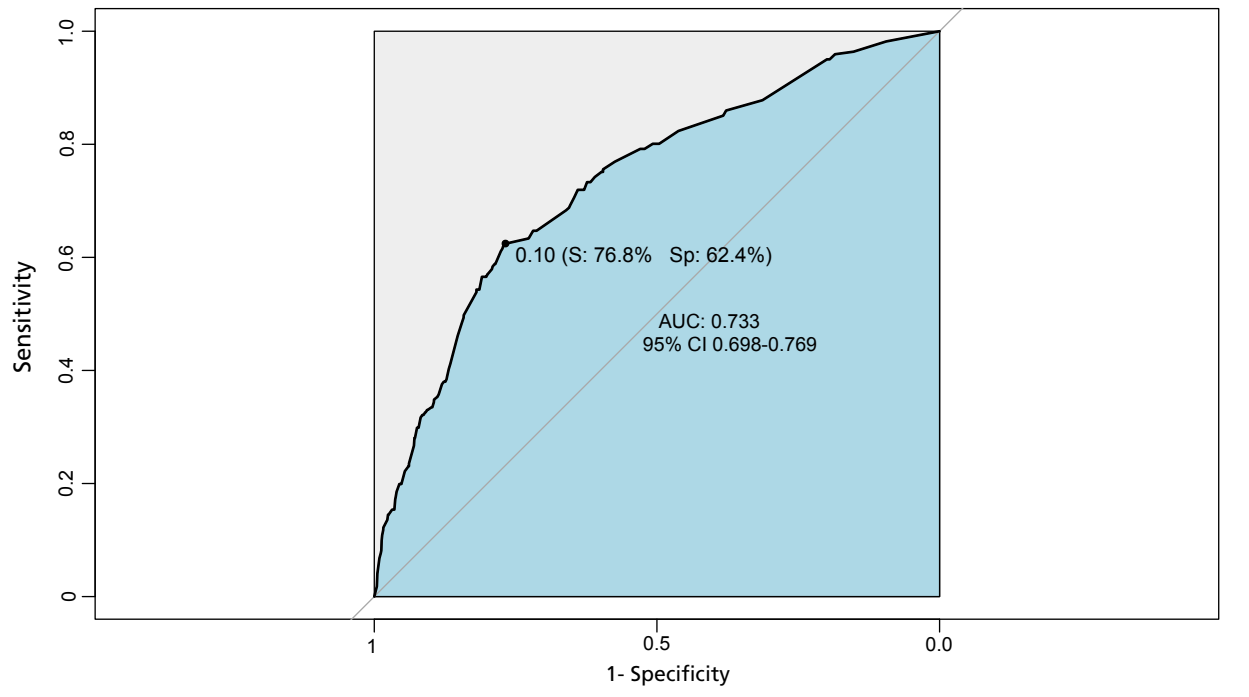
a prospective observational study published in 2003, analyzed patients with AMI (with and without ST-segment elevation) who underwent coronary angioplasty within 24 hours and found that the incidence of *de novo* AF was 7.7%. (18) Regarding national results, the incidence of in-hospital *de novo* AF in patients with AMI and unstable angina was 4.3% and 7.7%, respectively, according to data from the Buenos Aires I registry, which included patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). (19) Similarly, a previous publication from the ARGEN-IAM-ST registry showed that the incidence of *de novo* AF was 3.2%, and the predictor factors were advanced age, history of HT and previous coronary artery disease. (6) There are definitely no randomized studies comparing the incidence of *de novo* AF in patients with STEMI treated with fibrinolytics versus primary angioplasty, and the differences in the populations and methods used in the published studies preclude a correct assessment of the incidence of this complica-

Fig. 2. Predictors of *de novo* AF



AF: atrial fibrillation; LVEF: left ventricular ejection fraction

Fig. 3. ROC curve of the *de novo* AF predictive model

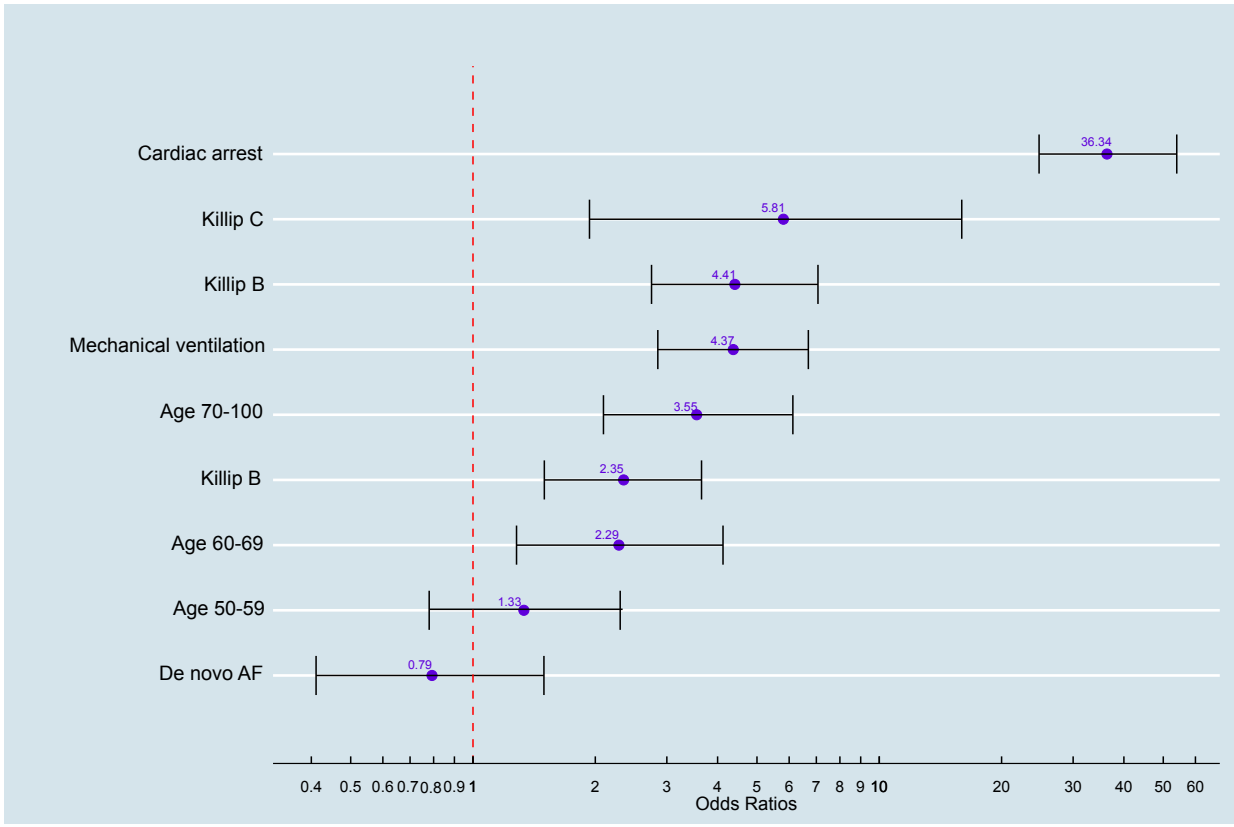


AF: atrial fibrillation; AUC: area under curve; ROC: receiver operating characteristic; S: sensitivity; Sp: specificity

tion and whether the type of revascularization has an impact on it.

In our cohort, age acted as an independent predictor of *de novo* AF, with the higher impact observed specifically between the ages of 70 and 100 years, with an OR of 3.98. As AF outside the setting of ACS, age was closely related to the incidence of this arrhythmia. In one of the largest studies including only patients aged ≥65 years from the Cooperative Cardiovascular Project database published in 2000, (11) the rate of *de novo* AF after ACS was 22%, significantly higher than in studies including patients of all ages. In addi-

Fig. 4. Predictors of in-hospital mortality



AF: atrial fibrillation

tion, the 2009 review by Schmitt et al., found that all studies published between 1992 and 2007 identified older age as an independent predictor of *de novo* AF after ACS. (20)

Although AF is the most frequent supraventricular arrhythmia in the general population, its incidence is significantly higher in patients with heart failure (HF). These two conditions are closely related to each other, and each perpetuates the presence of the other. (21) Our analysis showed that HF, as assessed by the Killip and Kimball score, was independently associated with *de novo* AF, as showed in the above mentioned GUSTO-I and III studies. Of note, a subanalysis of the international GRACE study, which included more than 21 000 patients with ACS and classified them according to the presence of *de novo* AF, previous AF, and no AF, identified a Killip score ≥2 as an independent predictor of *de novo* AF. (22) Similarly, tachycardia, probably secondary to HF, was also a predictor of *de novo* AF in our study and in the previously mentioned study. These results translate the impact of hemodynamic status within the pathophysiological mechanisms of AF in the setting of ACS and indicate that patients with altered hemodynamic status (HF, tachycardia, and/or hypotension) are at higher risk of AF.

In parallel, severely impaired LVEF (<35%) also functioned as an independent predictor of *de novo* AF in our analysis. Although the association between ventricular dysfunction and clinical presentation on admission (as reflected by the Killip and Kimball score and heart rate) is clear, other studies have not shown this variable to be an independent predictor of *de novo* AF.

LIMITATIONS

The registry ARGEN-IAM-ST is a voluntary participation registry with no audit strategy. Although a multivariate regression analysis was performed, we cannot completely exclude the possibility that unconsidered variables may have altered the results. Furthermore, although this is a multicenter study, it only represents the reality of the participating centers. Finally, it is not possible to determine when AF occurred during hospitalization, and thus the temporal relationship cannot be studied.

CONCLUSION

In this cohort of patients from the ARGEN-IAM-ST registry, *de novo* AF was a relatively frequent complication. Factors such as age, heart rate, hemodynamic profile on admission, and ventricular function were

shown to be predictors of *de novo* AF after an AMI during hospitalization. However, *de novo* AF was not independently associated with in-hospital mortality.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Relationship Between Ventricular-arterial Coupling and Stage of Extravalvular Damage in Aortic Stenosis

Relación entre la cupla ventriculoarterial y el estadio de daño extravalvular en la estenosis aórtica

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ABSTRACT

Background: A staging classification has been proposed for patients with severe aortic stenosis (AS) to evaluate the extent of extravalvular (anatomical and functional) damage with the aim of improving the indication and prognosis of aortic valve replacement (AVR) based only on the presence of symptoms or left ventricular ejection fraction (LVEF) < 50 %. However, such classification does not consider the vascular component of LV afterload. The characteristics of the arterial vasculature can have implications for LV function by influencing the ventricular-arterial coupling (VAC).
Objective: The aim of the present study was to evaluate the relationship between VAC and the different stages of extravalvular damage in AS.
Methods: We prospectively evaluated 205 patients (mean age 70 ± 11 years,117 men), with severe AS [aortic valve area (AVA) < 1 cm^2] using Doppler echocardiography. Ventricular-arterial coupling was calculated as the arterial elastance (Ea) to LV end-systolic elastance (Ees) ratio. Patients were divided into five groups according to the criteria for staging extravalvular cardiac damage: stage 0, no cardiac damage; stage 1: LV damage; stage 2: left atrial or mitral valve damage; stage 3: pulmonary hypertension or tricuspid valve involvement; and stage 4: right ventricular damage.
Results: There were no patients in stage 0. Symptoms were present in 40 % of stage 1 patients, 85 % of stage 2 and 100 % of stages 3 and 4. Ea increased from stage 2 to stage 4 while Ees remained unchanged in these groups but decreased from stage 1 to stage 2. Ventricular-arterial coupling exhibited progressive increase from stage 1 to 4.
Conclusions: As the stage of myocardial damage progresses, the impairment of VAC increases. The alteration of VAC that occurs from stage 2 to 4 is due to an increase in Ea without significant changes in the level of contractility (Ees). The progression of extravalvular myocardial damage appears to be associated not only with valvular disease but also with the characteristics of the arterial vasculature.

Key words: Aortic stenosis – Ventricular-arterial coupling – Effective arterial elastance

RESUMEN

Introducción: En pacientes con estenosis aórtica (EAo) grave se ha propuesto una clasificación en estadios para evaluar la extensión del daño extravalvular (anatómico y funcional) con la idea de mejorar la indicación y pronóstico del reemplazo valvular aórtico con base solo en la presencia de síntomas o fracción de eyección del ventrículo izquierdo (FEVI) < 50 %. Sin embargo, dicha clasificación no considera el componente vascular de la poscarga del VI. Las características de la vasculatura arterial pueden repercutir en la función del VI a través de la alteración de la cupla ventriculoarterial (CVA).
Objetivo: Evaluar la relación entre la CVA y los diferentes estadios de daño extravalvular en la EAo.
Material y métodos: Se estudiaron 205 pacientes, edad promedio 70 ± 11 años, 117 hombres, con EAo grave (área valvular aórtica, AVA, < 1 cm^2) con eco Doppler cardíaco. La CVA fue calculada mediante el cociente elastancia arterial efectiva (Ea)/ elastancia de fin de sístole del VI (Efs). Los pacientes fueron divididos en cinco grupos de acuerdo con la clasificación en esta¬dios de daño cardíaco extravalvular: estadio 0, sin daño cardiaco; estadio 1, daño del VI; estadio 2, daño de aurícula izquierda o válvula mitral; estadio 3, hipertensión pulmonar o compromiso de válvula tricúspide y estadio 4, daño ventricular derecho.
Resultados: No hubo pacientes en estadio 0. Los síntomas estuvieron presentes en el 40 % de los pacientes del estadio 1, 85 % del estadio 2 y 100 % de los estadios 3 y 4. La Ea se incrementó desde el estadio 2 al estadio 4 mientras que la Efs no presentó cambios en estos grupos, pero disminuyó del estadio 1 al 2. La CVA aumentó progresivamente del estadio 1 al 4.

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Conclusiones: El deterioro de la CVA aumenta a medida que avanza el estadio de daño miocárdico. La alteración de la CVA desde el estadio 2 al 4 se debe al incremento en la Ea sin cambios significativos en el nivel de contractilidad (Efs). La pro¬gresión del daño miocárdico extravalvular parece estar relacionado no solo con la enfermedad valvular sino también con las características de la vasculatura arterial.

Palabras clave: Estenosis aórtica - Cupla ventriculoarterial - Elastancia arterial efectiva

INTRODUCTION

Calcific aortic stenosis (AS) in adults is the valvular heart disease that most commonly requires surgical or endovascular treatment nowadays due to the aging of the general population. (1) According to the ACC/AHA (2) and ESC guidelines, (3) aortic valve replacement (AVR) is indicated when symptoms (angina, dyspnea or syncope) or impaired left ventricular ejection fraction (LVEF) develop, or in case cardiac surgery is necessary due to other causes. However, AS is not confined to the valve but rather should be considered a systemic disease involving all the cardiac chambers, as well as the pulmonary and systemic vascular systems. In light of this reasoning, a staging classification has been proposed for patients with severe AS to evaluate the extent of extravalvular (anatomical and functional) damage with the aim of improving the indication and prognosis of AVR. (4) However, it is important to note that LV afterload has a valvular component and a vascular component, (5,6) that is not evaluated in the staging classification. The characteristics of the arterial vasculature can have implications for LV function by influencing the ventricular-arterial coupling (VAC), which is evaluated by the relationship between effective arterial elastance (Ea) and LV end-systolic elastance (Ees). (7,8) If the value of the Ea/Ees ratio is ≤ 1 there is adequate coupling between the LV and the arterial vasculature, while a value > 1 indicates uncoupling, suggesting a loss of LV mechanical efficiency. Ea is a parameter of arterial mechanics that is influenced by characteristic impedance and peripheral resistance, (9) while Ees assesses LV contractility independently of preload and afterload. The rise in the age of patients with AS in recent decades has been accompanied by an increase in the prevalence of hypertension (HT), which places an additional load on the LV, in addition to valvular obstruction. (10,11)

The aim of the present study was to evaluate the relationship between VAC and the different stages of extravalvular damage in AS.

METHODS

We prospectively evaluated 205 patients (age 70 ± 11 years, 117 men), with severe AS [aortic valve area (AVA) < 1 cm^2] using Doppler echocardiography. The study protocol was approved by the Teaching and Research Committee of our institution. Patients with significant calcification of the mitral annulus, or with moderate or severe aortic or mitral regurgitation were excluded. History of hypertension was considered as the need for previous indication of antihypertensive treatment. History of ischemic heart disease was based on the presence of one of the following criteria or greater: 1) history of myocardial infarction, percutaneous coronary intervention or myocardial revascularization surgery; 2) coronary artery stenosis > 50% documented by angiography; and 3) akinetic segments documented by echocardiography. All the patients underwent complete anamnesis to detect the presence of coronary risk factors and symptoms, cardiovascular physical examination, blood pressure measurement, recording the carotid artery pulse waveform and complete Doppler echocardiography.

Doppler echocardiography: The study was performed with an ESAOTE Mylab 40 ultrasound machine with a 2.5 to 3 MHz transducer. M mode echocardiography and two-dimensional echocardiography were used to calculate LV endocardial fractional shortening (eFS), relative wall thickness (RWT), end-diastolic volume (EDV) estimated by the Simpson's method, end-systolic volume (ESV) and LVEF, according to American Society of Echocardiography (ASE) criteria. (12)

Peak aortic jet velocity, peak gradient (PG) and mean gradient (MG) across the aortic valve and velocity time integral (VTI) were recorded with continuous Doppler echocardiography from the apical view, right parasternal view, subcostal view and suprasternal view. Pulsed-wave Doppler was used to determine LV outflow tract flow from the five-chamber view. The dimensionless index was estimated by dividing the VTI of the left ventricular outflow tract by the VTI of the aortic valve jet. Effective AVA was calculated using the continuity equation, and the AVA index [AVA/body surface area, (BSA)], valvuloarterial impedance (Zva) and energy loss index (ELI) were also measured according to the ASE recommendations. (13) Stroke volume (SV) was calculated by multiplying the cross-sectional area of the LV outflow tract per the VTI of flow at that level; SV index (SVi) was estimated as the ratio between SV and BSA, and transaortic flow rate was calculated by dividing the SV by the LV systolic ejection period. Transmitral flow velocity was recorded by placing the pulsed Doppler sample volume at the level of the mitral valve tips in the four-chamber view to obtain peak E velocity and peak A velocity and thus calculate the E/A ratio. (14) Then, a tissue Doppler imaging sample volume was placed at the lateral and septal portions of the mitral annulus to acquire peak e' velocity in both sites, and the average of both was used to determine the E/e' ratio. (15) Peak tricuspid regurgitation velocity was recorded with continuous Doppler, and this parameter plus the right atrial pressure estimated through the diameter and collapse of the inferior vena cava were used to estimate the systolic pulmonary artery pressure. Right ventricular (RV) systolic function was quantified by the tricuspid annulus plane systolic excursion (TAPSE) and peak systolic velocity of the S wave at the lateral tricuspid annulus. In 168 patients LV longitudinal strain was estimated with two-dimensional speckle tracking echocardiography from the apical four-chamber, two-chamber and apical long-axis views, using the software provided by the device.

Pulse pressure (PP) was estimated as the difference between systolic and diastolic blood pressure measured with

a sphygmomanometer. Arterial compliance (AC) was calculated as the SV/PP ratio, (16,17) and for a better comparison between groups, SV was normalized to body surface area: SVi/PP. (18) Systemic vascular resistance (SVR) was calculated as (80 x MBP) /CO (where MBP: mean blood pressure and CO: cardiac output).

After performing Doppler echocardiography, carotid pulse tracing was recorded with a TPW – 01 A pulse transducer connected a TOSHIBA SSH140A machine, and blood pressure was measured in the right arm with the use of a sphygmomanometer. Carotid pulse tracing calibration was carried out according to the method used in our laboratory, (19,20) to obtain end-systolic pressure (ESP) (Figure 1).

Assessment of Ees, Ea and VAC: End-systolic elastance was estimated by the method by Senzaki et al. (21) (see supplementary material), Ea was calculated as the SV/ESP ratio and VAC as the Ea/Ees ratio (Figure 2).

Patients were divided into five groups according to the criteria for staging extravalvular cardiac damage proposed by Tastet et al. (22):

a) stage 0, no cardiac damage;
b) stage 1, LV damage (n = 10): LV hypertrophy (LV mass index > 115 g/m² in men and > 95 g/m² in women); LV diastolic dysfunction grade 2 or greater (E/e' ratio > 14); subclinical LV systolic dysfunction (LVEF < 60%, global longitudinal strain ≥ -15%);
c) stage 2, left atrial damage or mitral valve damage (n =88): left atrial volume index (LAVi) > 34 mL/m², ≥ moderate mitral regurgitation, atrial fibrillation;
d) stage 3, pulmonary hypertension or tricuspid valve involvement (n = 7): systolic pulmonary artery pressure ≥ 60 mm Hg, ≥ moderate tricuspid regurgitation;
e) stage 4, right ventricular damage or subclinical heart failure (n =100): RV systolic dysfunction (TAPSE < 17 mm, tricuspid tissue Doppler S wave < 9.5 cm/s), moderate to severe low flow (SVi < 30 mL/m²).

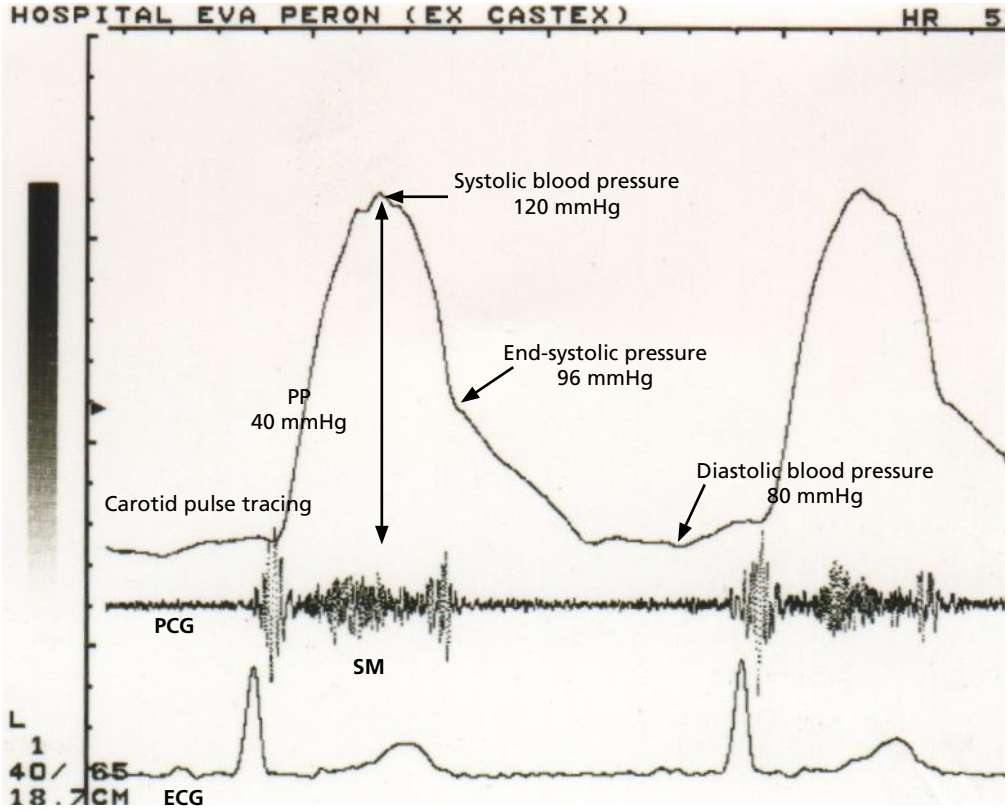
Patients were assigned to each group based on at least one criterion in the most advanced stage. For example, a patient with TAPSE < 17 mm was categorized as stage 4 even in the absence of pulmonary hypertension, mitral valve involvement or LVEF < 60%.

Statistical analysis

All the statistical calculations were performed using SPSS 25 software package. Continuous variables were expressed as mean ± standard deviation. The groups were compared using analysis of the variance. A p-value < 0.05 was considered statistically significant.

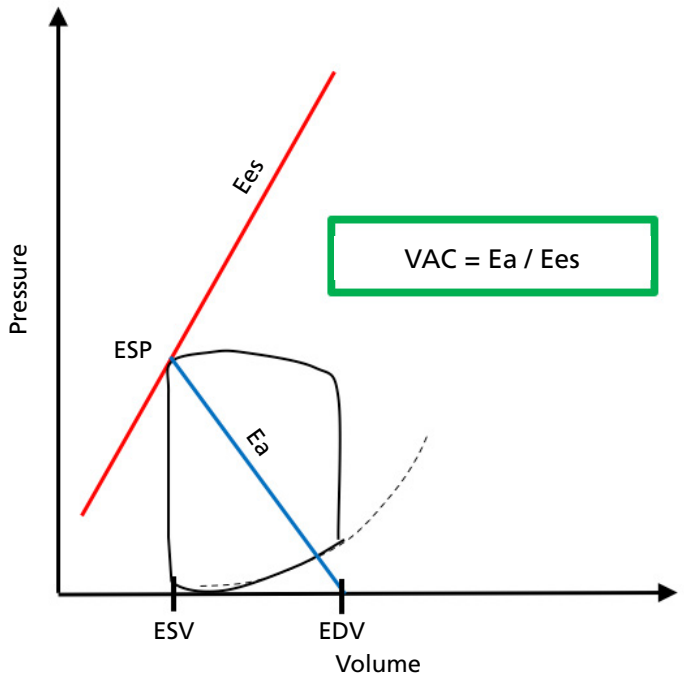
RESULTS

Table 1 shows the cardiovascular risk factors, comorbidities and symptoms of the patients evaluated. There were no patients in stage 0. Hypertension was the most common risk factor. Symptoms were present in 40 % of stage 1 patients, 85 % of stage 2 and 100 %



ECG: electrocardiogram; PCG: phonocardiogram; PP: pulse pressure; SM: systolic murmur recorded at the Erb's point.

Fig. 1. Estimation of end-systolic pressure using the carotid pulse tracing calibrated with blood pressure measured with a sphygmomanometer.



EDV: end-diastolic volume; ESP: end-systolic pressure; ESV: end-systolic volume

Fig. 1. Cardiac cycle in the pressure-volume system with the end-systolic elastance line (Ees) indicating the LV inotropic level and the effective arterial elastance line (Ea).The Ea/Ees ratio determines the value of ventricular-arterial coupling (VAC)

Table 1. Cardiovascular risk factors, comorbidities and patients' symptoms

Cardiovascular risk factors and comorbidities	%
Coronary artery diseases	24
Previous myocardial infarction	10
Hypertension	59
Diabetes	17
Dyslipidemia	30
Current smoking	28
Obesity (BMI > 30 Kg/m^2)	21
Chronic obstructive pulmonary disease	4
Symptoms (%)	%
Angina	15
Syncope	3
FC I-II dyspnea	27
FC III-IV dyspnea	48

BMI: body mass index; FC: functional class.

of stages 3 and 4. Class III-IV dyspnea was the most common symptom. Stage 1 patients were younger (57 ± 13 years, $p < 0.01$) compared to the rest of the patients (Table 2). There were no significant differences between the different groups when considering BSA, systolic blood pressure, diastolic blood pressure, ESP and heart rate.

LV systolic function (Table 3): ventricular dimensions and volumes exhibited a significant increase from stage 2 to 4 when compared to stage 1. According to LV mass index and RWT, concentric hypertrophy was the predominant geometry type in all groups. Left ventricular ejection fraction was significantly reduced in stages 3 and 4, although 40 % of patients in stage

Table 2. Clinical parameters

	Total n = 205	Stage 1 n = 10	Stage 2 n = 88	Stage 3 n = 7	Stage 4 n = 100
Age (years)	69 ± 11	57 ± 13	69 ± 11 *	73 ± 9 *	70 ± 11 *
Body surface area (m^2)	1.83 ± 0.2	1.72 ± 0.15	1.82 ± 0.2	1.76 ± 0.09	1.86 ± 0.21
Systolic blood pressure (mm Hg)	128 ± 23	130 ± 19	132 ± 21	132 ± 19	124 ± 25
Diastolic blood pressure (mm Hg)	74 ± 13	77 ± 11	75 ± 12	71 ± 19	74 ± 13
End-systolic pressure (mm Hg)	96 ± 19	95 ± 18	98 ± 19	91 ± 17	95 ± 19
Heart rate (beats per minute)	71 ± 13	71 ± 11	69 ± 11	72 ± 19	75 ± 13

Quantitative variables are presented as mean ± standard deviation. *p < 0.01 vs. Stage 1

Table 3. Incidence of the components of each stage of extravalvular damage

	Stage 1 n = 10 n (%)	Stage 2 n = 88 n (%)	Stage 3 n = 7 n (%)	Stage 4 n = 100 n (%)
Stage 1				
LV hypertrophy	9 (90 %)	83 (94 %)	7 (100 %)	90 (90 %)
LVEF < 60 %	4 (40 %)	32 (36 %)	6 (86 %)	70 (70 %)
E/e' ratio > 14		35 (40 %)	3 (43 %)	51 (51 %)
Global strain ≥ -15 % *		38/74 (51 %)	4/5 (80 %)	71/89 (80 %)
Stage 2				
LA enlargement		88 (100 %)	7 (100 %)	94 (94 %)
Atrial fibrillation		2 (2 %)	1 (14 %)	14 (14 %)
≥ moderate mitral regurgitation		8 (10 %)	4 (57 %)	29 (29 %)
Stage 3				
SPAP ≥ 60 mm Hg			6 (86 %)	10 (10%)
≥ moderate tricuspid regurgitation			5 (71 %)	13 (13 %)
Stage 4				
TAPSE < 17 mm				30 (30 %)
S-wave TDI < 9.5 cm/s				33 (33 %)
LV stroke volume index< 30 mL/m^2				82 (82 %)

LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annulus plane systolic excursion; TDI: tissue Doppler imaging. * % correspond to a total of 168 patients

1 and 36% in stage 2 had LVEF < 60% (subclinical systolic dysfunction). Left ventricular longitudinal strain presented a progressive reduction from stage 2 to 4, with statistically significant differences between groups. Stroke volume index and aortic flow were significantly lower in stage 4, with SVi < 30 mL/m^2 in 82% of patients in this group.

Aortic stenosis: there were no significant differences between patients in stages 1 to 3 when considering peak aortic jet velocity, PG and MG, AVA, aortic valve area index (AVAi), Zva and ELI (Table 4). Patients in stage 4 exhibited lower gradients but more severe aortic stenosis, as indicated by measurements of AVA, AVAi, Zva and ELI. This suggests a higher degree of disease involvement at the valvular level.

LV diastolic function: E/A ratio, E/e' and LAVi increased significantly from stage 2 to 4.

Mitral regurgitation: moderate mitral regurgitation or greater was more common in stages 3 and 4.

Tricuspid regurgitation, RV and systolic pulmonary artery pressure: mild tricuspid regurgitation occurred in one third of patients in stages 2, 3 and 4, whereas moderate or severe regurgitation was more frequent in stage 3 than in stage 4, probably because systolic pulmonary artery pressure was higher in stage 3 than in stage 4. Longitudinal RV systolic func-

Table 4. Echocardiographic parameters

	Total n = 205	Stage 1 n = 10	Stage 2 n = 88	Stage 3 n = 7	Stage 4 n = 100
LV systolic function					
LV diastolic dimension (cm)	5.3 ± 0.9	4.7 ± 0.9	5.1 ± 0.7 °	5.5 ± 1 *	5.4 ± 0.9 *
LV systolic dimension (cm)	3.7 ± 1	2.8 ± 0.6	3.3 ± 0.9 °	4 ± 1.2 *	4 ± 1.1 *
LV fractional shortening (%)	31 ± 11	41 ± 7	36 ± 10 °	29 ± 9 *	27 ± 11 *
LV posterior wall thickness (cm)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2
Interventricular septal thickness (cm)	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.3
Relative wall thickness	0.48 ± 0.11	0.52 ± 0.14	0.48 ± 0.09	0.49 ± 0.10	0.46 ± 0.13
LV mass (g)	291 ± 96	233 ± 99	283 ± 89	344 ± 116	300 ± 98
LV mass index (g/m^2)	158 ± 47	134 ± 52 #	154 ± 42 #	196 ± 66	162 ± 48
LV end-diastolic volume (mL)	119 ± 59	76 ± 59	105 ± 44 *	165 ± 48 * Δ	132 ± 66 * Δ
LV end-systolic volume (mL)	65 ± 54	32 ± 40	46 ± 36	104 ± 52 * Δ	81 ± 61* Δ
LV ejection fraction (%)	52 ± 19	65 ± 6	60 ± 16	40 ± 17 * Δ	46 ± 19 * Δ
LV stroke volume index (mL/m^2)	33 ± 11	40 ± 8	40 ± 10	41 ± 8	26 ± 8 * Δ #
LV stroke volume index< 30 mL/m^2, n (%)					82 (82)
Transaortic flow rate (mL/s)	184 ± 52	212 ± 44	208 ± 48	227 ± 47	156 ± 40 * Δ #
End-systolic stress (g/m^2)	50 ± 27	32 ± 12	42 ± 20	48 ± 17	59 ± 32
LV global longitudinal strain (%)	- 13 ± 4	- 20 ± 4	- 14 ± 4 *	- 10 ± 4 * Δ	- 10 ± 4 * Δ
Aortic stenosis					
Peak aortic jet velocity (m/s)	4 ± 0.93	3.95 ± 0.74	4.32 ± 0.83	4.18 ± 0.88	3.86 ± 0.99 Δ
Peak gradient (mm Hg)	70 ± 31	62 ± 25	76 ± 28	71 ± 27	64 ± 23 Δ
Mean gradient (mm Hg)	41 ± 19	35 ± 13	46 ± 18	40 ± 16	38 ± 21 Δ
Dimensionless index	0.21 ± 0.06	0.25 ± 0.06	0.22 ± 0.06	0.25 ± 0.08	0.19 ± 0.06 * Δ #
Aortic valve area (cm^2)	0.67 ± 0.21	0.79 ± 0.22	0.72 ± 0.20	0.81 ± 0.21	0.61 ± 0.20 * Δ #
Aortic valve area index (cm^2/m^2)	0.37 ± 0.12	0.46 ± 0.13	0.40 ± 0.11	0.47 ± 0.13	0.33 ± 0.11 * Δ #
Valvuloarterial impedance (mm Hg/mL/m^2)	5.4 ± 1.8	4.1 ± 1	4.4 ± 1	5.1 ± 2	6.3 ± 2 * Δ
Energy loss index (cm^2/m^2)	0. 42 ± 0.15	0.52 ± 0.16	0.45 ± 0.14	0.54 ± 0.17	0.37 ± 0.14 * Δ #
LV diastolic function					
E/A ratio	1.24 ± 0.9	0.72 ± 0.24	1 ± 0.47 *	2 ± 0.9 * Δ	1.5 ± 1.1 * Δ
E/e' ratio	16 ± 8	9 ± 2	15 ± 7 *	21 ± 12 *	17 ± 8 *
LA volume index (mL/m^2)	56 ± 19	29 ± 4	55 ± 17 *	71 ± 13 * Δ	58 ± 20 * Δ
Mitral regurgitation, n (%)		-	14 (16)	7 (100)	62 (62)
Tricuspid valve, right ventricle and systolic pulmonary artery pressure					
Mild tricuspid regurgitation, n (%)		1 (10)	26 (30)	2 (29)	32 (32)
≥ moderate tricuspid regurgitation, n (%)				5 (71)	13 (13)
Systolic pulmonary artery pressure (mm Hg)	46 ± 17	25	40 ± 12	67 ± 17 Δ °	43 ± 17 Δ
TAPSE (mm)	20 ± 6	22 ± 4	23 ± 5	20 ± 7 °	17 ± 6 *Δ
Tricuspid S-wave TDI (cm/s)	11 ± 3	12 ± 1	13 ± 2	10 ± 2 Δ	10 ± 3 Δ
Systemic arterial hemodynamics					
Arterial compliance (mL/mm Hg)	1.24 ± 0.53	1.4 ± 0.48 °	1.4 ± 0.53 °	1.4 ± 0.71	1.1 ± 0.48
Arterial compliance index (mL/m^2/mm Hg)	0.68 ± 0.29	0.82 ± 0.31 °	0.77 ± 0.28 °	0.8 ± 0.41 °	0.58 ± 0.24
Systemic vascular resistance (dynes/s/cm-5)	1905 ± 631	1664 ± 493 °	1639 ± 436 °	1605 ± 810 °	2181 ± 661
Ventricular-arterial coupling					
Ea (mm Hg/mL)	1.78 ± 0.69	1.45 ± 0.44	1.43 ± 0.46 °	1.57 ± 0.72 °	2.13 ± 0.71 *
Ees (mm Hg/mL)	2.15 ± 1.49	3 ± 1.25 Δ	2 ± 1.1	1.9 ± 1.2 *	2 ± 1.19 *
Ventricular-arterial coupling	1.13 ± 0.76	0.63 ± 0.41	0.88 ± 0.54	0.91 ± 0.61	1.40 ± 0.85 * Δ #

Ea: effective arterial elastance; Ees: end-systolic elastance; LA: left atrial; LV: left ventricular; TAPSE: tricuspid annulus plane systolic excursion.
Δ p < 0.01 vs. Stage 2; # p < 0.05 vs. Stage 3; ° p < 0.01 vs. Stage 4; * p < 0.01 vs. Stage 1

Quantitative variables are presented as mean ± standard deviation

tion assessed by TAPSE and peak systolic velocity at the lateral tricuspid annulus was reduced in stages 3 and 4.

Systemic arterial hemodynamics: AC and SVR were abnormal only in stage 4, with no significant differences between stages 1, 2 and 3.

Ventricular-arterial coupling: unlike AC and SVR, Ea increased from stage 2 to stage 4 indicating increased arterial stiffness and higher vascular load. End-systolic elastance, which assesses LV contractility, showed no changes in these groups (value greater than 1 in all stages) evidencing preserved contractility, although it decreased from stage 1 to 2 (3 ± 1.25 vs. 2 ± 1.1, $p < 0.01$). Ventricular-arterial coupling exhibited progressive alterations from stage 1 to 4, mainly as a result of the increase in Ea (Figure 3).

DISCUSSION

The main finding of the present study is that the progression of extravalvular damage in AS is related to the alteration of VAC, suggesting that such damage is not only due to the valvular component, but also to the characteristics of the systemic arterial vasculature. Généreux et al. (5) described a five-stage classification of extravalvular (anatomical and functional) damage in AS in 1661 patients from the PARTNER 2A and 2B studies who underwent AVR. Subsequently, the same authors published the impact of determining the stage of extravalvular damage at one year after AVR (23) and the correlation with quality of life according to the Kansas Cardiomyopathy Questionnaire. (24) To better define the compromise of LV function, global longitudinal strain was incorporated, improving the prognostic value of the previously described classification. (25) We use the stage classification proposed by Tastet et al., (9) which establishes a cut-off point for LVEF of less than 60% for stage 1. We consider this to be more appropriate than a value of less than 50% in the presence of concentric hypertrophy, a geometry that exaggerates the movement of the endocardium used to calculate LVEF. (26,27) In the aforementioned studies, stage 4 patients represent between 7.1% and 8.7% of the total population, while in our study 49%, were in stage 4 and no patients were in stage 0. This difference may be due to the lack of early diagnosis, as most patients with heart failure did not know they had valvular heart disease, a fact commonly observed in public hospitals.

With regard to the severity of AS, there were no differences between stages 1 to 3 in terms of gradients, AVA, AVAi and ELI. Therefore, we can consider that the valvular load was the same in the three stages. This did not occur in stage 4 patients, in whom AS was more severe. However, VAC exhibited progressive alterations from stage 2 to 4 at the cost of increased Ea with no decline in LV contractility (Ees) (Figure 3).

It should be noted that in AS the relationship with the afterload is more complex than would be expected (28-30) because of the effect of the obstruction of the left ventricular outflow tract (valvular load) added to the forces that resist ventricular ejection. These forces depend on the physical characteristics of the arteries (vascular load), (31) and include arterial impedance, determined by the phasic relationship between aortic pressure and aortic volume, SVR, aortic wall stiffness, (32) inertial properties of blood and properties of the reflection waves produced in arterial bifurcations. (33-35) Of the indexes evaluating arterial mechanics, Ea seems to be more adequate than AC, because it incorporates the characteristic impedance, resistance, compliance and cycle length. (36,37) A parameter that evaluates global (valvular and vascular) load in AS is Zva. However, despite an increase in Zva due to the high prevalence of hypertension, no significant differences were observed between the different stages, except for stage 4.

	Stage 1 n = 10	Stage 2 n = 88	Stage 3 n = 7	Stage 4 n = 100
Ea (mm Hg/mL)	1.45 ± 0.44	1.43 ± 0.46	1.57 ± 0.72	2.13 ± 0.71 °
Ees (mm Hg/mL)	3 ± 1.25 °	2 ± 1.1	1.9 ± 1.2	2 ± 1.19
VAC	0.63 ± 0.41	0.88 ± 0.54	0.91 ± 0.61°	1.40 ± 0.85 °

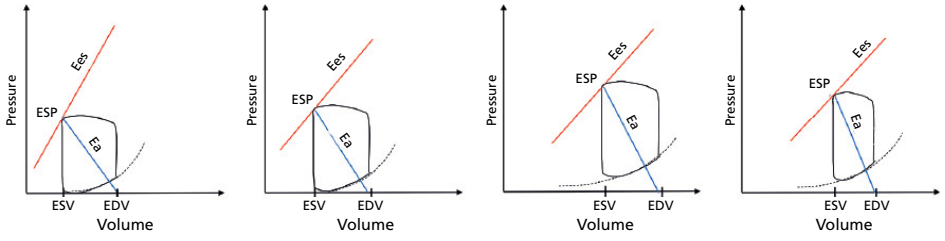


Fig. 3. Top: table with Ea, Ees and VAC values for each of the extravalvular damage stages.
Bottom: the same values are represented in the pressure-volume system. The values of end-systole volume (ESV), end-diastolic volume (EDV) and end-systole pressure (ESP) correspond to the average values of each stage. ° p< 0.01

The alteration of VAC correlates with the development of symptoms and heart failure, with the rise in Ea outweighing the decline in Ees. In the present study, LVEF was found to be diminished, particularly in stages 3 and 4 (86% and 70%, respectively), despite the presence of preserved contractility according to Ees. This is explained by the afterload mismatch, that is the uncoupling between afterload and inotropism between chamber function (LVEF) and muscle function (Ees) in AS. (16,39) The same concept could be applied to strain, which progressively decreased from stage 2 to 4 before the decline in LVEF, since strain had a positive correlation with the increase in Ea ($r = 0.43$, $p < 0.001$, $y = 0.0715.\ x + 2$) evidencing its dependence on afterload as it occurs with any index that evaluates fiber shortening. Therefore, it should be considered that the decrease in strain or LVEF is not only due to valvular load but also to vascular load.

CONCLUSIONS

As the stage of myocardial damage progresses, the impairment of VAC increases. The alteration of VAC that occurs from stage 2 to 4 is due to an increase in Ea without significant changes in the level of contractility (Ees). The progression of extravalvular myocardial damage appears to be associated not only with valvular disease but also with the characteristics of the arterial vasculature.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable

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ORIGINAL ARTICLE

Genetic and Clinical Characteristics of Patients with Congenital Long QT Syndrome- Genotype. Experiences During Long-Term Follow-Up

Características genéticas y clínicas de los pacientes con genotipo asociado al síndrome QT largo congénito. Experiencias durante un seguimiento a largo plazo

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ABSTRACT

Background: Congenital long QT syndrome (LQTS) is an inherited channelopathy with a broad genetic spectrum but with a common phenotypic manifestation, the prolonged QT interval. However, its clinical presentation and natural history are highly variable.
Objectives: The aim of this study was to define the genetic and clinical characteristics of patients with congenital LQTS during a long-term follow-up.
Methods: Retrospective cohort study of patients with congenital LQTS genotype. The incidence of serious events at follow-up was defined. Quantitative variables are expressed as median and interquartile range (IQR) and qualitative variables as frequency and percentage.
Results: Forty-four patients were included. Thirty percent of patients had LQTS1 genotype, 65% LQTS2 genotype and 5% LQTS3 genotype; 57% of cases carried the missense mutation, 11% the nonsense mutation and 32% the frameshift mutation. The corrected QT interval was 490 msec (IQR 462-498). The phenotype was present in 66% of patients, but it remained permanently only in 32%. Syncopal episodes occurred in 39% of patients. Cardiac arrest was the first manifestation in 7% of cases. Syncope recurred in 11% of patients even after pharmacological therapy, and 5% suffered sudden death. Seven patients received an implantable cardiodefibrillator (ICD). Among them, 29% received shocks due to ventricular tachycardia or ventricular fibrillation (VT/VF) and 58% presented device-related complications.
Conclusions: Most patients had the LQTS1 or LQTS2 genotype, the intermittent phenotype, and a good response to treatment. Implantation at an early age and the high rate of complications during long-term follow-up require careful evaluation when indicating an ICD.

Key words: Long QT syndrome - Sudden death - Syncope - Genetic mutation - Implantable cardiodefibrillators

RESUMEN

Introducción: El síndrome de intervalo QT largo (SQTL) congénito es una canalopatía hereditaria con un gran espectro genético pero una manifestación fenotípica en común, el intervalo QT prolongado. Sin embargo, la presentación clínica y la historia natural es muy variable.
Objetivos: Definir el perfil de las características genéticas y clínicas de los pacientes con SQTL congénito durante un seguimiento a largo plazo.
Material y métodos: Estudio de cohorte retrospectiva de pacientes con genotipo de SQTL congénito. Se definió la incidencia de eventos serios en el seguimiento. Las variables cuantitativas se expresan como mediana y rango intercuartilo (RIC) y las cualitativas como frecuencia y porcentaje.
Resultados: Fueron incluidos 44 pacientes. El 30% tenía el genotipo de SQTL1, el 65% el de SQTL2 y 5% el de SQTL3. El 57% tenía la mutación *missense*, el 11% *nonsense* y el 32% *frameshift*. El intervalo QT corregido fue de 490 mseg (RIC 462-498). El 66% manifestó el fenotipo, pero solo el 32% de manera permanente. El 39% tuvo episodios sincopales. El paro cardíaco fue la primera manifestación en el 7%. El 11% tuvo recurrencia de síncope aún luego de terapia farmacológica y el 5% padeció muerte súbita. Siete pacientes recibieron un cardiodesfibrilador implantable (CDI). De ellos, el 29% tuvo choques por taquicardia o fibrilación ventricular (TV/FV) y el 58% complicaciones asociadas a los dispositivos.
Conclusiones: La mayoría de los pacientes tenían el genotipo de SQTL1 o SQTL2, el fenotipo intermitente y una buena respuesta

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al tratamiento. La edad temprana del implante y la elevada tasa de complicaciones asociadas al largo plazo exigen una evaluación personalizada al momento de indicar el CDI.

Palabras claves: Síndrome QT largo - Muerte súbita – Síncope - Mutación genética - Cardiodesfibrilador implantable

INTRODUCTION

Congenital long QT syndrome (LQTS) is characterized by prolongation of the ventricular myocardial action potential due to increased sodium and calcium inward currents (INa and ICaL) or decreased potassium outward currents (IKs, IKr and IK1). So far, mutations in 20 different genes encoding cardiac ion channels and/or modulatory proteins directly or indirectly involved in the genesis of these currents have been identified. (1)

With a prevalence in the general population of 1 in 2000 individuals, it is no longer an exceptional situation to see a patient with a prolonged QT interval in daily medical consultation for sports, schooling or pre-employment. (2)

With the advance of computer technology and genetic engineering, hundreds of variants have been identified in each of the genes involved in LQTS that, through different types of mutations, alter the function of myocyte ion channels. Most mutations show an autosomal dominant inheritance pattern. Thus, individuals are born with the mutation causing the disease and live with it throughout their lives.

All affected individuals have a common phenotypic manifestation, the prolongation of ventricular repolarization duration. However, the existence of a broad clinical variability among patients raises questions about the epigenetic factors that modulate their phenotypic expression. Even when patients are born with the pathogenic genotype, the phenotype may never manifest itself, become evident late or, in some cases, only do so intermittently, expressing itself only on certain days, and remaining totally asymptomatic for prolonged periods of time. Similarly, the risk of suffering adverse cardiac events may vary among carriers of the same genetic variant and even in the same person, depending on the situation to which he/she has been exposed. (3)

In this study, we have evaluated the clinical and genetic characteristics of patients diagnosed with LQTS by means of a genetic study with massive parallel sequencing and long-term clinical follow-up for more than 10 years, thus allowing the assessment of both the natural history of the disease and the occurrence of adverse cardiac events (syncope, ventricular tachyarrhythmia and/or sudden cardiac death), the response to pharmacological treatment and/or implantable antiarrhythmic devices, and their associated complications.

METHODS

A retrospective study was designed selecting individuals with suspected congenital LQTS attending Hospital General de Ramos Mejía. The following inclusion criteria were used: men and women aged 5 to 70 years; clinical suspicion of congenital LQTS (QTc interval ≥480 milliseconds on the ECG or Schwartz score ≥3); and identification of a pathogenic variant of congenital LQTS in a genetic study. Those with any of the following criteria were excluded: LQTS acquired by medication; refusal to sign the informed consent; patients under 18 years of age, without parental or legal guardian consent; and negative genetic study. Simultaneous 12-lead ECG recordings were obtained from each patient. QT intervals were corrected for heart rate (QTc) using Bazett's formula ($QTc = QT/\sqrt{RR}$, in seconds).

For sequence analysis and deletion/duplication testing, massive parallel sequencing (NGS) was used with a panel of more than 150 genes for arrhythmias and cardiomyopathies (ABCC9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, BAG3, BRAF, CACNA1C, CACNA1D, CALM1, CALM2, CALM3, CASQ2, CBL, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, ELAC2, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GATA4, GATA5, GJA5, GLA, HCN4, HRAS, JUP, KCNE1, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYL4, MYLK3, NF1, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PPP1CB, PRKAG2, PTPN11, RAF1, RASA1, RBM20, RIT1, RYR2, SCN5A, SDHA, SGCD, SHOC2, SLC22A5, SOS1, SOS2, SPRED1, TAZ, TBX20, TCAP, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, VCL, A2ML1, AKAP9, ANK2, ANKRD1, CACNA2D1, CACNB2, CALR3, CAV3, CHRM2, CTF1, CTNNA3, DTNA, FHL2, GATA6, GATAD1, GPD1L, HAND1, ILK, JPH2, KCNA5, KCND3, KCNE2, KCNE3, KCNE5, KCNJ5, KCNJ8, KCNK3, KIF20A, KLF10, LAMA4, LDB3, LRRC10, MAP3K8, MED12, MYH6, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, NPPA, PDLIM3, PLEKHM2, PRDM16, RANGRF, RASA2, RRAS, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SLMAP, SNTA1, TMPO, TXNRD2), developed by Invitae® (1400 16th Street, San Francisco, CA 94103, USA). USA). Genomic DNA obtained from a peripheral blood sample was enriched for target regions using a hybridization-based protocol and sequenced using Illumina® technology. All target regions were sequenced to a depth ≥50× or supplemented with additional analyses. Readings were aligned to a reference sequence (GRCh37) and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. Enrichment and analysis were focused on the coding sequence of the indicated transcripts, 20 base pairs (bp) of flanking intronic sequence, and other specific genomic regions shown to be disease-causing at the time of assay design. Detected variants were evaluated by probing the following databases: dbSNP from NCBI (National Center for Biotechnology Information, https://www.ncbi.nlm.nih.gov/snp/), ExAC (Exome Aggregation Consortium, https://exac.broadinstitute.org), gnomAD (Genome Aggregation Database, https://gnomad.broadinstitute.org/) and OMIM (Online Mendelian Inheritance in Man, https://omim.org/).

The pathogenicity of variants was estimated using three different types of prediction software: SIFT (https://sift.bii.a-star.edu.sg/), PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/) and Align-GVGD (https://bio.tools/align-gvgd/).

Variants were classified as pathogenic or probably pathogenic, of uncertain significance, and probably benign or benign using an evidence scoring system based on the consensus of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. (4) Results were classified as positive, negative, carriers or uncertain, according to the classification of the identified variant and the inheritance pattern of the associated condition.

Statistical analysis

Quantitative variables are expressed as median and interquartile range (IQR) and qualitative variables as frequency and percentage.

Ethical considerations

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Hospital General de Agudos Dr. José María Ramos Mejía, Autonomous City of Buenos Aires, Argentina.

RESULTS

Forty-four patients with a genetic diagnosis of LQTS were followed-up for 46 months (IQR35-175). Among them, 26 (59%) were women, and median age was 30 years (IQR 20-49). Thirty-five patients (80%) reported a history of sudden cardiac death (SCD) in first- and second-degree relatives.

From the total number of patients, 13 (30%) corresponded to the LQTS type 1 genotype (KCNQ1 gene), 29 (65%) to LQTS type 2 (KCNH2 gene) and 2 (5%) to LQTS type 3 (SCN5A gene). The missense point mutation was identified in 25 patients (57%), five patients (11%) carried a nonsense mutation and a frameshift mutation was found in 14 patients (32%). The corrected QT interval was 490 msec (IQR 462-498). The phenotypic manifestation of LQTS (QTc >480 msec) was observed in 29 patients (66%). However, only 14 individuals (32%) manifested a permanent phenotype (Table 1).

Syncopal episodes were observed in 17 individuals (39%), especially during adolescence. Cardiac arrest was the first clinical manifestation in 3 patients (7%). The age at which symptoms began to be manifest was 17 years (IQR 14-25).

Ninety-three percent of cases were treated with beta-blockers (72% with propranolol), and 2 patients (5%) with a diagnosis of LQTS type 3 were treated with a sodium channel blocker (flecainide). Five patients (11%) had recurrence of syncope even after drug therapy. Two individuals with LQTS type 2 (5%) suffered nocturnal SCD at 17 and 66 years of age.

On the other hand, 7 patients required implantable cardiodefibrillator (ICD) at 18 years of age (IQR 16-26). Of these, 29% received shocks due to tachycardia or ventricular fibrillation (VT/VF) and 58% had complications associated with implantable devices (infection or catheter displacement/fracture) during the 161 month (IQR 83-229) follow-up (Table 2).

DISCUSSION

Congenital LQTS described by Jervell and Lange-Nielsen in 1957 and Romano and Ward in 1964 is an inherited channelopathy characterized by an alteration in ventricular repolarization and manifested by an abnormal prolongation in QTc interval duration. It predisposes to the onset of potentially lethal ventricular tachyarrhythmias (torsade de pointes and/

Table 1. Genetic and clinical characteristics (n=44)

Variable		
KCNQ1 (SQTL1)	13	30%
KCNH2 (SQTL2)	29	65%
SCN5A (SQTL3)	2	5%
Nonsense	5	11%
Missense	25	57%
Frameshift	14	32%
Relative with SCD	35	80%
Syncope	17	39%
Cardiac arrest	3	7%
QTc (msec)	490 (IQR 462-498)	
QTc ≥480 msec.	29	66%
Permanent phenotype	14	32%

SCD: sudden cardiac death.
Qualitative variables are presented as frequency and percentage, and quantitative variables as median and interquartile range (IQR)

Table 2. Treatment and adverse cardiac events during follow-up. (n=44)

Follow-up		
Beta-blockers	41	93%
Sodium channel blockers	2	5%
Recurrence of syncope	5	11%
SCD	2	5%
ICD Implant	7	16%
Implant age	18 (IQR 16-26)	
ICD replacement (number of devices/patient)	2.1	
ICD shock due to VT/VF	2	29%
ICD-associated infection	2	29%
Displacement or fracture of catheter	2	29%

ICD: implantable cardiodefibrillator; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

Qualitative variables are presented as frequency and percentage and quantitative variables as median and interquartile range (IQR). Percentages of shock, infection and catheter displacement refer to the 7 patients who received ICDs.

or ventricular fibrillation) that usually occur due to increased adrenergic tone following auditory stimuli, physical exercise or emotional stress. (5,6)

Over the past 25 years, 20 genes have been associated with congenital LQTS. However, a recent analysis reclassified several of these genes as having limited or controversial evidence. (7) This approach has left seven genes with definite or strong evidence of causality (KCNQ1, KCNH2, SCN5A, CALM1, CALM2, CALM3, and TRDN). All these genes encode ion channels involved in cardiac repolarization or proteins that regulate or modulate ion channel function.

Ninety percent of individuals with LQTS genotype carry mutations in one of the 3 major disease genes: KCNQ1 (LQTS type 1), KCNH2 (LQTS type 2), and SCN5A (LQTS type 3), which encode the alpha subunits of the Kv7.1 (IKs), Kv11.1 (IKr), and Nav1.5 (INa) ion channels, respectively (Figure 1). (8,9)

Approximately 40% of mutations correspond to nonsense mutations (consisting of a point mutation in the DNA sequence resulting in a premature termination codon), or frameshift mutations caused by the insertion or deletion of nucleotides in a DNA sequence, which generates a reading frame completely different from the original. These mutations alter protein synthesis and generate defective alpha subunits of ion channels. The remaining 60% are missense mutations, where a single nucleotide change alters an amino acid codon (Figure 2). These mutations can alter pore permeability, activation/deactivation or intracellular trafficking of ion channels. (10)

In our study, patients showed a genetic profile similar to the aforementioned studies. Ninety-five percent of the patients were carriers of the LQTS type 1 (KCNQ1) or LQTS type 2 (KCNH2) genotypes. The predominant genetic variants were due to missense point mutations with a single amino acid change in the protein sequence

Frequently, the intermittent nature of the LQTS phenotype manifestation hinders patient diagnosis. In our study, most patients (66%) manifested the LQTS phenotype (QTc >480 msec) but only one third had the permanent phenotype. These results were comparable to those of the study by Yoo et al. in which patients with LQTS showed significant QT interval oscillations in different measurements and only 20%

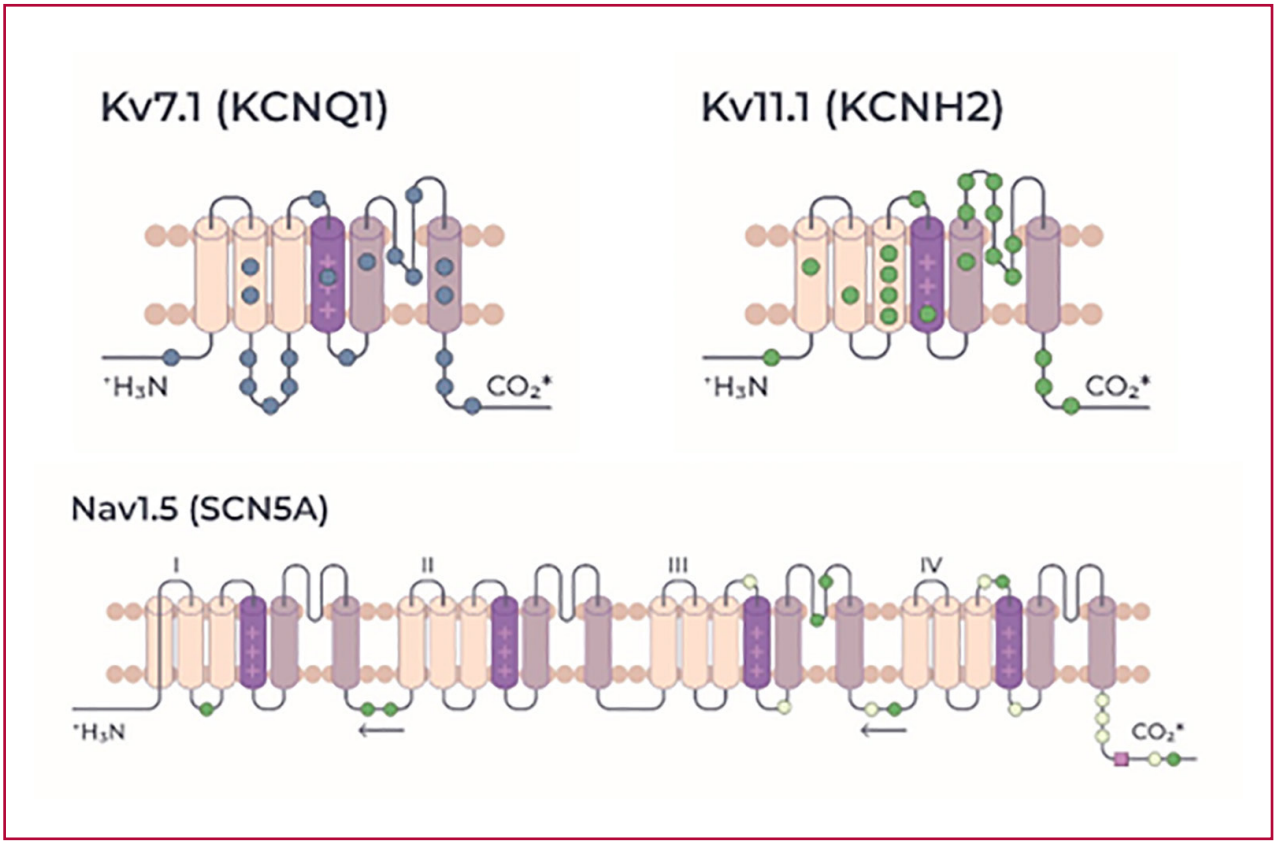
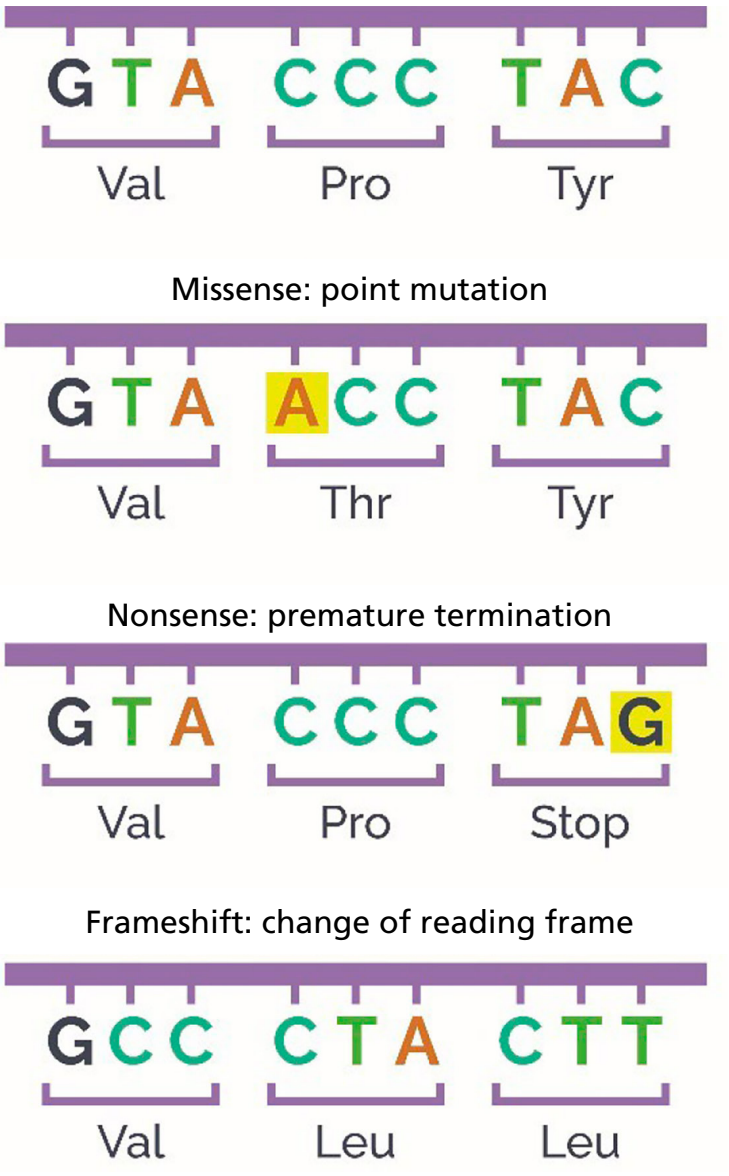


Fig. 1. Ion channels involved in LQTS type 1, type 2 and type 3. The KCNQ1 gene encodes the alpha subunit of the voltage-dependent potassium channel Kv7.1 (responsible for the slow delayed rectifier current, IKs) and the KCNH2 gene encodes the alpha subunit of the voltage-dependent potassium channel Kv11.1 (responsible for the rapid delayed rectifier current, IKr). The voltage-dependent sodium channel Nav1.5 (responsible for INa current) is encoded by the SCN5A gene. Modified from: Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev 2005;85:1205-53. https://10.1152/physrev.00002.2005



DNA sequence: A: adenine; T: thymine; C: cytosine; G: guanine. Amino acid sequence: Ser: serine; Val: valine; Pro: proline; Tyr: tyrosine; Thr: threonine; Leu: leucine; Stop: premature termination codon.

Fig. 2. Types of mutations. Missense: DNA point mutation that changes an amino acid. Nonsense: DNA point mutation that introduces a premature termination codon. Frameshift: insertion or deletion of DNA with a change of the reading frame. Modified from: Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev 2005;85:1205-53. https://10.1152/physrev.00002.2005

maintained the permanent phenotype. (11) These findings suggest that to achieve the diagnosis of congenital LQTS, patients should be thoroughly and continuously evaluated by serial ECG, stress ECG or dynamic recording with Holter monitoring on a periodic basis. In these circumstances, genetic testing to identify the responsible pathogenic variant becomes crucial for the early and accurate detection of patients with congenital LQTS.

Individuals with LQTS often manifest the phenotype and suffer syncopal episodes and/or sudden death at an early age. Mortality in patients with LQTS ranges from 1% to 2% at 5 years. (12) Beta-blockers are effective, especially in LQTS1 in which VT/VF is triggered by exertion. Non-compliance with treatment and the use of drugs that prolong the QT interval are mainly responsible for therapeutic failures. (13,14) In LQTS2 and LQTS3, lethal arrhythmic events are usually triggered at rest or by auditory or emotional stimuli. (15,16) Among individuals with ICD, the rate of recurrent events is approximately 3% to 28% within 5 years. (17,18)

There is still a tendency to consider it unnecessary to identify the genotype of patients with LQTS, once

the diagnosis has been made using clinical criteria. This conduct makes it impossible to initiate cascade screening of the affected family. Considering that the response to drugs (beta-blockers vs. sodium channel blockers) and the stimuli that act as arrhythmogenic triggers (exercise, auditory or emotional) are very different between genotypes, the lack of knowledge of the genetic cause makes it difficult to provide adequate therapy to patients. The consequences could result in avoidable deaths, especially among genotype-positive and phenotype-negative individuals. Thus, molecular biology should no longer be considered as an exclusive field of research but as an essential, everyday medical tool. (19)

In our study, ICD implantation was indicated between the second and third decade of life. The main reason was the occurrence of recurrent syncope even with beta-blocker therapy (primary prevention). The 2 women (one with LQTS1 and the other with LQTS2) who received an ICD for secondary prevention had adequate therapy for VT/VF 2 to 6 years after implantation. On the other hand, the rate of device-associated complications (infection or catheter displacement/fracture during long-term follow-up) was high. According to current guidelines, ICD implantation is indicated for secondary prevention (in individuals who have suffered resuscitated cardiac arrest, class I) and primary prevention (in those with recurrent syncope under beta-blocker treatment, class IIa). (20) Clearly, the decision to implant an ICD is life-saving in patients at high risk of SCD. However, in congenital LQTS, as in other hereditary channelopathies, the very early age of diagnosis and device implantation and the high rate (more than 20% in 5 to 10 years) of associated complications (infection, myocardial perforation, displacement, catheter wear and/or fracture, psychological consequences, etc.) that occur throughout the life of the patients, suggest that the decision to indicate an ICD should be based on a thorough and cautious evaluation. (21,22)

CONCLUSIONS

The genetic profile of our patients coincides with that reported in the literature. The identification of the genotype allows us to screen for asymptomatic carriers who do not express the phenotype permanently, thus achieving an accurate diagnosis and early treatment through the cascade screening strategy of relatives. Most patients respond favorably to beta-blockers. However, there is a high-risk group (previous VT/VF) that requires ICD implantation to prevent SCD. The early age of implantation and the high rate of associated long-term complications require a personalized and thorough evaluation at the time of implantation.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Extreme Living Conditions in Antarctica and Their Impact on the Cardiovascular System

Condiciones extremas de vida en la Antártida y su impacto sobre el sistema cardiovascular

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ABSTRACT

Background: Antarctica is one of the most challenging places to overwinter due to its meteorological characteristics, extreme light patterns, limited social interaction, and isolation.
Objective: To analyze cardiovascular function under conditions of confinement, circadian disruption, and prolonged isolation in a low-pollution area.
Methods: Observational, analytical, and longitudinal study in a group of 23 trained and healthy military personnel at the Argentinean Belgrano II Base in Antarctica. Body temperature, environmental and outdoor temperature were recorded. Abdominal waist circumference, body weight control and body composition were determined using bioelectrical impedance. The results of the exercise stress test and the 24-hour Holter ECG were recorded.
Measurements were made monthly for 12 months, including a baseline period, polar continuous darkness months, and continuous daylight months (confinement). Each individual was self-controlled. The baseline results were compared with those from the darkness and daylight periods and the darkness and daylight periods were compared with each other. Measurements were made between January 2023 and January 2024.
Results: The participants were trained males, with a mean age of 34.7 ± 5.1 years (range: 27-43), all exposed to the same diet, physical demands, and ambient temperature. No significant differences were observed in body composition parameters. The analysis showed a significant decrease in the heart rate (HR), systolic and diastolic blood pressure (BP) at rest, during maximal effort and during recovery on the exercise stress test, during the periods of darkness and daylight compared to baseline.
A similar trend was observed in the Holter ECG recordings, which showed significant changes in HR variability in the confinement phase compared to baseline. No differences were detected between the periods of darkness and daylight.
Conclusions: This behavior reflects autonomic nervous system activity on cardiac function and suggests an increased neurovegetative pattern, predominantly vagal. The implications of this study are relevant to the fields of healthcare, occupational performance in polar environments and space exploration.

Key words: Antarctic regions - Extreme environments - Circadian rhythms - Air pollution - Heart rate variability - Spaceflight

RESUMEN

Introducción: La Antártida es uno de los sitios más desafiantes para invernar, tanto por sus características meteorológicas, sus patrones de luz extremo, su interacción social limitada, como por sus condiciones de aislamiento.
Objetivo: Investigar el comportamiento de los parámetros cardiovasculares bajo condiciones de confinamiento, desajustes circadianos, aislamiento prolongado, y en una zona con escasa contaminación ambiental.
Material y métodos: estudio observacional, analítico y longitudinal, en un grupo de 23 militares entrenados y sanos, en la base argentina Belgrano II en la Antártida. Se realizaron determinaciones de temperatura corporal, ambiental y exterior, medición de cintura abdominal y control de peso, composición corporal por impedanciometría, ergometría, y ECG Holter de 24 horas.

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Las mediciones fueron mensuales, durante 12 meses incluyendo un basal, los meses de oscuridad-noche polar y los meses de luz permanente (confinamiento). Cada individuo fue control de sí mismo. Se compararon los estudios basales con los períodos de oscuridad y luz, además de ambos períodos entre sí. Las mediciones se realizaron entre enero 2023/enero 2024

Resultados: Los participantes fueron hombres entrenados, con edad media 34,7 ± 5,1 años (rango 27-43), bajo la misma alimentación, exigencias físicas y temperatura. No se registraron diferencias significativas en los parámetros corporales. El análisis reveló una disminución significativa en la ergometría de la frecuencia cardíaca (FC), tensión arterial sistólica y diastólica en reposo, en máximo esfuerzo y en la recuperación, en los períodos de oscuridad/luz respecto del basal. Igual tendencia se observó en el registro Holter, con una significativa variabilidad de la FC en la etapa de confinamiento comparada con la basal.

No se detectaron diferencias entre los períodos de oscuridad/luz.

Conclusiones: Este comportamiento refleja la actividad del sistema nervioso autónomo sobre la función cardíaca, y sugiere un patrón neurovegetativo incrementado, a predominio vagal. Las implicancias de este estudio se extienden a ámbitos relacionados con la salud, el trabajo en regiones polares y en la exploración espacial.

Palabras claves: Regiones Antárticas - Ambientes extremos - Ritmos circadianos - Contaminación atmosférica - Variabilidad de la frecuencia cardíaca - Vuelos espaciales

INTRODUCTION

Antarctica is the southernmost continent on Earth and one of the most hostile and inhospitable regions on the planet. Due to its geographic location and the tilt of the Earth's axis relative to the orbital plane, it receives less solar radiation, resulting in the low temperatures that characterize this continent, which can drop as low as —54 ºC during the winter. The climate is dry and there are strong winds. (1)

It has the cleanest air on Earth; it is an atmospheric region unaffected by human activity, and therefore, pollution carried by wind does not reach it.

Argentina occupies the territory known as the Argentine Antarctic Sector, which covers an area of approximately 1 461 597 km^2. Within the Argentine territory, there are 13 bases. One of them, Belgrano II Base, the southernmost, is located 1300 km from the South Pole. It is considered one of the most isolated bases, with very extremely limited access, and reaching it from other bases can take several days. (Photograph).

It is occupied and maintained each year by personnel from the Joint Antarctic Command, who remain at the base for a full year (January to January). During this period, there is no personnel turnover or short-term visits. They perform tasks related to the base maintenance, domestic duties and scientific activities following an eight-hour work schedule (9 AM to 6 PM) from Monday to Friday, with fixed times for breakfast, lunch and dinner. The diet is devoid of vegetables and relies heavily on canned food.

One of the most notable characteristics of the Belgrano II Base is its extreme photoperiod, with four months of continuous darkness (polar night) and four months continuous daylight (polar day). These conditions make it an ideal natural setting for studying the influence of natural light on circadian rhythms. Light is considered one of the main synchronization sources of the central biological clock, and limited or absent light exposure can lead to innumerable disruptions in human physiological functioning. (2)

Belgrano II is considered one of the most challenging bases for overwintering, due to its weather conditions, extreme photoperiods, limited social interaction and isolation. It is one of the most required and internationally recognized bases for studying these variables, and represents one of the most faithful experimental scenarios as a spatial analog, since it combines multiple specific environmental characteristics rarely found together in other places.

Our objective was to investigate the cardiovascular function under conditions of circadian disruption, confinement and prolonged isolation, particularly in a low-pollution area.

METHODS

This was an observational, analytical and longitudinal study conducted at the Argentine Antarctic Belgrano II Base. A total of 23 trained and healthy military personnel were included in the study and sent to the base. All participants agreed to participate in the project.

Participants underwent body weight monitoring, abdominal waist circumference measurement and body composition analysis using bioelectrical impedance (OMRON® HBF-514C). The body, environmental and outdoor temperature were recorded.

Exercise stress test was performed using Cardiovex® equipment on a Technogym® cycle ergometer, which automatically calculates metabolic equivalents (METs) of oxygen consumption. Measurements included baseline and maximal effort (Mx. effort) blood pressure (BP), recovery BP at 1 and 3 minutes, achieved METs, and peripheral oxygen saturation (SpO_2) at baseline and at maximal effort. The Astrand protocol was used, with ascending workload stages of 300, 600, 900, 1200, and 1500 kg'm. The same protocol was applied to all subjects.

Additionally, a 24-hour Holter ECG (Eccosur HT107®) was performed to determine the heart beats per day, maximum and minimum heart rate (Max. and Min. HR), heart rate variability (Standard Deviation of Normal-to-Normal (NN) intervals, SDNN) and the presence of arrhythmias.

Measurements were made in March (baseline), June, July, August (months of darkness) as well as in October, November and January (months of daylight).

Baseline results were compared with those from both darkness and daylight periods, and darkness and daylight periods were also compared with each other.

Statistical analysis

A Generalized Estimating Equations (GEE) approach was used to assess the variations in the ergometric variables in

the different evaluation timepoints. GEE allows modeling the correlation between repeated measurements from the same subject, thus allowing comparisons across time. Model validity was assessed using two types of correlation matrices: exchangeable or –1 autocorrelation. The exchangeable matrix assumes a similar correlation among all measurement pairs, while the –1 autocorrelation assumes that each measurement is correlated with the immediately preceding one, but not necessarily with the rest. The validity of models assuming both parametric and nonparametric distributions of the data was evaluated. It was assessed using the Quasi-likelihood under the Independence Model Criterion (QIC), and the model with the lowest QIC was selected. Pairwise comparisons were conducted using contrasts. This type of analysis imposes a penalty when making multiple comparisons. Holms' method was used to calculate the penalty.

Based on the GEE model, comparisons were made between the baseline values (at the beginning of the confinement phase) and those recorded during the confinement phase at the Base. Finally, contrasts within the GEE model were used to compare values from the winter (darkness months) and summer (daylight months) periods.

No covariates were included in the models.

Circular statistics were used to analyze the timing of the maximum and minimum HR values recorded in the 24-hour Holter ECG. Quantitative variables are expressed as means, standard deviation and 95% confidence intervals. Results are presented in hours, which are expressed in decimal format. Comparisons between groups were performed using the Watson-Williams test.

To compare winter (months of darkness) and summer (months of daylight) periods, contrasts on the adjusted GEE model including individual months were used.

The significance level was set at $\alpha = 0.05$. All statistical analyses were performed using R version 4.4 (The R Foundation, Vienna), with the geepack, modelbased, performance, parameters and circular packages. (3-5).

Ethical considerations

The 23 individuals who joined the study signed the informed consent, which was approved by the Bioethics Committee of the Hospital Central of the Province of Mendoza. The study was conducted in accordance with the Declaration of Helsinki and amendments.

RESULTS

The 23 participants were trained males with a mean age of 34.7 ± 5.1 years (range: 27-43). Smoking was the only cardiovascular risk factor, present in only 7 subjects (30%); all were exposed to the same diet, physical demands and ambient temperature (Table 1). Measurements were taken between January 2023 and January 2024. There were no significant differences in body parameters (Table 2).

Performance of exercise stress tests

The analysis revealed significant differences between the confinement (months of darkness and daylight) and baseline, with a decrease in HR: baseline 79.8 bpm (95% CI 75.4-85.9) vs. confinement 74.1 bpm (95% CI 71.4-78.5), p = 0.005 (Table 3).

A similar pattern was observed in systolic BP: baseline 118.26 mmHg (95% CI 114.06-122.78) vs. confinement 112.62 mmHg (95% CI 110.37-114.97), p <0.001; and in diastolic BP: baseline 76.15 mmHg. (95% CI 73.19-78.73) vs. confinement 69.84 mmHg (95% CI 66.81-70.94), p<0.001.

Table 1. Temperatures

	Baseline	Months of darkness	Months of daylight
Outdoor temperature	–12.6 ± 3.34	–22.8 ± 7.43	–7.51 ± 6.24
Indoor temperature	21.5 ± 1.78	23.1 ± 0.718	23.8 ± 0.415
Body temperature	35.7 ± 0.819	35.4 ± 0.516	35.4 ± 0.640

Temperatures are expressed in degrees Celsius.

Table 2. Body parameters

		Months of darkness			Months of daylight		
	Baseline (N=23)	06-2023 (N=23)	07-2023 (N=23)	08-2023 (N=23)	10-2023 (N=23)	11-2023 (N=23)	01-2024 (N=23)
Weight (Kg)	81.8 ± 13.9	81.6 ± 12.9	82.1 ± 13.1	82.0 ± 12.4	81.9 ± 12.0	81.4 ± 11.2	81.5 ± 11.2
BMI	27.2 ± 4.4	27.2 ± 4.1	27.1 ± 4.5	27.3 ± 4	27.3 ± 3.8	27.1 ± 3.6	27.1 ± 3.5
% Body fat	25.6 ± 7.3	26.3 ± 6.9	26.1 ± 7.6	26.3 ± 6.3	26.2 ± 6.0	26.1 ± 5.3	25.8 ± 5.4
% Muscle mass	35.9 ± 4.1	35.4 ± 3.9	35.2 ± 4.2	35.4 ± 3.6	35.5 ± 3.5	35.5 ± 3.0	35.7 ± 3.1
Basal metabolic rate (Kcal/day)	1780 ± 184	1770 ± 168	1780 ± 173	1780 ± 163	1780 ± 156	1770 ± 148	1770 ± 147
Relative visceral fat (%)	10.1 ± 4.2	10.2 ± 4.1	10.3 ± 4.3	10.5 ± 3.9	10.5 ± 3.7	10.3 ± 3.6	10.3 ± 3.5
Waist (cm)	93.3 ± 11.2	89.7 ± 8.4	89.9 ± 9.1	88.7 ± 8.5	88.8 ± 7.8	88.0 ± 7.1	88.7 ± 6.6

BMI: Body Mass Index.

Table 3. Performance of the exercise stress tests

	Baselineline	Months of darkness	Months of daylight	p
Exercise stress test (baseline)				
SpO_2	97.8 ± 1.4	97.9 ± 1.4	97.8 ± 1.3	0.324
HR	79.8 ± 12.9	74.3 ± 11.4	74.0 ± 11.3	<0.005
Systolic BP	118 ± 11.5	112 ± 7.2	113 ± 8.8	<0.001
Diastolic BP	76.1 ± 6.5	68.2 ± 8.1	69.9 ± 9.1	<0.001
Exercise stress test (max)				
SpO_2	96.8 ± 1.8	96.2 ± 2.1	96.1 ± 2.4	0.023
HR	177 ± 10.8	169 ± 11.7	168 ± 11.0	<0.001
Systolic BP	164 ± 15.6	153 ± 13.3	159 ± 14.3	<0.001
Diastolic BP	88.7 ± 6.9	91.6 ± 6.1	95.4 ± 8	<0.001
Exercise stress test (recovery. 1 min)				
SpO_2	97.7 ± 1.2	96.2 ± 2.1	96.2 ± 2.1	0.008
HR	147 ± 16.6	149 ± 13.6	151 ± 12.8	0.004
Systolic BP	153 ± 19.4	145 ± 13.3	153 ± 14.9	0.002
Diastolic BP	78.7 ± 9.7	81.2 ± 8.6	74.9 ± 8.5	<0.001
Exercise stress test (recovery. 3 min)				
SpO_2	98.1 ± 1.2	97.8 ± 1.2	97.3 ± 1.4	<0.001
HR	116 ± 15.0	108 ± 15.4	107 ± 15.1	<0.001
Systolic BP	129 ± 13.2	125 ± 14.0	125 ± 11.7	<0.001
Diastolic BP	77.0 ± 5.6	74.4 ± 8.9	73.2 ± 8.6	<0.005
Achieved METs	9.76 ± 1.5	10.0 ± 1.6	10.2 ± 1.42	0.184

HR: heart rate; max. maximal; METs: metabolic equivalents of O_2 consumption; SpO_2: peripheral oxygen saturation; BP: blood pressure.

Similar findings were obtained for HR at maximal effort: baseline 176.91 bpm (95% CI 172.72-181.32) vs. confinement 168.76 bpm (95% CI 165.31-172.36), p<0.001; and for systolic BP at maximal effort: baseline 163.94 mmHg (95% CI 158.00-170.34) vs. confinement 155.87 mmHg (95% CI 151.56-160.45), p<0.001.

In contrast, diastolic BP at maximal effort was higher during confinement: baseline 87.85 mmHg (95% CI 85.14-90.74) vs. confinement 92.38 mmHg (95% CI 90.74-94.08), p<0.001.

SpO2 at recovery showed a non-significant decrease: baseline 98.07% (95% CI 97.60-98.55) vs. confinement 97.49% (95% CI 97.20-97.79), p=0.003.

There were also significant differences in recovery values: HR: baseline 115.08 bpm (95% CI 108.68-122.27) vs. confinement 106.46 bpm (95% CI 100.95-112.61), p<0.001; systolic BP: baseline 128.52 mmHg (95% CI 123.54-133.93) vs. confinement 124.36 mmHg (95% CI 120.99-127.92), p=0.035; and diastolic BP: baseline 76.88 mmHg (95% CI 74.52-79.39) vs. confinement 73.48 mmHg (95% CI 71.03-76.11), p<0.001.

Figures 1, 2 and 3 show the performance of these variables during the exercise stress tests at baseline and during the months of daylight and darkness.

No differences were observed between the months of daylight and darkness, nor in the achieved METs.

Analysis of Holter ECGs

A decrease in minimum HR was observed during the months of darkness and daylight compared to baseline, with no significant differences between the two timepoints (p <0.005).

The maximum HR was recorded during the outdoor work times (snow shoveling), being significantly higher during the confinement (p <0.001).

A significantly greater HR variability was observed during confinement compared to baseline (p=0.005). There was no evidence of clinically relevant arrhythmias (Table 4).

DISCUSSION

Most studies conducted on the White Continent have focused on sleep patterns, with limited information on the impact of complex living conditions on the cardiovascular system. (6)

Extreme environments challenge the physiological capacity of human beings to adapt to complex situations resulting from the combination of different vari-

Photograph of Belgrano II Base located 1300 km from the South Pole and 4953 km from Buenos Aires

ables, such as climate, confinement, isolation and the absence of natural light. (7)

Studying how people live under these conditions may provide valuable information, with potential benefits for health or safety. Moreover, this is one of the most accurate experimental model settings as a space analog, as it shares many specific environmental features. (8,9)

This study aimed to demonstrate physiological changes in BP and HR related to human adaptation to extreme environments, through the longitudinal collection of continuous data over a maximum period of eleven months, allowing accurate observations of changes over time.

During the confinement, a clear decrease and a marked variability in HR were observed, along with a drop in BP.

This performance reflects the activity of the autonomic nervous system on cardiac function, and suggests an increased neurovegetative pattern, predominantly vagal.

Several factors influence HR variability as well as cardiac inotropism and chronotropism in general. Such is the case of the autonomic nervous system, which regulates cardiovascular parameters, such as HR, contractile force, redistribution of blood flow to areas with greater vascular demand and short-term BP control via different sympathetic and parasympathetic receptors. (10)

It is worth exploring which physiological mechanisms might explain this performance.

Circadian rhythm disruptions

The Earth rotates on its axis, resulting in two well-defined environments: daylight and darkness. Living beings have adapted by developing specific predictive mechanisms. This gave rise to the biological rhythms that repeat every 24 hours.

Findings related to chronotype and circadian activity rhythms confirmed the role of light in synchronizing the sleep phase. A decrease in sleep duration was observed, along with a delayed chronotype and increased social jet lag during the polar night. (11-12)

In this study, the circadian cycle did not appear to influence the physiological variables analyzed, as no differences in cardiovascular behavior were detected between the periods of darkness and daylight.

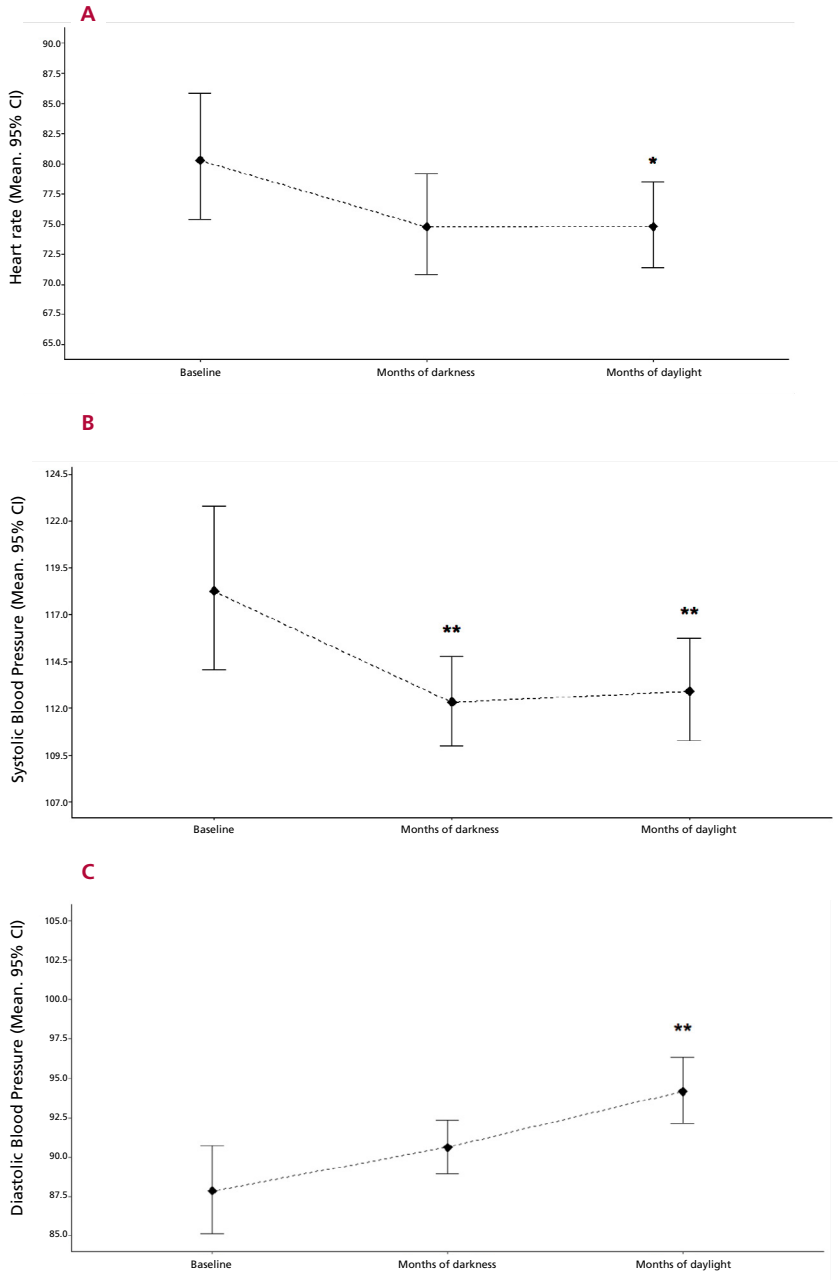
Environmental pollution

The environment is a major determinant of cardiovascular health. (13) Air pollution enters the body through the alveoli and contributes to the development of cardiovascular disease by activating several mechanisms, including inflammation, endothelial dysfunction, oxidative stress, autonomic dysfunction and thrombogenicity. (14)

Chronic exposure to air pollution has been associated with increased inflammation, promoting the production of interleukin-6 (IL-6) and C-reactive protein, among other inflammatory markers associated with a higher risk of disease. (15)

Several environmental pollutants can induce autonomic dysfunction by triggering reflex arcs that alter

Fig. 1. Exercise stress test: resting parameters at baseline and during the months of darkness and daylight



*** p <0.005 ** p <0.001**

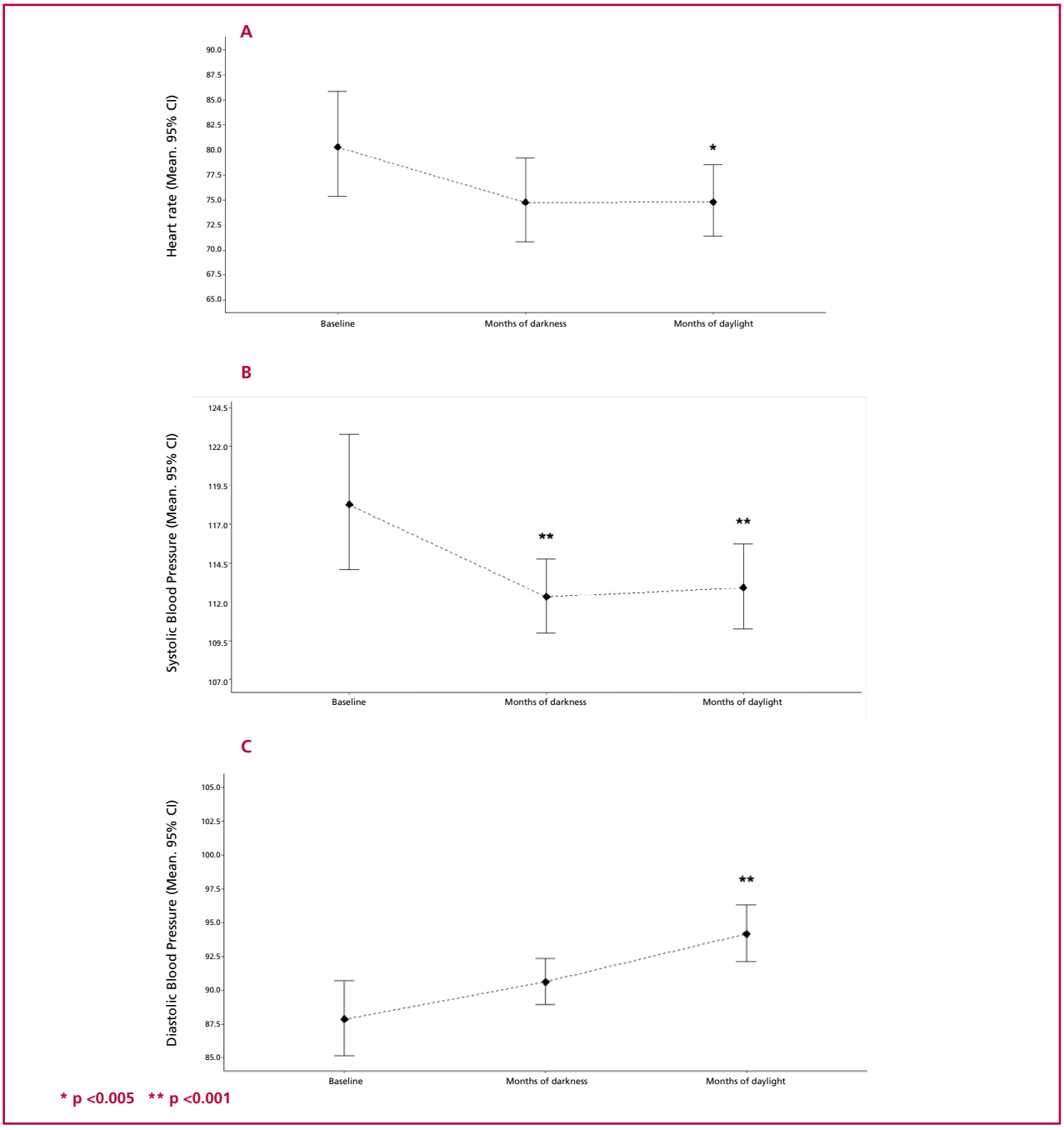
A. Heart rate; B. Systolic blood pressure; C. Diastolic blood pressure.

HR and favor the onset of arrhythmias. (16) Most epidemiological studies have reported negative associations between different indices of heart rate variability and levels of fine airborne particles with a diameter of less than 2.5 micrometers (PM2.5) as well as other pollutants. (17-18)

Lead, for instance, can replace calcium in calmodulin. This mechanism has been associated with the regulation of nitric oxide synthase, which affects nitric oxide production and plays a key role in endothelial function and the inhibition of platelet aggregation. (19)

Air in Antarctica contains fewer atmospheric aerosols and presents a much more heterogeneous and diverse chemical composition compared to that of the continental regions, which may explain the lower health impact observed in the health of the study population.

Fig. 2. Exercise stress test: maximal effort parameters at baseline and during the months of darkness and daylight.



A. Heart rate; B. Systolic blood pressure; C. Diastolic blood pressure.

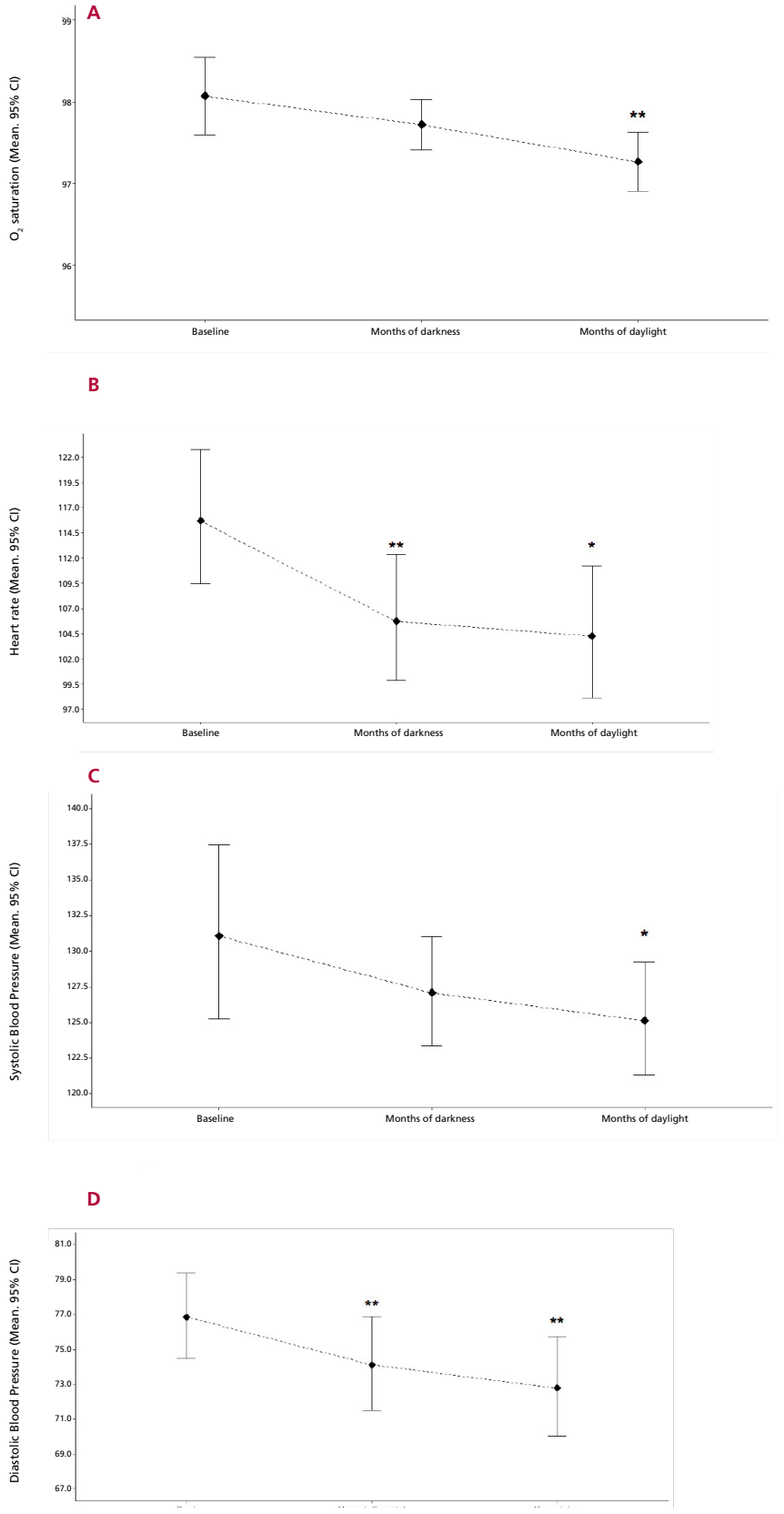
Exercise effect

Physical exercise leads to a reduction in resting HR, which is also evident during physical exercise in trained individuals when performed at submaximal intensities—a phenomenon directly related to an increase in stroke volume. (20) Among the mechanisms underlying bradycardia are the regulation of the autonomic nervous system with increased vagal tone, a decrease in the intrinsic heart rate, changes in baroreceptor sensitivity, and increased systolic volume.

Regular training reduces resting sympathetic activity, lowers plasma catecholamine levels (both at rest and during submaximal exercise) and modifies renal homeostasis by decreasing renal vascular resistance—all of which contribute to BP reduction.

Exercise programs with a high dynamic component lower BP in both normotensive and hypertensive adults. This effect is more marked in hypertensive in-

Fig. 3. Exercise stress test: recovery parameters at baseline and during the months of darkness and daylight.



*** p <0.005 ** p <0.001**

A. O_2 saturation; B. Heart rate; C. Systolic blood pressure; D. Diastolic blood pressure.

Table 4. Analysis of Holter ECGs

Holter	Baseline	Months of darkness	Months of daylight	p
Minimum heart rate	45.5 ± 10.3	42.0 ± 4.84	41.1 ± 4.17	0.012
Time (h)	5.56 ± 0.76	5.91 ± 0.79	5.62 ± 0.69	
Maximum heart rate	126 ± 14.3	129 ± 17.0	131 ± 17.6	<0.001
Time (h)	13.27 ± 1.44	12.84 ± 1.13	13.63 ± 1.01	
Differential heart rate	80.1 ± 19.1	86.6 ± 17.2	89.5 ± 16.7	
SDNN* (milliseconds)	155.0 ± 37.7	164.0 ± 38.7	177.0 ± 33.3	0.003

SDNN, Standard Deviation of Normal-to-Normal intervals.

dividuals, with a mean reduction of 6-7 mmHg in both systolic and diastolic blood pressure, compared to 3 mmHg reduction in normotensive individuals. (21)

The population included in our study was composed of individuals with a high level of physical training—an essential requirement for admission to the Antarctic program. Among many other reasons, candidates were selected for their strong adaptive capacity to exercise.

Furthermore, when body parameters (weight, abdominal waist circumference and body composition assessed by bioelectrical impedance) were analyzed, no differences were observed between baseline values and those recorded during the Antarctic stay. Therefore, it is unlikely that the results are influenced by the exercise effect.

Isolation and continuous stress

Antarctica is one of the most challenging environments to work in. In addition to extreme temperatures and photoperiods, Antarctic bases are remote and isolated locations usually inhabited by very few people, creating a context of limited interpersonal relationships and hostile conditions of confinement and isolation. (22-23)

During the 12-month period, the study group remained isolated, with no possibility of contact with the mainland, even in the event of an emergency. Both uncertainty and generalized fear have been described as negative factors in terms of psychological consequences. (24) Isolation lasting more than ten days has been identified as a significant risk factor for post-traumatic stress, fear, frustration, boredom and symptoms of anxiety and depression—conditions that may lead to cardiovascular alterations, such as increased HR and BP. (25)

Contrary to expectations, the mentioned cardiovascular variables tended to decrease. Positive psychological functioning was likely to act as a potential protective factor through the implementation of healthy mechanisms to cope with adversity. (26)

The military personnel voluntarily chose to participate in the expedition and undergo this experience, fully aware of the risks involved—a situation very different from imposed isolation, such as that experienced during the COVID-19 pandemic. (27)

Study Implications

The implications of this study extend to numerous areas related to healthcare, occupational health, and space exploration. Indeed, reduced HR and low BP were observed in astronauts on space shuttle missions. (28) The cardiovascular deconditioning that occurs during spaceflight includes a decrease in circulating blood volume and blood pressure—patterns very similar to our findings. (29)

In this regard, having scenarios that can rigorously replicate some of the conditions astronauts are expected to face is extremely valuable, as they offer useful contexts for advancing in space science.

New challenges in this field involve establishing permanent bases on the Moon and Mars, along with the possibility of incorporating tourist travel for untrained civilians. Therefore, the new challenges of space exploration require a deeper understanding of adaptation mechanisms in different populations. (30)

Limitations

Conclusions are limited by several factors. The sample size is small, although it worth noting that studies conducted in the Arctic or Antarctica typically involve small populations. A control group was not available, as it is almost impossible to find individuals living under the same temperature conditions and at sea level.

Another limitation is the absence of physiological parameters, such as the melatonin, cortisol and noradrenaline measurements. These assessments are planned for implementation in a future expedition.

CONCLUSIONS

The Belgrano II Base served as a model to explore the impact of extreme photoperiods and isolation in an environment free from atmospheric pollution on cardiovascular physiological variables. The findings suggest that under these conditions, neurovegetative activity increases. Future research is required to confirm these findings.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Heart Failure Registry in Santa Cruz de la Sierra, Bolivia. SEPE-HF Registry

Registro de insuficiencia cardíaca en Santa Cruz de la Sierra, Bolivia Registro SEPE-HF

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ABSTRACT

Background: Heart failure is a true pandemic affecting more than 64 million people worldwide. It is essential to know the local reality in order to implement the most appropriate diagnostic and therapeutic actions. We conducted a heart failure registry in Santa Cruz de la Sierra, Bolivia, the SEPE-HF registry.
Objective: The aim of the registry was to determine the epidemiological characteristics, clinical presentation, evaluation, treatment and outcome of heart failure in our region.
Methods: From January 2023 to April 2024, patients admitted to seven participating centers for heart failure were included in the study.
Results: We included 418 patients; mean age was 67.4± 13.1 years and 49% were men. Sixty-four percent had a history of hypertension, 21% diabetes mellitus, 20% atrial fibrillation (AF), and 12% ischemic heart disease. Most patients had Chagas cardiomyopathy (37%). Transthoracic echocardiography revealed that 51% had left ventricular ejection fraction (LVEF) ≤40%. Cardiovascular mortality was 5.5%. Chagasic patients tended to be older, with less history of hypertension, and a higher prevalence of right bundle branch block, AF and pacemaker rhythm. They presented more frequently depressed ventricular function, but no significant differences in in-hospital mortality.
Conclusion: The SEPE-HF registry reflects the characteristics and outcome of patients hospitalized for heart failure in Santa Cruz de la Sierra, Bolivia. Chagas disease accounts for more than one-third of the cases, making it imperative to advance the development of measures that facilitate early diagnosis and the eradication of the endemic disease.

Key words: Heart failure - Chagas disease - Ejection fraction - Santa Cruz de la Sierra - Epidemiology

RESUMEN

Introducción: La insuficiencia cardíaca es una verdadera pandemia, con más de 64 millones de personas con este síndrome en todo el mundo. Es fundamental conocer la realidad local para implementar las medidas diagnósticas y terapéuticas más adecuadas. Realizamos un registro de insuficiencia cardíaca en Santa Cruz de la Sierra, Bolivia, el registro SEPE-HF.
Objetivos: determinar las características epidemiológicas, clínica, evaluación, tratamiento y pronóstico de la insuficiencia cardíaca en nuestra región.
Material y métodos: Desde enero 2023 hasta abril 2024 fueron incluidos pacientes con historia de insuficiencia cardíaca internados por dicha causa en 7 centros participantes.
Resultados: Se incluyeron 418 pacientes, el 49 % hombres, con una media de edad de 67,4 ± 13,1 años. Tenía antecedentes de hipertensión arterial el 64 %, de diabetes mellitus el 21 %, de fibrilación auricular (FA) un 20 % y de cardiopatía isquémica el 12 %. La etiología predominante fue la chagásica (37 %). En el ecocardiograma transtorácico el 51 % presentaba fracción de eyección ventricular izquierda ≤40 %. La incidencia de mortalidad cardiovascular fue del 5,5 %. Los pacientes chagásicos tendieron a ser más añosos, con menos antecedente de HTA, mayor prevalencia de bloqueo de rama derecha, FA y ritmo de marcapasos. Presentaron con más frecuencia depresión de la función ventricular, pero no diferencias significativas en la mortalidad intrahospitalaria.

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Conclusión: El registro SEPE-HF refleja las características y evolución de los pacientes internados por insuficiencia cardíaca en Santa Cruz de la Sierra, Bolivia. La etiología chagásica es responsable de más de un tercio de los casos, lo que hace imprescindible avanzar en el desarrollo de medidas que favorezcan el diagnóstico precoz de la afección y la erradicación de la endemia.

Palabras clave: Insuficiencia cardíaca - Enfermedad de Chagas - Fracción de eyección, Santa Cruz de la Sierra - Epidemiología

INTRODUCTION

Heart failure (HF) is a clinical syndrome with symptoms and signs caused by a structural and/or functional cardiac abnormality, elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. (1) According to left ventricular ejection fraction (LVEF), heart failure (HF) is classified in: HF with reduced LVEF (LVEF ≤ 40%), mildly reduced LVEF (LVEF 41%-49%), and preserved LVEF (LVEF ≥ 50%). Among patients with HF with mildly reduced and preserved LVEF, patients with recovered LVEF, those with a baseline LVEF ≤ 40% and with improvement to LVEF > 40% and at least a ≥ 10% increase should be considered as a particular group. (2)

Heart failure is a global pandemic, affecting more than 64 million individuals worldwide and resulting in over 1 million hospitalizations per year in the United States and Europe. (3,4) It is estimated that the direct costs of HF account for 1-2% of the health budget in developed countries. (5) It is necessary to describe the characteristics of HF in a region from an epidemiologic and public health perspective. The PRICNASA registry, carried out in Bolivia in the city of Santa Cruz de la Sierra, observed particular characteristics in the population, such as high prevalence of Chagas disease (CD), the most common ethology of HF in the region. (6) In light of these findings, it became apparent that conducting a registry with the participation of multiple hospitals was essential to accurately reflect the regional epidemiology of HF. Santa Cruz de la Sierra, a city in the eastern plains of Bolivia, is currently the most populated city in the country, with a total population of approximately 1.6 million in 2024 and more than 3 million in the entire department of Santa Cruz. (7)

The SEPE-HF registry (Santa Cruz epidemiology and research on heart failure) is a multicenter registry, proposed by the *Sociedad Cruceña de Cardiología* and a group of research cardiologists, to evaluate the epidemiology of HF in Santa Cruz de la Sierra, Bolivia.

METHODS

The SEPE-HF REGISTRY is a prospective, cross-sectional, multicenter study with the participation of 7 healthcare centers in Santa Cruz de la Sierra that included tertiary health care hospitals (*Hospital Obrero nº3 Caja Nacional de Salud, Caja Petrolera de Salud and Hospital San Juan de Dios*), secondary health care hospitals (*Hospital Municipal Francés and Hospital Universitario Hernández Vera*) and private centers (*Clínica Incor* and *Clínica Foianini*). Patients hospitalized from January 2023 to April 2024 who were admitted with a diagnosis of HF due to signs and symptoms plus increased NT-proBNP (N-terminal pro-B-type natriuretic peptide) values, were included. Patients who met the inclusion criteria signed the informed consent form approved by the corresponding institutional review boards. Exclusion criteria were diagnosis of septic shock, ST-segment elevation myocardial infarction in the last 40 days, a life expectancy of less than three months, and any psychiatric disease. The aim of the registry was to determine the epidemiological characteristics, clinical presentation, evaluation, treatment and outcome of heart failure in the city of Santa Cruz de la Sierra, Bolivia.

Statistical analysis

All the statistical calculations were performed using Stata 18.0 software package. Quantitative variables are expressed as mean and standard deviation or median and interquartile range, according to their distribution. Means were compared using the t test or ANOVA, and the Wilcoxon test or Kruskal Wallis test were used to compare medians. Qualitative variables are presented as percentages and were compared using the chi-square test or Fisher's test. A p-value < 0.05 was considered statistically significant.

RESULTS

Between January 2023 and April 2024, 418 patients were included. Mean age was 67.4 ± 13.1 years and 51% were women. Mean age was 64.9 ± 13.1 years in men and 69.9 ± 12.7 years in women ($p < 0.001$). The baseline characteristics of the population are presented in Table 1.

Mean heart rate on admission was 84 ± 26.5 beats per minute, systolic blood pressure was 126.6 ± 29.6 mm Hg and diastolic blood pressure was 75.3 ± 16.2 mm Hg. Most patients were in functional class III and IV. The predominant signs and symptoms were dyspnea, jugular venous distension, bibasilar crackles and bilateral lower extremity edema. The admission laboratory showed slightly impaired renal function and a median NT-proBNP of 700 pg./mL (200-3142). The ECG showed sinus rhythm in 57.8% of patients and atrial fibrillation in 29.8%. Average QRS complex width was 110 ms.

Seventy-five percent of patients underwent transthoracic echocardiography; 51% presented LVEF ≤ 40%. Among patients with LVEF ≤ 40%, 62.4% were male versus 43% in those with higher LVEF; this difference was statistically significant ($p < 0.001$). The causes of HF decompensation included infection in 33%, treatment discontinuation in 31.3%, hypertensive emergency in 10.5%, cardiac arrhythmias in 7.1% and acute coronary syndrome in 4%.

The primary etiology of HF was CD (36.7%), followed by hypertension (29.9%), ischemic heart disease (19.2%), severe mitral valve disease (16%), arrhythmia (8.6%) and severe aortic valve disease (6.9%).

Table 1. Baseline characteristics of the patients

Characteristics	(n=418)
Age (years)	67.4 ± 13.1
Female sex	213 (51)
Comorbidities	
HTN	268 (64)
Type 2 DM	88 (21)
Chronic kidney disease	54 (13)
Ischemic heart disease	50 (12)
COPD	42 (10)
Tobacco use	21 (5)
Dyslipidemia	17 (4)
Previous hospitalization due to HF	109 (26)
Functional class (NYHA)	
II	62 (14.9)
III	223 (53.3)
IV	133 (31.8)
Signs and symptoms	
Lower limb edema	309 (73.9)
Cardiac enlargement	233 (55.7)
Dyspnea	327 (78.2)
Crackles	279 (66.6)
APE	22 (5.2)
Jugular venous distension	244 (58.3)
Pleural effusion	87 (21.2)
Nicturia	84 (20.0)
Nocturnal cough	77 (18.4)
Tachycardia	66 (15.7)
Heart rate (bpm)	85 (± 26.5)
SBP (mm Hg)	126.7 ± 29.6
DBP (mm Hg)	75.8 ± 16.2
Oxygen saturation (%)	94 ± 4.7
Electrocardiogram	
Atrial fibrillation	124 (29.7)
Pacemaker rhythm	44 (10.5)
RBBB	53 (12.7)
LBBB	47 (11.2)
LAH	54 (12.9)
Laboratory	
Creatinine (mg/dL)	1.29 (1-1.6)
NT-proBNP (pg/mL)	700 (200-3142)

APE: acute pulmonary edema; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; DM: diabetes mellitus; HF: heart failure; HTN: hypertension; LAH: left anterior hemiblock; LBBB: left bundle branch block; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; RBBB: right bundle branch block; SBP: systolic blood pressure.
Qualitative variables are presented as frequency and percentage, and quantitative variables are expressed as mean and standard deviation or median and interquartile range.

Table 2 presents the prevalent etiologies according to age range (< 50 years, 50-70 years, > 70 years).

A comparison of the characteristics of patients with CD and those without CD revealed that patients with CD tended to be older, had a lower prevalence of hypertension, and higher prevalence of right bundle branch block, atrial fibrillation (AF), and pacemaker rhythm. Patients with CD had higher prevalence of reduced LVEF. Prior use of diuretics, mineralocorticoid receptor antagonists and gliflozins was greater in these patients but the use of renin angiotensin system inhibitors and angiotensin II receptor blockers was lower. Table 3 shows the characteristics of both groups.

Treatment in the acute setting included the administration of intravenous bolus of loop diuretics in 90% of cases with an average dose of 68 mg/day. The use of noradrenaline was 9.5%, dobutamine 8.8%, nitroglycerin 5.5%, and dopamine 2.3%. Cardiovascular mortality was 5.5% (7.3% in patients with reduced LVEF). In these patients the incidence of cardiogenic shock was 11.5%. Cardiovascular mortality was not significantly higher in patients with CD.

The mean length of hospital stay was 14 days for all the patients in the registry. Heart failure treatment was optimized at hospital discharge, with indications for angiotensin-converting enzyme (ACE) inhibitors increasing from 8% to 28%, angiotensin II receptor blockers from 39% to 68%, sacubitril-valsartan from 4% to 15.8%, beta-blockers from 39% to 53%, mineralocorticoid receptor antagonists from 47% to 67%, and dapagliflozin from 16% to 58% (Figure 1).

DISCUSSION

The SEPE-HF registry included 418 patients in the city of Santa Cruz de la Sierra, Bolivia. We observed a heterogeneous population with advanced mean age and predominantly female, consistent with other cohorts. (5,8) The baseline characteristics of the patients and their cardiovascular risk factors reflect similar characteristics to the population of an important and recent registry such as the Argentine Registry of Heart Failure ARGEN-IC. (9) However, in our population the prevalence of tobacco use was much lower, and the history of CD was higher. The most common etiology of HF in various publications is mainly ischemic heart disease, but was only 19.2% in our registry, a low percentage compared to the ARGEN-IC registry where it was 26%. (9) In the population <50 years, the main causes were rheumatic heart disease and congenital heart disease. We should highlight that CD is the most common etiology in our registry (36.7%), which is high compared to other registries in countries where CD is present. The PRICNASA registry had already demonstrated a high prevalence of patients with CD in our region, confirmed by the SEPE-HF registry. (6) Chagas disease affects about 10-12 million people worldwide. (10) In the natural history of CD, cardiac impairment progressively develops 20-

Table 2. Etiology of heart failure

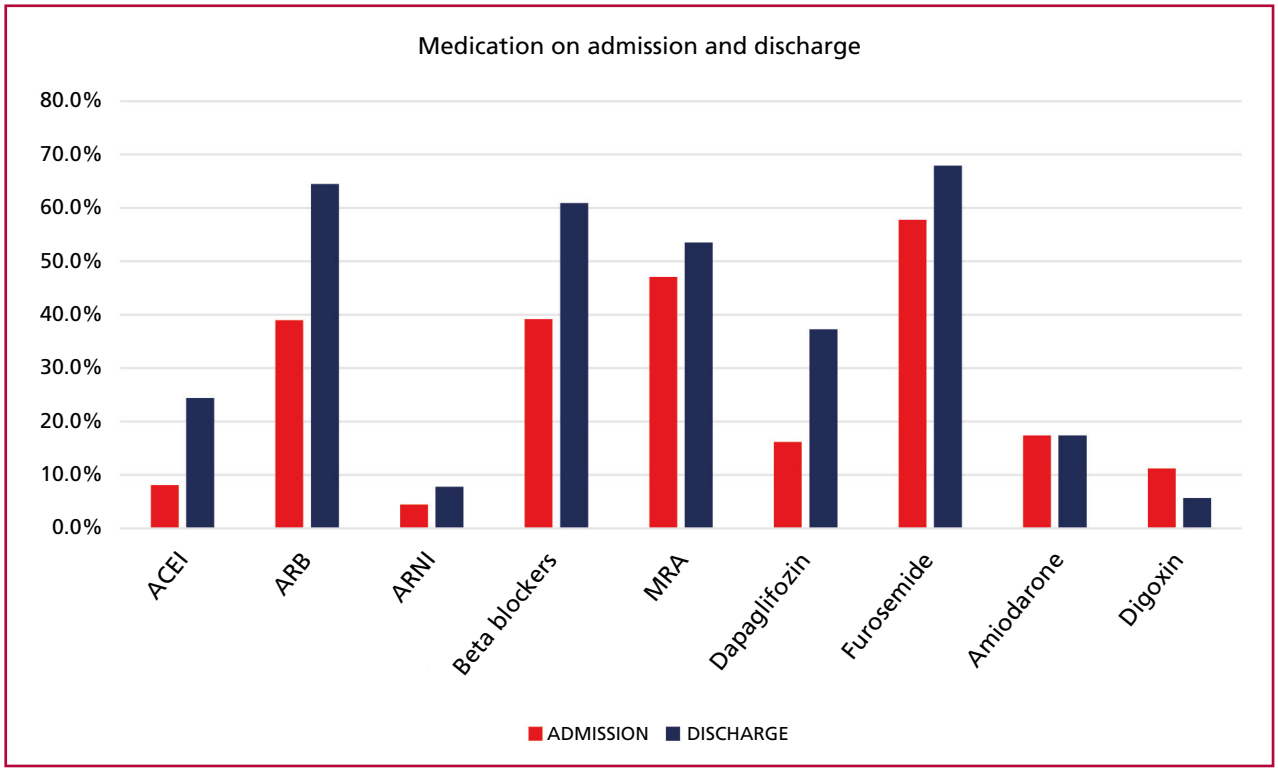
Etiology	< 50 years n = 42	50-70 years n =243	> 75 years n = 133	p
Ischemic heart disease	4 (10.2)	43 (17.8)	25 (19.2)	0.400
Severe mitral valve disease	13 (33.3)	56 (23.2)	9 (9.9)	0.001
Severe aortic valve disease	3 (7.6)	24 (9.9)	8 (6.1)	0.490
Hypertrophic cardiomyopathy	0 (0)	3 (1.2)	7 (5.3)	0.050
Idiopathic dilated cardiomyopathy	3 (7.6)	2 (0.8)	3 (2.3)	0.020
HTN	4 (10.2)	78 (32.3)	47 (36.1)	0.005
Induced by arrhythmias	1 (2.5)	27 (11.2)	16 (12.3)	0.190
Chagas cardiomyopathy	11 (28.2)	86 (35.6)	58 (43)	0.100
Congenital heart disease	5 (12.8)	1 (0.4)	0 (0)	1.000

Etiology of heart failure by age group
HF: heart failure; HTN: hypertension.
Qualitative variables are presented as frequency tables and percentages.

Table 3. Comparison of patients with and without Chagas disease

	With Chagas n=153 (36.6%)	Without Chagas n= 265 (63.4%)	p
Age, years	68.8 ± 11.9	66.5 ± 13.7	0.083
Female sex	72 (47.1)	131 (49.4)	0.714
HTN	76 (49.6)	186 (70.1)	0.001
DM	27 (17.6)	58 (21.8)	0.362
Tobacco use	8 (5.2)	14 (5.2)	1.000
Stroke	8 (5.2)	8 (3)	0.384
Ischemic heart disease	5 (3.2)	44 (16.6)	0.001
Pacemaker	40 (26.1)	3 (3.7)	0.001
CRT	3 (1.9)	1 (0.3)	0.280
ICD	1 (0.6)	1 (0.3)	1.000
Sinus rhythm	61 (39.8)	176 (76.4)	0.001
AF/atrial flutter	58 (37.9)	61 (23)	0.001
Pacemaker rhythm	34 (22.2)	10 (3.7)	0.001
RBBB	27 (17.6)	24 (9)	0.015
LBBB	19 (12.4)	28 (10.5)	0.676
Creatinine (mg/dL)	1.30 (0.91-1.62)	1.29 (1.02-1.65)	0.155
NT-proBNP	500 (107-2555)	805 (237-3612)	0.162
RASi	92 (60.1)	209 (78.8)	0.001
BB	77 (50.3)	132 (49.8)	1.000
MRA	90 (58.8)	132 (49.8)	0.093
SGLT2i	78 (50.9)	80 (30.1)	0.001
Diuretics	99 (64.7)	141 (53.2)	0.028
LVEF < 40%	91 (59.4)	72 (27.1)	0.001
LVEF 41-49%	17 (11.1)	41 (12)	0.273
LVEF >50%	16 (10.4)	79 (29.8)	0.001
Length of stay (days)	6 (3-12)	7 (2-12)	0.982
CV mortality	13 (8.4)	14 (5.2)	0.279

Comparison of HF patients' characteristics according to the presence or absence of Chagas disease
AF: atrial fibrillation; BB: beta-blockers; CAF: chronic atrial fibrillation; CRT: cardiac resynchronization therapy; DM: diabetes mellitus; HTN: hypertension; ICD: implantable cardioverter defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PM: pacemaker; RASi: renin-angiotensin system inhibitors; RBBB: right bundle branch block; SGLT2i: sodium-glucose co-transporter 2 inhibitor.
Qualitative variables are presented as frequency and percentage, and quantitative variables as mean and standard deviation or median and interquartile range.



ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor neprilysin inhibitors; MRA: mineralocorticoid receptor antagonists.

Fig. 1. Optimization of medical treatment at hospital discharge

30 years after the initial infection. (11) In Bolivia, CD has been historically endemic in approximately 60% of the national territory. In 1999, the domestic infestation rate in Bolivia was 55% and decreased to 1.5% in recent years, while the rate of houses intradomestically infested decreased from 24.2% to 0.4% in the same years. (12) Despite the high burden of morbidity and mortality associated with CD and the high cost to national healthcare systems, 70-90% of people with the disease are unaware of their diagnosis and only 1% receive adequate etiologic treatment. (13-15) However, once the disease progresses to more advanced clinical stages with severe cardiac involvement, etiologic treatment does not appear to provide clinical benefit. (16-18)

Because of the complexity of the pathophysiology and clinical characteristics of CD, this group of patients is not represented in any of the HF studies. There is little evidence on the management of these patients. It is imperative that registries and studies are conducted that continue to evaluate the outcome of HF in patients with CD, including treatment. The PARACHUTE HF trial will evaluate the effect of sacubitril-valsartan vs. angiotensin-converting enzyme inhibitors (ACEI) in patients with LVEF < 40% and CD, to provide randomized and contemporary evidence to guide medical decisions in these patients. (19)

Twenty-six percent of patients in the SEPE-HF registry had previous hospitalization for HF. About 84.9% had FC III-IV dyspnea. The clinical profile on admission was similar to the one observed in the ARGEN-IC registry. (9) Echocardiograms were conducted in 75% of patients. Not all patients were tested, perhaps due to lack of resources. In the ARGEN-IC registry, 90% of patients underwent echocardiography, with an average LVEF of 41%. Forty-nine percent of patients had reduced LVEF, a figure similar to the one in our registry. (9)

The low use of intravenous vasodilators was similar to that observed in the rest of the registries. Pharmacological treatment could be optimized at hospital discharge, in line with the scientific evidence available. Although treatment was optimized, it is imperative to closely monitor these patients to ensure continuous optimization of the mainstays of HF treatment. The SEPE-HF registry showed a deficit of influenza vaccination in our patients, suggesting that we should be more aware of the need for protocolisation.

In-hospital mortality (5.5%) is in the range of that observed in other registries: 7.9% in ARGEN-IC, (9) 4% in ADHERE, (8) and 6.7% in Euro Heart Failure Survey II. (20) This cohort provides us with the opportunity to obtain current information on the HF population in Santa Cruz de la Sierra, Bolivia, and to design new strategies and approaches for our patients hospitalized for HF.

CONCLUSIONS

The SEPE-HF registry is a representation of HF in our population. We observed similarities in terms of our incidence in many epidemiological factors, comorbidities, and clinical profile with the ARGEN-IC registry. Chagas disease remains a significant etiology of HF in our population, a factor that should be considered in future studies, strategies, and health policies. The mortality rate in our registry is consistent with global standards.

Conflicts of interest

None declared.

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

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BRIEF ARTICLE

Lymphatic Embolization of Protein-losing Enteropathy in the Fontan Kreutzer Circulation. Case Series

Embolización linfática de la enteropatía perdedora de proteínas en la circulación Fontan Kreutzer. Serie de casos

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ABSTRACT

Background: Between 3% and 20% of Fontan-Kreutzer surgery (FS) patients will develop protein-losing enteropathy (PLE), with high impact on survival. Selective hepatoduodenal lymphatic duct embolization (SHDLE) technique has been proposed as a novel therapeutic target.
Objective: The aim of this study was to evaluate the feasibility, complications and analytical clinical outcome of SHDLE in patients with FS and PLE.
Methods: A retrospective, single-center, case series of patients with FS was carried out, including 5 patients with PLE, who underwent percutaneous SHDLE.
Results: Five patients who underwent FS at a median age of 4 years (range: 3.5-4.3), developed PLE at a median postoperative time of 7 years (range 2.3-15.3). Seven SHDLE were performed, with catheter lymphography, under echocardiographic control. In all 5 patients dilated and tortuous hepatoduodenal lymphatic ducts draining into the small intestine were found, and their embolization was effectively achieved in all cases. Immediately after the procedure all these patients increased their serum albumin level. During a median follow-up of 20 months (range 12-43) 4 patients maintained their albumin levels, while one patient required two new embolizations due to persistent hypoalbuminemia. One patient required surgical intervention due to residual anatomical defect. All patients showed clinical improvement. There were no major complications related to the procedure; 3 patients presented a self-limited episode of melena.
Conclusions: SHDLE was a safe and beneficial tool. The procedure allowed improving serum albumin levels and symptoms in all our patients.

Keywords: Protein-losing enteropathy - Fontan-Kreutzer surgery - Selective lymphatic embolization.

RESUMEN

Introducción: Entre 3% y 20% de los pacientes con cirugía de Fontan-Kreutzer (CF) desarrollarán enteropatía perdedora de proteína (EPP), con alto impacto en la sobrevida. Se ha propuesto la técnica de embolización selectiva de conductos linfáticos hepatoduodenales (ESLHD) como un novedoso blanco terapéutico.
Objetivo: Evaluar la factibilidad, complicaciones y el resultado clínico analítico de la ESLHD en pacientes con CF y EPP.
Material y métodos: Serie de casos de pacientes con CF, retrospectiva, unicéntrica, que incluyó 5 pacientes con EPP, a los que se les realizó ESLHD por vía percutánea.
Resultados: Se incluyeron 5 pacientes con CF realizada a una mediana de edad de 4 años (rango: 3,5-4,3), quienes desarrollaron EPP a un mediana de tiempo postquirúrgico de 7 años (rango 2,3-15,3). Se realizaron 7 ESLHD, con linfografía por cateterismo, bajo control ecocardiográfico. En los 5 pacientes se hallaron conductos linfáticos hepatoduodenales dilatados y tortuosos que drenaban en el intestino delgado, y se logró su embolización de manera efectiva en todos los casos. Post procedimiento inmediato todos incrementaron el nivel sérico de albúmina. Durante una mediana de seguimiento de 20 meses (rango 12-43) 4 pacientes mantuvieron los niveles de albúmina, mientras que un p requirió dos nuevas embolizaciones por hipoalbuminemia persistente. Un paciente requirió intervención quirúrgica por defecto residual anatómico. En todos los pacientes se evidenció mejoría clínica. No hubo complicaciones mayores relacionadas con el procedimiento; 3 pacientes presentaron episodio autolimitado de melena.
Conclusiones: La ESLHD fue una herramienta segura y beneficiosa. El procedimiento permitió mejorar los niveles séricos de albúmina y sintomatología en todos nuestros pacientes.

Palabras clave: Enteropatía perdedora de proteínas - Cirugía de Fontan-Kreutzer - Embolización linfática selectiva

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INTRODUCTION

Fontan- Kreutzer surgery (FS) for patients with univentricular physiology consists in the generation of a "serial" circuit, with a single systemic ventricle as a pulsatile pump that maintains cardiac output, and directly connects the systemic venous return to the pulmonary artery without interposition of a functional subpulmonary ventricle. (1,2) Over time, this fragile hemodynamic model, characterized by elevated central venous pressure and chronic low output state, has deleterious effects on multiple organs. (3,4)

About 3% to 20% of patients will develop protein-losing enteropathy (PLE), defined as a severe loss of albumin and other proteins in the intestinal lumen, with a high impact on survival. It is suspected from the patient's history and physical examination, and is confirmed by the presence of hypoalbuminemia and elevated level of alpha 1 antitrypsin (AT) in the stools. (5) Survival at five years from diagnosis was initially described as low as 50%; however, with recent advances in early diagnosis and new treatments, survival at 5 and 10 years is currently 88% and 72%, respectively. (6-8)

The pathophysiology of PLE, although extensively studied, remains controversial and is not fully elucidated. Undoubtedly, the chronic increase in systemic venous pressure sustained over time is a determining factor, but it alone does not fully explain all the phenomena leading to protein leakage into the intestinal lumen. Two key observations have prompted the search for new answers: first, although all patients with Fontan-Kreutzer circulation have elevated systemic venous pressure, not all develop this complication; second, published studies have not shown a direct relationship between the value of central venous pressure and the severity of enteropathy. A better correlation has been found in those patients who, in addition to increased venous pressure, present a clearly decreased cardiac output, establishing increased peripheral resistance specially involving "non-vital" organs, such as the gastrointestinal system. In patients with PLE, diastolic flow in the mesenteric artery is markedly decreased or even absent. (9,10) This "compensatory" mechanism results in a significant reduction of perfusion flow and, at the cellular level, apoptosis, which compromises the integrity of the intestinal barrier and facilitates protein loss. (11) Protein-losing enteropathy occurs in gastrointestinal or systemic inflammatory diseases (such as Crohn's disease or systemic lupus erythematosus) and responds favorably to corticosteroids, further suggesting an inflammatory component in its pathophysiology. (12,13) Similarly, treatment with heparin has shown some effectiveness, acting by its chemical structure as a barrier for the passage of proteins into the enterocyte, given that both are negatively charged molecules. (14) Finally, the reduction of oncotic pressure due to protein loss causes generalized edema, even in the intestinal wall, which further hinders the adequate absorption of nutrients, creating a vicious circle that aggravates the already existing clinical condition.

In recent years and with the advent of new imaging modalities, such as nuclear magnetic resonance lymphography or catheterization, pathological dilatation of the hepatoduodenal lymphatic ducts, lymphangiectasias, collateralization of the lymphatic system and even the presence of retrograde lymphatic flow into cavities of lower pressure, such as the bronchi or intestine, have also been demonstrated

These findings suggest the existence of a congenital defect present in the lymphatic system of affected patients, which acts as another predisposing factor for the development of this entity. (15-20) Based on these observations, the technique of lymphatic duct embolization has been proposed as a novel specific therapeutic target with encouraging results, initially described by Itkin et al. (19-21)

OBJECTIVE

The aim of this study was to evaluate the feasibility, complications and clinical-analytical outcome of selective hepatoduodenal lymphatic embolization (SHDLE) in patients with Fontan-Kreutzer circulation and PLE.

METHODS

A retrospective review was carried out of the clinical history of patients with FS who evolved with PLE and underwent an SHDLE procedure. We defined PLE as the presence of compatible signs and symptoms (soft tissue edema, diarrhea and ascites) accompanied by decreased serum albumin levels (< 3.2 g/dL) and elevated alpha 1 AT clearance (Cl) in the stools (Cl 24 hs > 20 mL). The lymphography and percutaneous embolization technique was performed as described by Itkin et al. (19) We evaluated serum albumin levels 10 days and 4 months after the procedure, and at the last control of each patient.

RESULTS

Five patients (P1 to P5) with FS performed at a median age of 4 years (range 3.5-4.3) were included in this study. Three patients developed the characteristic clinical condition of PLE, and in two patients the presentation was subclinical, both by routine laboratory findings: one presented with isolated hypoalbuminemia, and the other with increased alpha 1 AT clearance in the stools and normal protein and albumin. The latter case was interpreted as incipient PLE. The patients included presented the diagnosis of PLE at a median time of 7 years (range 2.3-15.3) from the performance of the FS.

Patient characteristics are listed in Table 1.

Clinical presentation and initial management

Three patients had evident clinical signs of Fontan-Kreutzer system dysfunction, with generalized edema, including ascites, and one of them with disabling scrotal edema. Two patients presented with subclinical forms: patient P3 with mild lower limb edema and

patient P5 with loose stools and intermittent lower limb edema. In all patients, medical treatment was insufficient for the reversal of the condition. Patients with a more severe clinical presentation required a transfusion regimen with albumin.

Four patients were catheterized prior to lymphography to evaluate Fontan system functioning. In patient P5, who only had increased alpha 1 AT clearance, without hypoalbuminemia, no prior catheterization was performed. Only in one patient with flow restriction at the interatrial level, the catheterization showed an underlying treatable hemodynamic substrate. This patient required septectomy and fenestration of the system. The rest of the patients did not require interventional or surgical procedures to optimize their condition. Central venous pressure (CVP) was elevated in all patients, with a median of 15 mmHg (range 12-19) (Table 1).

Lymphography and embolization

A total of 7 procedures were performed in 5 patients. In all five patients dilated and tortuous hepatoduodenal lymphatic ducts draining into the small intestine were found. In only one patient, magnetic resonance lymphography was also performed previously, and in the rest of the patients, catheterization lymphography was executed. In all patients, SHDLE was effectively accomplished (Figure 1).

Surgical technique

Catheterization lymphography is performed in the interventional room under general anesthesia. The hepatic parenchyma is accessed under ultrasound control and guidance and a 22 G gauge 10 cm Chiba needle is placed near the portal vein. It is assumed that by anatomy the lymphatic ducts are contiguous to it. Under radioscopic guidance, water-soluble iodinated contrast material is gently injected while the needle is retracted until the hepatic lymphatic ducts draining into the duodenal lumen are visualized. When the lymphatic ducts are adequately opacified, and with the needle in the hepatic parenchyma, injection of contrast material is performed to confirm how the lymphatic ducts drain a large amount of lymph volume into the intestinal lumen. Then, they are embolized by injecting 1 to 2 mL of n-butylcyanoacrylate (n-BCA) glue diluted in ethylated oil (1/6) through the same hepatic access, to seal the lymphatic branches that go from the liver to the duodenum.

Outcome

After the first embolization, all patients showed good immediate response, with an increase in albumin values in laboratory controls performed within the first ten days of the procedure. Patients P1, P3 and P5 remained with albumin values within the normal range during their evolution, until the last control, with a median follow-up of 20 months (range 12-43) (Table 2 and Figure 2).

Patient P2 required 2 new embolizations due to failure to achieve desirable albuminemia values and persistent edema and ascites. These were performed 29 and 39 months after the first procedure, respectively. This patient did not reach normal albumin values during his evolution, but he did manage to reduce edema.

Patient P4 underwent atrial septectomy with fenestration of the system concomitant with SHDLE. At present he remains with slightly decreased serum albumin values, close to normal.

Clinically, all patients showed marked improvement in quality of life, with reduction of edema, including the patient with persistent hypoalbuminemia and the two subclinical cases, who reported improvement in self-perception of the skin and fit of their clothes.

All patients continue with the same pharmacological scheme prior to embolization, with interruption of corticosteroids at three months from the procedure.

No major intra- or periprocedural complications were observed. Regarding minor complications, 3 patients presented episode of mild self-limited melena immediately after the procedure.

DISCUSSION

Protein-losing enteropathy is a serious complication in patients with Fontan circulation. It has great impact on survival, with initially, 50% survival at five years after diagnosis. However, thanks to advances in early diagnosis and treatment in the last decade, the mortality rate has decreased significantly, and reported survival at 5 years after diagnosis is 88%, prolonging the time for the final indication of cardiac transplantation (6-8).

The incidence of PLE in FS described in the literature varies between 3% and 20% (6-8). In our case it was 5%. The pathophysiological mechanism underlying this condition is complex and multifactorial (9-11). In their initial series in 2017, Itkin et al. demonstrated in 8 patients that factors such as high central venous pressure, dilation and predisposing anatomy of the hepatoduodenal lymphatic connections play a crucial role in its development. These observations have led to a new approach on the importance of lymphatic circulation, offering a new paradigm for the management of this difficult-to-treat complication. Obliterating these lymphatic connections resulted in an effective reduction of protein leakage into the intestine, thus improving the patient's clinical status. (21) In our service we initiated the experience in 2019, with initially favorable results, although the number of patients treated has been limited, similar to what is observed in international cohorts.

According to the available literature, this complication can manifest itself both in the immediate post-surgical period as after many years. (9) In our series of patients, PLE presented at a median of 7 years after the performance of FS. Clinically, two patients

Table 1. Baseline characteristics

Pt	Sex	Age (years)	Type of SV	Surgery	FS (age in years)	PLE after Fontan (years)	SO_2 (%)	CVP (mmHg)	Time with PLE symptoms	Treatment for PLE
P1	Fem	8	HLVS	ECT (F) F permeable	4	2.5	88	19	19	aspirin, sildenafil, bosentan, enalapril, spironolactone, carvedilol, furosemide, anticoagulation. budesonide, albumin, diet
P2	Male	21	DILV criss cross type	ECT (F) F closed by catheterization	4	7	96	15	15	aspirin, sildenafil, bosentan, enalapril, eplerenone, atenolol, furosemide, anticoagulation, budesonide, albumin, diet
P3	Fem	20	DILV criss cross type	ECT (NF)	3.5	15.3	96	12	12	aspirin, anticoagulation, sildenafil, furosemide, spironolactone, diet
P4	Male	7	HLVS	ECT (F) Spontaneous closed F (later required surgical re F)	4.3	2.3	96	19	19	aspirin, sildenafil, enalapril, spironolactone, furosemide, anticoagulation, budesonide, albumin, diet. LPB angioplasty - Septectomy and fenestration of the system.
P5	Fem	19	HLVS	ECT (F) F closed by catheterization	3.9	14.9	97	not catheterized	not catheterized	aspirin, furosemide, spironolactone, enalapril, carvedilol, diet

CVP: central venous pressure; DILV: double inlet left ventricle; ECT: extracardiac tube; Fem: female; F: fenestration; FS: Fontan-Kreutzer surgery; HLVS: Hypoplastic left ventricle syndrome; LPB: Left pulmonary branch; NF: not fenestrated; PLE: protein-losing enteropathy; Pt: patient; SO2: arterial O2 saturation; SV: single ventricle.

diagnosed early showed mild or subclinical forms of the disease, while the other three had overt symptoms with severe impairment in their functional class and quality of life. The severity of hypoalbuminemia coincided with that of clinical symptoms, although no similar correlation was observed with alpha 1 AT clearance levels, and the more severe patients did not show higher levels of this protein in the stools. This could be due to a decrease in hepatic protein synthesis in the more severe cases. It is noteworthy that none of our patients presented alterations in the hepatogram during evolution. These observations underline the essential need for early detection of this complication in all patients with FS, by means of a detailed interrogation and serial analytical controls of serum albumin and alpha 1 AT in the stools.

Similary to Itkin et al. (21), and Maleux et al., (22) who have published the largest case series (with 8 and 7 patients, respectively), in our series we were also able to demonstrate, by magnetic resonance lymphography or catheterization lymphography, the presence of retrograde lymphatic flow from the liver to a dilated peri intestinal lymphatic network in the 5 patients presenting with PLE. Coincidentally with the aforementioned groups, adequate serum albumin levels were achieved in most of the treated patients

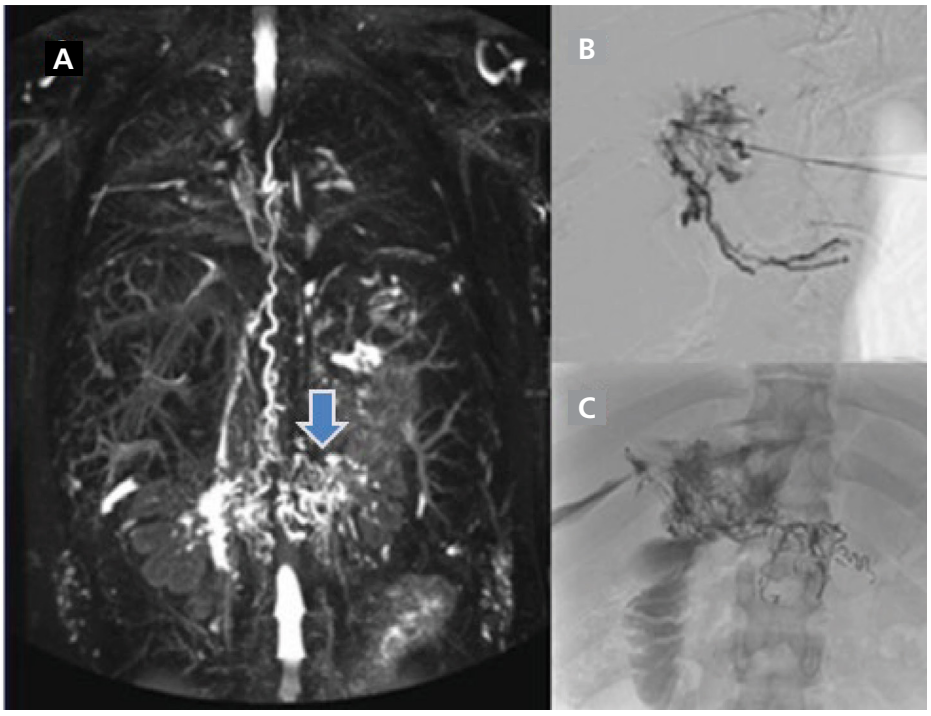

Fig. 1. A. Magnetic resonance lymphography, the arrow points to the tortuous and dilated hepatoduodenal lymphatic network. **B.** Lymphography by catheterization. **C.** Embolized hepatoduodenal lymphatic ducts.

Table 2. Results

Pt	alpha 1 AT Cl pre procedure (mL/24 h)	Alb. pre embolization (g/dL)	Alb. at 10 days (g/dL)	Alb. at 4 months (g/dL)	Alb. at last control (g/dL)	Follow-up time (months)
P1	1ww1069	2.6	3.7	4.8	4.16	23
P2	171.3	1.8	2.2	2	2.3	39
P3	217	2.5	2.69	4.85	5.12	43
P4	272.2	2.2	2.79	3.17	3.07	20
P5		4.04	4.26	4	4.2	12

Alb: albumin; Alpha 1 AT Cl: alpha 1 antitrypsin clearance; Pt: patient.
*Normal reference values: albumin: 3.2-5.3 g/dL; alpha 1 AT Cl: up to 20 mL/24 h

after the first embolization. However, as in their case, additional procedures were sometimes necessary. In our experience one patient required two new embolizations during follow-up due to persistent hypoalbuminemia, which revealed the development of new lymphatic connections. The most serious potential complications described include progression of the material used for embolization into the hepatic artery or vein, biliary tract, systemic veins or arteries, or the pulmonary artery. In addition, portal hypertension could be expected to develop during evolution and severe local bleeding could occur. (21) None of these complications were evident in our patients. Adverse events after the procedures were all minor, mostly intestinal bleeding, manifested as mild and self-limited melena. No patient died during follow-up.

Some questions that arise in our work team from the implementation of this new treatment include:

How long will the benefits of embolization last in each patient, taking into account that the same hemodynamic conditions will be maintained over time?

When is the right time to discontinue medical treatment instituted since the diagnosis of PLE?

When is the optimal time to perform embolization, and will the earlier the procedure is performed, the better the results?

Is it necessary to implement additional routine

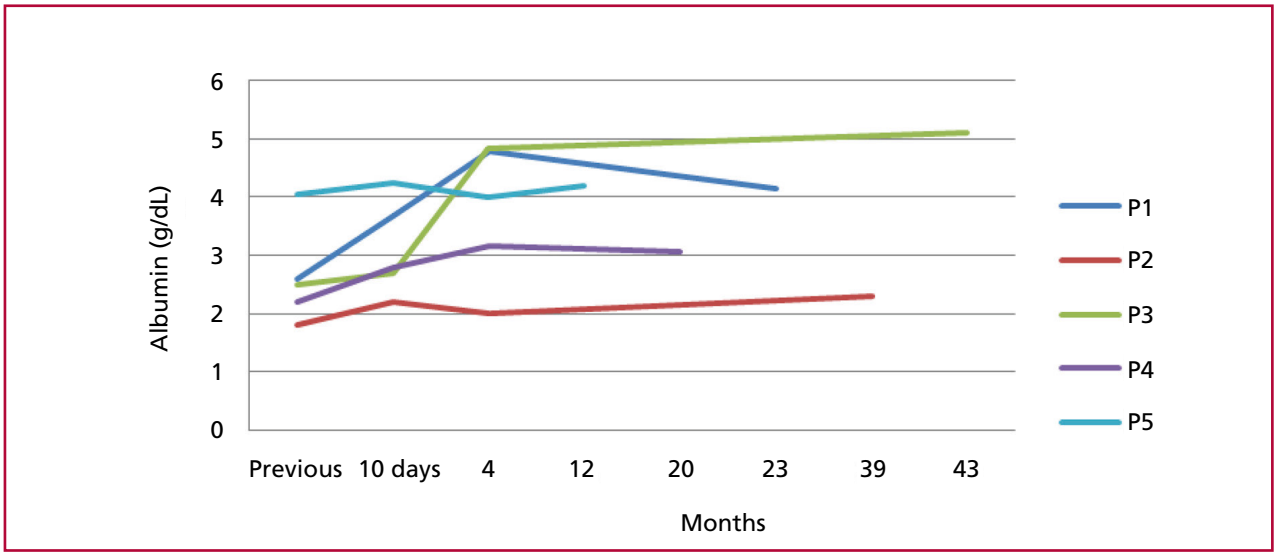

Fig. 2. Albumin values during follow up

lymphography during follow-up to evaluate persistent or newly established lymphatic connections?

When is the right time to evaluate a patient as a candidate for cardiac transplantation?

Limitations

Due to the low incidence rate of PLE in FS and the novelty of the proposed technique, the number of patients treated in our series was limited, leaving the answers to these questions unanswered.

CONCLUSIONS

Protein-losing enteropathy is a devastating complication in patients with Fontan circulation with great impact on quality of life and survival. Magnetic resonance imaging mapping and/or catheterization lymphography were key to delineate the lymphatic anatomy, lymphatic flow pattern and plan an interventional approach for embolization.

Although sample size was small, the results obtained in terms of increased serum albumin levels, clinical improvement and safety of the procedure were promising for patients with this complication. Larger scale studies will be necessary to define the long-term outcome.

Conflicts of interest

None declared.

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

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OPINION ARTICLE

Aortic Stenosis and Transcatheter Aortic Valve Replacement: A Real or Illusory Shift in the Landscape?

Estenosis aórtica y reemplazo valvular endovascular: cambio del escenario, ¿real o ficticio?

ARTURO CAGIDE[1, MTSAC], MARIANO FALCONI[1, MTSAC]

Two recently reported clinical trials aimed to address clinically relevant questions.

Their conceptual foundations were as follows:

a) The increase in afterload caused by aortic stenosis (AS), even moderate, may worsen left ventricular function. In symptomatic patients, transcatheter aortic valve replacement (TAVR) improves the quality of life and the long-term prognosis.
b) Asymptomatic severe AS without a current indication for TAVR tends to progress over a short period of time. In asymptomatic patients, TAVR prevents the onset of symptoms and potential deterioration of ventricular function, allowing the procedure to be performed in better clinical condition.

TAVR UNLOAD trial (1)

Objective

To estimate the probable superiority of TAVR in symptomatic patients with moderate AS and reduced ventricular function in relation to the conservative surveillance strategy and eventual intervention in case of progression to severe AS.

Design

Multicenter (66 centers in the United States, the Netherlands and Austria), controlled (open-label) and randomized study with assignment to TAVR or control arms.

Inclusion criteria

Moderate AS: valve area 1-1.5 cm2. If valve area ≤1 cm2 and suspected low-flow low-gradient at rest, dobutamine stress Doppler echocardiography is used to define the actual area.

Left ventricular ejection fraction (LVEF): 20% to 50%.

Symptoms: functional class (FC) II to IV.

Endpoint

Hierarchical combined endpoint of all-cause death, disabling stroke, heart-failure hospitalization, change from baseline on the Kansas City Cardiomyopathy Questionnaire (to assess patient's quality of life).

Statistics

Win Ratio (WR) with hierarchical endpoint according to the previous order.

Original sample size: 600 patients. There was an extension of the follow-up period due to the study low recruitment rate, which started in January 2017 and ended in December 2022.

Number of patients: 178; 89 in the TAVR arm and 89 in the control arm.

Mean follow-up: 23 months.

Baseline characteristics

Age: 77.4 ± 7.2 years; 20.8% women; Society of Thoracic Surgeons (STS) score: 4.4 ± 3.4; functional class (FC): 95% II/III; coronary artery disease: 76%; implantable cardioverter defibrillator (ICD): 62%; previous stroke: 9%; peripheral vascular disease: 22%; previous heart failure hospitalization: 45%; atrial fibrillation: 25%; frailty: 27%; Kansas score: 55.8 ± 23.1; aortic valve area: 1.2 ± 0.2cm^2; mean transaortic gradient: 21.9 ± 6.8 mmHg; LVEF: 39 ± 9.6%.

Crossover: 43% of the control arm crossed over to the TAVR arm due to progression from moderate to severe AS.

Results

This study did not demonstrate the superiority of TAVR over the control:

- No difference in the primary endpoint: WR 1.31 (95% CI 0.81-1.88), not significant.
- Significant difference in favor of TAVR over the

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Kansas score.
- No difference in mortality, major vascular events, stroke, hospitalization, and other outcomes.
- Feasibility of the procedure and a low complication rate.

Questions raised from the TAVR UNLOAD trial

a) Could the population characteristics have affected the result?

The high rate of associated comorbidities may suggest that the additional prognostic burden arising from the moderate AS is less significant. In symptomatic patients with moderate AS and reduced ventricular function, but a lower burden of comorbidities, the result is likely to differ.

b) What is the methodological question?

Lack of power: high false-negative rate, close to 70%, due to the small sample size.

Change in methodology: as a result, the follow-up period was extended, and due to the low enrollment rate, the statistical analysis was ultimately performed with the available data.

High crossover rate from the control group to the TAVR group

Although the WR is a validated methodology in multiple clinical trials, time-to-event analysis (Cox model) is the standard design in follow-up studies.

c) Why was there such a low enrollment rate?

There are several possible reasons:

The COVID-19 pandemic (although the study inclusion period extended beyond the pandemic itself).

Lack of an adequate referral strategy from low-to-high complexity centers within the study network (as suggested by the authors).

Perhaps for general practitioners, the objective of the study did not raise a clinically valid question, either because this was not appropriate to perform the TAVR, or, conversely, because the it was fully justified.

d) Does the symptomatic improvement reflected by the Kansas score alone justify the superiority of the procedure?

Although data is objective, it has less value because this was an open-label study, which limits the conclusions that can be drawn from it. Moreover, 43% of patients in the control group crossed over to the TAVR arm.

e) Why was crossover to the TAVR are not included in the combined endpoint?

It would not have substantially changed the results: in the control group, the rates of all-cause mortality, stroke and hospitalization were influenced by the patients who ultimately underwent TAVR. Furthermore, the indication for intervention was probably considered a more subjective criterion than the assessment of the functional status using the Kansas score.

f) How can the results of the TAVR UNLOAD trial be translated into clinical practice?

A logical conclusion would be to wait for the results of trials providing solid evidence without methodological flaws. However, from a strictly personal perspective, the clinical approach to managing symptomatic patients with moderate AS and reduced LVEF is unlikely to change. We will return to this point later.

EARLY TAVR trial (2)

Objective

To evaluate whether TAVR is superior to a conservative strategy (clinical surveillance) in patients with asymptomatic severe AS and preserved ventricular function.

Design

Multicenter (75 centers in the United States and Canada), controlled (open-label) and randomized study with assignment to TAVR or control arms.

Inclusion criteria

Age >65 years old.
Severe AS suitable for transfemoral TAVR.
LVEF >50%.
Absence of symptoms (assessed via exercise stress test in more than 90% of cases).

Endpoint

Combined endpoint of all-cause death, stroke, cardiovascular hospitalization (including crossover to TAVR in the control arm).

Statistics

Time to first event (Kaplan Meier, Cox model).

Original sample size: 900 patients. No changes to the original protocol

Number of patients: 901, 455 in the TAVR arm and 466 in the control arm, who were recruited from March 2017 to December 2021.

Mean follow-up: 3.8 years.

Baseline characteristics

Age: 76 ± 6 years; STS score 1.8; 30.9% women; coronary artery disease: 27%; previous stroke: 4.3%; peripheral vascular disease: 6%; possibility of performing exercise stress test: 90%; atrial fibrillation: 15%; aortic valve area: 0.85 ± 0.20 cm2; mean transaortic gradient: 47 ±10 mmHg; LVEF: 67.4 ± 6.6%.

Crossover: No crossover (the procedure in the control arm was included as part of the endpoint).

Results

The TAVR arm was superior to the conservative strategy control (Table 1).
- Significant reduction in the endpoint.
- No difference in mortality or stroke.
- Significant difference in unplanned hospitalization (motivated by the procedure in the control arm).
- 71% of control patients underwent the procedure at 24 months, one third of them due to advanced or severe symptoms.

QUESTIONS RAISED FROM THE EARLY TAVR TRIAL

a) Are there any methodological issues as in the TAVR UNLOAD trial?

Clearly not. As above noted, there was no crossover in the control arm, as the need to undergo TAVR in this arm was a component of the endpoint.

b) If the inclusion criterion was >65 years, why was the mean age 76 years and 95% of patients aged between 70 and 82 years?

This is striking. It is likely that younger patients were not referred because treating physicians usually recommend valve replacement in young patients with severe AS, even if they are asymptomatic.

c) Does the population included in this study differ from that of the TAVR UNLOAD trial?

The difference is evident in terms of comorbidities.

If prognosis is considered as the algebraic sum of the AS severity and the burden of comorbidities, in the TAVR UNLOAD trial it leaned more toward the associated diseases, whereas in the EARLY TAVR trial, it leaned more toward the valve disease itself.

In this study, all-cause mortality was 8.5% over a 47-month follow-up compared to 19% over an average 23-month follow-up in the TAVR UNLOAD trial.

d) How can the results of the study be translated into clinical practice?

The difference in favor of TAVR was driven by the high rate of intervention-related hospitalizations in the control group (86% at 3 years).

In a broader context, this was an open-label trial, in which the decision to perform the procedure was left to the physician's discretion, which, in the absence of differences in mortality, becomes a factor to be considered.

e) Therefore, is it feasible to wait and perform the procedure only upon the onset of symptoms?

In theory, based on the study results, it is feasible to wait, which could be defined as "watchful surveillance" with eventual intervention depending on progression. However, is this a usual strategy in everyday clinical practice? Probably. But in any case, the EARLY TAVR trial merely reinforces a common behavior, even if it is not always explicitly stated.

OVERALL CONCLUSION

It is highly likely that neither study will substantially alter the clinical approach followed in most high-complexity centers. Several factors support this conclusion.

In the presence of symptoms, a mean transvalvular gradient of 20 to 40 mmHg and associated comorbidities, the question often arises as to whether this represents true moderate AS or severe AS with low-flow low-gradient. Although different assessment criteria may be used (dobutamine stress Doppler echocardiography, calcium score, stroke volume), reaching a differential diagnosis is usually challenging.

The second issue concerns whether the symptoms are attributable to the valve disease or to associated comorbidities or, even better, in what proportion both conditions are involved.

Therefore, it is clear that, in the presence of symptoms, both aspects create a favorable scenario for TAVR to be considered a strong option, particularly when procedural risk is low.

A similar situation occurs in asymptomatic severe AS, where close and strict clinical surveillance is inherently challenging for several reasons. The progression of severity may be insidious, and its assessment is often complex due to the inherent variability of the assessment method. Moreover, the frequency of follow-up visits and the progressive limitation of physical activity on medical advice, may negatively impact the patient's lifestyle. In this context, such factors may become more limiting than those experienced after the procedure itself. Of course, a sine qua non condition is that the procedure must be a low-risk.

Although valve replacement for asymptomatic severe AS is not typically advocated at round tables, conferences or expert meetings, the proportion of patients managed with watchful waiting strategy alone may be minimal: when procedural risk is low, TAVR is often proposed at the slightest suspicion of symptoms –sometimes loosely related to the valve disease.

The above considerations are supported by evidence from the literature.

In the TAVR UNLOAD trial, at two years, 32% of patients in the control arm were hospitalized for heart failure. In addition, 43% underwent TAVR. By comparison, only 15% were hospitalized or underwent TAVR over two years in an observational study of patients with moderate AS and ventricular dysfunction. (3)

Similarly, in the EARLY TAVR trial, the likelihood of hospitalization leading to crossover to TAVR in the control arm was 71% at two years, significantly higher than that reported in an observational study by the Mayo Clinic (622 patients with asymptomatic severe AS), where only 33% developed symptoms or underwent the procedure. (4)

Taken together, these findings suggest that, in these trials, disease progression in the control arm was interrupted by the procedure in a much higher proportion than previously observed in observational studies. This may have influenced the results of the TAVR UNLOAD and EARLY TAVR trials.

It worth noting that in both studies, TAVR proved to be very safe –with no intraprocedural mortality and a low rate of serious complications– even in the higher-risk TAVR UNLOAD population. This is a key aspect, as physicians must consider procedural risk when making clinical decisions. The findings of both studies rely on the availability of a highly safe procedure. If the procedure risks were higher, the results and conclusions would likely differ significantly.

Another relevant aspect, particularly in the EARLY TAVR trial, is the relative safety of the close clinical surveillance strategy. Patients did not experience

Table 1. Primary endpoints of EARLY TAVR trial. Modified from (2)

Primary Endpoint	TAVR	Control	HR (95% CI)	p-value
Combined (%)	122 (26.8)	202 (45.3)	0.50 (0.40-0.63)	<0.001
Death (%)	38 (8.4)	41 (9.2)	0.93 (0.60-1.44)	-
Stroke (%)	19 (4.2)	30 (6.7)	0.62 (0.35-1.10)	-
Unplanned CV hospitalization (%)	95 (20.9)	186 (41.7)	0.43 (0.33-0.55)	-

CV, cardiovascular; HR, hazard ratio; 95% CI, 95% confidence interval; TAVR, transcatheter aortic valve replacement.

serious events; the main "consequences" were clinical progression, unscheduled hospitalizations or some deterioration in echocardiographic parameters. In other words, if access to a very low-risk TAVR is not available, the strategy of close clinical surveillance seems to be a good option –provided it includes frequent clinical follow-up visits, echocardiographic assessments and regular stress testing.

It is possible that, in the medium term, clinical practice guidelines will include this procedure in these patients as a Class IIa recommendation, provided that both the patient's risk profile and the center's outcomes ensure a very high probability of success in percutaneous implantation, with a very low rate of complications.

In conclusion, regardless of the results of both studies, it is likely that a significant proportion of symptomatic patients with moderate AS and ventricular dysfunction will continue to be referred for TAVR, just as occurs in cases of severe AS –even in the absence of symptoms. Those who choose clinical surveillance should implement it systematically and according to protocol in order to identify potential patients who may experience disease progression.

Conflicts of interest

None declared.
(See authors' conflict of interests forms on the web/Additional material).

Ethical considerations

Not applicable.

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Carcinoid Heart Disease with Double Valve Involvement Assessed by Multimodality Imaging

Enfermedad carcinoide cardíaca doble valvular valorada con imágenes multimodales

WALTER ALUSTIZA[1, MTSAC], JULIO BISUTTI[1], MARÍA P. MARTURANO[1, MTSAC], JAVIER VENTRICI[1]

We report the case of a 69-year-old female patient with a history of neuroendocrine tumor of the colon with liver metastases and episodic diarrhea. She completed chemotherapy with everolimus and sunitinib. During follow-up, she presented with 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) levels of 136 mg (normal value: 2-8 mg) and plasma chromogranin levels of 241 ng/mL (normal value: 19-98 ng/mL). The patient was admitted due to FC IV dyspnea, edematous syndrome and fatigue lasting more than one month. On physical examination the liver was enlarged, and ascites was present.

On transthoracic color-Doppler echocardiography (TTE), the left ventricular (LV) and right ventricular (RV) diameters and wall thickness were preserved. There was global LV hypokinesia and the ejection fraction (EF) was 36%. The left atrium was mildly dilated and the right atrium exhibited marked dilatation. The mitral valve had moderate regurgitation. The tricuspid valve leaflets were thickened, presented increased refringence suggestive of fibrosis with reduced opening and there was low implantation of the valvular plane with moderate regurgitation. The estimated systolic pulmonary artery pressure was 55 mm Hg and there was severe pulmonary valve regurgitation and an atrial septal aneurysm 2 L of the Olivares Reyes classification (Figure 1 A and B).

The transesophageal echocardiography (TEE) revealed increased transvalvular gradient across the tricuspid valve and thickening of the tricuspid subvalvular apparatus. The pulmonary valve was thickened, flail and retracted, lacking valve leaflet coaptation, and had increased velocities with severe regurgitation (Figure 2).

On cardiac magnetic resonance imaging (MRI) LV end-diastolic volume (EDV) was 32mL/m^2, end-systolic volume (ESV) was 22 mL/m^2 and the EF was 32%, with global hypokinesia and LV mass of 42 g/m^2. Right ventricular EDV was 34ml/m^2, ESV was 15 mL/m^2 and the EF was 65%. The left atrial volume was 65 mL and the right atrial volume was 75 mL. The LV walls presented intramyocardial edema in IR T2 and Triple IR sequences (Figure 1 C). The IR sequences showed non-ischemic gadolinium enhancement in the LV, with linear septal intramyocardial and epicardial distribution, and in the RV insertion zone, both atria, mitral valve and tricuspid valve.

Multimodality imaging exhibited findings suggestive of carcinoid heart disease, with involvement of both the tricuspid and pulmonary valves in a patient with ventricular dysfunction undergoing chemotherapy.

Carcinoid tumors are rare, with an incidence between 1.2 to 2.1 per 100 000 in the general population. Carcinoid heart disease occurs in about one third of patients with carcinoid tumors (particularly ileal carcinoid) with liver metastases and may be the initial manifestation. Cardiac involvement is characterized by the presence of an endocardial plaque comprised of fibrous tissue, resulting in valvular thickening and regurgitation. This carcinoid plaque is composed of muscle cells, myofibroblasts, extracellular matrix and an overlying endothelial cell layer. These deposits occur most commonly in the endocardium of the valve cusps. (1) Left-sided heart involvement does not occur in these patients, except in those with bronchial carcinoid or right-to-left shunts.

The most common finding on TTE is tricuspid valve involvement in approximately 90% of cases, with severe regurgitation and mild or moderate stenosis. The pulmonary valve is also commonly affected (50 to 69%) and shows similar changes in valve regurgitation or stenosis. (2) TEE allows for high-resolution images of the tricuspid valve with the fixed triangular orifice and thickened subvalvular apparatus. The use of multiplanar reconstruction (MPR) for planimetry of the tricuspid valve area in systole and diastole provides a quantitative measure of tricuspid regurgitation and tricuspid stenosis, presenting opportunities for the evaluation and monitoring of disease severity and progression. (3)

When TTE is anatomically inconclusive, cardiac

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Fig. 1. A. Three-dimensional transthoracic echocardiogram (TTE) images of the stenotic tricuspid valve from the right ventricular view. The septal leaflet is thickened, adhered to the interventricular septum and fused with the posterior leaflet. The anterior leaflet is significantly thickened.
B. Top: Two-dimensional echocardiography images in the apical 4-chamber (4C) view showing thickened tricuspid valve with reduced valve opening. Bottom: Three-dimensional echocardiography images in the apical 4C view showing thickened tricuspid valve with reduced valve opening.
C. Cardiac magnetic resonance imaging (MRI). Fast imaging employing steady-state acquisition (FIESTA). Tricuspid valve stenosis is observed in the short-axis sequence and four-chamber sequence.

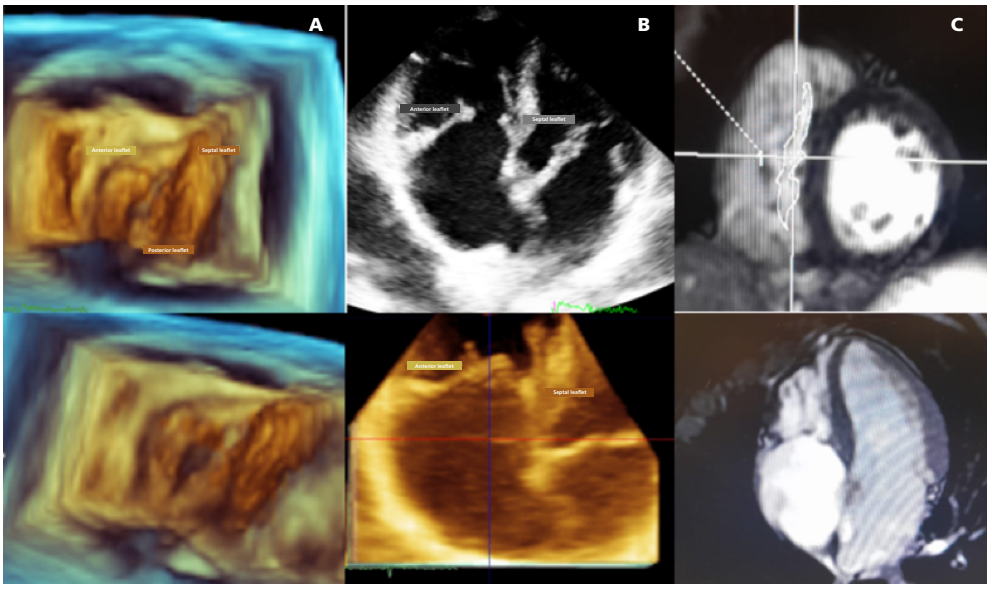
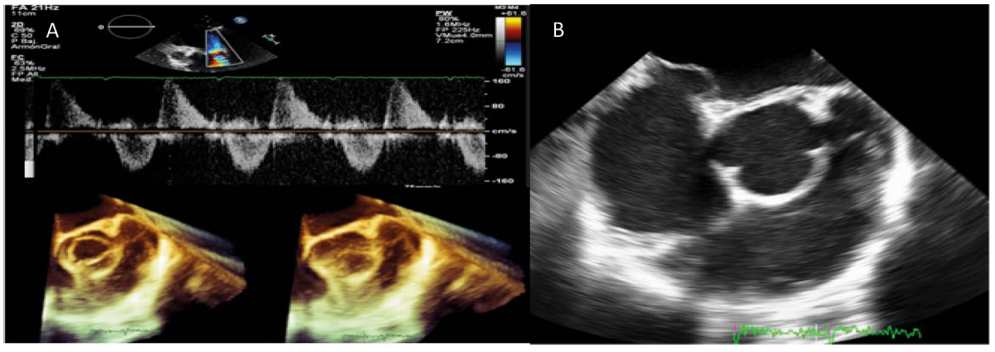


Fig. 2. A. Transesophageal echocardiography (TEE) with color-Doppler imaging of the pulmonary valve with increased transvalvular gradient and severe regurgitation. Three-dimensional TEE images showing a thickened and retracted pulmonary valve in systole and diastole. B. M-mode image of the pulmonary valve by transthoracic Doppler echocardiography at the level of the great vessels. The pulmonary valve is thickened and retracted.



MRI and/or CT scan may be performed.

Cardiac MRI is useful for risk stratification prior to treatment, surveillance, diagnosis and follow-up of cardiotoxic therapy, long-term effects, screening after treatment completion, and evaluation and follow-up of cardiac masses and infiltration. It also identifies the presence of myocardial edema, inflammation, and global and focal fibrosis. (4-5)

This patient is currently under joint evaluation with the Department of Oncology to assess the therapeutic course of action in the new scenario where double valve replacement surgery has been proposed as an effective strategy. (6)

Conflicts of interest

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

Ethical considerations

Not applicable.

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SCIENTIFIC LETTER

Recurrent Acute Myocardial Infarction in a Patient with Renal Cell Carcinoma Treated with Pembrolizumab

Infarto agudo de miocardio recurrente en una paciente con cáncer de riñón tratada con pembrolizumab

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The immune system plays an essential role in defending the body against pathogens and cancer cells. One of the strategies that are employed in order to prevent an excessive and harmful immune response to healthy tissues is regulation through immune checkpoints. The introduction of immune checkpoint inhibitors (ICIs) has resulted in a significant therapeutic breakthrough against cancer. These drugs are monoclonal antibodies that block inhibitory receptors expressed on T cells, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) or its ligand (PDL-1). As a result of this blocking, antitumor immunity is restored. (1) Immune checkpoint inhibitors have transformed the therapeutic paradigm for numerous tumors. These agents, whether administered as monotherapy or in combination with other drugs, including chemotherapy, targeted therapies, and ICI-ICI combinations, have yielded benefits that were previously unattainable for patients with advanced tumors that were resistant to other treatments.

These drugs can cause immune-mediated adverse effects in any organ of the body. Myocarditis is the most feared cardiovascular complication due to its high mortality; however, cases of non-inflammatory ventricular dysfunction, Takotsubo syndrome, pericarditis, conduction disorders and arrhythmias have also been reported. (2) A less common complication is acute myocardial infarction (AMI) due to thrombotic occlusion of an epicardial vessel (1%-3%).

We report the case of a 58-year-old female patient with a history of hypertension, morbid obesity, metabolic syndrome, nephrectomy and left adrenalectomy due to clear cell renal cell carcinoma and pulmonary metastases, who initiated a combination chemotherapy regimen with axitinib (an antiangiogenic drug) 5 mg twice daily and pembrolizumab (an anti-PD-1) every 21 days.

Five hours after receiving the seventh dose of pembrolizumab, the patients experienced a 15-minute episode of angina, which recurred at 24 and 72 hours. She presented to the cardiology clinic 12 days after the first episode, asymptomatic and with normal blood pressure, with no ST-segment abnormalities or changes relative to the electrocardiogram recorded one year earlier. On echocardiogram, the left ventricular ejection fraction was 70% and regional wall motion was normal. Hospitalization was decided because high-sensitivity troponin T level was 45.5 ng/L (VN up to 14 ng/L).

Fifteen hours after admission, the patient reported symptoms of angina and presented ST-segment elevation in the inferior and anterior leads (Figure 1 A). The coronary angiography revealed a sub-occlusion in the mid left anterior descending (LAD) coronary artery (Figure 2 A), and a non-significant stenosis in the proximal left circumflex artery (Figure 2 B). A drug-eluting stent was implanted in the LAD coronary artery with final TIMI 3 flow (Figure 2 C). The patient's progression was free from complications and she was discharged with dual antiplatelet therapy (aspirin and clopidogrel), carvedilol, valsartan, hydrochlorothiazide, amlodipine and rosuvastatin.

The oncologists decided to discontinue axitinib therapy and continue with pembrolizumab. The eighth dose was administered 35 days after the acute coronary syndrome (ACS). Ten days later, the patient exhibited an episode of angina with ST-segment de-

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Fig. 1. 12-lead electrocardiograms. **A.** First acute coronary syndrome. ST-segment elevation in leads DII, DIII, aVF, V4-V6. **B.** Second acute coronary syndrome. ST-segment depression in leads DI, V4-V6.

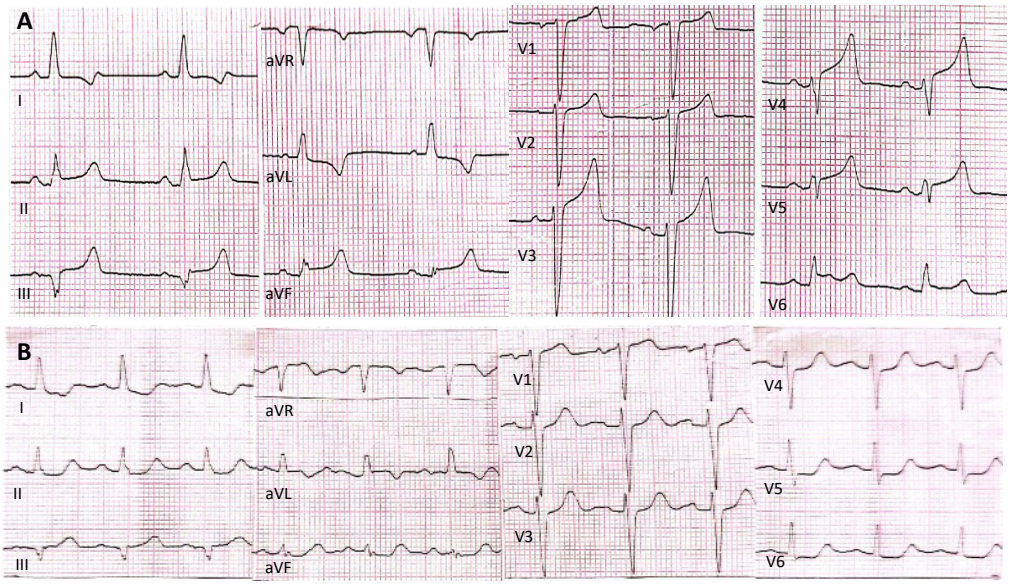
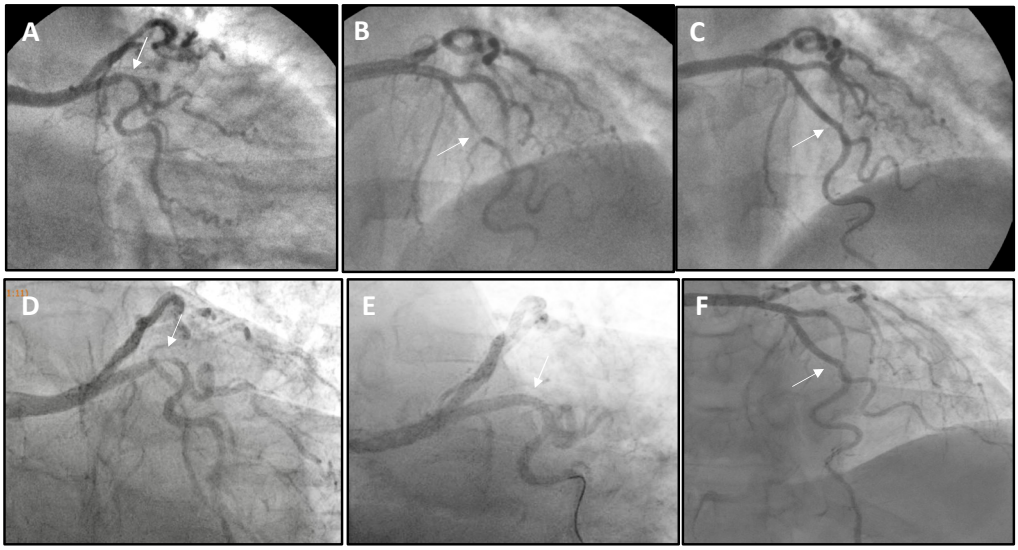


Fig. 2. Top: coronary angiography during the first acute coronary syndrome. **A.** Non-significant stenosis in the proximal left circumflex artery. **B.** Sub-occlusion in the mid left anterior descending coronary artery. **C.** Result after percutaneous coronary intervention with stent implant in the left anterior descending coronary artery. Bottom: coronary angiography during the second acute coronary syndrome. **D.** Significant stenosis in the proximal left circumflex coronary artery. **E.** Result after percutaneous coronary intervention with implantation of two stents in the left circumflex coronary artery. **F.** The stent in the left anterior descending coronary artery is patent.



pression in DI and from V3 to V6, accompanied by increased troponin levels (Figure 1B). Coronary angiography showed a severe stenosis in the proximal left circumflex artery (Figure 2 D) and the stent of the LAD was found to be patent (Figure 2 E). Two drug-eluting stents were successfully implanted in the left circumflex artery (Figure 2 F). The patient evolved with favorable outcome and was discharged with aspirin, clopidogrel, bisoprolol, valsartan, rosuvastatin and ezetimibe.

There is evidence suggesting that ICIs can aggravate pre-existing inflammatory diseases. Atheroscle-

rosis is a chronic vascular disease with an important inflammatory component and T cells play a key role in its initiation and progression. Immune checkpoints play a key role as negative regulators of the atherosclerotic process so their inhibition could accelerate its development. (3) Experimental studies have demonstrated that ICI treatment accelerates the progression of atherosclerosis and the formation of plaques with larger necrotic cores. A meta-analysis of 63 studies with 32 518 patients treated with ICIs showed a significant 1.51-fold increased risk of AMI and a 1.56-fold increased risk of ischemic stroke compared to the control group. (4) Atherothrombotic adverse events related to the use of ICIs occur more frequently during the first 6 months of treatment suggesting a potential destabilization of pre-existing atherosclerotic plaques.

There have been isolated case reports of an association between ICIs and ACS. Nevertheless, it is difficult to establish a cause-and-effect relationship. (5) Patients with active cancer have higher risk of developing arterial thrombosis and ischemic events particularly during the first year after diagnosis, in cases of advanced cancer and during active cancer treatment, and associated with coexistent cardiovascular risk factors, prothrombotic and inflammatory effect of the neoplasm and vascular toxic effects of cancer treatments.

In our patient, the first ACS was attributed to the use of axitinib because thromboembolic complications are more common than with ICIs. However, the rapid recurrence of ACS, involving a coronary artery that previously had a non-significant stenosis, and the temporal relationship with the administration of pembrolizumab suggest a causal link between ICI administration and ACS, a rare complication that necessitates the definitive discontinuation of treatment.

There is no evidence on the use of high doses of corticosteroids (methylprednisolone 1 g/day for 3-5 days followed by a dose reduction over 6 weeks) as recommended for other grade 3-4 adverse events (myocarditis, diarrhea or hepatitis), (6) although its empirical use has been reported in some publications on cases with ACS associated with treatment with ICIs. (5) In our case, we did not use corticosteroids.

This rare adverse effect should be suspected in cancer patients treated with ICIs.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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SCIENTIFIC LETTER

Genetics in Argentina: Identification of a New Variant Associated with Pulmonary Arterial Hypertension

Genética en Argentina: identificación de una nueva variante asociada con hipertensión arterial pulmonar

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Research on hereditary predisposition to pulmonary arterial hypertension (PAH) has led to the identification of variants in the gene encoding the bone morphogenetic protein receptor type II (*BMPR2*). About 70 to 80% of cases with hereditary PAH (HPAH) and up to 40% of idiopathic cases (IPAH) are caused by genetic variants in *BMPR2*. (1)

More than 800 different variants have been described; however, the penetrance is reduced, since only 20 to 30% of carriers develop PAH. The latter suggests the contribution of other genetic, epigenetic, environmental and hormonal factors in the modulation and development of the disease (2-4).

Bone morphogenetic protein receptor type II is part of one of the two major signaling pathways that make up the transforming growth factor-β (TGF-β) superfamily: the bone morphogenetic protein (BMP)-growth differentiation factor (GDF) pathway. Cross-communication between this pathway and its counterpart, the TGF-β-activin-nodal pathway, plays a central role in numerous cellular processes that regulate cell proliferation and differentiation. (5)

Variants in *BMPR2* result in reduced expression of the functional protein, which alters BMP signal transduction, often together with an increased activin-mediated response. This imbalance is now known to contribute to the pathogenesis of PAH by generating endothelial cell dysfunction, as well as proliferation, resistance to apoptosis, and contraction of pulmonary vascular smooth muscle cells. These mechanisms result in increased pulmonary vascular resistances, increased pulmonary arterial pressure and consequent right ventricular remodeling. The loss of balance between the BMP-GDF and TGF-β-activin-nodal pathways is currently considered the main molecular defect with a critical role in the predisposition and progression of PAH, as well as a novel therapeutic target. (6)

We present the case of a 31-year-old woman, with no medical history, who was admitted to the emergency room of the Fundación Favaloro University Hospital with progressive dyspnea as the main symptom. Initial evaluation included a chest angiotomography that ruled out acute pulmonary thromboembolism and a Doppler echocardiogram that showed findings suggestive of pulmonary hypertension (PH): tricuspid regurgitation velocity of 4.02 m/s and right ventricular systolic dysfunction. Further evaluation of PH included pulmonary function tests, pulmonary ventilation-perfusion scintigraphy, liver function tests, viral serologies and collagenogram, with results within normal parameters. In the 6-minute walk test, the distance covered was 420 m (59% of the predicted value), with desaturation (from 96% to 86%). Based on these results, a right heart catheterization was performed, which showed mean pulmonary artery pressure of 52 mmHg; pulmonary artery wedge pressure of 6 mmHg; mean right atrial pressure of 2 mmHg; cardiac output of 4.3 L/min; cardiac index of 2.95 L/min/m^2 and pulmonary vascular resistance of 11 Wood units. The diagnosis of IPAH was reached and specific treatment was started with double therapy: tadalafil 40 mg/day and ambrisentan 10 mg/day.

Genetic testing by whole-exome sequencing and

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*Clarification of shared authorship: Drs. María J. Banchio Dal Bó and María B. Fontecha share first authorship..

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subsequent bioinformatic analysis was performed at the Pharmacogenomics Laboratory of the Institute of Experimental Medicine (IMEX). A new heterozygous variant was detected in the BMPR2 gene: NM_001204.7:c.663del (p.Leu222Trpfs*8) located in exon 6. Confirmation was performed by polymerase chain reaction (PCR) and Sanger sequencing. The variant consists of a cytosine deletion at position 663 that induces a change in the reading frame and the replacement of leucine by tryptophan at codon 222. This generates a premature termination codon 8 triplets later (Figure 1) leading to the synthesis of a shorter BMPR2 protein, with loss of function. Classification of the variant was performed according to the recommendations of the American College of Medical Genetics and Genomics. It was determined that this variant was not previously described in the general population or in patients with PAH. Based on the analysis performed, it was classified as a probably pathogenic variant.

With the results obtained and following current international recommendations, clinical and genetic evaluation of first-degree relatives was initiated. A direct molecular study of the variant was performed by PCR amplification of exon 6 and Sanger sequencing in both parents. The patient's father, who also reported compatible signs and symptoms at the time of interrogation, was diagnosed with PAH, which was also positive in the genetic test. The diagnosis of PAH in the father and the detection of the c.663del variant confirmed the familial segregation (Figure 2) and supports the reclassification of this variant as pathogenic. Thus, the diagnosis of both patients as carriers of HPAH was modified.

The data obtained indicate that c.663del is a causal variant of PAH unknown until now and also the first *BMPR2* variant reported in Argentina. The identification of this variant allowed us to confirm the molecular diagnosis of hereditary disease, of importance both for the clinical and therapeutic management and for the genetic counseling of the patient and her relatives.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

The study was approved by the institutional ethics committees of the participating centers, in accordance with current national and international ethical guidelines.

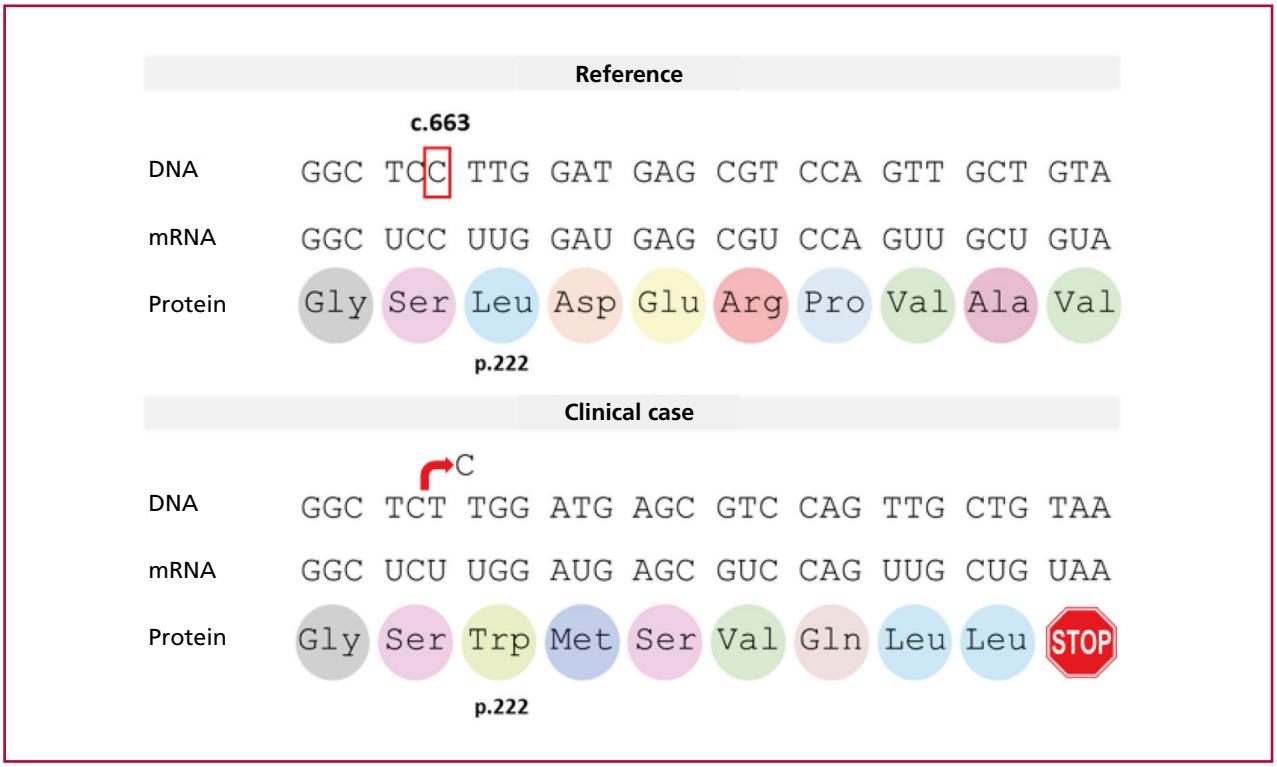
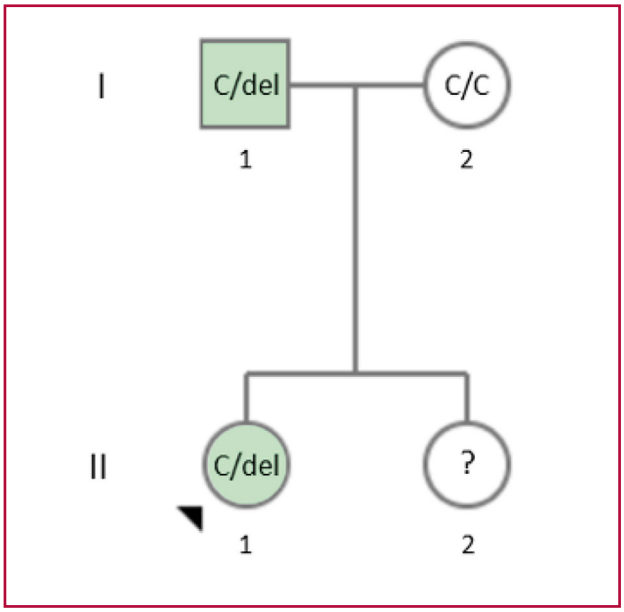


Fig. 1. Analysis of the c.663del variant in the *BMPR2* gene. DNA, mRNA and protein sequences are compared between the case and the reference. The case shows the deletion of one cytosine (C) in the 663 nucleotide (red arrow), which causes a frameshift and results in a premature stop codon (STOP). The BMPR2 reference sequence are: NG_009363.1 (gene), NM_001204.7 (transcript) and NP_001195.2 (protein)



C: Cytosin; del: deletion.

Fig. 2. Pedigree of the patient with the c.663del variant. The relatives diagnosed with PAH are identified in green. The variant was found in heterozygosity in the index case and her father (C/del). The mother´s genotype was C/C and hence does not present the variant, while the sister has not been studied yet.

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SCIENTIFIC LETTER

Results of Conventional and EVAR Abdominal Aortic Aneurysm Repair

Resultados de la reparación de aneurisma de aorta abdominal convencional y EVAR

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Abdominal aortic aneurysm (AAA) is defined as a 30-mm diameter or greater dilation of the aorta at the abdominal level, exhibiting a prevalence of 1.5%-5.9% in people aged 50 years or older, and even higher in smokers. In addition to smoking, it is associated with risk factors such as atherosclerosis, hypertension and dyslipidemia. (1)

The introduction of endovascular techniques for the repair of ruptured AAAs has emerged as an alternative to conventional open surgery and is now considered the first option in cases with favorable anatomy. (1)

The aim of our study was to analyze the results in the management of patients with asymptomatic and complicated AAA in our center, comparing conventional surgery with endovascular aneurysm repair (EVAR).

We conducted a descriptive and retrospective study of 45 patients with a diagnosis of asymptomatic or complicated AAA presenting with vital signs (palpable peripheral pulses, detectable blood pressure or audible heart sounds), who underwent surgery at Hospital Italiano de Córdoba between January 2016 and November 2020. Follow-up was extended to 5 years after hospital discharge. Statistical analysis was performed with InfoStat® version 2016e. Student's t-test and the chi-square test were used for the analysis of significant differences, considering $p < 0.05$ as level of significance.

Thirty-five men and 10 women aged between 51 and 85 years, with average age of 73.3 years, were included in the study. A high proportion of patients had risk factors and concomitant diseases: hypertension in 39, smoking in 40, ischemic heart disease in 10 and obstructive pulmonary disease in 8.

Of the 45 patients operated on, 25 (55.5%) were asymptomatic and 20 (44.4%) had complicated or ruptured aneurysm. Conventional surgery was used in 27 (60%) and EVAR in 18 (40%).

Among the 25 asymptomatic aneurysms, 8 (32%) were repaired conventionally and 17 (68%) by EVAR. In the case of the 20 complicated aneurysms, 19 (95%) were repaired with conventional surgery and 1 (5%) by EVAR (this only repaired patient in the complicated group because of a previous endoleak.).

The type of clinical presentation was an important factor for choosing the type of surgery: conventional surgery was performed in 8 asymptomatic and 19 complicated patients, and EVAR in 17 asymptomatic patients and only in 1complicated patient ($p < 0.0001$).

Mean AAA diameter differed significantly between asymptomatic and complicated (ruptured) cases: 66.16 mm vs 82.4 mm ($p=0.0061$).

Hospital length of stay was also significantly different: 9.6 ± 9 days for conventional surgery versus 2.7 ± 1 for EVAR ($p<0.001$). This logically had its correlation with the different length of hospitalization according to the admission condition, with means of 3.6 days in asymptomatic patients and 11.7 days in complicated patients.

Overall mortality of the series of 45 patients was 33.3% (n=15). Among the 25 asymptomatic patients there were 2 deaths (8%), none in the 17 patients with EVAR vs. 2 among the 8 patients with conventional surgery, $p=0.093$. Among the 20 complicated patients there were 13 deaths ($p < 0.001$ versus asymptomatic ones), all among the 19 patients who underwent conventional surgery. The 2 patients who died among the elective patients were due to sepsis, and almost half of the deaths among the complicated patients were due to multiple organ failure.

When comparing the 60-month long-term survival with conventional surgery vs. EVAR in discharged patients, no significant difference was observed (92.6% vs. 88.9%, $p=0.587$).

The results of the present analysis show a higher incidence of interventions in the male sex and at an advanced age, which coincides with the literature

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consulted. Age is usually considered an important risk factor in all the reported experiences. However, there is sufficient evidence that morbidity and mortality depend in part on predictable, modifiable or controllable factors. Coinciding with the fact that most of the patients included in the sample were over the sixth decade of life, more than half of them had several associated comorbidities. Evidence of the association between smoking and AAA was first provided by the Framingham study in 1967. Other studies also showed similar results, where smoking and hypertension increased the risk of having an aortic aneurysm by 30-40% and 70-80%, respectively. (2)

The type of clinical presentation was an important element in choosing the type of repair. In most studies, hemodynamic instability is one of the exclusion criteria for EVAR: patients undergo immediate conventional or open surgery because the necessary studies to plan EVAR cannot be performed. However, these adverse factors can be overcome by following an appropriate protocol that employs the use of a hypotensive hemostatic approach and transfemoral aortic balloon occlusion technique. (3)

Recent publications show that small AAA can be observed periodically, with strict clinical controls, without a higher rupture rate if those that present accelerated growth or reach a diameter equal to or greater than 5.5 cm are operated on. In the present series, the average size of AAA in asymptomatic operated patients was 6.6 cm, and in complicated patients 8.2 cm, which reveals a conservative attitude in the surgical indication.

Beyond the risk imposed by the disease, surgical intervention per se significantly influences perioperative risk, related to underlying complications and stress associated with tissue injury; treatment by EVAR is less aggressive and this is reflected by shorter hospital stay. In our registry, hospitalization was shorter in asymptomatic than in complicated patients, and longer in both cases with conventional treatment, similar to what has been described in other national registries. (4)

The postoperative mortality of complicated AAA is reported to be approximately 30-50%. In our study overall mortality was 33.3%. Despite our small sample size, we can agree with the meta-analysis of Qin et al, (5) which demonstrated significant differences in favor of EVAR in terms of mortality in the first 30 days after surgery.

With respect to asymptomatic aneurysms, we obtained 8% mortality with conventional surgery and 0% in the case of EVAR, similar to that reported by large studies where endovascular treatment decreased in-hospital mortality, as for example in the EVAR study, where mortality was 1.8% with endovascular surgery and 4.3% with conventional surgery. (6)

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable.

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SCIENTIFIC LETTER

Observational Analysis of Patients with Infective Endocarditis Managed with a Multidisciplinary Approach

Análisis observacional de pacientes con endocarditis infecciosa abordados multidisciplinariamente

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Currently, the mortality rate due to infective endocarditis (IE) remains high, with an incidence of 25.5% in our country, as reported by the EIRA III registry. This percentage applies to both medically and surgically treated patients. (1)

The indication for surgery in IE is usually reserved for patients with heart failure (HF), refractory sepsis, embolism prevention or complications such as abscess or fistula. All these situations are associated with high clinical risk. (2) The percentage of patients undergoing surgical treatment in the acute phase is close to 30%; however, a non-negligible percentage undergo surgery during follow-up. (3) Early surgical intervention may offer benefits that surpass those of conservative medical treatment. (4) We decided to evaluate the results in our population with both treatments. For this purpose, we used a comprehensive criterion based on the clinical, surgical and imaging findings to determine the characteristics of the population of patients with active IE, the rate of complications and treatment outcomes, considering early surgery when it was indicated.

We conducted a single-center retrospective cohort study in a high-complexity hospital center. We included patients > 18 years admitted with a diagnosis of IE according to modified Duke criteria between March 2012 and January 2020. All patients were managed by a multidisciplinary team made up of cardiologists, internists, infectious disease specialists, imaging specialists, and cardiovascular surgeons ("IE team").

The following criteria were considered an indication for surgery: fungal endocarditis, endocarditis associated with implantable catheters with a definite diagnosis of vegetation, new acute severe aortic or mitral regurgitation, HF, high pure embolic risk or associated with another criterion, perivalvular extension or persistent sepsis without extravalvular focus. For patients with high surgical risk, the indication for surgery was determined by the "IE team." Early surgery was defined as a procedure that was performed during hospitalization with < 7 days after the diagnosis was made. The risk was assessed using global surgical risk scores (EUROSCORE II) and specific scores for IE surgery (RISKE). The study was approved by the institutional review board of Hospital Universitario Austral.

A total of 64 patients with a diagnosis of acute IE were included. In total, 45.3% (n = 29) of the subjects received exclusive medical treatment (MT), while 54.7% (n = 35) received surgical treatment (ST). The early surgery rate was 68.5%. Of the 29 patients with MT, 23 (79%) presented valve involvement: 14 in the aortic valve and 9 in the mitral valve. Among the 35 patients with ST, 28 (80%) had valve involvement: 17 in the aortic valve and 11 in the mitral valve. Valve replacement with mechanical prostheses was more common (47.1%) in the ST group. In the mitral valve group, while mechanical valve replacements were prevalent (45.5%), a significant number of valve repairs (36.4%) were also performed. A special section should be considered for the removal of leads and stimulation devices, which accounted for a total of 9 cases, representing 25.7% of the total number of surgical procedures.

Thirty-one patients (48.4%) exhibited a clinical event on initial presentation. The most common complications were embolism (n = 11), predominantly peripheral, HF (n = 10) and acute renal failure (n = 4).

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The main indications for ST were extravalvular involvement/persistent sepsis in 12 patients, HF in 11 and risk of embolism in 7.

In patients undergoing surgery, the overall results of EUROSCORE II and RISKE preformed for preoperative risk assessment were 18.7 and 24.3, respectively.

Of the 35 patients who underwent surgery, 11 developed postoperative complications; of these, vasoplegic shock was the most common, occurring in 3 patients. Total mortality was 4.7% (n = 3, 2 patients with MT and 1 with ST).

There were no significant differences in the baseline characteristics between patients with IE in the MT group and those in the ST group, except for age, with a higher incidence of young patients in the ST group. This could indicate a selection in the ST group, with a direct impact on the results. The percentage of mechanical valve replacements was high due to the significant number of young patients. Regarding the surgical approach employed in mitral valve surgery, a significant proportion of patients underwent mitral valve repair, as is currently recommended in the literature. (5)

Despite the rate of complications was around 30%, total mortality rate among patients diagnosed with IE and treated at our institution using an interdisciplinary approach was 4.7%, even when most patients (54%) underwent cardiovascular surgery.

The operative mortality of 2.9% is well below the average mortality of 15-20% published in the literature (1) and below the predicted mortality assessed by the current risk scores.

These results reflect the need for a multidisciplinary approach in patients with IE, considering early surgery as a feasible alternative in patients with IE in teams with low operative mortality. (6) Additionally, the study calls for a modification of scores in high complexity centers.

It is necessary to increase the number of patients in order to determine whether the findings are consistent with those published for the overall population.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable.

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"Doctor, Should I Be Worried About This?"

"Doctor, ¿Me tengo que preocupar por esto?"

LUCIANO BATTIONI[1, MTSAC]

If we could differentiate the universal goals of the medical sciences, we might conclude that there are three: diagnosis, prognosis, and treatment.

Their relative importance differs between patients and doctors. The question I have chosen to title this letter is probably the most important to the patient. However, it is the one that has received the least scientific and technical development.

In daily practice we use prognostic tools consistently and even dogmatically. In fact, many times we try to use scores generated to predict an event X in one population and extrapolate them to an event Y in another. (1) Most of these tools have areas under the ROC curve ranging from 0.60 to 0.85. (2,3) If we offered someone these tools to detect fraudulent banking transactions, they would quickly shake our hand and show us the way out.

This poor current predictive performance is due not only to multiple limitations and difficulties associated with healthcare data management, but also to the tools that have been used so far. In the work entitled Events Prediction Ability in Patients with Hypertension using Artificial Neural Network Analysis of Ambulatory Blood Pressure Monitoring Compared to Clinical Risk Stratification, Di Gennaro et al. developed a simple neural network model capable of predicting what will happen to our patients more accurately. (4)

Beyond the limitations acknowledged by the authors, it is worth highlighting what this work represents: the introduction of Artificial Intelligence (AI) tools into clinical practice. The integration of AI into medicine will change our practice in ways we cannot yet imagine. By integrating multiple variables, creating ones that we did not know existed or linking facts that elude human analysis, we will be able to provide precision medicine. (5)

But not all that glitters is gold. For example, neural networks tend to overfit, i.e. they have high internal validity, but when validated in external cohorts their performance can drop significantly.

To conclude, this work represents one of the first instances of using AI tools in medicine at a national level and, despite its design limitations, it gives us a very small sample of what this integration could represent and encourages us to continue research in this area.

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 would like to thank Dr. Luciano Battioni for his accurate and enriching comments on our work entitled Events Prediction Ability in Patients with Hypertension using Artificial Neural Network Analysis

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of Ambulatory Blood Pressure Monitoring Compared to Clinical Risk Stratification. We agree that, while classical risk stratification models are used in the development of risk stratification models, the incorporation of new methodological tools, such as the analysis using artificial neural networks represents an opportunity that would allow us to optimize the diagnostic and prognostic accuracy of different variables, such as those described in this study. These technologies make it possible to simultaneously integrate a large amount of data, identify patterns and generate more accurate predictions compared to the methodological analysis tools that we usually use.

We recognize, as Dr. Battioni points out, that these models are not exempt from limitations, such as the risk of overfitting and the need for external validation. However, we believe that their development and implementation, carefully evaluated, can complement our clinical analysis and act as a valuable supportive tool to make more accurate decisions.

We hope that this work will contribute to the promotion of dialogue and interdisciplinary research between clinical medicine and data science, and we thank you once again for the careful reading and the valuable contributions you have made in your letter.

Yours sincerely,

Federico Di Gennaro

Target Organ Damage in Special Situations: Are we Measuring Correctly?

Daño de órgano blanco en situaciones especiales. ¿Estamos midiendo bien?

BRUNO GUARINO[1]

I have read with interest the study by Travetto et al.: "Detection of Subclinical Cardiac Damage by Echocardiography in a Hypertensive Population with a High Prevalence of Obesity: Discrepancies According to the Indexing Method Used". (1) This descriptive, observational and prospective study included 150 adult patients with hypertension (HT). The differences and agreements between normalization of cardiac chambers measurements using allometric height-based indexing (AHI) and body surface area-based indexing (BSAI) were evaluated. In my opinion, it represents a bold attempt to leverage the resources available in any echocardiography laboratory to achieve a more accurate interpretation of the prevalence of target organ damage (TOD) in populations considered to be at high cardiovascular risk, such as patients with obesity and HT with left ventricular hypertrophy (LVH) or left atrial enlargement (LAE).

Since the 1980s, there have been ongoing efforts to normalize echocardiographic values, particularly for patients with increased left ventricular mass or left atrial dilatation, as a manifestation of elevated pressure in the left circuit. (2) The difficulty of adequately assessing obese patients with HT can be overcome by using AHI rather than BSAI. Interpreting LAE using the standard echocardiographic measurements can be challenging in cases with body mass index (BMI) > 35 kg/m^2. Therefore, the use of AHI is of high clinical value for early diagnosis, underscoring the limitation of the most commonly used method in the echocardiography laboratories, such as normalization using BSAI in this population. (3)

An example of the usefulness of this paper is the reclassification rate of LAE in the total population (28.5%) compared to that in the population with BMI > 40 kg/m^2 (55.4%). Given that the most recent survey on cardiovascular risk factors revealed that the prevalence of obesity was 61.6%, it is clear that accurate measurement of TOD in patients with obesity will pose a significant challenge in the coming years. (4) The greatest discrepancy between the methods appears to be LAE measured by AHI, particularly in hypertensive patients with BMI > 35 kg/m^2.

Clinical practice guidelines on cardiovascular prevention developed by various scientific societies include the use of AHI as a validated method. However, its daily use in cardiac imaging laboratories remains limited, despite its potential to reclassify patients,

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particularly those with more extreme values of BSAI. This could be achieved by replacing this method or by associating it with the echocardiographic assessment for LVH and LAE in patients with obesity grade I-II or greater and with a history of HT.

The incorporation of automatic normalization using AHI in echocardiography devices, as well as its systematic, use particularly in patients with HT and BMI > 35/40 kg/m², has the potential to facilitate early diagnosis of TOD and to intensify treatment in this type of special 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

We thank Dr. Bruno Guarino for his interest in our work and agree with his words. The identification of valid indexes for the standardization of echocardiographic parameters related to body size in subjects with obesity is a complex issue. Many of these parameters vary according not only to height, weight, muscle mass, total body fat mass but also to body fat distribution, and the coexistence of other metabolic disorders associated with obesity. (1)

For those parameters with methods and cut-off values defined in clinical practice guidelines for the obese population, we consider it important to reinforce the need to incorporate them into routine practice. For those for which there is no consensus, it is crucial to always bear in mind the limitations of body surface area as an indexing method, especially in subjects with severe or morbid obesity.

Conversely, in the context of medical practice, it is crucial for healthcare professionals to acknowledge that "clinical obesity," characterized by alterations in tissue or organ function due to excess adiposity, (2) is not merely a cardiovascular risk factor but rather a distinct disease entity, adversely impacting health and well-being. Therefore, a specific and multidisciplinary approach is necessary to prevent the development of its complications, among which cardiovascular, metabolic, and renal diseases stand out. (2-4) It is imperative to acknowledge clinical obesity as a salient problem within the office setting so that people suffering from this condition can understand their risks and initiate treatment that will help them improve their quality of life and outcome.

Carolina Travetto

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Correlation of Ergospirometry with Echocardiography in Pulmonary Arterial Hypertension

Correlación de ergoespirometría con ecocardiograma en hipertensión arterial pulmonar

GUILLERMINA SORASIO[1,2,3, MTSAC]

Pulmonary arterial hypertension (PAH) is a heterogeneous, chronic and progressive entity that leads to remodeling of the pulmonary arterioles with subsequent increase in pulmonary vascular resistance (PVR) and right ventricular function impairment, the main predictor of mortality (1).

It is essential to perform adequate baseline risk and follow-up stratification in these patients in order to initiate early treatment based on known risk scores. (2)

Although the 6-minute walk test is the most accessible and simple technique to assess functional capacity, it has certain limitations such as the influence of sex, age, height, weight, comorbidities and learning curve, among others. For this reason, ergospirometry or cardiopulmonary exercise test (CPET) is the ideal method to determine exercise limitation, though it is not very accessible and expensive. (3)

As mentioned above, stratifying patients with PAH at baseline and during follow-up is a priority, and CPET with variables such as peak oxygen consumption (peak VO_2) and ventilation to carbon dioxide production ratio (VE/VCO_2) is an important part of it. (4)

Among the echocardiographic variables, the relationship between the tricuspid annular plane systolic excursion distance (TAPSE) and pulmonary artery systolic pressure (PASP) as a surrogate of ventricular arterial coupling, and the reduction of the stroke volume index (SVI) have been associated with poor prognosis in PAH.

The prognostic association between CPET variables, mainly VE/VCO_2 ratio and VO_2, and echocardiographic variables, as the TAPSE/PSAP ratio, is not well established.

The study by D' Amelio et al. evaluated the predictive ability of echocardiographic right ventricular function parameters in relation to exercise capacity, and compared CPET with the echocardiogram. Seven patients were included, most of them with PAH and chronic thromboembolic pulmonary hypertension (CTEPH). A statistically significant correlation was observed in the linear regression between TAPSE/PSAP ratio and peak VO_2. Although the number of patients is limited for decision making, it is an interesting hypothesis when it comes to correlating the more accessible echocardiogram with CPET, thus allowing the assessment of the functional capacity of patients with PAH, which is an important prognostic parameter. The rest of the CPET variables such as the VE/VCO_2 slope and Doppler echocardiogram variables, as fractional area and right atrial diameter change did not show statistical association. (5)

This is a very interesting study that when applied to a larger number of patients will allow us to evaluate other significant associations of echocardiographic variables with CPET and enable their application to daily clinical practice.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

I would like to thank Dr. Sorasio for her detailed and clear summary of the role played by each variable analyzed in the risk stratification of patients with PH. In response, I would like to highlight as a strength of the study that we found the correlation between TAPSE/sPAP and peak VO_2 in chronic patients treated according to the risk established for each one, and without modifying the therapeutic the last two months. So, the possibility of using an echocardiogram variable as a surrogate for CPET could have application in the risk stratification of those patients in follow-up.

Nicolás D´Amelio

Retraction notice

The Argentine Journal of Cardiology retracts the article: "Shaggy Aorta: Ideal Substrate for Disaster" by Kevin Velarde-Acosta et al., published in the Argentine Journal of Cardiology 2025; 93 (1): 25-30.

The article, which was originally submitted in English, underwent a thorough review process that included translation, multiple corrections, and collaborative discussions with the authors during the final months of 2024 and the early months of 2025. After its publication, we became aware that the same paper, with minor differences, had been published in English in Archivos Peruanos de Cardiología y Cirugía Cardiovascular in September (see Archivos Peruanos de Cardiología y Cirugía Cardiovascular 2024;5(3):143-152). This constitutes a violation of the principles of originality and duplicate publication established by our editorial policy and international guidelines for scientific publications. During the course of the communication process, the author did not inform us that the article had been just published in another journal.

The Argentine Journal of Cardiology deeply regrets this situation, extends its apologies to Archivos Peruanos de Cardiología y Cirugía Cardiovascular and reiterates its commitment to scientific integrity and compliance with ethical standards in academic publishing.

Jorge Thierer
Editor-in-chief of the
Argentine Journal of Cardiology

The Argentine Society of Cardiology and the Forum of Scientific Societies

La Sociedad Argentina de Cardiología y el Foro de Sociedades

The Argentine Society of Cardiology (SAC) has recently announced the establishment of the **Forum of Scientific Societies** to its members and the general public. This forum, made up of 21 distinguished scientific societies with significant academic background in our country, represents a range of specialties in the medical sciences (the participating societies are listed on the website sac.org.ar).

FOUNDING OBJECTIVES OF THE FORUM

The founding objectives of the Forum are as follows:

1. **Positioning the medical community:** Establish the medical community as a key player in the Argentine health system and promote its relevance in formulating health policies.
2. **Visibilizing health system issues:** Raising awareness among government authorities and the public of the persistent issues the health system faces and their impact on the performance of healthcare professionals. Efforts will be made to generate a deep understanding of these issues so that they become a priority for Argentine society.
3. **Proposing solutions:** Presenting public and private solutions to improve the working conditions of healthcare professionals. Job insecurity and moonlighting, direct consequences of deteriorating income levels, negatively impact the quality of patient care.
4. **Promoting human resources training:** Encourage continuous training and professional development of human resources in the healthcare field to ensure the quality and sustainability of the system.
5. **Generate innovative proposals:** Develop comprehensive proposals that rethink budgetary resources and optimize the health management system, considering the increase in life expectancy and the impact of new technologies.

The primary objective is to ensure that every patient receives quality, equitable healthcare, which is a fundamental right.

SPECIFIC INTERVENTION STRATEGIES

Along with creating the forum, the SAC is developing specific intervention strategies for clinical settings. Implementing proven programs with minimal investment can significantly reduce mortality and morbidity in the short term.

Data from the ARGEN-IAM-ST Registry, (1) which includes more than 7000 patients, reveal an alarming stagnation in mortality from acute myocardial infarction (AMI) at 8% over the last ten years. This figure significantly exceeds the one recorded in the international community. The mortality rate due to AMI indicates the promptness and effectiveness of access to emergency treatments, such as angioplasty or thrombolysis; therefore, it is a crucial indicator of the effectiveness of the healthcare system. In this registry, hypertension is the most prevalent risk factor, present in 60% of patients.

The RENATA (National Registry of Hypertension) Registry is an initiative of the SAC, together with other societies, with the aim of evaluating and improving the diagnosis, treatment, and control of hypertension in the population. (2) The data provided reveal a worrying reality: approximately 40% of the adult population in Argentina has hypertension. The prevalence of hypertension among the patients surveyed was 70%, and less than 30% of hypertensive patients had their blood pressure adequately controlled (below 140/90 mm Hg). In addition, around 55% of patients were not receiving antihypertensive treatment. Adherence to antihypertensive medications ranges from 30% to 50%, and patients from lower socioeconomic strata have less access to medical care and adequate treatment, which exacerbates the problem.

INTERDISTRICT CONFERENCE IN BARILOCHE AND THE DIGITAL MEDICINE COUNCIL MEETUP

The Interdistrict Conference was recently held in the city of Bariloche, together with the **Council on Digital Medicine Meetup**, in collaboration with the Balseiro Institute. Over the course of two days, members of our society who study advances in artificial intelligence and digital tools generated a powerhouse of ideas and projects applicable in two crucial scenarios: acute myocardial infarction and blood pressure control.

In these settings, the SAC, in line with the Forum

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of Societies, is developing a work group with the districts, Stent Save a Life initiative, ARGEN-IAM, and the Council on Digital Medicine for the creation of myocardial infarction networks in Argentina. This group will be responsible for providing advice and structuring networks in different communities across the country to optimize reperfusion times and define the appropriate strategy for each region, using digital medicine and artificial intelligence tools for the diagnosis of infarction and informed decisions on reperfusion strategies.

With regard to high blood pressure, PAHO's Hearts program is an excellent tool that we can apply in different regions of the country. (3) This program has proven to be an invaluable tool in the fight against hypertension and cardiovascular diseases, providing solid evidence to support a comprehensive approach to primary care.

CALL TO ACTION

The actions of the SAC within this strategic framework are not limited to the diagnosis of the problem. In context of this health system, it is imperative that our society becomes an active player, offering evidence-based organizational solutions and adapting them to the realities of our country.

At this critical time, the members of the SAC must come together to address the challenges that our health care system is facing. It is imperative to not only identify the issues pertaining to organization, financing, and expenditure, but also to raise awareness about these issues. We are also committed to training human resources who are dedicated to the cardiovascular epidemiological reality of our region and to implementing effective and proven strategies that contribute to reducing cardiovascular mortality in our country.

We embody a profound responsibility towards our patients. Let us work with determination and commitment for a more efficient, equitable, and humanized healthcare system.

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President of the Argentine Society of Cardiology

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