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EDITORIAL

Cardiogenic Shock: Evolution According to Gender in Latin America

Shock cardiogénico: evolución conforme al sexo en América Latina

HOLGER THIELE[1]

Cardiogenic shock is still the most important cause of death in patients hospitalized with acute myocardial infarction. The randomized SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK) trial set the basis for an early invasive management of these patients, (1) with subsequent increase in early revascularization strategies across the globe. This strategy has dramatically improved outcome and reduced in-hospital mortality of cardiogenic shock patients from the former 70-80% to nowadays 40-50%. (2)

Currently, only few large-scale landmark randomized controlled trials have been performed in the cardiogenic shock setting including the above-mentioned SHOCK trial in 1999, (1) the IABP-SHOCK II trial, (3-5) the CULPRIT-SHOCK trial, (6,7) the ECLS-SHOCK trial, (8) and the recent DanGer-Shock trial. (9) Accordingly, only few measures rely on strong clinical evidence in the treatment of cardiogenic shock. (10,11)

When insufficient evidence is available and mortality still high, evidence from observational data is important and additive to randomized data. This is particularly true for sex specific differences in cardiogenic shock because often women are underrepresented in the large-scale randomized controlled trials. This is partly an effect because women are older and many large-scale randomized controlled trials had an upper age limit for inclusion which automatically leads to less women for inclusion because of the higher age in women presenting with cardiogenic shock. Therefore, it is even more important in clinical practice to measure the outcome of acute coronary syndromes and the complications including cardiogenic shock with respect to sex specific differences. Only by measuring outcome, measures can be implemented to improve outcome for women and also men. As such, it can only be supported to see the publication of the LATIN Shock registry from Argentina, Bolivia, Chile, Ecuador, Honduras, Paraguay and Peru. (12) The in-hospital mortality of 49% in women and 54% in men shows the still very high mortality in cardiogenic shock in the current era of early revascularization. (13) Interestingly, despite the older age in women there was no difference in mortality, which has also been shown in other analyses such as the CULPRIT-SHOCK and IABP-SHOCK II sex specific subanalyses. (14,15) In contrast, other observational data suggest less invasive treatment in females presenting with cardiogenic shock with subsequent higher mortality. (16) Accordingly, the LATIN Shock registry supports no relevant outcome differences in cardiogenic shock based on sex.

Interestingly, still the majority of patients is treated by intraaortic balloon pumping where the evidence does not support to use this device. (3-5) On the other hand evidence for active mechanical circulatory support is also limited and currently only the DanGer-Shock trial and a meta-analysis of all trials comparing active mechanical circulatory support versus control supports the use in very selected patients with ST-elevation myocardial infarction and no risk of hypoxic brain injury. (9,17)

The authors should be congratulated to put this LATIN Shock registry together. More efforts should be directed towards cardiogenic shock registries and a higher number of patients will help to define the best treatment strategies to improve outcome in cardiogenic shock also with respect to sex specific differences.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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EDITORIAL

The Road to Early Diagnosis of Transthyretin Cardiac Amyloidosis in Argentina

El camino hacia un diagnóstico temprano de la amiloidosis cardíaca por transtiretina en Argentina

SANTIAGO DECOTTO[1, MTSAC], DIEGO PEREZ DE ARENAZA[1, MTSAC]

Transthyretin cardiac amyloidosis (ATTR-CA) is a significant but underdiagnosed cause of heart failure in older adults. (1) In recent years, its diagnostic incidence has shown a considerable increase. This growth can be attributed to greater medical knowledge, the growing availability of noninvasive diagnostic tools such as bone scintigraphy with bisphosphonates, and the advent of new therapies modifying the course of the disease. (2) The concept of red flags aims to facilitate diagnosis by identifying combinations of clinical signs and symptoms yielding higher probability of cardiac amyloidosis detection. (2) Several of the red flags include clinical, electrocardiographic and echocardiographic elements, the most relevant being a history of bilateral carpal tunnel, wall thickening with low ECG voltages, altered ventricular filling, low tissue velocity or decreased global longitudinal strain (GLS) in the basal and medial segments, with apical preservation. (3) Nevertheless, the diagnosis of ATTR-CA continues to be made predominantly in elderly patients and in advanced stages, which limits therapeutic options and significantly reduces the positive prognostic impact that an early intervention could offer.

The importance of generating one's own knowledge

With this issue in mind, Gobbo et al. present the *deteCTTAR* score, a predictive model developed entirely from local data, (4) which ensures that the diagnostic tools are truly useful in our setting. Many predictive models developed in other regions do not necessarily reflect the characteristics of our populations, which can lead to diagnostic underestimation or implementation of ineffective strategies.

The model proposed by the authors is based on clinical, electrocardiographic and echocardiographic variables that are easily obtained in routine clinical practice and are considered red flags for the search of the disease in question. We believe that the inclusion of predictor variables such as history of bilateral carpal tunnel, interventricular septal thickness (≥16 mm) and pseudonormal or restrictive diastolic relaxation pattern makes it easily applicable, with information obtained simply from a correct anamnesis and a transthoracic Doppler echocardiogram, a widespread practice. On the other hand, the score showed remarkable sensitivity and specificity for the detection of cardiac amyloidosis (AUC 0.88), with better performance than other international scores already validated in different cohorts. These scores have been developed in larger multicenter studies for the diagnosis of ATTR-CA and light chain (AL) amyloidosis. Among these, one of the most important was that of Boldrini et al. who studied 1187 patients with suspected cardiac amyloidosis. In this study, 332 patients were diagnosed with AL amyloidosis and 339 with ATTR-CA. The parameters that were predictive for the diagnosis of AL amyloidosis were relative wall thickening, E/e' ratio, tricuspid annular plane systolic excursion (TAPSE) and GLS, while for ATTR-CA the apex-to-base systolic ratio was also added. (5) The study published in the Argentine Journal of Cardiology has the great value and originality of using local data.

Fitting the model: have we chosen the adequate septal thickness threshold?

One of the aspects that we believe is important to discuss is the choice of an interventricular septal thickness ≥16 mm as the cutoff point. This seems to be a solid criterion, but could limit the sensitivity of the model. In patients with earlier forms of the disease, a lower threshold, such as ≥12 mm, the cutoff point used in other international scores, could have better sensitivity, and thus potentially improve the model's ability to detect early-stage disease. In fact, in the

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study published by Gobbo et al, (4) 39% of patients diagnosed with ATTR-CA had septal thickness between 12 and 16 mm. This type of adjustment can be useful to ensure that we not only identify those who already have advanced disease, but also those in whom early intervention can make a difference.

The importance of red flags

The use of red flags as predictor variables in the model is one of the work's strengths. A history of bilateral carpal tunnel, for example, not only has a strong association with ATTR-CA, but also represents a unique opportunity to identify patients in subclinical stages. Incorporating this variable into clinical practice could foster greater diagnostic sensitivity among non-cardiologists, such as traumatologists and rheumatologists, expanding the opportunities for early diagnosis.

On the other hand, the pseudonormal or restrictive diastolic relaxation pattern, variables widely recognized in echocardiography, highlights the value of this method as an accessible and useful tool for the detection of ATTR-CA. Taken together, these variables reinforce the idea that the early diagnostic approach does not necessarily require complex technologies, but rather a correct identification of the key findings in the clinical and imaging evaluation.

Prospective validation, next steps and concluding remarks

Although the results of the *deteCTTAR* score are promising, its implementation in clinical practice will require prospective validation in independent cohorts. This step is crucial to confirm the robustness of the model and to adjust for possible biases derived from the population used in the initial analysis.

Its development marks a significant advance in the field of cardiac amyloidosis in our country. Beyond its figures and results, this work points to the importance of prioritizing local research and fostering a culture of knowledge generation adapted to our needs.

Today's medicine faces the challenge of being more accurate and earlier. In diseases such as ATTR-CA, where the time of diagnosis is a critical factor for the future prognosis of the compromised patient, tools such as the *deteCTTAR* score not only represent an opportunity to improve the diagnosis of cardiac amyloidosis, but also to optimize the prognosis through early treatment.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Characteristics and Evolution of Cardiogenic Shock According to Gender in Latin America. LATIN Shock Registry Data

Características y evolución del shock cardiogénico de acuerdo con el sexo en Latinoamérica. Datos del registro LATIN Shock

YANINA CASTILLO COSTA[1, MTSAC], FLAVIO DELFINO[2, MTSAC], JOSÉ MACÍAS[2], MIGUEL QUINTANA[3], MARIANO ADAMOWSKI[4], FABIOLA RODRÍGUEZ CABALLERO[1, 5], MA DE LOS ÁNGELES NAVARTA NAVARRO[1, 6], GABRIELA VELAZCO[1, 7], VÍCTOR MAURO[1, MTSAC], ON BEHALF OF LATIN SHOCK GROUP

ABSTRACT

Background: Cardiogenic shock (CS) as a complication of myocardial infarction is a condition with high mortality that, due to biological or equity differences, may have different characteristics according to gender.
Objectives: The aim of this study was to evaluate whether there are differences in the presentation, clinical evolution and treatment of patients with CS, according to gender.
Methods: We analyzed the patients of the LATIN Shock registry and evaluated whether there were differences according to gender.
Results: A total of 278 patients (30% women) were included. Seventy-five percent of patients presented ST-segment elevation acute coronary syndrome. Women were older and men were heavier smokers, and there were no differences in the prevalence of other cardiovascular risk factors, history, or comorbidities between genders. Revascularization was similar in men and women (86%) and there were no differences in the indication for pulmonary catheterization (11% vs. 20%, p=0.082). Women received less mechanical support with intra-aortic balloon counterpulsation (14% vs. 26%, p=0.032), while use of other mechanical support procedures was scarce, only in 1% of women and in 3% of men (p=0.678). Mortality in women was 48% vs. 54% in men, not reaching statistical significance (p=0.470).
Conclusions: Women with CS due to infarction are older and receive similar treatment except for mechanical supports, which are more frequently used in men. In our study there were no significant differences in mortality according to gender, which was high in both groups.

Key words: Cardiogenic Shock - Myocardial Infarction - Gender - Registry.

RESUMEN

Introducción: El shock cardiogénico (SC) como complicación del infarto agudo de miocardio (IAM) es una patología con alta mortalidad que por diferencias biológicas o de equidad podría tener distintas características de acuerdo con el sexo.
Objetivos: Evaluar si hay diferencias en la presentación, evolución clínica y tratamiento de acuerdo con el sexo en los pacientes con SC.
Material y métodos: Se analizaron los pacientes del registro LATIN Shock y se evaluó si existían diferencias de acuerdo con el sexo.
Resultados: Se incluyeron 278 pacientes (30 % mujeres), el 75 % con síndrome coronario agudo con elevación del segmento ST (SCACEST). Las mujeres fueron más añosas y los hombres más frecuentemente tabaquistas. No hubo diferencias en la prevalencia de otros factores de riesgo cardiovascular, antecedentes ni comorbilidades entre ambos sexos. Hombres y mujeres recibieron revascularización en forma similar (86 %). No hubo diferencias en la indicación de cateterismo pulmonar (11 % vs 20 %, p = 0,082). Las mujeres recibieron menos soporte mecánico con balón de contrapulsación (14 % vs 26 %, p=0,032).
El empleo de otros soportes mecánicos fue escaso (1 % de las mujeres y 3 % de los hombres, p= 0,678). La mortalidad de las mujeres fue del 49 % y la de los hombres 54 %, sin diferencia significativa (p= 0,470).

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Conclusiones: Las mujeres con SC por IAM son más añosas que los hombres y reciben similar tratamiento, excepto soportes mecánicos, más utilizados en hombres. No encontramos diferencias significativas de acuerdo con el sexo en la mortalidad, que fue elevada en ambos grupos.

Palabras clave: Shock cardiogénico - Infarto de miocardio - Sexo - Registro

INTRODUCTION

Cardiovascular disease is the leading cause of death in both men and women. (1) It has been shown that in myocardial infarction, female gender, usually underrepresented in published works, (2,3) is associated with longer delays in consultation, lower rates of primary angioplasty, higher probability of developing heart failure and cardiogenic shock (CS), (4-6) and higher mortality. (7-10). In CS, a condition with mortality ranging between 40-60%, (11) differences in presentation, treatment received and evolution between men and women are not clearly defined. This "indefinition" is particularly relevant today, since there is evidence that biological gender (considering the different hormonal influence) implies some differences in physiological responses and in the action of certain drugs (12) that influence clinical disorders [as in sepsis (13, 14)], and should therefore be taken into special account. (1) Similarly, equity in access to health care is a current objective of many scientific societies. (15) To determine whether there is equity or differences in relation to gender, the contribution of regional multicenter registries, in our case the LATIN Shock registry, (16) is essential, since it has also been shown that there are differences in access to health care depending on whether high or low-income countries are evaluated. (17,18)

To date, there is scarce literature worldwide on the implications of gender differences in the characteristics, evolution and treatment of CS, and none in Latin America.

OBJECTIVES

1) To analyze whether there are differences in the clinical presentation, treatment received, and clinical evolution according to gender in patients with CS in the context of acute coronary syndromes (ACS), and 2) To establish whether gender is an independent predictor of in-hospital mortality.

METHODS

LATIN Shock is a multicenter, observational, prospective and consecutive registry of ACS complicated with CS. The Research Area of the Argentine Society of Cardiology provided computer and statistical support for the study.

Cardiogenic shock was defined as the presence of systolic blood pressure (SBP) <90 mmHg for at least 30 minutes or requirement of vasopressors and/or inotropic drugs to maintain SBP ≥90mmHg, associated with signs of hypoperfusion and signs of pulmonary congestion.

The inclusion criteria were: patients over 18 years of age, hospitalized in a coronary care unit or multipurpose critical care unit for ST-segment elevation ACS (STE-ACS) or non-ST-segment elevation ACS (NSTE-ACS), who presented CS since admission or developed it during hospitalization.

Data were collected by the responsible investigators of the different centers in an electronic file designed ad hoc with the RedCAP platform. In-hospital events were analyzed.

Further details on the characteristics of the participating centers can be found in LATIN Shock. (16)

Statistical analysis

The information obtained through RedCAP was exported in Excel and the database was analyzed using Epi-info 7. Continuous variables were expressed as mean and standard deviation for those with normal distribution and as median with interquartile range 25% -75% (IQR) for those non normal distribution. The statistical analysis of continuous variables was performed using Student's t test or the Wilcoxon rank sum test, as appropriate. Discrete variables were expressed as percentages and comparisons were performed using the chi-square test with Yates correction or Fisher's exact test, as appropriate.

Contingency tables were built to analyze variable association or independence. Linear and/or multiple logistic regression analyses were carried out to determine the existence of associations and/or independent predictions between the different variables involved and mortality. All statistical comparisons were two-tailed and values of $p<0.05$ were considered statistically significant.

Ethical considerations

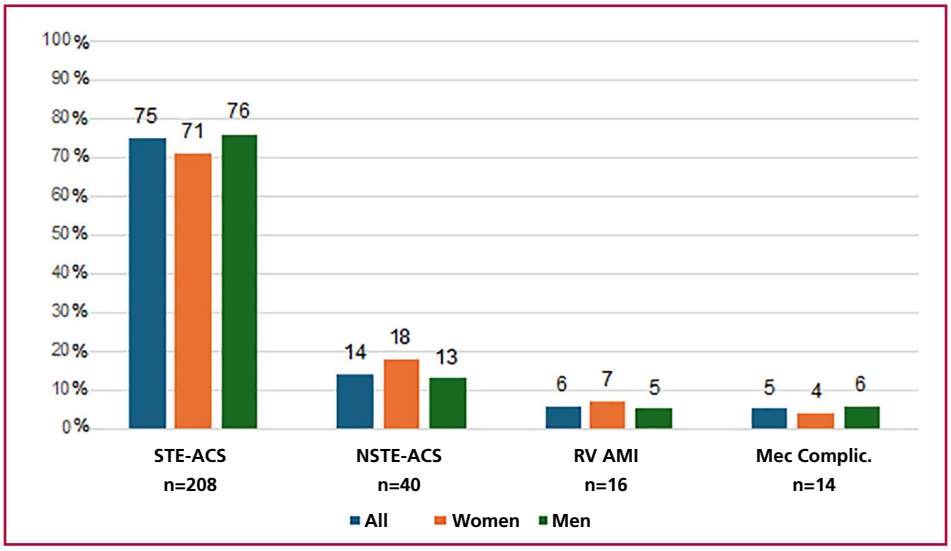
The study was conducted in accordance with current national and international regulations: Declaration of Helsinki of the World Medical Association, the ICH E6 Good Clinical Practice Guidelines, Resolution 1480/11 of the National Ministry of Health and GCBA Law 3301/09. The protocol was approved by the Bioethics Committee of the Argentine Society of Cardiology (SAC). Informed consent was waived since no sensitive data were recorded and only in-hospital follow-up was performed.

RESULTS

Forty-one Latin American centers from seven counties (Argentina, Bolivia, Chile, Ecuador, Honduras, Paraguay and Perú) participated in the registry, recruiting 278 patients from October 2021 to September 2023. Seventy percent of patients were men (n=195) and overall median age was 66 years (IQR 59-75). Women were older [median age 71 years (IQR 61-78) vs. 64 years (IQR 58-73) in men, $p<0.001$]. Most CS (75%) were due to STE-ACS. Details of the causes of CS are shown in Figure 1.

CS was present from admission in 60% of cases (66% in women and 57% in men; $p=0.181$). In those admitted with another Killip, 81% developed CS on

Fig. 1. Causes of CS



CS: Cardiogenic shock; Mec Complic: mechanical complications; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; RV AMI: right ventricular acute myocardial infarction; STE-ACS: ST-segment elevation acute coronary syndrome

Table 1. Baseline characteristics of the population.

	Total (n=278)	Female (n=83)	Male (n=195)	p
Age (years)	66 (59-75)	71 (61-78)	64 (58-73)	<0.001
Hypertension	206 (74)	66 (80)	140 (72)	0.179
Dyslipidemia	95 (34)	28 (34)	67 (34)	0.920
Smoking	72 (26)	13 (16)	59 (30)	0.011
Type 2 diabetes	117 (42)	35 (42)	82 (42)	0.494
Obesity	79 (29)	26 (31)	53 (27)	0.483
COPD	19 (7)	3 (4)	16 (8)	0.165
Chronic anemia	14 (5)	5 (6)	9 (5)	0.623
Chronic kidney disease	17 (6)	4 (5)	13 (7)	0.556
Previous AMI	44 (16)	8 (10)	36 (19)	0.065
Previous HF	20 (7)	6 (7)	14 (7)	0.483
Previous stroke	15 (5)	4 (5)	8 (4)	0.781

AMI: Acute myocardial infarction; COPD: Chronic obstructive pulmonary disease; HF: Heart failure. Quantitative variables are presented as median and interquartile range, qualitative variables as frequency and percentage.

the first day of hospitalization, 13% on the second day and 6% on the third day, with no differences according to gender.

Baseline characteristics according to gender are shown in Table 1

The use of vasoactive agents was 97.8%, with no differences by gender according to the type of drug used, except for vasopressin, which was used in 7.2% of women and 16% of men (p=0.041). Mechanical ventilation was used in 52.5% of cases in both genders, Swan Ganz catheter in 17% (11% in women and 20% in men, p=0.073), intra-aortic balloon counterpulsation in 22.2% (14% in women and 26% in men, p=0.032) and extracorporeal membrane oxygenation (ECMO) in 1% of women and 3% of men, p=0.676). No other supports were used.

The culprit vessel was revascularized in 81% of the overall population, with no differences according to sex (80% of women vs. 82% of men, p= 0.768). The prevalence of multivessel disease was 71% (63% in women and 73% in men, p=0.113) and there was no difference in the prevalence of revascularization of other vessels, (40% in women and 31% in men, p=0.408).

In-hospital evolution by gender is detailed in Table 2.

The median (IQR) hospital stay was 6 days (1-16). Overall in-hospital mortality was 52.7%, with no differences between ACS with or without ST-segment elevation or according to gender: women 49% vs. men 54%, p=0.470).

The variables shown in Table 3 were considered for the analysis of univariate predictors of mortality

In the multivariate analysis model that included age, gender, diabetes, reperfusion and use of intra-aortic balloon counterpulsation, only age maintained its prognostic value (odds ratio 1.025, 95% CI 1.002-1.048, p=0.011).

In patients with STE-ACS without mechanical

complications on admission (n=208) there were no differences in baseline characteristics; median (IQR) time to overall consultation was 300 min (120-780); 360 min (120-540) in women and 274 min (120-870) in men, p=0.196. AMI was anterior in 68% of cases (women: 55.9% vs. men: 72.5%, p=0.012) and percutaneous coronary intervention (PCI) was performed in 88.9% of women and 82% of men (p=0.149) and the door-to-balloon time was 120 min (60-240), without differences according to gender. There were 19.1% of failed PCI in women and 21.2% in men (p=0.398). Mortality in women was 54.2% and 55.4% in men (p=0.437).

DISCUSSION

LATIN shock, the first Latin American study of CS in the context of ACS, allows us to learn about the reality of CS management in low-moderate income countries and at the same time, with a culture different from the European/American one, which could entail disparities according to gender.

It is well known that the proportion of women with CS due to infarction is higher than that of men, as shown by the Argentine ARGEN IAM ST registry (6) or the French FAST AMI study, in which it is almost twice that of men. (19) This is probably due, among other things, to the fact that women have a longer life expectancy and, in general, are older at the time of infarction with shock. In our case, women had a median age 7 years older than men.

The prevalence of women with CS in the different published studies and registries ranges from 21% to 37%. (20-25) In our study it was 30%. Women were older and did not present more risk factors or comorbidities than men, as has been observed in some studies. (22-25)

Revascularization is the mainstay in the treatment of CS, (26) but some studies reveal considerable differences according to gender. (27) It even emerges from the analysis of the National (nationwide) Inpa-

Table 2. In-hospital evolution according to gender

Variable	Total (n=278)	Female (n=83)	Male (n=195)	p
Revascularization (CV)	222 (81)	65 (80)	157 (82)	0.768
Angina/ reAMI	9 (3)	4 (5)	5 (3)	0.331
Arrhythmias	88 (32)	26 (31)	62 (32)	0.939
AF	27(10)	6 (7)	21 (11)	0.362
VT/VF	39 (14)	11 (13,2)	28 (14,3)	0.808
AV block	16 (6)	7 (8)	9 (5)	0.211
Transient PM	15 (5)	2 (2)	13 (7)	0.151
ECV	36 (13)	7 (8)	29 (15)	0.143
Fever	36 (13)	11 (13)	25 (13)	0.922
Dialysis	20 (7)	6 (7)	14 (7)	0.988
Transfusion	21 (8)	7 (8)	14 (7)	0.717
Mortality	146 (53)	41(49)	105 (54)	0.470

AF: atrial fibrillation; CV: culprit vessel; ECV: electrical cardioversion; PM: pacemaker; reAMI: reinfarction; VT/VF: ventricular tachycardia/ventricular fibrillation
Qualitative variables are presented as frequency and percentage.

Table 3. Univariate analysis for mortality

	Dead (n= 146)	Alive (n= 132)	p
Age (years)	68 (60-78)	65 (57-76)	0.010
Female gender	41 (28)	42 (32)	0.470
HTN	113 (77)	93 (71)	0.223
Smoking	35 (24)	36 (28)	0.504
Type 2 diabetes	59 (40)	58 (44)	0.516
Previous AMI	30 (20)	14 911)	0.025
STE-ACS	114 (78)	93 (71)	0.175
Revascularization	111 (77)	111 (87)	0.041
Swan Ganz	25 (17)	22 (17)	0.988
Balloon counterpulsation	37 (26)	24 (19)	0.170
MVD	106 (73)	91 (69)	0.551

AMI: acute myocardial infarction; HTN: Hypertension; MVD: Multiple vessel disease; STE-ACS: ST-segment elevation acute coronary syndrome
Quantitative variables are presented as median and interquartile range, qualitative variables as frequency and percentage.

tient Sample (NIS) database, with more than 134 000 elderly patients (≥75 years) with CS, that women were less likely to receive angiography, angioplasty and mechanical support compared with men. (28) In our study there were no significant differences in revascularization between men and women, probably because most of the participating centers had available angioplasty and current guideline recommendations were followed, (29,30) but there was a difference in the indication of mechanical support, which was significantly lower in women, with the indication for balloon counterpulsation being half that of men. Extracorporeal membrane oxygenation was used in less than 4% of cases, which reflects the lack of availability and/or implementation given the socioeconomic conditions in Latin America. However, with the results of the IABP-SHOCK II trial, (31) those of ECMO-CS (32) and of ECLS-SHOCK, (33,34) which did not show benefits in survival, its routine use is not proposed for either men or women. The DanGer Shock study (35) in which Impella was used on a randomized basis, showed lower mortality with the use of the device in the included population, but in the subgroup analysis, only men benefited from its use. In Latin America, Impella was not used in any patient, although it should be noted that the registry was carried out prior to the publication of that study.

Mortality in our environment was high and there were no differences by gender as in other studies; (36,37) however, it is on this point where there is more controversy, since some recent studies report higher mortality in women. (38-40)

It should be noted that women may have some different baseline characteristics and that they are usually underrepresented in studies, but there have been no significant outcome differences with respect to gender, neither with revascularization (SHOCK trial), nor with the use of balloon counterpulsation (IABP-SHOCK II), or with revascularization of only the culprit vessel (CULPRIT-SHOCK). (41,42) There were also no differences according to gender in the use of other mechanical supports, except in the DanGer Shock study (35) in which the benefit of Impella was limited to the male group. In any case, it cannot be ruled out that this is due to the low number of women included. With the current data, both genders should continue to be treated equally. (43,44)

The heterogeneity of populations, treatment received and evolution makes it essential to have local and regional epidemiological data. Only by measuring and becoming aware of our own situation it is possible to evaluate whether it is necessary to implement change actions.

Limitations

The SCAI classification was not used, the registry did not report cardiac arrest at admission and there was no external audit of the data.

CONCLUSION

Latin American women who present with CS in the context of ACS are older than men, are revascularized in a similar manner, and have an equally high mortality. Although the use of mechanical supports was lower in women, this has not had an impact on mortality, nor has it had an impact on the results of randomized studies.

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Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Transthyretin Cardiac Amyloidosis. Development of a Prediction Model and Scoring Scale for Diagnosis: the *deteCTTAR* Score

Amiloidosis cardíaca por transtiretina. Desarrollo de un modelo de predicción y escala de puntuación para el diagnóstico: score deteCTTAR

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ABSTRACT

Background: To verify the diagnosis of transthyretin cardiac amyloidosis (ATTR-CA) in its early stages, certain warning signs or "red flags" have been lately identified to guide suspicion. However, to date, there is little evidence regarding the diagnostic sensitivity and specificity of each red flag or whether there is any combination of variables that can reliably predict the presence of ATTR-CA.
Objective: The aim of this study was to develop a prediction model based on clinical, electrocardiographic and/or echocardiographic variables to establish a scoring scale to guide the diagnosis of ATTR-CA.
Methods: The medical records of 342 patients with cardiac scintigraphy (CS) for suspected ATTR-CA were analyzed: 171 patients with a positive diagnosis were compared with the same number of patients with a negative diagnosis. Clinical, electrocardiographic and echocardiographic data were analyzed and included in univariate and multivariate logistic regression models. A 0-8 scoring scale was built and a receiver operating characteristic (ROC) curve was generated. The area under the curve (AUC) with its 95% CI was then calculated.
Results: The following variables were identified as predictors of ATTR-CA in univariate and multivariate logistic regression models: interventricular septum (IVS) ≥16 mm (OR 3.6, 95% CI 1.8-7.1), male gender (OR 7.9, 95% CI 3.6-17.1), grade II or III diastolic dysfunction with pseudonormal or restrictive relaxation pattern (OR 12.7, 95% CI 6.1-26.3), and history of bilateral carpal tunnel syndrome (CTS) (OR 24.4, 95% CI 6.0-97.8).
Based on the OR obtained, a scoring scale was created showing an AUC of 0.88 (95% CI 0.84-0.91, p<0.001), and a value ≥3, with high sensitivity and specificity, was identified to predict ATTR-CA (AUC 0.82 95% CI 0.77-0.87).
Conclusions: The prediction model allowed the development of a scoring scale that demonstrated high sensitivity and specificity to strongly guide the diagnosis of ATTR-CA.

Key words: Amyloidosis - Prealbumin- Restrictive Cardiomyopathy - Diastolic Heart Failure - Systolic Heart Failure

RESUMEN

Introducción: Con el objetivo de establecer el diagnóstico de amiloidosis cardíaca por transtiretina (AC-TTR) en etapas precoces, en los últimos años, se lograron identificar ciertas señales de alerta o ¨banderas rojas¨ para orientar la sospecha. Sin embargo, hasta el momento, contamos con escasa evidencia acerca de la sensibilidad y especificidad diagnóstica de cada bandera roja o de si existe alguna combinación de variables que pueda predecir en forma confiable la presencia de AC-TTR.
Objetivo: Desarrollar un modelo de predicción basado en variables clínicas, electrocardiográficas y/o ecocardiográficas que permita establecer una escala de puntuación para guiar el diagnóstico de la AC-TTR.
Material y métodos: Se analizaron las historias clínicas de 342 pacientes con centellograma cardíaco (CC) por sospecha de AC-TTR: 171 pacientes con diagnóstico positivo fueron comparados con igual número de pacientes con diagnóstico negativo. Se analizaron datosclínicos, electrocardiográficos y ecocardiográficos, los cuales fueron incluidos enmodelos de regresión logística uni y multivariados. Se construyó una escala depuntuación de 0-8 y se generó una curva de característica operativa del receptor (ROC). Posteriormente, se calculó el área bajo la curva (AUC) con su IC del 95%.
Resultados: En modelos de regresión logística uni y multivariados, se identificaron como predictores de AC-TTR: el septum interventricular (SIV) ≥16mm (OR 3,6, IC 95% 1,8-7,1), sexo masculino (OR 7,9, IC 3,6-17,1), disfunción diastólica grado II y III con patrón de relajación seudonormal o restrictivo (OR 12,7, IC 95% 6,1-26,3) y el antecedente de túnel carpiano bilateral, TCB (OR 24,4, IC 95% 6,0-97,8).

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En función de los OR obtenidos se creó la escala de puntuación que mostró un AUC 0,88 (IC 95% 0,84-0,91; p< 0.001) y se identificó el valor ≥3, con alta sensibilidad y especificidad para predecir AC-TTR (AUC 0,82, IC 95% 0,77-0,87).
Conclusión: El modelo de predicción obtenido permitió desarrollar una escala de puntuación que demostró una alta sensibilidad y especificidad para orientar fuertemente el diagnóstico de AC-TTR.

Palabras clave: Amiloidosis - Prealbúmina - Cardiomiopatía Restrictiva - Insuficiencia Cardíaca Diastólica - Insuficiencia Cardíaca Sistólica

INTRODUCTION

Transthyretin cardiac amyloidosis (ATTR-CA) is an infiltrative cardiomyopathy caused by the extracellular deposition of amyloid as a consequence of transthyretin disaggregation and/or misfolding. (1)

Although its prevalence remains uncertain, in certain clinical scenarios such as hypertrophic cardiomyopathy (HCM), severe aortic stenosis (SAS) or heart failure with preserved left ventricular ejection fraction (HFpEF) it is usually more frequent, ranging between 13% and 17% of cases. (2-5)

In recent years, the emergence of cardiac scintigraphy (CS) with phosphonates as a non-invasive diagnostic method, together with the advent of new drugs for specific therapy, have led to a growing interest in this pathology, generating a notable increase in the diagnosis. (6)

A great advance in this regard was the identification of certain clinical, electrocardiographic and imaging variables as warning signs or "red flags" to guide suspicion and attempt to detect patients in earlier stages of the disease. However, so far, we have little evidence about the diagnostic sensitivity and specificity of each red flag, or whether there is any combination of variables that can reliably predict the presence of ATTR-CA. (7)

It is known that ATTR-CA is a slow and progressive disease, with a long asymptomatic or subclinical period. It is precisely in these stages where early diagnosis can be crucial to improve the clinical evolution and prognosis of those who suffer from this disease. Phosphonate CS imaging is highly sensitive and specific for diagnosis, when performed in the appropriate clinical context. However, to delineate when it is appropriate to perform it or not is still a challenge.

We conducted this study with the aim of developing a predictive model and subsequently a scoring scale, based on clinical, electrocardiographic and echocardiographic variables, to guide the early diagnosis of ATTR-CA.

METHODS

A single-center and retrospective study was designed. The electronic medical records of 342 patients referred to our service between January 2016 and April 2024 for CS with Tc99m-hydroxymethylene diphosphonate (HMDP) for suspected ATTR-CA were analyzed. Cardiac scintigraphy with HMDP was performed according to current guidelines. The images obtained were analyzed qualitatively according to the Perugini scale. A positive diagnosis of ATTR-CA was considered in the presence of cardiac uptake with grade 2 or 3 HMDP (in the absence of light chains in serum and urine). A negative diagnosis for ATTR-CA was considered for cardiac uptake grade 0. (8,9) Patients without previous consultations and/or studies in our institution were excluded from the analysis.

A total of 171 patients with a positive diagnosis of ATTR-CA were compared with an equal number of patients with a negative diagnosis, randomly selected from our database from a total of 564 CS with HMDP presenting with grade 0 uptake. The populations were not matched for gender or age, as both variables were shown to be predictors in other previously published scoring scales.

Clinical, electrocardiographic and echocardiographic data were analyzed in both groups. All red flags were included, except for proteinuria, global longitudinal strain and late gadolinium enhancement, which were excluded from the analysis due to high data loss.

Definition of variables

Left ventricular relaxation pattern was defined according to the following echocardiographic parameters: (10,11)

- grade I diastolic dysfunction: E/A ratio ≤0.8 + E wave ≤ 50 cm/s, and the absence of 2 or 3 of the following parameters: (a) E/e' ratio >14, (b) tricuspid regurgitation (TR) jet velocity >2.8 m/s, and (c) indexed left atrial (LA) volume >34 ml/m^2;
- grade II diastolic dysfunction: E/A ratio ≤0.8 + E wave >50 cm/s, or E/A ratio > 0.8 and <2, and the presence of 2 or 3 of the (a), (b) and (c) parameters mentioned in the previous section;
- grade III diastolic dysfunction: E/A ratio ≥2
- indeterminate diastolic dysfunction when it does not meet the above criteria.

Interventricular septum (IVS) hypertrophy was defined as diastolic interventricular septum thickness ≥12 mm (12), and bilateral carpal tunnel syndrome (CTS) as the surgical history or presence of current symptoms compatible with this syndrome. (13)

Pseudo infarction pattern was defined as the presence of QS complexes in leads V1-V2, in the absence of a history of myocardial infarction, and microvoltage as the presence of QRS complexes <5 mV in frontal leads or <10 mV in precordial leads.

Statistical analysis

Quantitative variables were expressed as median with their corresponding interquartile range (IQR) and were compared with the Mann-Whitney test. Qualitative variables were expressed as percentages and were compared using the multiple chi-square test.

All the data collected were included in univariate logistic regression models. Those with statistical significance were subsequently included in multivariate logistic regression models to evaluate their predictive value in TTR-CA diagnosis.

Variables identified as predictors in the multivariate models were used to build a prediction scale with a 0-8 score.

According to the ORs obtained, 1 point was assigned for ORs between 1 and <7; 2 points for ORs between 7 and 21, and 3 points for ORs >21.

Sample calibration was evaluated by the Hosmer-Lemeshow statistical test. To determine the predictive capacity of the scoring scale, a receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) with its 95% CI was calculated as a measure of discrimination.

The level of statistical significance was established as $p < 0.05$.

SPSS Statistics version 26 was used to perform the analyses.

Ethical considerations

The study was approved by the Research Committee of our institution and by an independent Ethics Committee.

RESULTS

Table 1 summarizes baseline characteristics of both groups with the variables included in the univariate analysis.

In the ATTR-CA group, male gender, incidence of bilateral CTS, peripheral neuropathy, atrioventricular block, and grade II or III diastolic dysfunction pattern were significantly more prevalent. In the group without ATTR-CA, diabetes, smoking, history of coronary artery disease, HF with left ventricular ejection fraction (LVEF) ≥50%, marked LA dilatation, and severe AS were significantly more prevalent.

Statistically significant differences in IVS thickening were also observed: most patients without ATTR-CA had thickness <12 mm or between 12 and 16 mm, with a median (IQR) of 13.3 mm (12.6-14.1), while in the ATTR-CA group the majority showed an IVS thickness ≥16mm, with a median (IQR) of 16.6 mm (16.1-17.2) .

In our analysis, microvoltage and pseudoinfarction pattern (predictor variables of ATTR-CA in other models) showed no significant differences between the two groups.

There were no patients with grade 1 cardiac uptake, nor patients with grade 0 uptake and positive serum and urine light chains.

Within the group with positive ATTR-CA, 13 patients (8%) had IVS thickness ≥12 mm without any red flag. Another 3 patients (2%) although they had red flags, did not have increased IVS thickness and, in addition, one patient had neither condition.

Four patients presented positive genetic test (hereditary ATTR-CA), the most frequent mutation being Val50Met and only one of them presented the Val142Ile variant.

Table 2 shows the multivariate analysis of the significant variables in the univariate analysis. Table 3 shows the variables identified as predictors of AC-TTR in the multivariate analysis and the score assigned to each of them, for the preparation of our prediction scale (*deteCTTAR* score).

In the ROC curve analysis, the scale showed an AUC of 0.88 (95% CI 0.84-0.91, p <0.001) (Fig. 1A). A value ≥3 was identified as having the best combination of sensitivity and specificity for predicting ATTR-CA, with an AUC of 0.82 (95% CI 0.77-0.87) (Fig. 1B and C), and OR 22.9 (95% CI 12.3- 42.5, p<0.001) for having the disease.

There was no evidence of significant differences in the number of red flags present between the groups, nor that a greater number of red flags implies a higher risk of ATTR-CA.

DISCUSSION

In our work, male gender, IVS thickness ≥ 16 mm, grade II or III diastolic dysfunction (also known as pseudonormal or restrictive relaxation pattern) and bilateral CTS were predictors of ATTR-CA.

Lack of differences in the number of red flags between patients with and without the disease confirms the low specificity of these conditions to arrive at a diagnosis.

In recent years, two scoring scales for the early diagnosis of ATTR-CA were published. One of them, the transthyretin amyloid cardiomyopathy score (ATTR-CM score) searched for ATTR-CA among patients with IVS hypertrophy and HF with LVEF ≥40%. (14)

However, according to our results, of the total number of patients with a positive diagnosis of ATTR-CA, only 44 patients (26%) had HFpEF, 73 patients (42%) showed no signs/symptoms of HF, while 54 (32%) had decreased LVEF.

Although it is known that ATTR-CA is a pathology historically related to HFpEF, it should be remembered that the natural evolution of the disease without specific treatment leads to progressive deterioration of myocardial histoarchitecture and function. Initially, the isolated deposition of amyloid fibrils affects diastolic function, but later, with excessive accumulation, sarcomere coupling is affected, damaging systolic function. (15)

Therefore, in our study, patients with decreased LVEF could be a consequence of the natural evolution of the disease (and hence, of a late diagnosis) or could be due, in some cases, to the coexistence of other diseases. It is important to emphasize that 21% of this subgroup of patients had a history of coronary artery disease. This highlights the fact that the search for ATTR-CA should not only focus on cardiomyopathies of unexplained etiology, since coexistence with ischemic-necrotic cardiomyopathy can be frequent.

In the other scale (the T-Amylo score), patients had to present as a necessary condition an IVS thickness ≥12 mm associated with one or more red flags to establish the risk of presenting ATTR-CA. (16) However, in our study, 17 patients (10%) with a diagnosis of ATTR-CA did not have increased IVS thickness or red flags.

Although the presence of ATTR-CA in patients without IVS thickening is not widely reported, one study found 5% prevalence of the disease in patients with HFpEF and IVS <12 mm. (17) This could be ex-

Table 1. Baseline characteristics of both groups and variables analyzed in the univariate model.

	ATTR-CA (n=171)	No ATTR-CA (n=171)	p
Clinical Variables			
Age (years)	82 (76-86)	82 (75-87)	0.820
Male gender	155 (90%)	95 (55%)	< 0.001
Hypertension	133 (78%)	138 (80%)	0.505
Diabetes	29 (17%)	47 (27%)	0.019
Dyslipidemia	104 (60%)	110 (64%)	0.502
Smoking	72 (42%)	92 (53%)	0.031
History of coronary artery disease	36 (21%)	71 (42%)	< 0.001
Narrow medullary canal	8 (5%)	2 (1%)	0.054
Atrial fibrillation	89 (52%)	101 (59%)	0.191
Biceps rupture*.	0	0	-
Bilateral carpal tunnel syndrome*.	43 (25%)	3 (2%)	< 0.001
HF, LVEF ≥ 50%*.	44 (26%)	102 (59%)	< 0.001
HF, LVEF <50%*.	54 (32%)	39 (23%)	0.068
Hypotension - normotension* +	4 (2%)	2 (1%)	0.410
Autonomic dysfunction*.	4 (2%)	0	-
Peripheral neuropathy*.	9 (5%)	0	-
PPM Implantation*	44 (26%)	53 (31%)	0.283
Family history *	0	0	-
Skin bruising*.	0	0	-
Electrocardiographic variables			
Microvoltage *	26 (15%)	28 (16%)	0.766
Pseudoinfarction pattern*.	54 (32%)	48 (28%)	0.478
AVB*	42 (25%)	22 (13%)	0.005
LBBB	47 (27%)	48 (28%)	0.903
RBBB	22 (13%)	20 (12%)	0.741
Echocardiographic variables			
IVS <12 mm	4 (2%)	57 (33%)	< 0.001
IVS ≥12 and <16 mm	67 (39%)	86 (50%)	0.038
IVS ≥16 mm	100 (58%)	28 (16%)	< 0.001
IVS (mm)	16.6 (16.1-17.2)	13.3 (12.6-14.1)	< 0.001
LA mild dilation (35 to 41 mL/m^2)	61 (36%)	45 (26%)	0.061
LA moderate dilation (42 to 48 mL/m^2)	55 (32%)	44 (26%)	0.189
LA severe dilation (>48 mL/m^2)	27 (16%)	69 (40%)	< 0.001
E/e' ratio ≥15	77 (45%)	61 (36%)	0.077
LVEF >50%.	90 (53%)	107 (63%)	0.062
Severe AS*	8 (5%)	44 (26%)	< 0.001
Normal relaxation pattern	16 (9%)	38 (22%)	0.002
Grade I diastolic dysfunction pattern (impaired relaxation)	41 (24%)	68 (39%)	0.003
Grade II diastolic dysfunction pattern (pseudonormal)	38 (22%)	15 (9%)	0.001
Grade III diastolic dysfunction pattern (restrictive)	58 (34%)	1 (<1%)	< 0.001
Indeterminate relaxation pattern	18 (11%)	49 (28%)	< 0.001
0 red flags	14 (8%)	8 (5%)	0.260
1 red flag	63 (37%)	75 (44%)	0.185
2 red flags	69 (40%)	54 (32%)	0.909
3 red flags	22 (13%)	26 (15%)	0.533
4 red flags	2 (1%)	8 (5%)	0.054
5 red flags	1 (<1%)	0	-

ATTR-CA: Transthyretin cardiac amyloidosis; AS: aortic stenosis; AVB: atrioventricular blockade; HF: heart failure; IVS: interventricular septum; LA: left atrial; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; PPM: permanent pacemaker; RBBB: right bundle branch block.

Tabla 2. Multivariate analysis

Variable	OR	95% CI	p
Male gender	7.9	(3.6-17.1)	<0.001
BCT	24.4	(6.0-97.8)	<0.001
LVEF >50%	1.2	(0.4-4.2)	0.682
AVB	0.6	(0.1-3.1)	0.632
IVS≥16mm	3.6	(1.8-7.1)	<0.001
Severe LA dilation	0.1	(0.1-0.2)	0.042
Severe AS	0.1	(0.1-0.4)	<0.001
Normal relaxation pattern	0.3	(0.1-0.8)	0.014
Impaired relaxation pattern	2.6	(0.9-7.3)	0.076
Pseudonormal relaxation pattern	4.1	(1.2-12.9)	0.017
Restrictive relaxation pattern	10.3	(7.2-23.4)	0.034
Indeterminate relaxation pattern	0.2	(0.1-1.22)	0.083

AS: Aortic stenosis; AVB: Atrioventricular block; BCT: Bilateral carpal trunnel; IVS: Interventricular septum, LA: left atrial; LVEF: Left ventricular ejection fraction; OR: Odds ratio

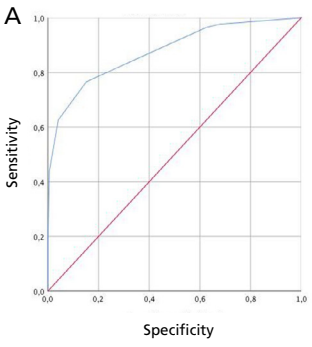
Table 3. Variables identified as predictors in the *deteCTTAR* score

Variable	Points	Prediction	OR (95% CI)	p
MasCuline	2 points		7.9 (3.6-17.1)	<0.001
BCT	3 points		24.4 (6.0-97.8)	<0.001
Increased Thickness IVS ≥ 16mm	1 points		3.6 (1.8- 7.1)	<0.001
Pseudonormal or restrictive Relaxation pAttern	2 points	0 20 40 60 80 100 120	12.7 (6.1-26.3)	<0.001

BCT: Bilateral carpal tunnel; IVS: Interventricular septum.

B

POINTS	SENSITIVITY	SPECIFICITY	AUC	95% CI
≥0	100%	0%%	0.5	(0.43- 0.56)
≥1	97%	33%	0.65	(0.59-0.70)
≥2	96%	38%	0.67	(0.61-0.73)
≥3	76%	85%	0.82	(0.77-0.87)
≥4	62%	95%	0.79	(0.74-0.84)
≥5	44%	96%	0.71	(0.66-0.77)
≥6	17%	100%	0.58	(0.52-0.64)
≥7	13%	100%	0.56	(0.50-0.62)
8	6%	100%	0.52	(0.46-0.59)



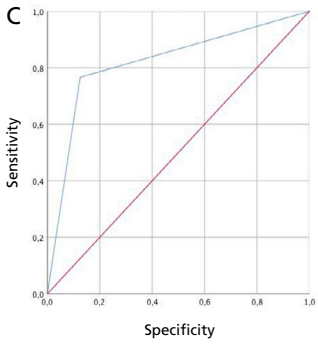


Fig. 1. (A) ROC curve of the prediction model; (B) Sensitivity, specificity and area under curve (AUC) according to each score; (C) ROC curve of the ≥3 value in the scoring scale.

plained in a manner analogous to what occurs with the ischemic cascade, in which molecular methods can detect it even before changes in the electrocardiogram, motility alterations or symptoms become evident.

Both phenomena (myocardial ischemia and ATTR-CA) have a long subclinical period, in which early diagnosis is fundamental to change the prognosis of the disease. (18)

Possibly, in the case of ATTR-CA, if we wait to meet more suspicious conditions (greater IVS thickness or greater number of red flags), the diagnosis is achieved with more advanced disease and with myocardial damage already established. In addition, the new drugs approved in our country do not remove myocardial amyloid deposits, but rather stabilize the TTR molecule to prevent its disintegration, thus avoiding further accumulation. All this leads to the need of trying to establish an early diagnosis, even before the increase in IVS thickness becomes evident. (19)

Thus, the *deteCTTAR* score could be more comprehensive than the T-Amylo score and the ATTR-CM score, since it could discriminate the risk of ATTR-CA among patients, regardless of whether or not they meet the classic warning signs for suspicion and the LVEF value (Fig. 2 and 3)

It is known that CS with phosphonates has a high sensitivity and specificity for the noninvasive diagnosis of ATTR-CA. However, there is currently no agreement in the literature on the appropriate moment to perform it.

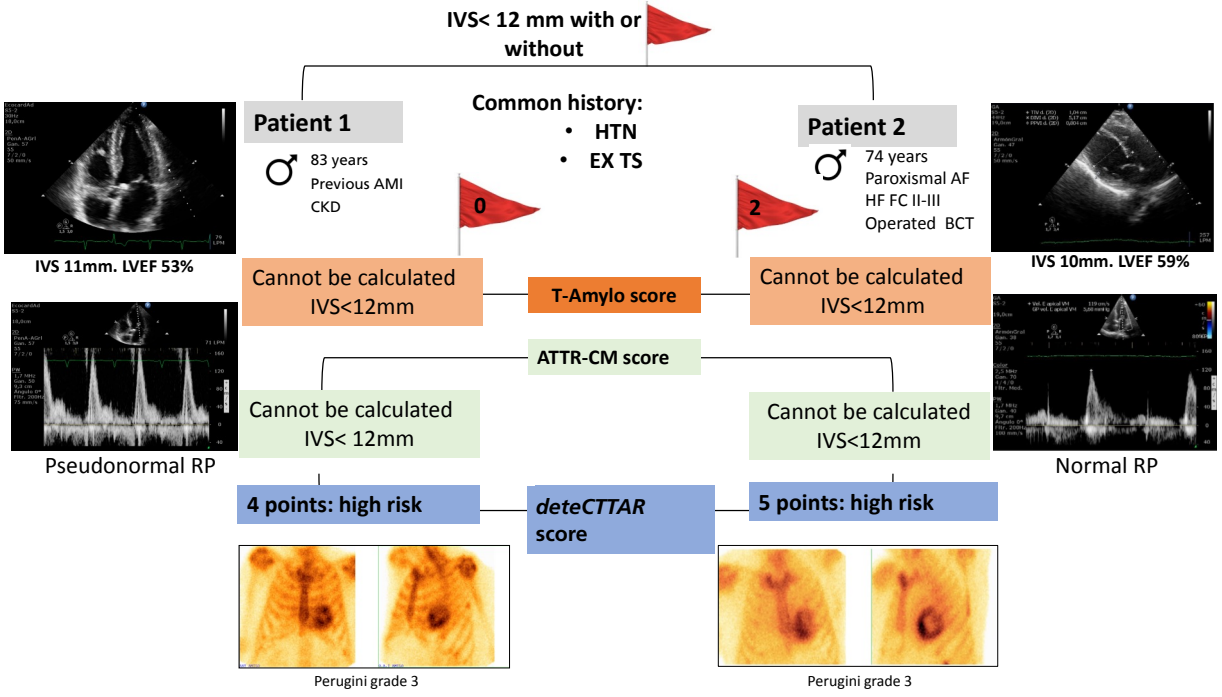
Some guidelines propose that it should be performed directly in certain clinical scenarios, without the need to apply scoring scales to determine the risk of each patient. For others, CS should be requested only in the presence of increased IVS thickness associated with one or more red flags, HFpEF or severe AS. (20-23)

Although it is more common to find ATTR-CA among patients over 65 years of age with HFpEF and severe AS than in the general population, these variables alone were not shown to be predictors of the disease. (2-5, 24-26)

As for IVS thickness, there is no doubt that if it is severely increased, the difference that could exist in the measurement between different operators or machines would not have too much repercussion. However, in values close to 12 mm, an error in the measurement (due to poor technique, poor acoustic window or lack of operator experience) according to the scoring scales in force to date, would mean ruling out the diagnostic suspicion of ATTR-CA.

Previously to the ATTR-CM and T-Amylo scores,

Fig. 2. Patients without IVS hypertrophy with ATTR-CA diagnosis. Patient 1, additionally, had no red flags and patient 2 had two red flags. The three scoring scales for ATTR-CA risk assessment were compared. In both the T-Amylo score and the ATTR-CM score it is not possible to establish risk due to IVS <12mm, whereas the *deteCTTAR* score identified both patients as being at high risk for the disease.



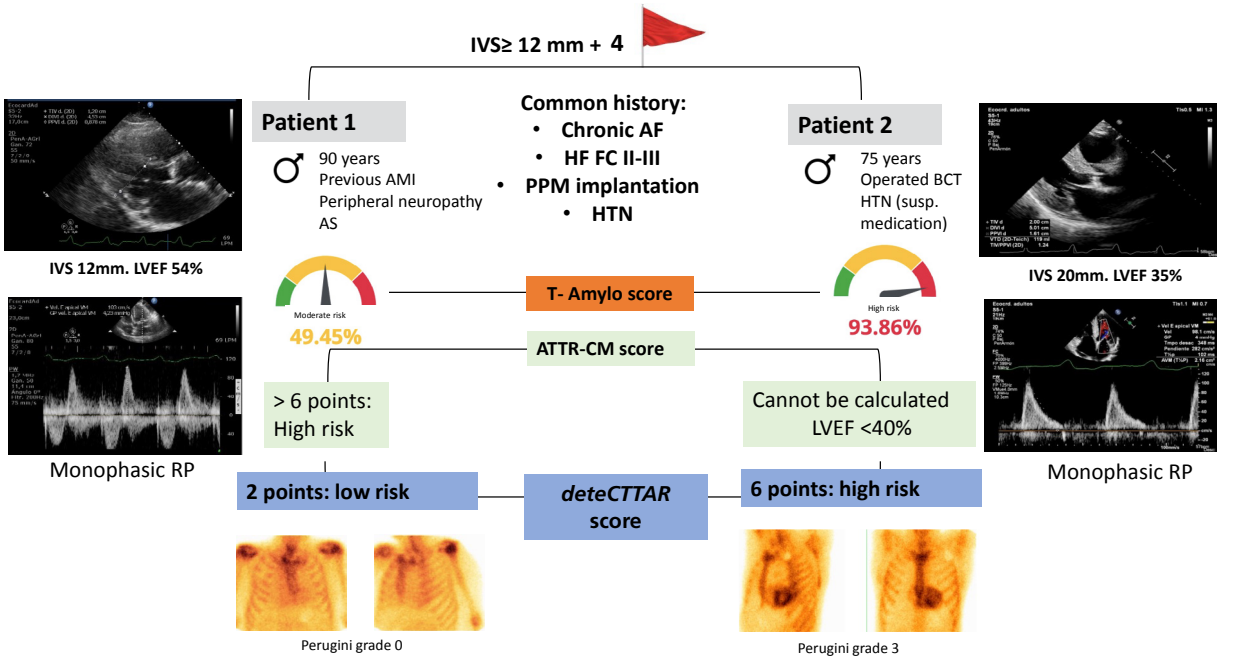
AF: Atrial fibrillation; AMI: Acute myocardial infarction; BCT: Bilateral carpal tunnel; CKD: chronic kidney disease; EX TS: Ex-tobacco smoker; HF FC. Heart failure functional class; HTN: Hypertension; IVS: Interventricular septum; LVEF: Left ventricular ejection fraction; RP: Relaxation pattern.

other prediction models were published but, unlike these, they only included echocardiographic and/or electrocardiographic parameters. (27,28) However, in our study, most of the variables included in these models were not predictors of ATTR-CA, with the exception of the relaxation pattern and IVS thickness.

Regarding clinical history, including red flags such as dysautonomia, peripheral neuropathy, hypotension-normotension, etc., the only one that showed a relationship with the diagnosis was having bilateral CTS.

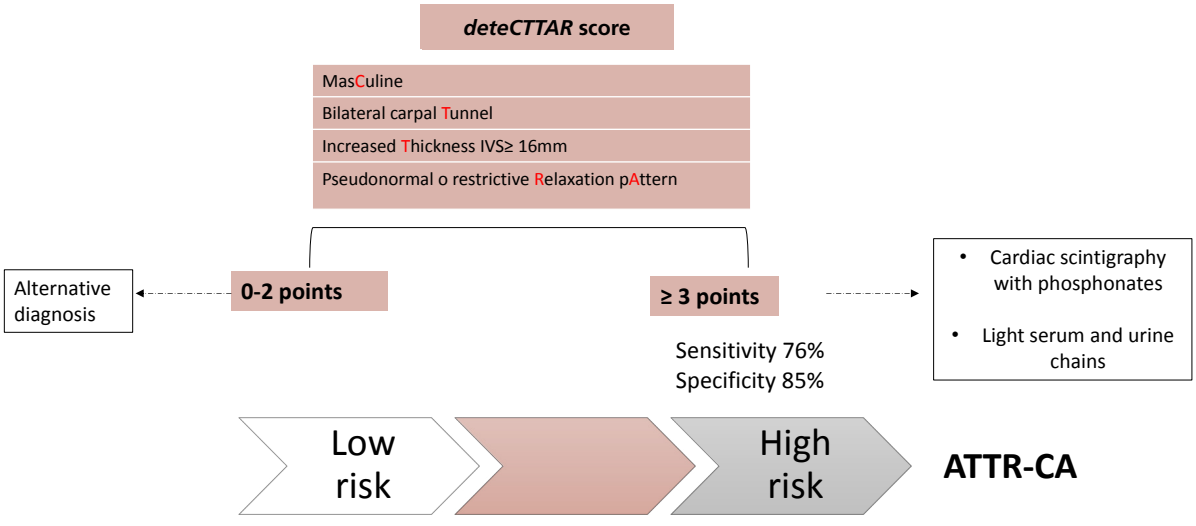
In our scale, a score ≥3 considerably increases the risk of ATTR-CA, so that only in these cases it would be indicated to perform a CS with phosphonates. In

Fig. 3. Patients with IVS increased thickness and 4 red flags. The three scoring scales for risk assessment of ATTR-CA were compared. For patient 1 (negative ATTR-CA), the T-Amylo score predicted an intermediate risk of ATTR-CA, the ATTR-CM score a high risk, while the *deteCTTAR* score, a low risk. In the case of patient 2, the T-Amylo score and the *deteCTTAR* score predicted a high risk of developing the disease, whereas the ATTR-CM score could not be applied due to the degree of LVEF impairment.



AF: Atrial fibrillation; AMI: Acute myocardial infarction; AS: Aortic stenosis; BCT: Bilateral carpal tunnel; HF FC: Heart failure functional class; HTN: Hypertension; IVS: Interventricular septum; LEFV: Left ventricular ejection fraction; PPM: Permanent pacemaker; RP: Relaxation pattern; susp: suspended

Fig. 4. Diagnostic algorithm proposed according to the *deteCTTAR* score



ATTR-CA: Transthyretin cardiac amyloidosis ; IVS: interventricular septum

those patients with a score between 0-2, it would not be necessary to perform it, and an alternative diagnosis should be considered (Fig. 4). If clinical suspicion persists, a cardiac magnetic resonance imaging could be performed, since its high negative predictive value would finally rule out the disease.

According to our scale, the mere presence of bilateral CTS (3 points) would be a sufficient condition to request a CS with phosphonates. In these cases, in particular, the time since diagnosis and/or surgery should be considered, since amyloid infiltration of the median nerve usually precedes cardiac involvement by 5 to 9 years. Thus, a negative CS may not exclude the disease if it was performed early, so a strict cardiological follow-up would be appropriate. (29)

It should be noted that the greatest challenge encountered by all scoring scales for ATTR-CA is in patients with HCM. In the differential diagnosis with this entity, the physician's experience at the time of suspicion is fundamental, since epidemiology, family history and most of the time the electrocardiogram, can contribute to differentiate them, without the need to apply scoring scales.

The *deteCTTAR* score is the first score for the prediction of ATTR-CA developed with patients in our country. It can be applied in the office to any patient without the need to wait for conditions (red flags) that may delay diagnosis, using data obtained from the interrogation and a baseline echocardiogram.

Limitations

The study design was single-center, retrospective, with a relatively small database, so there could be an overfitting of the model.

The low number of patients causes the 95% CI of some predictors to be very wide, which implies lower prediction accuracy.

Although our data are encouraging, they require external validation in the future with a larger sample of patients.

CONCLUSIONS

The presence of increased IVS thickness associated with one or more red flags was not a necessary condition for the diagnosis of ATTR-CA.

The prediction model obtained allowed the development of a scoring scale that demonstrated high sensitivity and specificity to strongly guide the diagnosis of ATTR-CA.

A score ≥3 in the *deteCTTAR* score significantly increases the risk of ATTR-CA.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the web)

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ORIGINAL ARTICLE

2023 SONQO-CALCHAQUÍ III Program. Evaluation of Cardiovascular Variables in Native Communities of the Calchaqui Valleys (Northwest Argentina)

Programa SONQO-CALCHAQUÍ III 2023. Evaluación de variables cardiovasculares en comunidades originarias de los Valles Calchaquíes (Noroeste Argentino)

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ABSTRACT

Background: Previous reports of our work group demonstrated that the native population of Quilmes (Tucumán) has a high rate of overweight and obesity and a Western pattern diet. The 2023 SONQO-CALCHAQUÍ III program was designed to evaluate whether these characteristics are shared by other native communities in the Calchaqui Valleys.
Objective: The aim of this study was to evaluate the cardiovascular variables in three native communities of the Calchaqui Valleys and their possible differences.
Methods: We conducted a cross-sectional study in the communities of Cachi, Colalao del Valle and Fuerte Quemado. The participants answered questionnaires and were evaluated with electrocardiogram, anthropometric determinations and endurance and muscular strength testing.
Results: A total of 819 inhabitants were included (Cachi: 292; Colalao del Valle: 251; Fuerte Quemado: 276). Mean age was 52.9 ± 0.6 years. A high proportion of patients had not checked their cardiovascular risk factors; 39.5% were overweight, 28.1% were obese, 38.9% had normal waist circumference; 9.5% presented carotid atherosclerotic plaques and 39.1% had reduced hand grip strength. The Edmonton Scale revealed that the population was non-frail. The Mini-Mental test indicated mild to moderate cognitive impairment. Colalao del Valle had the best health status but residents of Fuerte Quemado had better sleep quality and self-esteem.
Conclusions: The population is not homogeneous, and each community has its own characteristics. In general, physical fitness is acceptable, but the rate of overweight and obesity is high, regardless of the community in which they live, indicating a Western diet pattern. There are, however, local factors with a protective role in cardiovascular disease that should be further investigated in this population.

Keywords: Native population - South America - Middle and high mountains - Cardiovascular variables – Epidemiology

RESUMEN

Introducción: En reportes anteriores de nuestro grupo de trabajo se demostró que la población originaria de Quilmes (Tucumán) presenta un alto índice de sobrepeso y obesidad y un régimen alimentario occidentalizado. Para evaluar si estas características son compartidas por otras comunidades originarias de los Valles Calchaquíes se llevó a cabo el Programa SONQO-CALCHAQUÍ III (Edición 2023).
Objetivo: Evaluar variables cardiovasculares en tres comunidades originarias de los Valles Calchaquíes y sus posibles diferencias.
Material y métodos: Estudio descriptivo transversal en las comunidades de Cachi, Colalao del Valle y Fuerte Quemado. Se realizaron cuestionarios, electrocardiograma, ecocardiograma, determinaciones antropométricas, y pruebas de resistencia y fuerza muscular.
Resultados: Se incluyeron 819 pobladores (Cachi: 292; Colalao del Valle: 251; Fuerte Quemado:276). La edad promedio fue 52,9±0,6 años. Alta proporción de pacientes no controlaba el estado de sus factores de riesgo cardiovascular. El 39,5 % tenía sobrepeso y 28,1 % obesidad. El 38,9 % presentaba un perímetro de cintura normal. Un 9,5 % presentaba placa aterosclerótica carotídea y 39,1 % tenía la fuerza prensil disminuida. Según la escala de Edmonton la población se encontraba en rango no frágil. El Minimental test indicó deterioro cognitivo leve a moderado.

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En Colalao del Valle se detectó un mejor estado de salud, pero en Fuerte Quemado se evidenció una mejor calidad de sueño y autoestima.
Conclusiones: No se observó una población homogénea, teniendo cada comunidad características diferenciadas. En general el estado físico es aceptable pero con un alto índice de sobrepeso y obesidad, independientemente de la comunidad donde viven, indicando una occidentalización de los hábitos alimenticios. Sin embargo existen factores locales con un rol protector cardio¬vascular que deben ser estudiados más a fondo en esta población.

Palabras clave: Población originaria- Sudamérica - Media y alta montaña - Variables cardiovasculares – Epidemiología

INTRODUCTION

The SONQO-CALCHAQUÍ I and II Programs (years 2018 and 2022) evaluated the Quilmes native community (Colalao del Valle, Tucumán), descendants of the people who settled in that area at the end of the 15th century. (1) The inhabitants had a high rate of overweight and obesity, (2) with a prevalence of cardiovascular risk factors similar to that described in urban centers. (3) The diet was based on flour. Yet, the physical condition was acceptable. (4)

Because of the characteristics of the native communities living in the Calchaqui Valleys (scattered settlements with distinctive historical, geographic and sociocultural characteristics), the question arises whether these findings would be similar in other communities in the same location. The 2023 SONQO-CALCHAQUÍ III Program studied the native communities of Cachi (province of Salta, 2530 m above sea level); Colalao del Valle (province of Tucumán, 3500 m above sea level) and Fuerte Quemado (province of Catamarca, 1795 m above sea level). Therefore, the aim of the present study was to evaluate three native communities of the Calchaqui Valleys, which, despite having similar sociocultural characteristics, present local particularities that could influence the variables studied.

METHODS

We conducted a cross-sectional descriptive study carried out on volunteers ≥ 18 years who attended the SONQO-CALCHAQUÍ III Program in Cachi, Colalao del Valle and Fuerte Quemado from September 23 to October 1, 2023. In order to evaluate only the native population, we worked together with the community delegate. The following determinations were carried out in offices implemented in the local schools:

Office 1 (Surveys):

- Targeted cardiovascular survey. (3,4)
- Mini-Mental State Examination, that evaluates cognitive impairment. (5)
- 24-hour dietary recall (6)
- Food frequency questionnaire: semi-quantitative questionnaire that includes 19 food items indicating the frequency of consumption (daily, weekly or monthly) in the last year.
- 12-Item Short Form Survey (SF-12): assesses self-perceived health status on a scale of 0 to 48. (7)
- 10-item Rosenberg Self-Esteem Scale on a scale of 0 to 40. (8)
- Pittsburgh Sleep Quality Index. (9)
- Frailty test (Edmonton Scale). (10)

Office 2 (Anthropometry, blood pressure and pulse oximetry):

Body mass index (BMI), expressed in kg/m^2, was calculated and values ≥18,5 and < 25 were considered normal. Waist circumference (normal ≤ 88 cm in women and ≤ 102 cm in men) and neck circumference (normal ≤ 43 cm) were measured.

Blood pressure (BP) was measured with an automatic BP monitor (Omron ® 7120) according to the guidelines of the Argentine Consensus on Hypertension. (11)

Oxygen saturation (%) and heart rate (bpm) were measured by plethysmography using a pulse oximeter (Contec® CMS50N).

Office 3 (Electrocardiogram):

12-lead electrocardiogram with a digital machine (Jotatec® TaurusTouch).

Office 4 (Echocardiography):

The dimensions (mm) and areas (cm2) of the cardiac structures (Esaote® MyLab 30 Gold) were recorded, and the left ventricular ejection fraction (LVEF) was calculated using the Simpson biplane method. (12)

Office 5 (Peripheral vascular ultrasound):

The neck vessels were evaluated using Doppler ultrasound (Esaote® MyLab 30 Gold).

Office 6 (Endurance and muscular strength testing):

The Ruffier-Dickson test was used to assess endurance to physical stress. (13). The Ruffier index was calculated as the sum of resting heart rate plus exercise heart rate plus post-exercise heart rate minus 200 and divided by 10. The following scale was considered: 0: very good; 0.1 to 5: good; 5.1 to 10: average; 10.1 to 15: insufficient and 15.1 to 20: poor.

The maximum hand grip strength was measured by means of a hydraulic dynamometer (Jamar®) in the dominant hand and was calculated as the average of 3 trials. The normal values considered were ≥ 27 kg and ≥16 kg in women. (14)

Exclusion criteria: people with sensory, cognitive or motor disabilities.

Statistical analysis

The results were expressed as mean ± standard error. Nominal variables were analyzed using the chi-square (χ^2) test (2) or Monte Carlo simulation (when data was 0). The Student's t-test was used for pooled data and ANOVA for numerical variables. A p value < 0.05 was considered statistically significant. All the statistical calculations were performed using Prism 5.0.2 software package.

Ethical considerations

The study was approved by the Research Ethics Committee of the SI.PRO.SA Research Department (Decision 34/2022).

All patients gave their informed consent before participating in the study.

RESULTS

Of the 880 inhabitants who participated in the SONQO-CALCHAQUÍ 2023 Program, 819 were included in this study (Cachi: 292, Colalao del Valle: 251, and Fuerte Quemado: 276); 510 were women and 309 were men. There were no differences in the distribution by sex in the communities. Mean age was 52.9±0.6 years (Cachi: 53.3±1.0 years, Colalao del Valle: 51.6±1.1 years and Fuerte Quemado: 53.7±1.0 years; p = 0.392).

Office 1

Socioeconomic and educational data:

Illiteracy was found in 11.5% of the population; 43.3% had completed primary education, 29.7% had secondary education, 10.4% had tertiary education and 2.6% were university graduates. A total of 3.1% participants did not answer this question. A different distribution was found in the three communities, with a lower proportion of illiteracy and more university students in Colalao del Valle (p = 0.041).

Occupation: 23.1% were housewives, 12.4% were unemployed, 41.5% were active workers and 14.0% were retired. A total of 4.0% participants did not answer this question. There were no differences between the three communities.

Medical coverage: 36.8% had no coverage, 32.4% had social security, 22.1% had PAMI (a medical retirement plan) and 5.6% had prepaid medical insurance. A total of 2.7% participants did not answer this question. There were no differences between the three communities.

Mobile telephone: 52.4% did not own a mobile telephone (42.5% in Cachi; 63.7% in Colalao del Valle and 52.5% in Fuerte Quemado; p<0.001). All the participants answered this question.

Targeted cardiovascular survey:

The distribution of self-reported cardiovascular risk factors is shown in Table 1. Approximately 30% of patients had not had their blood pressure checked, while more than 60% and more than 75% had not had their blood sugar and cholesterol levels measured, respectively, in the past year. Of the 258 inhabitants with hypertension, 26.0% were not receiving pharmacological treatment (52.0% in Cachi. 12.3% in Colalao del Valle and 17.6% in Fuerte Quemado; p < 0.001).

The 95 smokers smoked 5.6 ± 0.8 cigarettes per day (with no differences between the three communities).

Of the 126 inhabitants with known diabetes, 27.8% were not receiving pharmacological treatment (13.3% in Cachi, 56.0% in Colalao del Valle and 42.3% in Fuerte Quemado; p < 0.001).

Of the 72 inhabitants with known dyslipidemia, only three were receiving pharmacological treatment.

Mini-Mental State Examination

The average score was 15.0 ± 0.1 points (with no differences in this item in the three communities), indicating a population with mild to moderate cognitive impairment.

Diet

a) 24-hour dietary recall:

Breakfast: 49.0% drank *yerba mate* and 36.5% another infusion; 63.1% of them also ate (mainly homemade) bakery and 7.6% did not have breakfast (4.5% in Cachi, 8.8% in Colalao del Valle and 9.8% in Fuerte Quemado; p = 0.038).

Snack: 7.9% drank water alone, 8.5% drank water with other foods (mainly seasonal fruits) and 44.9% ate other foods; 38.6% did not eat snacks (30.8% in Cachi, 41.4% in Colalao del Valle and 44.2% in Fuerte Quemado; p= 0.002).

Lunch: 21.2% ate some kind of stew, 13.6% ate meat, 7.9% chicken, 14.9% pasta, 21.0% rice and 13.6% ate some other kind of food; 12.9% of respondents had consumed a dessert (usually seasonal fruit) and 7.8% did not have lunch (without differences between the three communities).

Afternoon snack: 44.4% drank *yerba mat*e and 38.0% had another infusion accompanied by (mainly homemade) bakery in 57.9% of the respondents; 17.6% did not eat an afternoon snack (15.4% in Cachi, 23.9% in Colalao del Valle and 14.1% in Fuerte Quemado; p = 0.006); 10.6% ate something between the afternoon snack and dinner (19.5% in Cachi, 6.0% in Colalao del Valle and 5.4% in Fuerte Quemado; p < 0.001).

Dinner: 52.9% had dinner, generally the same meal as lunch (Cachi: 63.7%, Colalao del Valle: 43.8% and Fuerte Quemado: 48.9%; p < 0.001).

b) Food frequency questionnaire: the main results in the three communities are shown in Figure 1. There was higher consumption of meat, vegetables and fruits in Colalao del Valle and of bakery products in Cachi. The number of sugar and water servings per month was similar in the three communities (Cachi: 36.6 ± 7.1, Colalao del Valle: 36.5 ± 2.7 and Fuerte Quemado: 31.4 ± 3.2 and Cachi: 106.9 ± 5.1, Colalao del Valle: 106.5 ± 4.7 and Fuerte Quemado: 110.2 ± 4.8, respectively).

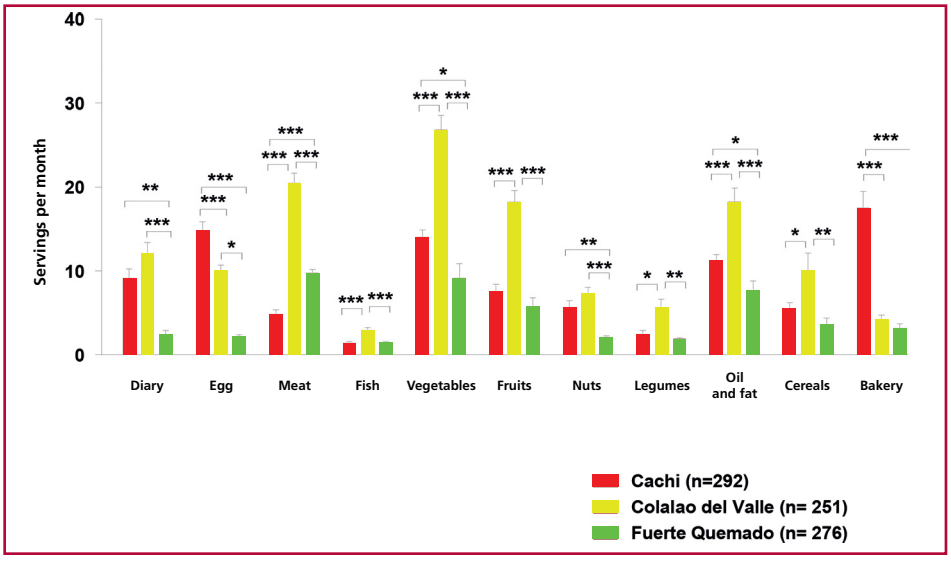
Quality of life, self-esteem, sleep quality, and frailty questionnaires

a) SF-12: mean score was 35.6 ± 0.2 points (Cachi: 36.0 ± 0.4 points, Colalao del Valle: 36.3 ± 0.4 and Fuerte Quemado: 34.5 ± 0.4; p = 0.003).
b) Rosemberg Self-Esteem Scale: mean score was 28.9 ± 0.2 points (Cachi: 28.5 ± 0.2 points, Colalao del Valle: 28.5 ± 0.2 and Fuerte Quemado: 29.8 ± 0.3; p = 0.003).
c) Sleep assessment: sleep quality was rated very good in 23.1%, fairly good in 55.8%, fairly bad in 16.9% and very bad in 4.2%. There were no differences between the three communities. 20.3% took

Tabla 1. Targeted cardiovascular survey

		Cachi (n=292)	Colalao del Valle (n=251)	Fuerte Quemado (n=276)	Total (n=819)	p
Did you check your BP in the last year?	YES	71.2%	74.9%	61.2%	69.0%	0.002
Do you have HTN?	YES	25.7%	32.3%	37.0%	31.5%	0.025
	NO	59.2%	54.2%	46.4%	53.4%	
	IDK	15.1%	13.5%	16.7%	15.1%	
Do you smoke?	YES	11.6%	11.2%	12.0%	11.6%	<0.001
	NO	84.6%	76.1%	79.0%	80.1%	
	FORMER	3.8%	12.7%	9.1%	8.3%	
	SMOKER					
Did you check your blood sugar levels in the last year?	YES	25.7%	47.0%	40.6%	37.2%	<0.001
Do you have diabetes?	YES	25.7%	10.0%	9.4%	15.4%	<0.001
	NO	63.0%	88.4%	87.3%	79.0%	
	IDK	11.3%	1.6%	3.3%	5.6%	
Did you check your cholesterol in the last year?	YES	30.8%	25.9%	13.4%	23.4%	<0.001
Do you have dyslipidemia?	YES	24.3%	0.4%	0.0%	5.6%	<0.001
	NO	15.8%	0.0%	0.0%	8.8%	
	IDK	59.9%	99.6%	100%	85.6%	
Did you suffer a MI?	YES	13.4%	2.8%	3.3%	6.7%	<0.001
	NO	79.8%	88.0%	85.9%	84.4%	
	IDK	6.8%	9.2%	10.9%	8.9%	
Did you suffer a stroke?	YES	20.2%	2.8%	5.1%	9.8%	<0.001
	NO	76.4%	92.4%	87.3%	85.0%	
	IDK	3.4%	4.8%	7.6%	5.3%	

BP: blood pressure; HTN: hypertension; IDK: I don't know; MI: myocardial infarction
In the case of only "yes" or "no" questions, only the affirmative answer is presented. When there was also the option "I don't know" the data of the three possible answers are presented



*p<0.05; **p<0.01; ***p<0.001

Fig. 1. Food frequency questionnaire in the communities studied

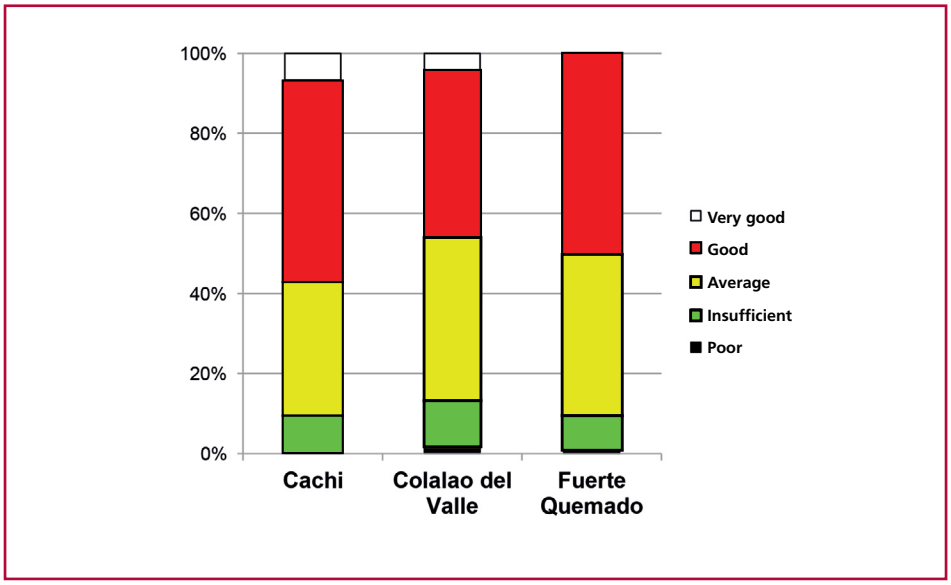


Fig. 2. Results of the Ruffier-Dickson test

p = 0.045

medicine to sleep at least once in the last month (Cachi: 29.8%, Colalao del Valle: 11.2% and Fuerte Quemado: 18.5%; p < 0.001). A total of 45.3% reported drowsiness at some time during daily activities (Cachi: 36.0%, Colalao del Valle: 46.2% and Fuerte Quemado: 54.3%; p < 0.001).

d) Frailty test (Edmonton Scale): the value obtained was 3.6 ± 0.1 points (range considered as non-frail). There were no differences between the three communities.

Office 2

Mean BMI was 28.3±0.3 kg/m² (overweight). Of the population, 0.8% was undernourished, 31.6% had adequate weight, 39.5% were overweight and 28.1% were obese, with no differences between the three communities. The mean waist circumference was 98.5 ± 0.7 cm (Cachi: 96.5 ± 0.9 cm, Colalao del Valle: 97.3 ± 0.9 and Fuerte Quemado: 100.9 ± 1.3; p = 0.014). Waist circumference was within normal ranges in 38.9% of the population, with no differences between the three communities. Neck circumference was also not significantly different, with a mean value of 38.6 ± 0.5 cm, normal in 82.9% of the inhabitants (Cachi: 78.1%, Colalao del Valle: 89.9% and Fuerte Quemado: 79.9%; p = 0.022).

Systolic blood pressure was 128.9 ± 0.9 mm Hg (26.6% presented elevated values), diastolic blood pressure was 77.2 ± 1.4 mm Hg (11.0% with elevated values), and heart rate was 71.0 ± 0.5 beats per min. There were no differences in these parameters between the three communities. Oxygen saturation was 95.4 ± 0.1% (Cachi: 94.4 ± 0.5%, Colalao del Valle: 95.8 ± 0.2% and Fuerte Quemado: 96.1 ± 0.2%; p = 0.004).

Office 3

The ECG was abnormal in 26 subjects (two had atrial fibrillation; nine had right bundle branch block and two had left bundle branch block).

Office 4

The echocardiogram was abnormal in 15.8% of the inhabitants (Cachi: 20.5%, Colalao del Valle: 13.9% and Fuerte Quemado: 12.3%; p = 0.017). These abnormalities included two cases of congenital heart disease, six of valvular calcifications, two cases of valvular stenosis, seven of valvular regurgitation and one case of pericardial effusion.

Office 5

No aneurysms, tumors or vascular malformations were found. Atherosclerotic plaques were detected in 9.5% of the inhabitants, with no significant differences between the three communities.

Office 6

The Ruffier-Dickson test was performed on 596 subjects. Resting heart rate was 71.5 ± 0.5 bpm, increased to 101.3 ± 0.7 bpm during exercise (43.1 ± 0.9% increase; p < 0.001) and decreased to 78.8 ± 0.6 bpm post-exercise (a 21.8 ± 0.4% decrease; p < 0.001). The inhabitants of the community of Colalao del Valle presented greater increase and lesser decrease in heart rate. The number of squats performed was 24.1 ± 0.3 (without significant differences).

The Ruffier index was 5.2 ± 0.1. Mean Ruffier index (Cachi: 4.9 ± 0.2, Colalao del Valle: 5.8 ± 0.3 and Fuerte Quemado: 5.1 ± 0.3; p = 0.038) and its distribution (Figure 2) were different between the three communities.

Hand grip strength was evaluated in 667 inhabitants using a dynamometer. The mean value was 25.2 ± 0.6 kg (Cachi: 22.8 ± 0.9 kg, Colalao del Valle: 28.7 ± 1.2 and Fuerte Quemado: 24.8 ± 1.1; p = 0.002). Hand grip strength was reduced in 39.1% of the inhabitants, with no significant differences.

It should be noted that 14 patients were referred to a more complex care center as a result of the results obtained.

DISCUSSION

In this new phase of the SONQO-CALCHAQUÍ Program we were able to compare some parameters related to cardiovascular health in the inhabitants of three native communities of the Calchaqui Valleys.

There were differences in the variables under study in the three communities. Colalao del Valle inhabitants have better health status because their educational level is higher, patients with hypertension and diabetes are better treated and a higher percentage of the population has normal neck circumference. However, residents of Fuerte Quemado have better sleep quality and self-esteem. These differences indicate that the inhabitants of the Calchaqui Valleys are not a homogeneous population, but that each community has its own characteristics. Follow-up studies should be conducted to assess the future impact of these different characteristics on cardiovascular health.

According to the records reviewed, the sample represents 4.4% of the total population of Cachi and 11.1% of the total population of Colalao del Valle. (15) Fuerte Quemado lacks recent statistics, so this data could not be calculated. Interestingly, the records reviewed do not differentiate between native and non-native inhabitants, so it can be assumed that the sample recorded in this study is representative of the native communities studied.

Although the three communities have some different features, they share similar characteristics in terms of non-frail populations with good self-esteem, good sleep quality, and mild to moderate cognitive impairment.

It is worth noting that the average BMI was in the overweight range and that 67.6% of the population was overweight. One bias of the present study may be the lack of sampling, as the population evaluated consisted of individuals who voluntarily agreed to participate. However, this finding was already observed in previous editions of the SONQO-Calchaquí Program (2,4) and has been reported by other authors. (16) In addition, high levels of overweight have been reported in other native populations in Argentina, such as the Wichi (17) and Toba communities. (18) A recent study showed that the inhabitants of Northwest Argentina have a high rate of overweight and obesity. (19) The high BMI may be due to dietary changes. In the present study, the 24-hour dietary recall questionnaire showed low intake of fruits, nuts, and legumes. To underscore this point, the 24-hour recall indicates a diet based on stew, rice and pasta, with low intake of dairy products. Archaeological studies indicate that the diet of the Calchaqui Valleys has been based on carbohydrates since prehistoric times. (20) This difficult access to food has persisted to the present day, with the difference that the access to processed food is increasing. The low consumption of nuts (which have proven cardiovascular benefits) (21) is particularly noteworthy, given that this area is a producer of nuts. Several factors are likely to be involved in the poor choice of food, especially economic factors: (22) more than half of the population is not employed and does not have tertiary education. This is coupled with the difficult access observed in this geographical area since prehistoric times, (20) as well as the difficulty of storage and social factors. This poor dietary choice should be further investigated as it has a direct impact on the cardiovascular health of the population. It is noteworthy that the low consumption of ultra-processed food and the high consumption of yerba mate suggest that the process of westernization is not yet complete.

Regarding economic factors, it has been shown in other populations that people of low socioeconomic status have low protein diets, mainly due to the higher cost of healthy food. (23,24)

The decreased hand grip strength found in 39.1% of the population could indicate sarcopenia. However, the Ruffier index was found to be within the average to good range, with a limited number of subjects in the insufficient range, indicating adequate cardiac endurance during exercise. (25) In this regard, it is important to consider the potential protective role that their lifestyle and socioeconomic status may play in other health domains (sleep quality and self-esteem). It can be hypothesized that deep-rooted traditions, coupled with a social background that accompanies and gives identity to the person, together with a rough terrain which implies greater physical activity, would be important factors in this protective role. In this sense, further studies are needed to validate this hypothesis.

The absence of atherosclerotic lesions in most of the population studied (only 9.5% of the population had plaques on neck vessel Doppler ultrasound) would support the existence of local factors with a cardiovascular protective role. In other populations, it is difficult to find patients with elevated BMI without atherosclerotic plaques. Whether this protection is genetic or epigenetic remains to be determined in future studies.

In conclusion, the inhabitants of the Calchaqui Valleys are not a homogeneous population, and each community has its own characteristics. In general, their physical fitness is acceptable, but the rate of overweight and obesity is high, regardless of the community in which they live, indicating a Western diet pattern. There are, however, local factors with a protective role in cardiovascular disease that should be further investigated in this population.

Conflicts of interest

None declared.

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

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APPENDIX I
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ORIGINAL ARTICLE

Performance of Myocardial Work as a Marker of Ischemia in Dipyridamole Stress Echocardiography

Comportamiento del trabajo miocárdico como marcador de isquemia en el ecocardiograma estrés con dipiridamol

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ABSTRACT

Background: There is scarce evidence about the assessment of myocardial work during dipyridamole stress echocardiography (DSE).
Objective: The aim of the present study was to evaluate the performance of myocardial work during DSE and to define its differences between patients with and without myocardial ischemia .
Methods: This retrospective study included 30 patients; mean age was 69.9 ± 10 years and 45% were men.
Results: Eight patients (27%) presented ischemia. After dipyridamole infusion, global myocardial work index (GWI) and global constructive work (GCW) decreased in the groups with and without ischemia. In patients with ischemia, global wasted work (GWW) increased and global work efficiency (GWE) decreased. In patients without ischemia, GWW decreased while GWE remained unchanged or significantly improved.
Conclusions: In DSE myocardial ischemia was associated with increased GWW and decreased GWE. These findings warrant further studies to elucidate the responsible mechanisms.

Key words: Myocardial work - Dipyridamole stress echocardiography - Strain

RESUMEN

Introducción: Existe escasa evidencia sobre la evaluación del trabajo miocárdico (TM) durante el eco estrés con dipiridamol (EED).
Objetivos: Estudiar el comportamiento del trabajo miocárdico durante el EED y definir sus diferencias entre pacientes con y sin isquemia.
Material y métodos: Estudio retrospectivo. Se incluyeron 30 pacientes, 45 % hombres, con una edad de 69,9 ± 10 años.
Resultados: Ocho pacientes (27%) presentaron isquemia. Con el apremio con dipiridamol, en los grupos con y sin isquemia disminuyó el índice de trabajo miocárdico global (ITG) y el trabajo constructivo global (TCG). En los pacientes con isquemia se evidenció un aumento del trabajo desechado global (TDG) y una disminución de la eficiencia del trabajo miocárdico (ETG), mientras que en los pacientes sin isquemia el TDG disminuyó y la ETG se mantuvo o mejoró significativamente.
Conclusiones: La isquemia en el EED se acompañó de un mayor desaprovechamiento y una menor eficiencia del trabajo miocárdico. Dichos hallazgos justifican más estudios al respecto, para desentrañar los mecanismos responsables.

Palabras clave: Trabajo miocárdico - Ecocardiograma estrés dipiridamol - Strain

INTRODUCTION

Dipyridamole stress echocardiography (DSE) is a first-line stress test for the diagnosis and/or prognosis of coronary artery disease, particularly in patients unable to exercise maximally. Although the sensitivity of DSE is lower in single-vessel disease, the diagnostic accuracy is similar to that of dobutamine stress echocardiography in protocols that include atropine or handgrip exercise in the final stage and employ a fast infusion rate. (1)

This type of stress also allows for the measurement of other parameters with a high degree of feasibility. These parameters include coronary flow reserve (CFR) in the left anterior descending (LAD) coronary artery and the assessment of myocardial deformation using speckle-tracking echocardiography. This is pos-

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sible because the drug has vasodilator properties and produces lower increase in contractility and in heart rate (HR) compared to dobutamine, which makes it an ideal complement for the analysis of myocardial strain. It has been previously demonstrated that the information provided by these techniques increases the sensitivity of the test without significantly affecting its specificity and provides additional prognostic value. (2)

While myocardial strain quantification offers a more sensitive means of detecting early signs of myocardial dysfunction that may otherwise go undetected in subjective wall motion analysis, one of its limitations is its dependence on myocardial loading conditions. It has been suggested that measuring the pressure-strain loop is an effective method for estimating myocardial work (MW). This allows for a more comprehensive evaluation of myocardial function by considering the global myocardial work index (GWI), the global constructive work (GCW), the global wasted work (GWW), and the global work efficiency (GWE). The GWI is derived from the area of the pressure-strain loop. The GCW represents shortening of the myocardium during isovolumetric contraction and lengthening of the myocardium during isovolumetric relaxation. The GWW represents the amount of work that is not useful in this context (lengthening of the myocardium during systole or shortening during isovolumetric relaxation). Finally, the GWE is defined as the ratio between constructive work and the sum of constructive and wasted work. (3)

The aim of the present study was to evaluate the behavior of different MW parameters during an DSE study in a consecutive population of patients and the differences between those with and without ischemia.

METHODS

Study population

This single-center study had a retrospective and analytical design. The study population consisted of consecutive patients who underwent DSE in the echocardiography laboratory of Hospital de Clínicas José de San Martín between August 2023 and March 2024. Patients with atrial fibrillation, inadequate ultrasound window and significant (moderate or severe) valvular heart disease or congenital heart disease were excluded from the study.

Stress echocardiograph

Patients fasted for at least 4 hours and avoided xanthine containing beverages or medications 12 hours before the study. Dipyridamole was the stressor used in intravenous infusion of 0.84 mg/kg/min over 4 minutes. (4) A Vivid E95 ultrasound machine (GE HealthCare) with a 5 MHz matrix array transducer was used to acquire two-dimensional images at a frame rate of 60 to 70 frames/second. The evaluation of the standard ultrasound parameters was performed following the guidelines of the American Society of Echocardiography (ASE). (5)

Analysis of longitudinal strain and myocardial work

Global longitudinal strain (GLS) was analyzed semiautomatically from the apical 4-, 3-, and 2-chamber views and was considered as the average of the values obtained in a 17-segment model. The first step to calculate myocardial work was to visualize the opening and closure of mitral and aortic valves from the apical 3-chamber view and to measure cuff blood pressure in the patient's right arm to obtain the pressure-strain loop. The analysis of the pressure-strain loop allowed us to determine the following parameters: GWI, GCW, GWW and GWE according to the myocardial deformation during the different periods of the cardiac cycle (Figure 1). These values were measured both at baseline and 8 minutes after the end of dipyridamole infusion, and the delta was defined as the difference between both measurements. (6)

Ethical considerations

The study was approved by the local ethics committee.

Statistical analysis

All calculations were performed using IBM SPSS Statistics 20 software package. Qualitative variables were expressed as percentages and quantitative variables as mean and standard deviation or median and interquartile range according to their distribution. The groups were compared using the corresponding hypothesis tests (chi square test, Student's t test or the Mann-Withney test) depending on the type of variable and distribution of data. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 30 patients were consecutively included; mean age was 69.9 ± 10 years and 45% were men. One third had a history of coronary artery disease and the prevalence of cardiovascular risk factors was high. The main reason for performing DSE was to assess the preoperative risk of cardiac events before peripheral vascular intervention. These characteristics are summarized in Table 1.

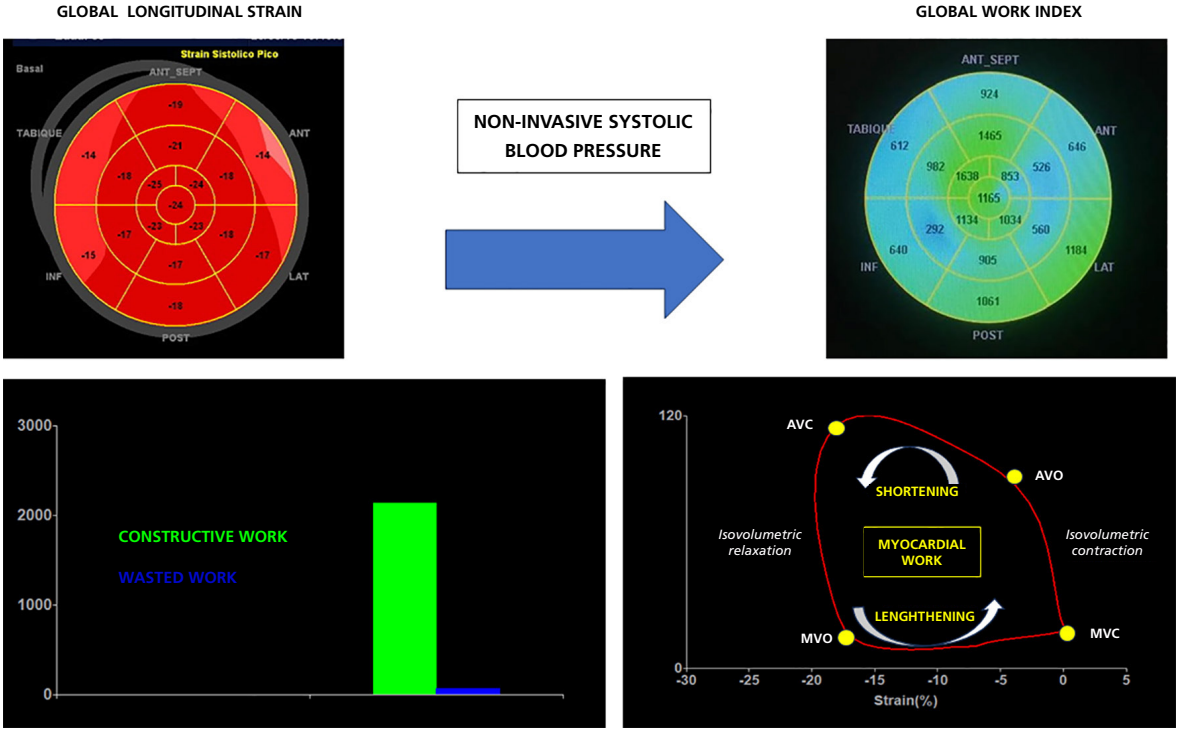
Myocardial ischemia was evident in 8 patients (27%) according to the visual analysis of wall motion. These patients exhibited a trend toward higher prevalence of previous MI and cardiovascular risk factors. There were no differences in the baseline HR and blood pressure at rest and during pharmacologic stress. Left ventricular volumes had no differences in patients with and without ischemia but left ventricular ejection fraction (LVEF) and GLS were significantly lower in patients with dipyridamole-induced ischemia. The CFR in the LAD coronary artery was lower in patients with ischemia, and these patients had a trend toward lower contractile reserve. Table 2 summarizes the characteristics of the 2 groups.

When the different parameters of MW were analyzed, GWI and GCW decreased in both groups, although there was a tendency for a smaller decrease in patients without ischemia. In contrast, the GWW and GWE performed differently. In patients with ischemia, the GWW increased and the GWE decreased. In patients without ischemia, the GWW decreased while the GWE remained unchanged or significantly improved (Table 2, Figure 2 and 3)..

DISCUSSION

Stress echocardiography is still a first-line test for the diagnosis and prognosis of coronary artery disease.

Fig. 1. Based on the values of global longitudinal strain (top-left) and noninvasive arterial pressure, the global myocardial work index (GWI) is automatically determined (top-right). The opening and closing times of the mitral and aortic valves are used to assess myocardial deformation at different stages of the cardiac cycle (bottom).



AVC: aortic valve closure; AVO: aortic valve opening; LVP: left ventricular pressure; MVC: mitral valve closure; MVO: mitral valve opening.

Table 1. Patients' clinical characteristics

Variable	Value
Age (years)	69.9 ± 10
Male sex	45%
HTN	78%
DM	33%
Smoking habits	16%
Obesity	26%
Previous MI	29%
PCI	8%
Beta blockers	44%
ACEI	32%
ARB	32%
Statins	56%
Aspirin	43%

ACEI: angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; DM: diabetes mellitus; HTN: hypertension; MI: myocardial infarction; PCI: percutaneous coronary intervention.

About 20-30% of patients cannot exercise maximally and the use of high-dose dipyridamole administered over 4 minutes is an excellent option in this scenario. However, the main limitation of this approach is the subjectivity inherent in visual analysis of wall motion, particularly in less experienced operators. This is a relevant consideration given that the drug does not increase contractility and heart rate in a proportionate manner to that observed with dobutamine, and that a considerable proportion of patients are already receiving beta-blocker therapy.

To address these limitations, the concurrent measurement of CFR in the LAD coronary artery and the analysis of myocardial deformation through two-dimensional strain have been proposed. The CFR allows for a comprehensive evaluation of the coronary vascular tree and numerous studies have demonstrated its significant prognostic value beyond the presence or absence of wall motion abnormalities. Therefore, its measurement is strongly recommended in all patients undergoing stress echocardiography. (8,9) Nevertheless, its implementation in routine clinical practice is limited due technical considerations, namely the necessity for an optimal configuration of imaging parameters, the fact that not all operators know how to use it, and economic reasons in our setting.

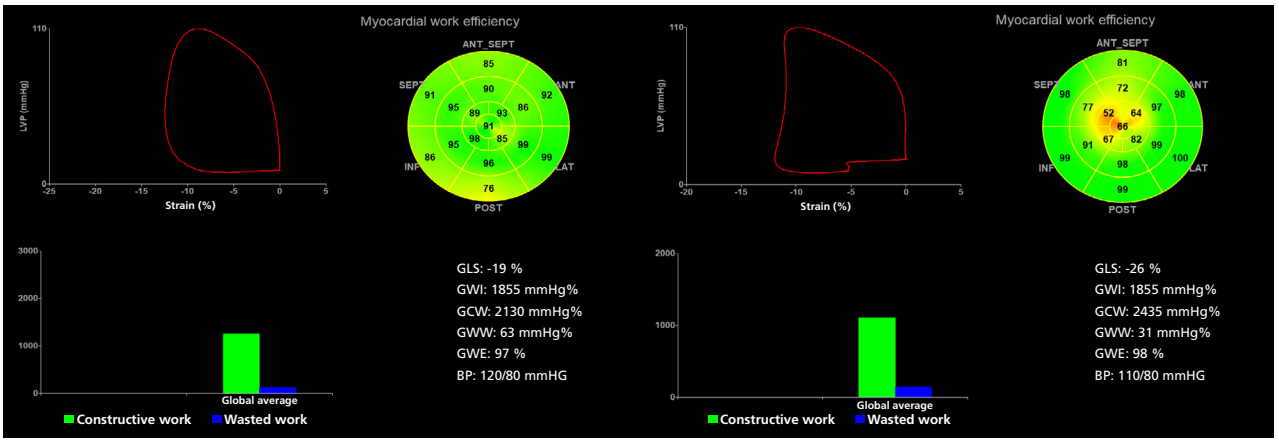
The quantification of myocardial deformation by analyzing GLS represents another valuable tool for enhancing the sensitivity of the test without signifi-

Tabla 2. Clinical and echocardiographic characteristics of patients according to the presence of myocardial ischemia.

Variable	Ischemia (n=8)	No ischemia (n=22)	p
CLINICAL CHARACTERISTICS			
Male sex	50%	38%	0.601
Age (years)	73.6 ± 9.1	68.7 ± 10.1	0.293
HTN	100%	78%	0.225
DM	48%	29%	0.412
Previous MI	88%	10%	0.113
Beta blockers	60%	48%	0.467
ACEI	38%	30%	0.822
ARB	32%	28%	0.783
Statins	65%	52%	0.676
Aspirin	65%	35%	0.432
SBP (mm Hg)	130 ± 9	134 ± 15	0.603
Stress SBP (mm Hg)	127 ± 39	125 ± 25	0.893
DBP (mm Hg)	72 ± 7.5	77 ± 8	0.226
Stress DBP (mm Hg)	72 ± 12	72 ± 10	0.868
HR	67 ± 18	68 ± 10	0.871
Stress HR	82 ± 12	87 ± 17	0.532
ECHOCARDIOGRAPHIC PARAMETERS			
EDV (mL)	94 ± 57	79 ± 31	0.468
Stress EDV (mL)	95 ± 57	85 ± 36	0.645
ESV (mL)	55 ± 54	37 ± 24	0.521
Stress ESV (mL)	57 ± 56	35 ± 24	0.452
LVEF (%)	50 ± 14	56 ± 11	0.248
Stress LVEF (%)	49 ± 15	61 ± 11	0.031
Longitudinal strain (%)	-15 ± 4	-18.2 ± 4	0.099
Stress longitudinal strain (%)	-14 ± 5	-20.8 ± 4.1	0.003
CFR in the LAD coronary artery	1.6 ± 0.24	2.3 ± 0.35	0.001
LV contractile reserve	17%	37%	0.349
Wall motion score index	1.41 ± 0.49	1.11 ± 0.23	0.191
Stress wall motion score index	1.64 ± 0.41	1.10 ± 0.22	0.019
MYOCARDIAL WORK PARAMETERS			
GWI (mmHg%)	1493 ± 513	1946 ± 481	0.828
Stress GWI (mmHg%)	1164 ± 470	1850 ± 24	0.005
Delta GWI (mmHg%)	-329 ± 163	-96 ± 255	0.050
GCW (mmHg%)	1697 ± 572	2229 ± 612	0.068
Stress GCW (mmHg%)	1358 ± 580	2136 ± 640	0.014
Delta GCW (mmHg%)	-338 ± 183	-93 ± 312	0.081
GWW (mmHg%)	130 ± 105	123 ± 87	0.885
Stress GWW (mmHg%)	143 ± 93	82 ± 53	0.171
Delta GWW (mmHg%)	14 ± 95	-41 ± 64	0.108
GWE (%)	90 ± 9	93 ± 5	0.435
Stress GWE (%)	85 ± 12	95 ± 3	0.123
Delta GWE (%)	-5 ± 6	2 ± 3	0.019

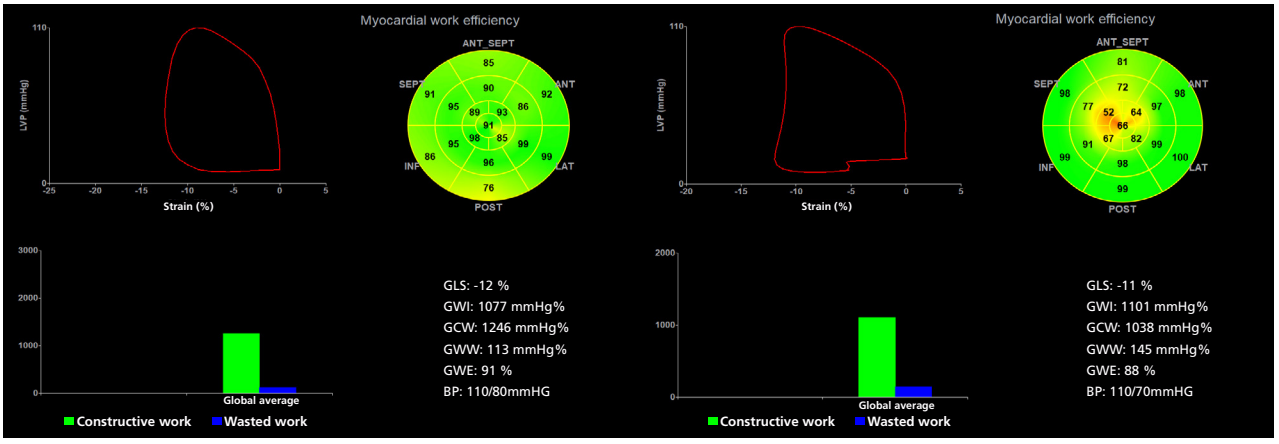
Quantitative variables are presented as mean ± standard deviation and qualitative variables as percentages
ACEI: angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; DBP: diastolic blood pressure; DM: diabetes mellitus; EDV: end-diastolic volume; ESV: end-systolic volume; GCW: global constructive work; GWE: global work efficiency; GWI: global myocardial work index; GWW: global wasted work; HR: heart rate; HTN: hypertension; LAD: left anterior descending; LV: left ventricular; LVEF: left ventricular ejection fraction MI: myocardial infarction; PCI: percutaneous coronary intervention; SBP: systolic blood pressure.

Fig. 2. Study of a patient without myocardial ischemia showing a decrease in GWW (baseline 63 mmHg% and stress 31 mmHg%) and stable GWE (baseline 97 mmHg% and stress 98 mmHg%). Left: baseline study; right: stress test



BP: blood pressure; GCW: global constructive work; GLS: global longitudinal stress; GWE: global work efficiency; GWI: global myocardial work index; GWW: global wasted work; LVP: left ventricular pressure

Fig. 3. In a patient with myocardial ischemia, we observed a decrease in GWE (baseline 91 mmHg% and stress 88 mmHg%) and an increase in GWW (baseline 113 mmHg% and stress 145 mmHg%). Left: baseline study; right: stress test.



BP: blood pressure; GCW: global constructive work; GLS: global longitudinal stress; GWE: global work efficiency; GWI: global myocardial work index; GWW: global wasted work; LVP: left ventricular pressure

cantly reducing its specificity. In this case, the slight increase in HR and contractility, which was previously regarded as a limitation of the method, is, in fact, an advantage. DSE is considered the ideal scenario for the use of two-dimensional strain. The analysis of the performance of subendocardial fibers, which are more sensitive to ischemia, allows for the detection of incipient abnormalities and helps in the interpretation of myocardial wall motion, as demonstrated in a study by Lowenstein et al. in which the inclusion of GLS increased the sensitivity of the test from 50% with visual analysis to 83.3% ($p = 0.001$). (2) The close relationship between the performance of CFR and GLS was demonstrated in a publication by Arbucci et al., in which both parameters were evaluated with DSE in a population of 179 patients. Both values showed a significant correlation, that was higher when the regional strain of the apical segments was considered. (10)

Myocardial work assessment has the advantage of incorporating loading conditions to conventional two-dimensional strain and the pressure-strain loop is proportional to myocardial oxygen uptake. (11) Its usefulness has been demonstrated in numerous clinical scenarios such as patients with arterial hypertension, valvular heart disease, coronary artery disease, heart failure and cancer, among others. (12,13) However, there is little evidence on its usefulness during stress echocardiography. Recently, Borrie et al. analyzed 60 patients who underwent exercise stress echocardiography. Of these patients, 30% exhibited evidence of ischemia, as indicated by wall motion abnormalities. With exercise, GWI increased and GWE remained unchanged in individuals without ischemia while in

those with ischemia GWI remained unchanged (i.e., did not increase) and GWE showed a significant decrease (from 93% to 87%). This study determined that the best cut-off point for identifying patients with myocardial ischemia was a 25% increase in GWI, with a sensitivity of 90% and a specificity of 85%. (14) These findings suggest that this tool could have additional value in patients with a good ultrasound window. The study by Edwards et al. reaches similar conclusions. (15) One of the main limitations to the use of MW during exercise stress echocardiography is the quality of the ultrasound window and the elevated HR during exercise that hinders accurate analysis of myocardial wall motion during the cardiac cycle.

In a study using pharmacological stress echocardiography, Leitman et al. analyzed MW with the use of dobutamine in 119 patients without ischemia. Dobutamine stress echocardiography resulted in a decrease in all MW parameters despite improvement in GLS. The authors suggest that the dose of up to 40 mcg/kg/min until 85% of maximum heart rate is reached may have deleterious effects on contractility. (16) More recently, Liu et al. reported a study performed with adenosine in 78 patients with microvascular angina and evaluated the performance of MW according to the presence or absence of CFR. The main finding was that patients with microvascular disease (abnormal CFR) had increased GWW and decreased GWE, in addition to a trend towards a smaller increase in GWI and GCW. (17) Similar findings are reported in an abstract published by Lofrumento et al. in 50 patients with suspected macrovascular disease, where it is evident that the analysis of GWE and GWW has an additive role beyond GLS when implemented in a DSE. (18)

The results obtained in our study are in line with those studies evaluating MW with exercise and adenosine in terms of increased wasted work and decreased efficient work in patients with ischemia, which is related to the percentage of post-systolic strain. It should be noted that, in contrast to the effects observed during exercise, the use of vasodilators such as dipyridamole is expected to result in stable and potentially decreased blood pressure values. Consequently, it can be expected that the GWI and GCW will not increase or even decrease slightly during exercise.

Study limitations

This study has several limitations. Firstly, it is a retrospective study, which makes it difficult to draw comparisons between groups. Secondly, the number of patients involved is small, which limits the ability to perform regional analysis of the different MW parameters. Finally, there is no definition of the anatomical correlation with coronary artery lesions.

CONCLUSION

The introduction of new quantitative analysis tools, such as MW, could assist in the interpretation of signs of myocardial ischemia in DSE. Further verification of these observations is required in larger patient cohorts with the inclusion of additional stressors such as exercise and dobutamine.

Conflicts of interest

None declared.

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

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OPINION ARTICLE

New 2024 European Society of Cardiology Guidelines for the Management of Chronic Coronary Syndromes. Highlights and Comparison with Other Clinical Practice Guidelines

Nueva guía europea de síndromes coronarios crónicos 2024. Aspectos destacados y comparación con otras guías de práctica clínica

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The new 2024 European Society of Cardiology (ESC) clinical practice guidelines (CPG) for the management of chronic coronary syndromes (CCS) (1) revise the previous 2019 version (2) and the 2018 myocardial revascularization guidelines, (3) so that they serve as a double document. Their analysis is relevant as they are the first CPG on chronic coronary artery disease (CAD) developed by the ESC published after the ISCHEMIA study (4) appeared in 2020. This document involves professionals from 41 countries in Europe and is endorsed by the European Association for Cardio-Thoracic Surgery. The process of voting and approval of the recommendations requires an agreement from at least 75% of the members. Following multiple rounds of double-blind peer review by external experts, the guidelines are signed off by all the experts in the Task Force for their publication.

The aim of this article is to highlight the state-of-the-art in CCS and compare the selected classes of recommendations (COR) and levels of evidence (LOE) with the previous versions of the guidelines developed by the ESC, American Heart Association (AHA) and American College of Cardiology (ACC).

NEW DEFINITION

"*CCS are a range of clinical presentations or syndromes that arise due to structural and/or functional alterations related to chronic diseases of the coronary arteries and/or microcirculation. These alterations can lead to transient, reversible, myocardial demand vs. blood supply mismatch resulting in hypoperfusion (ischemia), usually (but not always) provoked by exertion, emotion or other stress, and may manifest as angina, other chest discomfort, or dyspnea, or be asymptomatic. Although stable for long periods, chronic coronary artery diseases are frequently progressive and may destabilize at any moment with the development of an ACS*".

The 2024 definition differs from the previous one in the emphasis on functional alterations and microcirculation, which has been discussed in a section dedicated to INOCA/ANOCA (ischemia/angina with non-obstructive coronary arteries). Accordingly, from a pathophysiologic perspective, the CCS umbrella encompasses macrovascular and microvascular alterations, and, from the clinical point of view, the following five scenarios:

1. The symptomatic patient with reproducible stress-induced angina or ischemia with epicardial obstructive CAD.
2. The patient with angina or ischemia caused by epicardial vasomotor abnormalities or functional/structural microvascular alterations in the absence of epicardial obstructive CAD (ANOCA/INOCA).
3. The non-acute patient post-ACS or after a revascularization procedure.
4. The non-acute patient with heart failure (HF) of ischemic or cardiometabolic origin.
5. The asymptomatic patient in whom epicardial CAD is detected during an imaging test for refining cardiovascular risk assessment.

These five scenarios are identical to those used by the 2023AHA/ACC CPG for the management of chronic CAD. (5)

Like the 2019 ESC CPG, this document involves the use of steps, in this case four (instead of six), to describe the patient evaluation process: general clinical examination, further evaluation, confirming diagnosis and initial treatment, followed by pharmacologic treatment and revascularization.

The second step, called "further evaluation", introduces one of the greatest and most controversial

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changes; the risk factor-weighted clinical likelihood (RF-CL) model derived from the publication by Winther et al. (6) The document defends this model because it is patient-centered and accurate compared with more advanced models requiring computed calculation, and categorizes three times more subjects as being at very low risk compared with the 2019 CPG. This model includes sex, age, symptoms (chest pain and/or dyspnea) and risk factors (family history, smoking, dyslipidemia, hypertension and diabetes). Thus, the estimated pretest likelihood values range from 0 to 45%. The symptom score replaces the previous terminology of anginal pain symptoms (typical, atypical and non-cardiac/non-anginal), which the ESC now considers potentially misleading. Individual adjustment of the likelihood may be necessary for subjects with severe single risk factors or comorbidities such as familial hypercholesterolemia, severe renal dysfunction, rheumatic/inflammatory diseases, and peripheral vascular disease (PVD).

The CPG highlights that: "*In general, individuals with a very low (≤ 5%) likelihood of obstructive CAD do not require further diagnostic testing unless symptoms persist and non-cardiac causes have been excluded. In patients with a low (> 5%-15%) likelihood, the benefit of diagnostic testing is uncertain, but may be performed if symptoms are limiting and require clarification. Patients with moderate (> 15%–50%), high (> 50%–85%), and very high (> 85%) likelihood of obstructive CAD are encouraged to undergo further diagnostic testing*".

In addition, they expand the concept of RF-CL and recommend adjusting for the following six complementary clinical data or risk enhancers (COR I, LOE C): resting ECG changes, exercise ECG with abnormal findings, ventricular dysfunction, ventricular arrhythmia, acute pulmonary edema (APE), and coronary artery calcification on pre-existing computed tomography (CT) scan. In the particular case of low-risk patients (without enhancers), the CPG weight the combination of the coronary artery calcium score (CACS) with the RF-CL model, as it shows the strongest potential to defer diagnostic testing (COR IIa, LOE B) to reclassify subjects as very low likelihood of obstructive CAD.

To summarize, the maximum estimated pretest likelihood is 45%, and higher percentages can be reached with the use of risk enhancers. The difficulty arises because the CPG do not provide any tool to use risk enhancers to calculate high or very high pre-test likelihood. How can this calculation be made? The document does not provide definitive insights on this pivotal matter. Nevertheless, the following discussion on the X social media platform helps to a better understanding. In a post dated September 6, 2024, Dr. Capodanno (CPG reviewer and renowned editor-in-chief of EuroIntervention) points out this problem. Dr. Christiaan Vrints, chair of the CPG, answers: "*The idea is to make a 'clinical' judgment, not a calculation, based on the number and severity of the 'likelihood enhancers'. If you are convinced about 'very high' CL, go directly to invasive coronary angiography; if you estimate 'high' CL, order functional imaging*." (7) Although Dr. Vrints emphasizes that the decision is based on clinical judgment, there is a discrepancy, as the CPG suggests percentages for estimating the risk.

CONFIRMING DIAGNOSIS

Once patient's risk has been obtained using the RF-CL model, the document suggests first-line tests and management strategies in symptomatic patients with suspected CCS:

- Very low risk (≤ 5%): defer further testing.
- Low risk (>5-15%): consider CACS to re-estimate the risk or coronary computed tomography angiography (CCTA).
- Moderate risk (> 15 -50%): CCTA or functional tests as single photon emission-computed tomography (SPECT), stress echocardiography or cardiac magnetic resonance imaging (MRI).
- High risk (> 50-85%): functional test (SPECT, stress echocardiography or cardiac MRI).
- Very high risk (> 85%): invasive coronary angiography.

The document highlights the added value of CACS performed simultaneously with nuclear medicine imaging, e.g. PET-CT (COR I-LOE B). It also emphasizes that there is growing support for the use of CCTA as a first-line test in the low to moderate probability group (>5%-50%) (COR I, LOE A), and introduces CCTA-derived fractional flow reserve (FFR-CT) as a novel approach for risk stratification in proximal left anterior descending coronary artery stenosis ≥70% (COR I, LOE B).

In very high-risk patients, invasive coronary angiography via the radial access (COR I, LOE A) is indicated with selective assessment of functional severity of intermediate diameter stenoses to guide the decision to revascularize, using the following tools:

- FFR or iFR (instantaneous wave-free ratio), significant with values ≤ 0.8 or ≤ 0.89, respectively (COR I, LOE A). *A similar recommendation is provided by the 2023 AHA/ACC CPG for the management of chronic CAD*.
- QFR or quantitative flow ratio, significant with value ≤ 0.8 (COR I, LOE B). *Not mentioned in the 2023 AHA/ACC CPG for the management of chronic CAD*.

TREATMENT

Pharmacological novelties

- The CPG propose rearranging antianginal medications, eliminating the concept of first-line or second-line drugs. Without new drugs, the document reinforces the concept that medical therapy should be tailored to each patient (COR I, LOE C).
- The recommendation to use clopidogrel as an alternative to aspirin is now stronger (COR I, LOE

A) due to its efficacy and safety. *The 2023 AHA/ACC CPG for the management of chronic CAD do not recommend it as antiplatelet monotherapy*.

In addition, two cardiometabolic drugs and one anti-inflammatory drug have been incorporated:

- Sodium glucose co-transporter 2 inhibitors for patients with diabetes (COR I, LOE A). *The same recommendation is provided by the 2023 AHA/ACC CPG for the management of chronic CAD*.
- Glucagon-like peptide-1 receptor agonists (GLP-1 RA) in patients with overweight and obesity (COR IIa, LOE B). *The 2023 AHA/ACC CPG for the management of chronic CAD have stated that there is no evidence yet to recommend these drugs in patients without diabetes*.
- Low-dose colchicine (COR IIa, LOE A). The results of the COLCOT (8) and LoDoCo2 (9) studies provided the basis for the introduction of a drug with a direct anti-inflammatory mechanism and a high level of recommendation for the treatment of chronic CAD. *For the 2023 AHA/ACC CPG for the management of chronic CAD this drug has a COR IIb, LOE B*.

Revascularization

Revascularization is defined by symptoms, risk and coronary anatomy, similar to the definition of the 2023 AHA/ACC CPG for the management of chronic CAD. The recommendations emphasize the participation of the Heart Team (HT). The most relevant recommendations are:

- Coronary artery bypass graft (CABG) surgery (COR I, LOE A) is recommended for patients with severe left main coronary artery (LMCA) disease, LMCA with multivessel disease (MVD) or MVD with diabetes.
- CABG surgery (COR I, LOE A) is recommended for patients with three-vessel disease and preserved left ventricular ejection fraction (LVEF). *This key point is the opposite of the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization, (10) in which the recommendation was class IIb, resulting in significant controversy worldwide*. The level of disagreement was such that the American Association for Thoracic Surgery and the Society of Thoracic Surgeons withdrew from the document. Although this was amended in the 2023 AHA/ACC CPG for the management of chronic CAD with a COR IIa, LOE B, the debate continued. (11,12)
- Percutaneous coronary intervention (PCI) is recommended for LMCA disease of low complexity with a SYNTAX score ≤ 22 (COR I, LOE A), or as an alternative to surgery in three-vessel disease, preserved left ventricular function and absence diabetes, with a SYNTAX score ≤ 32 (COR I, LOE A). *Regarding this last point, the 2021 ACC/AHA/SCAI CPG also provided a low COR (IIb) versus medical treatment. Subsequently, this recommendation was modified in the 2023 AHA/ACC CPG for the management of chronic CAD to IIa B*.
- In patients with MVD and LVEF ≤ 35%, CABG surgery is recommended to improve survival (COR I, LOE B). *This COR and LOE are in line with those of the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization and 2023 AHA/ACC CPG for the management of chronic CAD*.
- In patients with functionally significant MVD and LVEF ≤ 35% who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG surgery (COR IIb, LOE B). The evidence derived from the REVIVED-BCIS2 study has downgraded the recommendation for PCI in ischemic heart disease, representing a notable development. (13) *This scenario was defined as multifactorial (HT, anatomy, possibility of complete revascularization, diabetes and comorbidities) in the 2018 ESC CPG on revascularization with a COR IIa, LOE C. The 2021 AHA/ACC/SCI revascularization guideline recommended PCI only for patients with contraindication to cardiac surgery via the HT, without providing a COR. Finally, the 2023 AHA/ACC guidelines for the management of CAD stated that PCI is reasonable as an alternative to surgery to reduce events (COR IIa, LOE B)*.

Based on the study by Perera et al., (13) the determination of viability did not obtain any recommendation in this section.

INOCA/ANOCA

This document features an extensive section dedicated to ischemia/angina with non-obstructive coronary arteries (INOCA/ANOCA), which is a notable shift from the 2019 CPG, where this topic was mentioned for the first time. The GPG include a solid algorithm for making the diagnosis, highlighting the role of angiography with coronary functional testing to define the endotype and to improve quality of life (COR I, LOE B). This is the current, widely accepted approach outlined by the leading CPG on the subject. (14) *The 2023 AHA/ACC CPG for the management of chronic CAD provided a lower COR (IIa) with the same LOE (B). Non-invasive functional testing has been downgraded to a COR IIb, LOE B*.

CONCLUSION

This long-awaited document requires a detailed reading due to its length, the quantity of information it contains, and the value of the changes it proposes. The workup process has evolved and the current role of ischemia, functional testing and CCTA merits a separate article. Medical treatment has incorporated significant advances, and the recommendations demonstrate its prognostic power compared to intervention. Coronary anatomy continues to be what ultimately defines revascularization and, finally, INOCA/ANOCA is positioned as a central issue in the diagnostic algorithm.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

Impact of Gender-Affirming Hormone Therapy on Cardiovascular Health

Impacto de la terapia hormonal de reafirmación de género en la salud cardiovascular

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ABSTRACT

Despite advances in the management of cardiovascular risk factors, the approach to the transgender population receiving hormone therapy is not completely defined. Transgender patients are those who present with "gender incongruence," that is, a discrepancy between the individual's expressed gender and the designated gender, which generally corresponds to the biological sex. In these cases, hormonal treatment differs from the "traditional" approach in that it is a "crossover" hormonal treatment. Multiple studies have evaluated the relationship between gender affirming hormone therapy (GAHT), the development of cardiovascular risk factors and the occurrence of cardiovascular events, both for the transfeminine and transmasculine population. These findings are particularly relevant, as cardiovascular disease is the second leading cause of mortality in the transgender population. However, studies that have attempted to stratify this group according to their cardiovascular risk have faced notable difficulties and limitations. The aim of this review is to investigate the impact of GATH on cardiovascular health, to assess the need to reconsider risk stratification and therapeutic targets for these patients, and to discuss the applicability of general recommendations to this specific population.

Keywords: Transgender people - Hormone replacement therapy - Cardiovascular disease

RESUMEN

A pesar de los avances en el manejo de factores de riesgo cardiovascular, el abordaje de la población transgénero que recibe terapia hormonal no está completamente definido. Los pacientes transgénero son aquellos que presentan "incongruencia de género", es decir, una discrepancia entre el género expresado por el individuo y el género designado, el cual generalmente se corresponde con el sexo biológico. En estos casos el tratamiento hormonal difiere del enfoque "tradicional" al tratarse de una hormonización "cruzada". Múltiples estudios han evaluado la relación entre la terapia hormonal para la reafirmación de género (THRG), el desarrollo de factores de riesgo cardiovascular y la ocurrencia de eventos cardiovasculares, tanto para la población transfemenina como transmasculina. Estos hallazgos son particularmente relevantes, ya que la enfermedad cardiovascular es la segunda causa de mortalidad en la población transgénero. Sin embargo, los estudios que han intentado estratificar a este grupo según su riesgo cardiovascular han enfrentado notables dificultades y limitaciones. El objetivo de esta revisión es investigar el impacto de la THRG en la salud cardiovascular, evaluar la necesidad de reconsiderar la estratificación del riesgo y las metas terapéuticas para estos pacientes, y discutir la aplicabilidad de las recomendaciones generales a esta población específica.

Palabras claves: Personas transgénero - Terapia de reemplazo hormonal - Enfermedad cardiovascular.

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. (1) Despite significant advances in the management of cardiovascular risk factors (CVRF) and the publication of numerous clinical practice guidelines, the approach to certain subpopulations in relation to cardiovascular prevention is still not completely well defined. (2) Within this group are patients receiving hormonal treatments, including those receiving gender affirming hormone therapy (GAHT), for whom specific recommendations on cardiovascular prevention, which are very clear for the general population, are not adequately defined. Given that numerous studies have reported the impact of these therapies on CVRF and an association between hormone treatments and the occurrence of cardiovascular events, the aim of this review is to investigate the impact of GAHT on cardiovascular health, to analyze

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whether risk stratification and therapeutic goals for these patients need to be reconsidered, and to discuss whether recommendations for the general population are applicable to this specific population.

Gender incongruence and "crossover hormonization"

Transgender patients are those who present "gender incongruence", that is, a discrepancy between the gender expressed by the individual and the biological sex. (3) The incorporation of this term by the World Health Organization is intended to facilitate the diagnostic approach to issues related with gender identity, understood as the individual's perception of gender, and to guarantee access to health services for this population. Similarly, the term "gender dysphoria" refers to the distress experienced as a result of the aforementioned incongruence. (4) A transgender man is an individual whose biological sex is female, but whose gender identity is male, professing a gender transition from female to male. A transgender woman has a male biological sex, but with a female gender identity, posing a transition from male to female.

As part of the depathologization of gender identities, the Gender Identity Law (Law No. 26,743) stipulates that all persons have the right to the free development of their person in accordance with their gender identity, and in this context, GAHT is presented as a therapeutic strategy whose objective is to eliminate the physical characteristics associated with the biological sex and to develop those of the perceived gender. (5,6) Hormone therapy protocols for these patients are based on the administration of estrogens and testosterone, and are detailed in Table 1. (5)

Hormonization, risk factors and cardiovascular health: what evidence do we start from?

Multiple associations have been established between hormone replacement therapies, the development of CVRF and the occurrence of cardiovascular events. The effects of hormone replacement therapy have been documented mainly in men with hypogonadism and in postmenopausal women.

Estrogens, metabolism and cardiovascular events.

Regarding the impact of estrogens on the metabolic profile, numerous studies have shown a clear association between estrogen treatment and an improvement in the lipid profile. This treatment is associated with a decrease in low-density lipoprotein cholesterol (LDL-C) levels and an increase in high-density lipoprotein cholesterol (HDL-C) concentrations, although an increase in triglyceride levels is also observed. In turn, oral formulations have been found to cause more significant changes in these concentrations compared with transdermal formulations, and these effects are influenced by the dose administered. (7-10) In addition, a 25% reduction in lipoprotein(a) [(Lp(a)] levels was reported in women treated with oral estrogens, and that the association between this lipoprotein levels and the development of coronary heart disease would be modified by hormone treatment. (10,11) Moreover, estrogens have been associated with a reduction in insulin resistance and an increase in C-reactive protein levels secondary to the use of oral formulations (not with transdermal formulations). (10)

However, despite its beneficial impact on multiple components of the metabolic profile, the large randomized clinical trials HERS and WHI in postmenopausal women demonstrated that estrogen treatment carries an increased risk of major cardiovascular events, such as myocardial infarction, stroke, and venous or pulmonary thromboembolism, to such an extent that the WHI study had to be prematurely stopped. (7-9) This could be explained, in part, by a reductive effect on protein S activity, which is involved in the degradation of coagulation factors, as well as by the potentially dual role of estrogens in the atherogenic process. Estrogens may have a beneficial effect on the healthy

Table 1. Hormone schedules for gender-affirming therapy. Adapted from the National Ministry of Health. (5)

Estradiol: administration routes and dosage

Route of administration	Presentation	Schedule	Dose
Oral	17β-estradiol valerate	1 or 2 daily intakes	2 to 6 mg
Transdermal	17β-estradiol 0.06% gel.	1 or 2 daily applications	0.75 to 3 mg (1.25 to 5 mg of gel)
	Estradiol patch	Replacement every 3 or 4 days	50 to 100 mg

Testosterone: administration routes and dosage

Route of administration	Presentation	Scheme	Dose
Intramuscular	Injectable enanthate	Application every 15 to 21 days	250 mg
	Injectable cypionate	Application every 15 to 21 days	250 mg
	Undecanoate injection	Quarterly application (every 10 to 12 weeks)	1000 mg
Transdermal	1% testosterone gel	Daily application	25 to 100 mg (2.5 to 10 g of gel)

endothelium, but a negative impact on atherosclerotic disease with established plaques. (10,12-14)

Testosterone, metabolism and cardiovascular events

Studies in men with hypogonadism have shown conflicting results regarding the impact of testosterone on the metabolic profile. Testosterone has been found to inhibit lipogenesis and promote lipolysis, which could have a beneficial effect on obesity and insulin resistance associated with this condition. However, in men with hypogonadism treated with exogenous testosterone, abrupt discontinuation of treatment may lead to increased fasting glucose levels. (15) On the other hand, although the use of anabolic androgens has been associated with an increased risk of hypertension, treatment with doses that equal physiological testosterone concentrations could have a beneficial effect on blood pressure. (15-17) Nevertheless, the effects of testosterone on atherosclerotic disease are still unclear. While some studies have found that treatment with physiological doses of testosterone is associated with a reduction in carotid intima-media thickness, other studies suggest opposite results. (15)

Notably, the effects of androgens may differ significantly between the male and female cardiovascular systems. In women with hyperandrogenic polycystic ovary syndrome (PCOS), an association has been reported between this disorder and the development of left ventricular hypertrophy, impaired ventricular ejection fraction, and alterations in mitral filling. A tendency towards arterial hypertension has also been observed, which could be related to an impaired release of nitric oxide due to oxidative stress and activation of pathways leading to endothelial dysfunction. (18,19)

Regarding the association with cardiovascular events, the TOM clinical trial observed that, in a group of men of approximately 75 years of age with testosterone levels in the hypogonadism range and a high prevalence of cardiovascular comorbidities, the use of exogenous testosterone was associated with a higher incidence of adverse cardiovascular events. (20) Other observational studies obtained similar results, with a higher cumulative incidence of all-cause death, hospitalization for major myocardial infarction or ischemic stroke in hormone-treated patients. (21-23) However, the recent TRAVERSE randomized clinical trial demonstrated, in a non-inferiority analysis, that hormone replacement therapy with testosterone in men with pre-existing or high risk of presenting cardiovascular disease has no significant difference compared with placebo in the occurrence of major cardiovascular events. (24)

Association of "crossover" hormonization with risk factors and cardiovascular events in transgender patients

In transgender patients receiving GAHT, changes have been observed in CVRF as well as in the rate of cardiovascular events. This aspect is of particular interest, since in these cases the hormonal treatment differs from the "traditional" approach as it is a "crossover" hormonization.

Estrogen crossover therapy and cardiovascular health in the transfeminine population.

Several studies have assessed the impact of crossover hormonization on CVRF in transgender women. Regarding its influence on blood pressure, the results of these studies have been contradictory. Overall, most of these studies suggest that crossover hormonization with estrogen is associated with an increase in blood pressure values, with documented increases of up to 4 mmHg in systolic blood pressure and 6.5 mmHg in diastolic pressure after only 1 year of treatment. (25) However, multiple studies that assessed changes in blood pressure did not observe significant differences when comparing these results with those of men in the general population. (26,27) According to a review article, endogenous testosterone in these patients would induce a vasopressor response mediated by the renin-angiotensin-aldosterone system (RAAS). (28,29) Moreover, differences in the distribution of estrogen receptors in the female compared with the male cardiovascular system would contribute to oxidative stress and endothelial dysfunction, mechanisms underlying the development of hypertension. (29)

In relation to the lipid profile, although some studies have shown no variations after treatment initiation (25) most have shown that estrogen therapy in transgender women is associated with favorable changes in lipid parameters, similar to those observed in postmenopausal women using oral estrogens. Among the most representative studies in this regard is the ENIGI study, conducted in four European gender clinics with a total of 144 transgender women. In this study, it was observed that the transwoman population experienced a reduction in total cholesterol of 7.66 mg/dL (95% CI 2.94-12.39) and a reduction of 4.65 mg/dL in LDL-C levels (95% CI 0.74-8.56) compared with baseline values after treatment initiation. (30)

In terms of glucose metabolism, parameters of insulin resistance and reduced incretin response have been observed in transgender women under hormone treatment. (25,31) According to the American Heart Association (AHA), transgender women have a higher prevalence of diabetes compared with cisgender groups. The likelihood of developing diabetes in this group is twice as high as in women in the general population and six times higher than in men. (32) Changes in weight and body mass index (BMI) after initiation of hormone treatment could account for changes in the glycemic profile. (25,33)

In relation to documented cardiovascular events reported in the population of transgender women, a higher incidence of myocardial infarction, venous thromboembolic events, and ischemic stroke has been observed, as in postmenopausal women, com-

pared with the general population. (32) One of the largest studies evaluating the incidence of events in 2842 transgender women, found a higher incidence of thromboembolic events and stroke in transgender women compared with men and women in the general population. In addition, a higher incidence of myocardial infarction was observed in the transwoman population compared with the reference cohort of women, although it was not higher than the incidence observed in the reference male cohort (Table 2). (34) Other studies have obtained similar results, (35-37) and one of them revealed that transgender women had an infarction rate of 7.8%, significantly higher than that of women in the general population. However, this study did not specify whether the patients included were receiving hormone treatment. (38)

Testosterone crossover therapy and cardiovascular health in the transmasculine population

In contrast to what has been observed in the transfeminine population, most studies in transgender men receiving androgen therapy have shown a clear association between hormone treatment with testosterone and an increase in blood pressure values. (28,32,33) An increase of almost 11 mmHg in systolic blood pressure and up to 9 mmHg in diastolic blood pressure has been observed after one year of treatment. (25) Different studies have proposed that impaired endothelial function is an underlying mechanism in the development of hypertension in transgender men receiving androgen crossover treatment. Investigations comparing arterial stiffness, brachial vasodilator response (measured as brachial artery diameter after occlusion with an inflated blood pressure cuff at supra-systolic values) and pulse wave velocity in testosterone-treated transgender men with values obtained in premenopausal women in the general population and in transgender men without hormone treatment, found a decrease in the vasodilator response and an association between androgen treatment and increased vascular system stiffness in these patients. (39,40)

Possible causes of increased blood pressure in this group include altered activity of the endothelin-1 system, due to suppression of a receptor involved in nitric oxide synthesis, together with increased RAAS activity. (29) These mechanisms have also been previously observed in women with hyperandrogenic PCOS. (18)

Several studies have revealed that testosterone treatment in transgender men has an adverse effect on the lipid profile. A retrospective longitudinal study showed a statistically significant increase in plasma total cholesterol levels, with baseline concentrations of 166 ± 35.1 mg/dL and 175.6 ± 38.2 mg/dL at 2 years. An increase in LDL-C levels was also observed, from 103.8 ± 28.7 mg/dL to 112.8 ± 30.3 mg/dL. Triglycerides increased from 70.6 ± 30.7 mg/dL to 102.3 ± 68.5 mg/dL, and HDL-C levels decreased from 52.2 ± 12.2 mg/dL to 45.4 ± 13.8 mg/dL. (33) Other studies obtained similar results. (25,30)

Results on the impact of testosterone treatment on glucose metabolism in transgender men are contradictory. While some studies have observed a statistically significant increase in glycosylated hemoglobin levels associated with treatment, (25) a systematic review suggests that testosterone therapy does not affect insulin sensitivity and, instead, could be associated with an improvement in glycemic control. (41) However, as in transgender women on estrogen therapy, an in-

Table 2. Incidence of cardiovascular events in the transwoman population

Cohort and event of interest	Transwoman cohort		Adjusted HR (95% CI)*	
	Cardiovascular events (n)	Incidence† (95% CI)	vs. men in the general population	vs. women in the general population
Overall transwoman cohort (n=2842)				
Venous thromboembolism	61	5.5 (4.3-7.0)	1.9 (1.4-2.7)	2.0 (1.4-2.8)
Ischemic stroke	54	4.8 (3.7-6.3)	1.2 (0.9-1.7)	1.9 (1.3-2.6)
Myocardial infarction	33	2.9 (2.1-4.1)	0.9 (0.6-1.5)	1.8 (1.1-2.9)
Transwoman estrogen initiation cohort (n=853).				
Venous thromboembolism	17	6.6 (4.1-10.6)	3.2 (1.5-6.5)	2.5 (1.2-5.0)
- At 0-2-year follow-up	6	4.3 (1.9-9.6)	1.5 (0.5-5.1)	1.7 (0.5-5.5)
- At >2-year follow-up	11	9.3 (5.2-16.8)	5.1 (2.1-12.6)	3.2 (1.3-7.6)
Ischemic stroke	17	6.6 (4.1-10.6)	2.3 (1.2-4.3)	2.9 (1.5-5.5)
- At 0-6-year follow-up	9	3.8 (2.0-7.3)	1.3 (0.6-2.9)	2.3 (1.0-5.4)
- At >6-year follow-up	8	36.2 (18.1-72.4)	9.9 (3.0-33.1)	4.1 (1.5-11.4)
Myocardial infarction	4	1.5 (0.6-4.1)	1.0 (0.3-3.2)	2.4 (0.6-9.4)

HR, hazard ratio; CI, confidence interval; vs, versus.
*Comparison with reference cohorts. Adapted from Getahun et al. (34)
†Calculated as number of cases per 1000 patients/year.

crease in BMI has also been observed in testosterone-treated transgender men, though this increase could be attributed to the fact that testosterone therapy increases the lean mass and decreases the fat mass. (25,41,42) On the other hand, the ENIGI study found no significant variation in BMI with hormonization. Although transgender men showed a higher long-term risk of cardiovascular disease than the optimum calculated according to biological sex, as estimated by the Framingham risk calculator based on this index, these results did not change after two years of androgen treatment. (30)

Regarding cardiovascular events in transgender men, the first observational study, published in 1989, found no statistically significant differences in infarction rates or infarction-associated mortality compared with the general population. (26) Another study showed incidence curves for venous thromboembolism, stroke, and myocardial infarction with similar patterns in transgender men on hormone treatment (n=2118) and the general population. In relation to myocardial infarction, HR values were 0.7 (95% CI 0.3-1.8) relative to men in the general population and 1.3 (95% CI 0.5-3.9) relative to women. (34) These results partially differ from those observed in other studies. (26,38) Alzahrani et al. found that the transmasculine population had a probability of myocardial infarction twice that of men in the general population (OR 2.53; 95% CI 1.14-5.68; p=0.02) and almost five times that of women (OR 4.90; 95% CI 2.18-10.90; p<0.01), after adjusting for other CVRF. (38)

Cardiovascular risk stratification in transgender patients.

Cardiovascular disease is the second leading cause of mortality among the transgender population, exceeded only by suicide in overall all-cause mortality. (43) Studies that sought to stratify transgender patients according to their cardiovascular risk encountered notable difficulties and limitations. The ENIGI study, which estimated the 30-year cardiovascular risk of transgender patients using the Framingham score based on the lipid profile according to their biological sex, (1) demonstrated a significant increase in risk after GAHT initiation. The study revealed that both transgender men and women have a higher baseline cardiovascular risk (i.e., pre-hormonization) than the general population, suggesting the presence of cardiovascular risk factors in addition to the traditional ones. In the case of transgender men, such risk increased after initiation of hormone treatment, whereas in the case of transgender women it was slightly decreased after GAHT initiation but not statistically significant . (30)

According to a retrospective study that estimated cardiovascular risk in 427 transgender patients without hormone treatment, employing the ASCVD risk calculator system, the transgender population would be the majority in the highest cardiovascular risk categories compared with the general population (Figure 1). (44) Furthermore, the mean values of the calculated risk for the transgender population aged 45-65 years using the QRISK3 and ASCVD risk calculator scores were 12.2% and 8.3%, respectively. The difference observed between the two risk calculators could be explained in part by steroid use, high rates of mental health disorders, and substance use in this population, factors that are only considered in the QRISK3 score

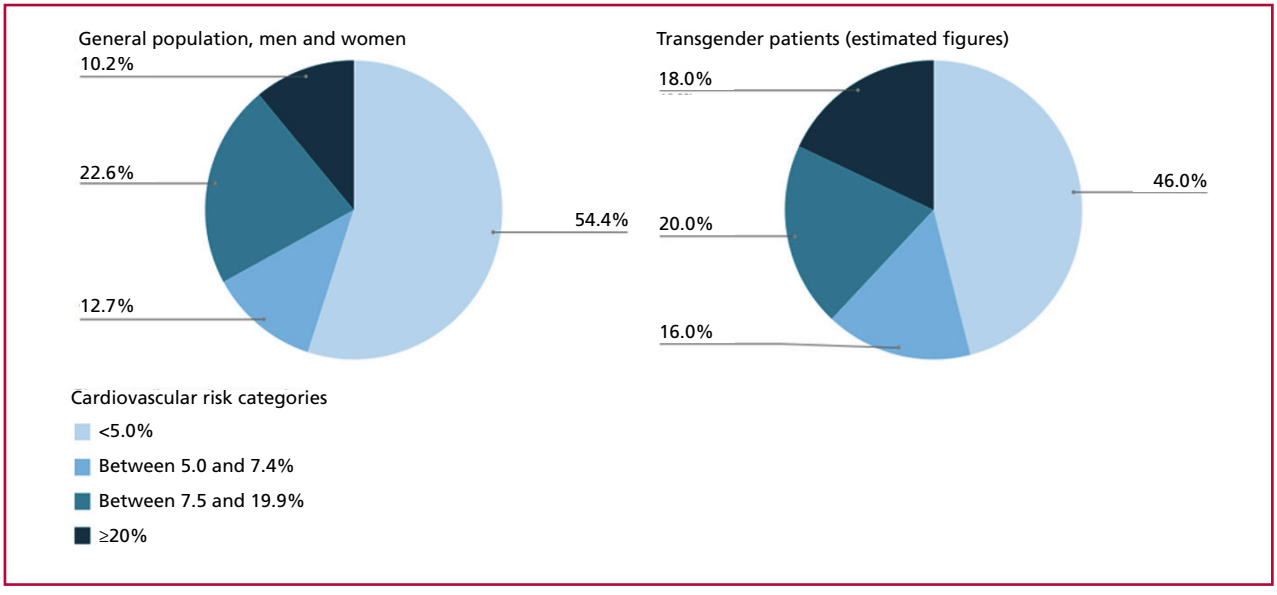

Fig. 1. Proportion of transgender patients and the general population (aged 40-79 years) in the different risk categories (*QRISK3* system). Adapted from Denby et al.(44)

Final reflections and conclusions

The influence of sex hormones on cardiovascular health is complex. The impact of crossover hormonization in transgender patients has been evaluated in numerous studies, but these have clear methodological limitations, as they tend to be retrospective studies and, in many cases, with small number of patients. Based on the effects of hormonization described for the general population in large randomized clinical trials, a key question arises: can these results be directly extrapolated to the transgender population receiving crossover hormone treatment? It has been recognized that there are sex differences in cardiovascular health, attributable both to genetic variations associated with biological sex and to the dynamic interaction between hormones. Epigenetic mechanisms play a crucial role in this context and could explain the differences in the response of the heart and blood vessels to sex hormones observed in individuals of male and female biological sex. (45)

When determining the cardiovascular risk of patients receiving GAHT, both the physiological mechanisms of the hormones and the effects of crossover treatment and nontraditional CVRF associated with their minority status come into play. In this regard, there are no studies that have evaluated how traditional risk scores apply to this population. Therefore, rethinking the tools for cardiovascular risk stratification in this specific population, through the development of adapted estimators, represents a major challenge for current cardiology.

In recent years, there has been an increase in the number of transgender patients seeking access to hormone therapies to improve their well-being and reduce the stress and nonconformity associated with gender dysphoria. The metabolic effects of gender-affirming hormone therapy, combined with the effects of crossover treatment and the nontraditional CVRF associated with their condition, notably impact on the cardiovascular health of these individuals.

In this context, it is essential to implement a specialized cardiological follow-up program for these patients. The formation of multidisciplinary teams with expertise in the subject could contribute to the development of better recommendations in future cardiovascular prevention guidelines, since the general recommendations are not fully applicable to this very particular population.

Conflicts of interest

None declared.

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

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SCIENTIFIC LETTER

Heart Transplantation in a Cardiac Patient after the Fontan Procedure

Trasplante cardíaco en paciente cardiópata en estadio Fontan

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As a result of advances in diagnosis and surgical techniques, even patients with complex congenital heart disease can survive into adulthood with a high risk of end-stage heart failure. Therefore, the number of patients with congenital heart disease requiring heart transplantation has increased in recent decades.

For patients with single ventricle physiology heart disease, staged palliative operations culminating in the Fontan procedure which involves the complete bypass of the right heart remains the gold standard. Unfortunately, even the ideal candidate with a "perfect" Fontan surgery and adequate follow-up undergoes slow functional deterioration with development of progressive heart failure and a survival of 86% at 5 years and 74% at 15 years.

Patients with Fontan surgery and advanced heart failure are a cohort of patients candidate for heart transplantation.

Before placing a patient with a complete right heart bypass on the transplantation list, the possibility of optimizing the Glenn-Fontan circulation by hemodynamic or surgical interventions should be considered. If this is not possible, the pre-transplantation assessment process should be initiated.

As these patients have undergone multiple operations, they usually have a history of blood product transfusions and exogenous material implants, which increases the titers of lymphocytotoxic antibodies, as well as a history of multiple vascular accesses, which predisposes to thrombosis of the vascular accesses.

Regarding the surgical technique, in addition to the difficulties inherent in reoperation (mostly third or fourth sternotomy), there are aspects of the univentricular pathophysiology that require technical variations compared to the biventricular physiology.

For these reasons, transplantation after Fontan surgery is a challenge not only from a surgical point of view, but also from the time of pre-transplantation assessment to the distant postoperative follow-up.

We present the case of an 18-year-old patient diagnosed with dextroisomerism, type II B tricuspid atresia, double-sided superior vena cava and partial anomaly of pulmonary venous return.

Regarding surgical history, a left systemic-to-pulmonary anastomosis and later a right one were performed in neonatal stage. At the age of 3, the patient underwent bilateral Glenn surgery, Fontan surgery with fenestration with a 20 mm polytetrafluoroethylene (PTFE) conduit, correction of the anomalous pulmonary venous return and plastic surgery of both pulmonary artery branches, in one-stage surgery. At the age of 5, the patient underwent catheterization and attempted fenestration closure with cribriform Amplatzer™ but had residual shunt; thus, at the age of 8, a stent was placed to close it.

He then developed severe mitral regurgitation which led to ventricular dysfunction and eventually heart failure. As a result, he was placed on the heart transplantation list.

The pre-transplantation echocardiogram showed heterotaxia, dextroisomerism, permeable extracardiac conduit (EC) with biphasic flow velocity of 0.39 m/sec, closed fenestration without residual shunt, collector with laminar flow velocity of 0.49 m/sec, wide atrial septal defect, right atrioventricular (AV) valve atresia, left AV valve with severe regurgitation caused by coaptation, single dilated and trabeculated ventricle with moderate to severe dysfunction, left ventricular diastolic diameter (LVDD) 8.5 cm, left ventricular systolic diameter (LVSD) 6.8 cm, shortening fraction 20%, mitral annulus plane systolic excursion (MAPSE) 9 mm, E/A inflow pattern 0.7, bilateral Glenn procedure

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with biphasic flow, the left one with a velocity of 0.34 m/sec and the right one of 0.5 m/sec.

Pre-transplantation catheterization was performed and showed pressures of 16 mmHg in bilateral Glenn and Fontan procedures and 95/56 (63) mmHg in aorta. A Qp/Qs ratio of 0.96 and a Rp/Rs ratio of 0.07 were obtained (Figure 1).

An HLA panel study was performed and showed sensitization of 18% for group I and of 37% for group II, for which the patient received gamma globulin (3 doses), and plasmapheresis in extracorporeal circulation was programmed at the time of heart transplantation.

Given the complexity of the setting due to the clinical and anatomical conditions and the requirements of highly complex medical technology, a transplantation simulation was performed in the operating room in the presence of cardiologists, cardiovascular surgeons, perfusionists, hematologists, anesthesiologists, surgical instrument technicians and intensivists. This allowed us to optimize time and reduce potential errors and adverse events, as these are not procedures we usually perform on other patients.

On the day of transplantation, femoral cannulation was performed, and the patient was placed in extracorporeal circulation via the femoral route due to adhesions between the single ventricle and the sternum. Following re-sternotomy, left Glenn cannulation was carried out. The patient was placed in deep hypothermia, the aorta was clamped and the heart was explanted. Subsequently, implantation was performed by anastomoses of the left atrium, the pulmonary artery and the aorta. The cardiac cavities were purged, and the aorta was declamped. Implantation was completed by anastomosis of the inferior vena cava and ligation of the superior vena cava, leaving both cavopulmonary anastomoses permeable, bilateral Glenn. (Figure 2)

In extracorporeal circulation, the plasmapheresis protocol was followed during cardiopulmonary bypass, which is indicated for patients with heparin-induced thrombocytopenia (HIT), patients with antiphospholipid syndrome (APS) and hypersensitized patients who remain on the heart transplantation list, as in this case.

The patient progressed favorably and was extubated

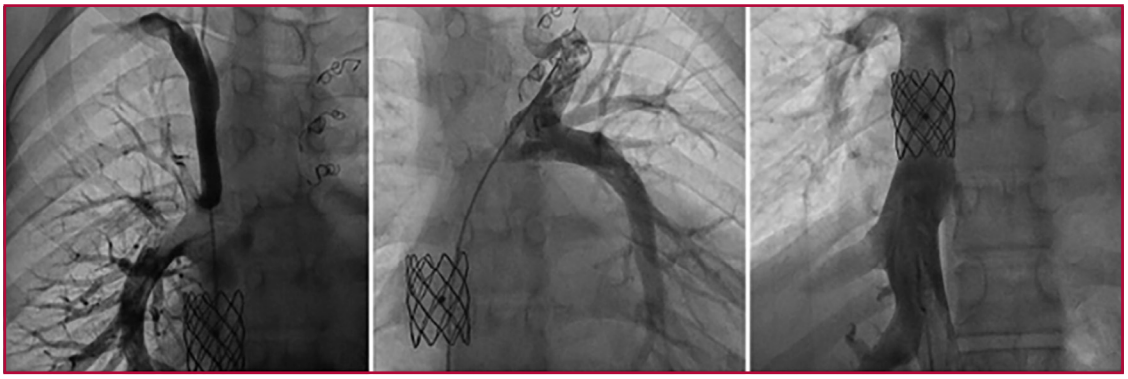

Fig. 1. Pre-transplantation catheterization. a) Right Glenn procedure. b) Left Glenn procedure. c) Extracardiac conduit with implanted stent to close fenestration.

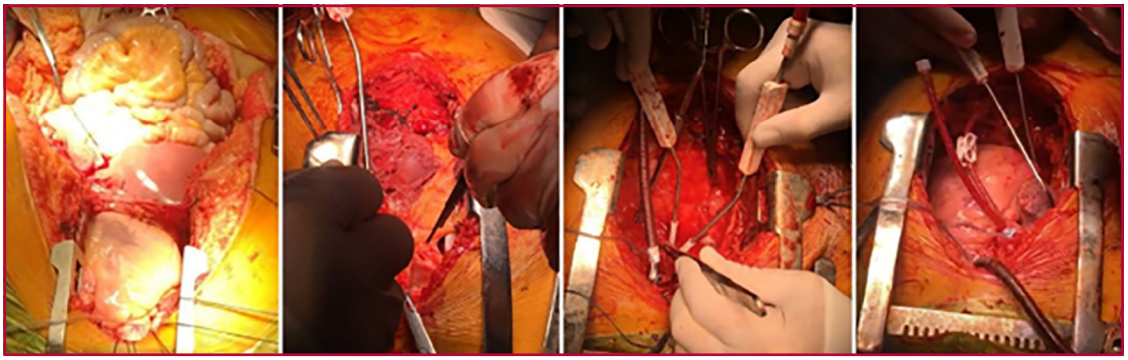

Fig. 2. Surgical images. a) Multi-organ ablation. b) Opening; patient in extracorporeal circulation via femoral approach; clamping; lesion in the anterior wall of the single ventricle. c) Empty mediastinal cavity; left Glenn cannulation. d) Implanted beating heart and declamped aorta.

48 hours after transplantation. He is currently receiving outpatient treatment with immunosuppressants, corticosteroids, diuretics, prophylactic antibiotics and insulin for diabetes secondary to glucocorticoids.

The control echocardiogram showed preserved ventricular function, LVDD 4.7 cm, LVSD 3 cm, shortening fraction 36%, left ventricular ejection fraction by Simpson method 65%, MAPSE 18 mm, tricuspid annulus plane systolic excursion (TAPSE) 14.4 mm, both outflow tracts free, competent aortic valve, trivial pulmonary valve regurgitation, bilateral Glenn with preserved and pulsatile flow.

Catheterization and biopsy were performed 2 months after surgery and showed no signs compatible with rejection.

Patients with univentricular circulation are usually candidates for heart transplantation in the long term. In our opinion, adequate patient selection and pre- and post-operative planning are necessary to improve the quality and success of transplantation in patients with congenital heart disease. Simulation with all the professionals involved in the transplantation made it easier to organize and optimize the operating time.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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The Importance of National Registries in Cardiac Surgery

Importancia de los registros nacionales en cirugía cardíaca

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Coronary artery bypass grafting (CABG) remains a widely used surgery to treat coronary artery disease, thanks to its long-term benefits, especially in patients with multi-vessel disease, proximal left anterior descending artery involvement, left main coronary artery disease, and also in patients with diabetes and moderate to severe left ventricular dysfunction, with left ventricular ejection fraction <35%. While its effects on reducing all-cause mortality versus optimal medical therapy are still unknown, current cardiology guidelines continue to position CABG as the first-choice option for these patients. In addition, they emphasize the need to perform an individual assessment of perioperative risks in all cases and to consider the patient's decision together with the Heart Team. (1)

Awareness of local outcomes is essential for decision-making in this population, since heterogeneous socioeconomic backgrounds may override the extrapolation of data from international registries. In this context, the study titled *Cirugía de revascularización miocárdica en Argentina. Subanálisis del Registro ARGEN-CCV (Coronary Artery Bypass Grafting in Argentina. Subanalysis of the ARGEN-CCV Registry) by Alustiza et al*., (2) provides valuable information on the current situation of CABG in this country. This is the first national registry conducted a decade after the previous registry, CONAREC XVI. This ARGEN-CCV subanalysis, which included 700 patients, revealed a higher in-hospital mortality than international registries (6.9% vs. 2.5% of STS 2022) and an increase compared to the previous national registry (4.3%). In addition, a significantly higher mortality was observed in patients with left ventricular dysfunction versus those without a history of this condition (13.1% vs. 5.1%).

This increase in mortality could be partly due to the fact that the registry was conducted during the COVID-19 pandemic, when, as the authors and several studies point out, cardiovascular mortality increased, scheduled cardiovascular surgeries were dramatically reduced, and the observed/expected postoperative mortality ratio increased notably. (3)

However, it is important to consider the existing discrepancy in terms of postoperative results across different sites in Argentina, some of which have reported individual results comparable to international registries. (4) These differences could be partly explained by the socioeconomic inequality in Argentina (Gini coefficient = 0.46 in the first quarter of 2024), which has been associated with a significant increase in postoperative in-hospital mortality after cardiovascular surgery, according to a recent study. (5) Patients with lower household income had a lower rate of health insurance coverage, a higher rate of emergency surgery, a higher rate of comorbidities and less access to health care in specialized institutions.

Continued efforts are essential to develop national registries, such as the one above, reflecting the cardiovascular surgery scenario in Argentina. This is vital to support informed decisions when managing these patients.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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AUTHORS' REPLY

We are very grateful to Dr. Avellaneda for her comments on our article. We are aware that it allows us to know about the situation of our quality of care indicators, impacted by socioeconomic level, education, medical training, lack of control of top-quality results and urgent political actions, showing that results can be heterogeneous across the country.

Analysis of mortality results, well above the accepted 5% indicators, evidences the inequity of a vulnerable society, with just 8.9% having access to this procedure (62 out of 700 patients) in the public sector, and a large proportion of them in a complex condition (urgency/emergency), with absence of actions by the second-level of primary care (early diagnosis and timely treatment) and by outcome controlling entities in different surgery institutions. Patients undergoing revascularization surgery are considered the most severe population, with a higher proportion of them experiencing left main coronary artery disease (38% versus only 19% in previous registries), diabetes in 38%, acute myocardial infarction (AMI) in less than 30 days in 19%, and heart failure and variables omitted in previous registries, such as frailty. This is because endovascular procedures are now used to treat increasingly complex patients, leaving surgery only for extremely severe cases. This also makes it very difficult to classify them based on predicted mortality estimations, since some variables are not included in the scores (STS, EuroSCORE, ArgenSCORE), for example, the proportion of myocardial fibrosis, fragility, etc., all independent mortality predictors.

Although there are surgery institutions that maintain optimal quality of care indicators, this is not the case in the entire country. *The Coronary Artery Bypass Grafting in Argentina. Subanalysis of the ARGEN-CCV Registry Study* shows true data on a harsh and heterogeneous reality in our beloved Argentine Republic, where we all work. As Dr. Avellaneda says so well, it is essential to continue working on our own data registry to introduce any necessary improvements required by the health system.

As Dr. René Favaloro used to say, "You should always do your best for yourself, your family, and society. Memories are all we have".

Walter Alustiza[MTSAC]

Is It Possible to Predict the Development of Heart Disease in Patients with Chagas Disease?

¿Es posible predecir el desarrollo de cardiopatía en pacientes con enfermedad de Chagas?

CAROLINA B. PUTARO[1, 2]

In Argentina, 1.5 million people live with chronic Chagas infection. Despite advances in diagnostic and therapeutic methods, cardiovascular complications continue to be a concern for cardiologists.

Thirty percent of infected patients in the indeterminate phase will develop structural heart disease, which can result in arrhythmia, sudden death, and/or dilated cardiomyopathy of different grades of severity. In addition, many patients have a reduction in parasympathetic nerves, leading to various types of dysautonomia, which, sometimes, precede heart disease. (1)

This heterogeneous occurrence and progress of the disease could be due to several factors, such as the parasite strain, individual genetic propensity, and subsequent immune response. (2) In turn, the pathophysiology of chronic infection, characterized by a latent period from 10 to 20 years, is both an opportunity for early diagnosis and a challenge to establish appropriate strategies during follow-up.

In this context, it is essential to collect heart disease predictors. This is the basis of the study titled Presence of Dysautonomia as a Predictor of Development of Structural Heart Disease in Patients with Chagas Disease, by Chirino Navarta et al. (3) The authors prospectively enrolled 200 patients with a positive serology test for Chagas disease and without

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structural heart disease (asymptomatic with normal electrocardiogram, 24-hour Holter monitoring, and echocardiogram). These patients had continuous electrocardiographic recording while doing the Valsalva maneuver. An abnormal Valsalva ratio (VR) was defined as the ratio of the longest R-R to the shortest R-R being less than 1.1. This procedure allowed them to identify the VR as an independent predictor of heart disease in the study population during a 3-year follow-up period.

This study is innovative because, while previous analyses have shown impaired autonomic function in patients with Chagas disease, comparisons were limited to healthy individuals only. (4) In addition, it is essential to highlight that this technique is easy to reproduce and does not require many resources.

In the future, it would be interesting to perform a specific evaluation of the different types of structural heart disease to determine whether the VR can be used in some or all cases. Similarly, extending the study to analyze long-term outcomes could provide more detailed and valuable information.

Therefore, it is important to develop validated tools to identify patients at higher risk of Chagas heart disease, especially in Argentina, where patients are distributed over a vast territory and, in many cases, have poor regular access to healthcare systems. In this respect, results could be the starting point of future research, helping to improve the follow-up of Chagas disease patients.

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 kindly thank Dr. Putaro for her valuable comments on our study. We fully agree with the concern regarding prognostic evaluation challenges still present in Chagas disease, as well as its relevance as an important public health issue in our country and the continent. Therefore, it is essential to identify early predictors of structural heart disease to address this issue.

Autonomic dysfunction has long been described as being present in Chagas disease. (1) The causes of dysautonomia are not fully understood, and multiple potential mechanisms have been suggested. As the doctor points out, most studies have compared dysautonomia in Chagas disease patients versus healthy controls. (2) This has led us to hypothesize whether the presence of dysautonomia might be a predictor of structural heart disease. We selected the Valsalva rate due to its simplicity, reproducibility, and low cost. This technique can be performed at the doctor's office in about 10 minutes, making daily administration practical.

The suggestion to perform a specific assessment of the different types of structural heart disease is highly relevant and interesting. We intend to continue with our cohort follow-up, although we admit that it would be essential to expand the sample and extend follow-up beyond three years, as in our initial study. This may help to better identify progression to arrhythmia, dilated cardiomyopathy, or sudden death, and to evaluate whether the Valsalva rate has a differential predictive value according to the type of complication. To move in this direction, it would be interesting to collaborate with other research groups interested in the subject.

Finally, we share your concern about geographic and health care access barriers affecting Chagas disease patients in our country. We also appreciate Dr. Putaro's observations and discussion on this vital subject. It is our hope that this will lead to further promotion of strategies for the improvement of health care for this vulnerable population.

Daniel Chirino[MTSAC]

Current Situation of Cardiologists in our Country. Results of the Health Policy Area Survey

La situación actual de los cardiólogos en nuestro país. Resultados de la encuesta del Área de Políticas de Salud

CECILIA M. MARPEGAN[1]

It is well known that there is an increasing exodus of specialized physicians from our country, probably encouraged by, or perhaps as a consequence of, the current economic situation, poly-employment, low salaries, burnout syndrome, among other factors.

Cardiology is not exempt from this problem, as shown by the recently published article *La situación actual de los cardiólogos en nuestro país. Resultados de la encuesta del Área de Política Sanitaria.* (1)

The survey assessed the opinion of 393 cardiologists on working conditions, satisfaction with their salary, and their representation by the Argentine Society of Cardiology, as well as the forms of continuing medical education. As expected, more than 90% of the respondents disagreed with their income and salary, were personally dissatisfied and had a discouraging outlook for the future. These results are in line with the alarming prevalence of burnout syndrome among cardiologists in Argentina, affecting almost 70% of professionals. (2) It should be noted that the prevalence in the United States is less than 30%. (3) The data are consistent with the results of the CONAREC survey (4) presented at the last Congress, in which 83% of future cardiologists were considering leaving the country.

Regarding the system of specialty training, currently a subject of debate in all medical specialties, the respondents agreed that a medical residency was still the best method of training. They also considered that it should be complemented with postgraduate studies (a doctorate or a master). Despite specialists' agreement, for the past two years, recently graduated Argentine physicians have accounted for less than 70% of the applicants interested in this type of training.

Another interesting point is the growing desire to work in care networks. Only half of the professionals responding to the survey currently do so. Not only would this improve the times of care, but it would also focus specialists, ideally in multidisciplinary teams, on the treatment of more complex but less common pathologies, allowing better use of health resources, combining knowledge and experience, and improving the satisfaction of both patients and professionals, with a likely reduction in health costs.

We cardiologists agree on the current situation of our health system, our training, our day-to-day work, our remuneration and our problems, but few of us know that the Argentine Society of Cardiology has a Health Policy Area where these issues are discussed and where we can participate to achieve a better present and future.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

Dear Dr. Marpegan, thank you for the important contribution to our publication. There are several points that have been mentioned and that need to be devel-

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oped in depth in our survey, in which we seek to obtain answers to daily concerns. We would like to tell you and the cardiology population that at the Health Policy Area, the Board of Directors and other areas of our Society we are working hard to change these figures and future perspectives, which currently seem discouraging. This survey, as well as others that have taken place this year will help us to begin this change with renewed knowledge. With this objective in mind, we will continue on this path and we invite all doctors and non-doctors to participate actively in the SAC and in the Health Policy Area to bring about deep changes in society, in our training, in our daily professional development and in our medical actions, and so that the population can receive the best care with the highest standards in the world.

Diego Novielli[MTSAC,]

Dr. Hernán Claudio Doval (1941-2024)

Hernán Claudio Doval received his medical degree from Universidad Nacional de Buenos Aires, completed his residency in Internal Medicine at CEMIC (Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno) and at the end of the 1960s was summoned by Raúl Oliveri together with Oscar Bazzino to set up the Coronary Care Unit at Hospital Italiano de Buenos Aires. Carlos Bertolasi had created the first Coronary Unit in Latin America at Hospital Argerich, specially oriented to acute ischemic heart disease. A new stage of Cardiology began, a cycle of assistance at the bedside of the intensive care unit patient with ceremonial rounds associating staff physicians and residents, a practice that continued with Doval until the day of his stroke a few months ago. Except for a few years in which he was head of Cardiology at Sanatorio Otamendi, his institutional work was fully concentrated at Hospital Italiano. The physiopathological thinking governed the conducts, and the availability of multiple resources of blood gas measurements together with the Swan Ganz catheter, allowed a thorough individual hemodynamic exploration. At that time he carried out researches on the hemodynamics of infarction, oxygenation evaluated through the divergence between ventilation and perfusion and anatomical shunt, and he invented a nomogram for the management of the acid-base status, and a peculiar device that allowed the measurement of oxygen consumption through a carbon dioxide filter and a parachute. His greatest achievement at that moment was the creation of the "Doval catheter", a modification of the K31 catheter, that with an electrode placed near its end allowed guiding its placement by electrocardiography without requiring expensive monitors to measure pulmonary pressure. He never patented this catheter, which was widely used in low complexity intensive care units in our country and in many others. Already in the 70's the Hospital Italiano was consolidated as a school of cardiology that has maintained its excellence to this day, with Doval as one of its central protagonists.

The 80s, with the Oxford manifesto that led to the ISIS studies in Great Britain and collaterally to the GISSI study, brought about a historical change in medicine, with cardiology as its leading specialty in the evaluation of "simple questions with large studies". On the basis of scientific evidence that proved beyond any doubt, for example, that aspirin reduced mortality in acute myocardial infarction, a new paradigmatic concept emerged and was adopted as hegemonic in contemporary medicine: the "evidence-based" practice, better translated as practice based on scientific evidence with clinical benefit on relevant events. This new reality, which implied generating information that could be taken up by the community to improve the population health on an irrefutable basis, was Doval's passion. Since the first Council of Emergencies in Cardiology, Doval felt encouraged to design studies to evaluate thrombolytics and surveys of different pathologies. He formed and led the GESICA Group that carried out the multicenter study of amiodarone, which showed for the first time that a drug could improve survival in patients with advanced heart failure. This finding, which was based on the hypothesis of the antiarrhythmic effect of the drug, and which was surprising because it also reduced death due to advanced heart failure, provided a rational basis for the convenience of reducing heart rate in this condition, later supported by studies with beta-blockers. Not only was it published in The Lancet with the

generous collaboration of Peter Sleight (leader of the group of young people such as Salim Yusuf in Oxford) and the JACC but it also involved multiple international presentations, conferences and dialogues with the acknowledgement of the leaders in this field.

The late 80's and 90's were thus a time of explosion of national and international multicenter projects, in Argentina ECLA, GEMICA, and ENAI from the Argentine Society of Cardiology (SAC). Doval preferred to maintain GESICA as an independent group with the intention of exploring his own ideas and not being part of the canned studies that were later multiplied as a routine form of exploration of new molecules by the pharmaceutical industry.

With the desire to promote independent national research, he formed the GEDIC group, and since the late 90s he began to teach a training course for clinical researchers, at a time when these concepts were little known in our setting, hosting more than 1000 health professionals for more than 25 years. He taught his last class three days before his stroke. From this course came the idea of a conference on Evidences in Cardiology that brought together a select group of young scholars and resulted in the risky attempt of a self-financed book on the subject in a small format in the year 2000, a few months before the launching of Salim Yusuf's immense book. Evidencias en Cardiología (Evidences in Cardiology) under Doval's leadership was adopted as a kind of textbook for the practice of cardiology by young physicians and residents, and grew slowly from four volumes to reach its tenth edition in 2023, with the addition of national and international contributions.

The GESICA group was consolidated as an example of national independent research, with the virtues and limitations that this implies: remaining independent of the pharmaceutical industry except for minor collaborations, and with national research agencies that have completely ignored clinical research until very recently. It carried out projects such as DIAL, a telephone intervention through nursing that proved to reduce the rate of hospitalizations in heart failure in a practical and economical way, and later studies on Omega 3 in atrial fibrillation. In recent years, there was also an exploration of risk factors in slum areas, which showed a doubling of the concentration of these factors with respect to the national survey that omits this sector of the population. The research led to the training of population agents in the same environment for prevention and early treatment interventions.

In the 2000s, the SAC decided to change the editorial policy of the Journal and summoned Raúl Oliveri, who was succeeded by Doval as editor. Based on his thorough knowledge of the leading journals, of which he had always been a daily reader in the library of Hospital Italiano, he proposed not only an aesthetic change, but also multiple modifications and the tradition of writing editorials on various topics of contemporary medicine. In these editorials, some of them compiled in a first book, he unfolded the approach to health in all its cultural and socioeconomic dimensions, the ethics of medical practice, and made inroads into all the advances of contemporary science, from genetics to regenerative medicine. Concerning concepts on health-disease his guide was Canguilhem, who participated in the French resistance to Nazism and later published The Normal and the Pathological, the cornerstone of the functional-valuative criterion as opposed to the naturalistic-objective-biologistic one. This dimension leads to a medicine more attentive to subjective and psychosocial aspects, which makes its ethical dimension. This stage of the journal marked not only an improvement of its contents, which unfortunately was not enough for its indexation, but it also became a sort of weekly "debate club" on the most diverse topics of medicine and contemporary society. He also occupied the role of director of the Ethics Committee of the SAC for many years.

At Hospital Italiano, together with Dr. Enrique Beveraggi, he created the Family and Preventive Medicine Unit, which gave conceptual basis to the successful Health Plan. Despite being a cardiologist (or not, because he never obtained or claimed that formal title) he maintained a strong commitment to general and family medicine. An in-depth expert on the history of Social medicine since Bismarck, he collaboratively wrote the book Salud. Crisis del sistema. Propuestas desde la medicina social. (Health Crisis of the system. Proposals from Social Medicine). The "causes of causes" approach, as Salim Yusuf called the socioeconomic and cultural factors underlying risk factors, was applied by Doval to each of the topics he addressed.

His training as a great reader of the philosophy of science and his scientific culture in general, allowed him to transmit in the training courses for researchers very creative concepts of the emergence and maturation of ideas. Thus Galileo, Newton, Poincaré, Popper, Bradford Hill, Bateson converged in an epistemological thinking applicable to clinical research.

Throughout his life, he maintained a very committed ideology with the claim for the need for a socioeconomic change as a contribution to a more egalitarian society, an essential part of his medical thinking and many of his projects.

In these brief lines I tried to summarize the dimensions of his professional career, his scientific production, his teaching in research, cardiological publications, his contributions to medical ideas, Argentine society and the ethical dimension. Personally, I did my residency at Hospital Italiano from 1977 to 1981, and I collaborated with Doval in the Emergency Council, in the Argentine Journal of Cardiology and in GEDIC, that is, many hours of joint work that only increased my admiration for his gigantic human and professional dimension, which makes him an undisputable Master of Argentine Medicine. Thus, I witnessed the controversial development of many of his projects, the

emergence from nothing to their maturation in unthinkable concretions, the passionate (and stubborn) defense of his ideas, and the only tears I saw him shed when we shared a presentation on death in cardiology, from an evocative account of his first experiences. And from a distance, I believe that the hundreds of young physicians who have passed through the cardiology residency program at Hospital Italiano or his courses bear the imprint of an intellectual, very human clinical perspective and an ethical dimension, perhaps one of his greatest legacies embodied in the practice of his disciples.

Finally, I would like to share this poem that Doval found at a book fair on a poster in the Chinese pavilion, attributed to Bertold Brecht, although he was never able to verify it even with the help of ChatGPT. I used to read it in the methodology course when the topic of observation and emergence of research ideas was addressed.

To observe you must learn to compare.
To compare you need to have observed.
Observation generates knowledge
and knowledge is necessary to observe.
Observes wrongly
he who cannot do anything with what is observed.
For the apple tree the farmer has a sharper eye
than the stroller,
but man is not exactly seen
by who is not aware that man is man's destiny.

Carlos D. Tajer[MTSAC]

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Hernán Claudio Doval

Loyalty and Commitment of an Irreplaceable Person

Hernán Claudio Doval

Fidelidad y compromiso de una persona irremplazable

Many words and concepts defined Hernán Doval. Some of them come quickly. He was intelligent, cultured, tenacious, and hardworking. While admirable, these were not the qualities that made him irreplaceable. Hernán was that, but he added some key characteristics that are harder to see: he was a loyal, committed, honest, and humble person.

It can be said that it is natural and healthy to change over the years. Therefore, it is difficult to establish loyalty as a virtue. What would be virtuous about being loyal if it were possible to change? But loyalty is not stubbornness. Doval's loyalty was always an act of will that transcended external changes. He was always loyal to a commitment that involved choosing again and again, even in the face of difficulties, to recognize the importance of constant engagement with others in order to build something meaningful. His loyalty was an act of authenticity, of free choice, not of the inertia of past decisions. An avowed admirer of Rudolf Virchow, it is hard not to think of Hernán when reading the great German pathologist and politician: "Medicine is a social science, and politics is nothing but medicine on a grand scale. The physicians are the natural attorneys of the poor, and the social problems should largely be solved by them." Like Virchow, Doval was a man of integrity and his character as a physician was always inseparable from his political and social creed. He practiced medicine without seeking a central role. He had a way of being among others, never above or behind them. Another rare quality.

We do not say goodbye to a person like Hernán. He will be remembered. He will remain present in the memory of those of us who knew him, in the generations of colleagues he inspired, and in the ideas and values he defended. Hernán's legacy is his permanence, his immortality and his transcendence in the consciousness of all those who loved him.

Javier Mariani[MTSAC], **Alejandro Macchia**, **Gianni Tognoni**

Dr. Eduardo Mele (1948-2024)

On November 25, 2024, Dr. Eduardo Fernando Mele passed away at the age of 76 in the city of Buenos Aires where he was born on October 9, 1948.

Dr. Mele received his medical degree from the University of Buenos Aires (UBA) in 1972, his certification as a university cardiologist in 1979, and his Doctor of Medicine degree in 1998, also from UBA. He completed his residency program in cardiology and was chief resident at *Hospital Torcuato de Alvear* in Buenos Aires from 1972 to 1977. From 1978 to 2000 he was a staff physician in the Department of Cardiology and Head of the Coronary Care Unit at *Hospital de Clínicas José de San Martín* of the UBA. From 1985 to 2001 he held the position of Head of the Intensive Care Unit at *Sanatorio Anchorena* in Buenos Aires, and from 1999 to 2001 he was Head of Cardiology at the same institution. Finally, from 2007 until recently, he served as a staff physician at the Department of Cardiology of *Sanatorio Güemes* in Buenos Aires, where he was responsible for overseeing the care of inpatients. Throughout his extensive career, Dr. Mele received unanimous recognition from his peers for his perceptive spirit, intelligence, knowledge, and academic brilliance.

Another facet of Dr. Mele's professional activity was his contribution to clinical research, reflected in publications in national and international journals. He also participated as a speaker in numerous national and international congresses and academic conferences.

In addition to his clinical work, Dr. Mele developed a fruitful teaching career. He was Professor of Medicine at the UBA, General Coordinator of the Center for Continuing Education of the Argentine Society of Cardiology, Deputy Director of the Cardiology Specialist Course of the UBA, *Sanatorio Güemes* venue, and Member of the Academic Committee of the Cardiology Specialist Course of the UBA. In this extensive commitment to teaching Dr. Mele demonstrated a deep vocation and a dedicated and caring spirit.

Dr. Mele's remarkable participation in institutions, particularly the Argentine Society of Cardiology (SAC), reflects his dedication to service and professional commitment. Became Full Member in 1982 and was elected president of the institution in 2008 when the World Congress of Cardiology was held in Buenos Aires.

At the international level, Dr. Mele did an outstanding work. Was fellow of the American College of Cardiology, European Society of Cardiology, and Interamerican Society of Cardiology. In 2017, he held the position of Governor of the Argentine Chapter of the American College of Cardiology.

Dr. Mele was a highly regarded clinician, an astute researcher, and a dedicated educator. His personality was characterized by discipline, perseverance, scientific knowledge, and dedication to service. But beyond his unquestionable scientific values, his affability, balanced character and moral integrity consistently earned him the well-deserved recognition of patients and colleagues.

I met Eduardo in 1977 when we were both students of the Cardiology Specialist Course directed by Prof. Dr. Albino M. A. Perosio. Since then we built a solid friendship. In 2004, when I was Vice President of the SAC, I had to assume the role of President on numerous occasions due to the illness and subsequent passing of our beloved President Mario Ciruzzi. This was an additional responsibility, apart from the organization of the Congress of Cardiology to be held that year. I sought the assistance of someone who could help me in that task and Eduardo was an excellent collaborator. Furthermore, he assumed a prominent role in the organization of the Congress. Since that time,

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I am indebted to him for his invaluable contributions.

As a world reference said, "in the fleeting time we have on this Earth, what matters is not wealth, or status, or power, or fame—but rather, how well we have loved, and what small part we have played in making the lives of other people better." Dr. Eduardo Mele loved and made the lives of many people better and perhaps, also made all of us better.

It is with profound sadness that we bid a final farewell to our colleague, peer, and friend, and we extend our deepest sympathies to Ana Salvati, his cherished and devoted partner, his children Pablo, Verónica, and Fernando, his grandchildren Olivia, Juan, Tomás, Clara, and Luca, and to all those who knew Dr. Eduardo Fernando Mele.

The journey is over, may you rest in peace, Eduardo.

Daniel José Piñeiro[MVSAC]
Consulting Professor, Universidad de Buenos Aires
Former President, Argentine Society of Cardiology

Closing Speech of the 2024 SAC Academic Ceremony

Discurso de cierre del acto académico 2024

Dear members of the SAC,

It has been a year since the new Board of Directors and Executive Committee took over the management of our Society. This very challenging year, which began with considerable political and economic uncertainty, has gone by very quickly. But with hard work and dedication, our Society has done very well. We had a great academic and a good financial year, which is very important to maintain the logistics and structure of the Argentine Society of Cardiology, the SAC. I am going to break with the tradition or habit of reading the accomplishments. I am convinced that it is not necessary, given the enormous work done by the Instructional Resources Area (ARI) and the Press and Communication Area of the SAC, which weekly informs all members of the Society of all our activities through digital, audiovisual and graphic media.

I thought about showing a slide with the most important 10 or 15 accomplishments of the year. I was not convinced with this idea. It seemed to me that it would be like not recognizing the work that each member of the SAC does every day. Writing an abstract, a case conference, a book page, a webinar, a podcast, or attending or participating in a course. This vocation is the true essence and spirit of our Society.

That is why I would just like to take these few minutes to publicly express my gratitude and acknowledge the true lead actors of this management.

1. Firstly, to each member of the SAC for their invaluable contributions and sense of belonging.
2. To the Board of Directors, particularly Pablo Stutzbach and Sergio Baratta. We agreed on ideas and actions, which allowed us to enhance the management.
3. I would like to thank my two closest collaborators. Our academic secretary, Silvia Makhoul, and our treasurer, Diego Pérez de Arenaza. I would not have been able to carry out my work without Silvia's global knowledge of the SAC and without Diego's expertise in economic matters.
4. To the members of the Advisory Board, whose political and personal support, suggestions and recommendations facilitated our work.
5. To Jorge Thierer, who in collaboration with the editorial team of the Argentine Journal of Cardiology, are undertaking an exceptional job to achieve the long-awaited goal of being indexed in Pubmed.
6. To Ana Salvati, a relentless worker who has expanded the boundaries of our Society to the community, overcoming significant challenges.
7. I should also like to recall Hernán Doval and Eduardo Mele, who will forever remain in our memories as mentors of a life of commitment, self-improvement and love for cardiology and for people.
8. To Sebastián Galdeano, our second Vice-President, presidents and members of SAC PAÍS, who disseminated the message of cardiovascular healthcare through conferences targeting cardiologists, physicians in general and the community, to every corner of our country.
9. To each of the directors of the councils and areas, nurses, and technicians, who are the true generators of scientific content and its dissemination and who, following an idea of Mario Fitz Maurice, collaborated with him in the development the SAC Manual of Cardiology, a seminal work for our Society.
10. To Hector Deschle for his profound teaching vocation along with the establishment of the Institute of Continuing Education. This will serve as the nexus for all teaching activities within the SAC and reaffirms the path of the primary objective, the University Institute.
11. To all the staff of the SAC, always willing to work with consistent availability and dedication to self-improvement. I want to highlight Marina, our great secretary, who is always present for any concern and solves any situation. And Dr. Analia Llanos, our administrator. Her organization and efficiency have allowed us to work in a planned and professional manner, fundamental qualities for the success of each of our activities.

Personally, it has been a great honor to have presided over our society. I will always remain at your disposal.

Víctor Mauro MTSAC,
President of the Argentine Society of Cardiology

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