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Summary

ORIGINAL ARTICLE

Impact of a Specifically Designed Model of Care in an Outpatient Coronary Angioplasty Program

Impacto de un modelo asistencial específicamente diseñado en un programa de angioplastia coronaria ambulatoria

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ABSTRACT

Background: An outpatient model of care for percutaneous coronary procedures called Radial Lounge (RL) was designed at our center. Patients wear their own clothes throughout their stay, with no mobility restrictions and without fasting. Before and after the procedure, they remain in an armchair accompanied by a family member until discharge, without continuous monitoring, under the supervision of a nurse dedicated exclusively to this area.
Objectives: The aim of this study was to evaluate the safety and efficacy of the RL model of care, the same-day discharge (SDD) rate, patient experience, and major adverse cardiovascular events (MACE): in-hospital mortality, overall mortality, and re-hospitalization at 30 days
Methods: A retrospective observational cohort study was conducted at a cardiovascular center, including consecutively enrolled patients undergoing elective percutaneous coronary intervention (PCI) in the RL.
Results: A total of 2102 elective PCI procedures were included under the RL model. The SDD rate was 85.3% in the first year of its implementation (2018) and reached 89% in 2022. Assessing patient experience, the average score obtained through the Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey was 9.61/10. The rate of MACE was not higher than that reported in the literature.
Conclusion: The PCI program in the RL proved to be a safe and effective model in our experience.

Keywords: Percutaneous Coronary Intervention - Length of Stay – Patient experience

RESUMEN

Introducción: Desarrollamos en nuestro centro un modelo asistencial ambulatorio para procedimientos coronarios percutáneos denominado *Radial Lounge* (RL). Los pacientes visten su propia ropa durante toda la estadía, sin restricciones de movilidad y sin necesidad de ayuno. Antes y después del procedimiento permanecen en un sillón acompañados por un familiar hasta el alta, sin monitoreo continuo y controlados por un enfermero dedicado exclusivamente a esta área.
Objetivos: Evaluar la seguridad y eficacia del modelo asistencial del RL, la tasa de alta el mismo día (AMD), experiencia del paciente y eventos cardiovasculres adversos mayores (ECAM): mortalidad intrahospitalaria, mortalidad y rehospitalización a 30 días.
Material y métodos: Se realizó un estudio observacional de cohorte retrospectiva en un centro cardiovascular, en que se incluyeron consecutivamente pacientes sometidos a una angioplastia transluminal coronaria (ATC) electiva en el RL.
Resultados: Se incluyeron 2102 procedimientos de ATC electivas realizadas bajo el modelo RL. La tasa de AMD fue del 85,3% en el primer año de su implementación (2018) y alcanzó un 89% en 2022. Al evaluar la experiencia de los pacientes, el puntaje promedio obtenido a través de la encuesta de *Consumer Assessment of Healthcare Providers and Systems* (HCAHPS) fue 9,61/10. La tasa de ECAM no fue mayor que la reportada en la literatura.
Conclusiones: El programa de ATC en RL demostró ser un modelo seguro y efectivo en nuestra experiencia.

Palabras clave: Angioplastia coronaria transluminal percutánea – Tiempo de internación – Satisfacción del paciente.

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INTRODUCTION

Currently, percutaneous coronary intervention (PCI) is the treatment of choice in cases of severe symptomatic coronary artery disease with favorable anatomy. (1,2) As a rule, patients undergoing elective PCI are monitored in a closed unit for at least 24 hours due to the risk of vascular access complications and acute events. (3) With advances in the angioplasty technique and new antithrombotic therapies, together with the new generation of stents and, fundamentally, the progressive and sustained shift from femoral to radial access, same-day discharge (SDD) is an increasing alternative. (4,5)

Multiple studies have demonstrated the safety of this strategy. (6,7) Both the American Society for Cardiovascular Angiography and Interventions Expert Consensus (updated in 2018) and the 2021 American College of Cardiology Expert Consensus have incorporated SDD as the standard of care for elective PCI. (8,9)

The implementation of SDD protocols following elective PCI has optimized the use of hospital resources by reducing the length and cost of hospital stay, while providing safe and effective patient care. (10) Early mobilization, along with early return to the home environment, represents a valuable strategy to mitigate physical deterioration and reduce the risk of infections and delirium associated with hospitalization. (11,12) In addition, a shorter hospital stay can have a positive impact on cost reduction by optimizing the use of limited medical resources, both in physical space and medical staff. (13) However, the lack of a model of care specifically designed for outpatient percutaneous procedures may affect the effectiveness of the program. (14)

In our center the PCI with SDD program was first implemented in the conventional inpatient area in 2015, and then, due to the increase in elective PCI volume and evidence support, an exclusive outpatient model of care was implemented in 2018 in a specific area, called Radial Lounge (RL). The RL is adjacent to a new cath lab with the highest standards of complexity and safety. It follows a defined medical program in terms of inclusion and exclusion criteria, and is prepared to treat a broad spectrum of cardiovascular diseases. This model has shown promising results in terms of operational efficiency and patient experience, but its impact on the outpatient PCI program has not been thoroughly studied.

The aim of this study was to evaluate the impact of the RL model in the PCI program with SDD, considering its safety, efficacy and patient experience.

METHODS

We conducted a retrospective observational cohort study in a high-complexity center, including patients undergoing elective PCI between 2018 and 2022 under the LR model of care.

Radial Lounge

The RL opened in July 2018 as an area dedicated to outpatient percutaneous procedures. It has 10 armchairs, a bed in a separate room (femoral box), a nursing office, an administrative area and a healthy snack bar. In all cases, patients are evaluated in a pre-procedure consultation with a cardiologist of the service, who reviews each case and considers the feasibility of SDD according to the pre-procedure checklist recommended by the 2021 ACC expert consensus. (9) In addition, the informed consent form specifying the risks of the procedure is explained and handed out on paper. Patients without exclusion criteria are received in the RL by a nurse who checks vital signs on admission, places an intravenous line and assigns them to a chair where they will wait until the procedure accompanied by a family member. Previous fasting is not required. (15) Subsequently, they are admitted to the hemodynamics room in their own clothes. In all cases, the operator chooses the access site. For radial (proximal or distal) or ulnar (left or right) access, hemostasis is performed using the Terumo™ TR Band radial compression device or compressive bandage for distal radial punctures. For femoral access, puncture is performed under ultrasound guidance and the Angio-Seal (Terumo™) arterial occluder device is used. After PCI, the patient remains in the LR chair for a minimum of 4 hours in case of radial or ulnar access and 6 hours in case of femoral access, except for those cases in which the interventional cardiologist in charge indicates hospitalization in a monitored unit due to some intercurrence during the procedure. The following complications of the procedure are considered: altered flow, side vessel compromise that generates precordial pain, untreated dissection, arterial perforation, vascular access complication or allergic reaction to the contrast medium. Observation in the RL ends with an evaluation by a clinical cardiologist and all patients are discharged with a follow-up appointment within 10 days after the procedure.

PCI program in the RL

All outpatients with an indication for a percutaneous procedure are previously evaluated in a consultation by a member of the Interventional Cardiology team. Clinical and social exclusion criteria have been developed for the admission of patients to the RL. In these cases, patients are referred to the conventional hospitalization area.

RL clinical exclusion criteria:

- Requirement of permanent oxygen therapy (home oxygen).
- Left ventricular ejection fraction <30%.
- Weight >150 kg.
- Need for dialysis or creatinine clearance <30 ml/min.

RL social exclusion criteria:

- Lack of family support or patient's refusal.
- Psychiatric disorders or advanced cognitive impairment.
- Need for bed rest for any other reason.

Complexity of the procedure

Procedural complexity is not part of the RL exclusion criteria. Therefore, patients with a complex anatomy can be admitted and treated in this setting. To assess the complexity of the procedures performed, the following criteria are taken into account: the Syntax score, use of rotational atherectomy (Rotablator), intravascular ultrasound (IVUS)-guided PCI, PCI for left main coronary artery (LMCA) and/or proximal left anterior descending artery and/or venous graft and/or bifurcation and/or chronic total occlusion.

Patient experience

Scores obtained from the Hospital Consumer Assessment of Healthcare Providers and Systems Survey (HCAHPS) are

used to assess patient experience. (16) HCAHPS is a standardized survey tool that measures patients' perceptions of their hospital experience, including communication with healthcare providers, hospital environment hygiene and quietness, pain management, and overall hospital rating. We collected HCAHPS scores from patients who underwent elective PCI under the RL model and voluntarily completed the questionnaire.

Major adverse cardiovascular events (MACE)

To evaluate the safety of the RL model, in-hospital mortality, overall mortality, coronary reintervention and rate of 30-day rehospitalization were considered.

Data collection

Data were collected from the electronic medical records registration system and the digitized reporting system. Demographic data, clinical characteristics, procedure details, and outcomes were collected for all patients included in the study.

Ethical considerations

The present study was submitted to and approved by the institutional Ethics Committee.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range, as appropriate. Categorical variables are expressed as frequencies and percentages. The t test or Mann Whitney test were used to compare continuous variables, according to their distribution, and the chi-square test or Fisher's exact test were used to compare categorical variables between groups. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 2102 PCIs were included under the LR model of care. Among treated patients, 86.7% were male, and mean age was 67.1 ± 9 years. The mean number of vessels treated was 1.3 ± 0.5, and the mean number of stents implanted was 1.9 ± 1.0. Complexity criteria were identified in 46.7% of all the PCIs performed. The complete distribution of risk factors and complexity are presented in Table 1.

From 2018, when the RL program began, there was a sustained and progressive increase in the rate of PCIs with SDD over the years, and the number of hospitalizations for more than 24 hours in elective PCI procedures decreased (Figure 1). The RL SDD rate was 85.3% in the first year of implementation (2018) and reached 89% in 2022 (Figure 2).

The voluntary response rate to the HCAHPS of patients undergoing elective PCI in the LR was 39.5%. The mean score received was 9.61/10.

Regarding PCI with SDD in the LR MACE, in-hospital and 30-day mortality was 0.1%; there was 0.4% coronary reinterventions and 0.5% rehospitalizations at 30 days (Table 2).

Table 1. Distribution according to risk factors and complexity of the procedure performed.

Characteristics	Radial Lounge (n = 2102)
Age, years, mean±SD	67.1±9
Male sex, n (%)	1822 (86.7)
Dyslipidemia, n (%)	1830 (87.1)
Hypertension, n (%)	1723 (81.9)
Obesity, n (%)	586 (27.9)
Diabetes, n (%)	714 (33.9)
Chronic kidney disease, n (%)	183 (8.7)
Previous angioplasty, n (%)	538 (25.6)
Vascular access, n (%)	
Radial	1912 (91.0)
Femoral	140 (6.7)
Cubital	15 (0.7)
Humeral	4 (0.2)
Treated vessels, mean±SD	1.3 ±0.5
Stents implanted, mean±SD	1.9 ±1.0
LMCA, n (%)	103 (4.9)
Chronic total occlusion, n (%)	101 (4.8)
Rotablator, n (%)	2 (0.1)
IVUS, n (%)	208 (9.9)
Left anterior descending artery, n (%)	605 (28.8)
Venous graft, n (%)	23 (1.1)
Bifurcation, n (%)	389 (18.5)
Syntax Score >32, n (%)	57 (2.7)
Complex angioplasty *, n (%)	982 (46.7)

*defined according to the Syntax score, use of Rotablator, IVUS-guided PCI, PCI to left main artery and/or proximal left anterior descending artery and/or venous bridge and/or bifurcation and/or chronic total occlusion.
IVUS: intravascular ultrasound; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; SD: standard deviation

DISCUSSION

The main finding of our analysis was a significant increase in the volume of elective PCI with SDD since the introduction of the RL, currently reaching almost 80 % of all elective PCIs. The PCI program in the RL did not affect safety in terms of adverse events during hospitalization or at 30 days. These results are in line with the current approach of healthcare institutions that seeks to optimize resource utilization, and improve patients' satisfaction without affecting their safety. (17-19)

Reducing the length of stay is essential to prevent the development of complications associated with hospitalization and the time to social reintegration of patients. This is especially beneficial in elderly populations, as it decreases the potential harms associated with hospitalization, such as infections, falls or cognitive impairment. (20) Many reports have estimated that each additional night in the hospital increases the risk of adverse drug reactions by 0.5% and the risk of infections by 1.6%. (21,22) In addition, this has had a significant impact on hospital resources by avoiding unnecessary bed occupancy, especially in light of the latest COVID-19 pandemic. In our study, out of the total number of elective PCIs performed in the RL

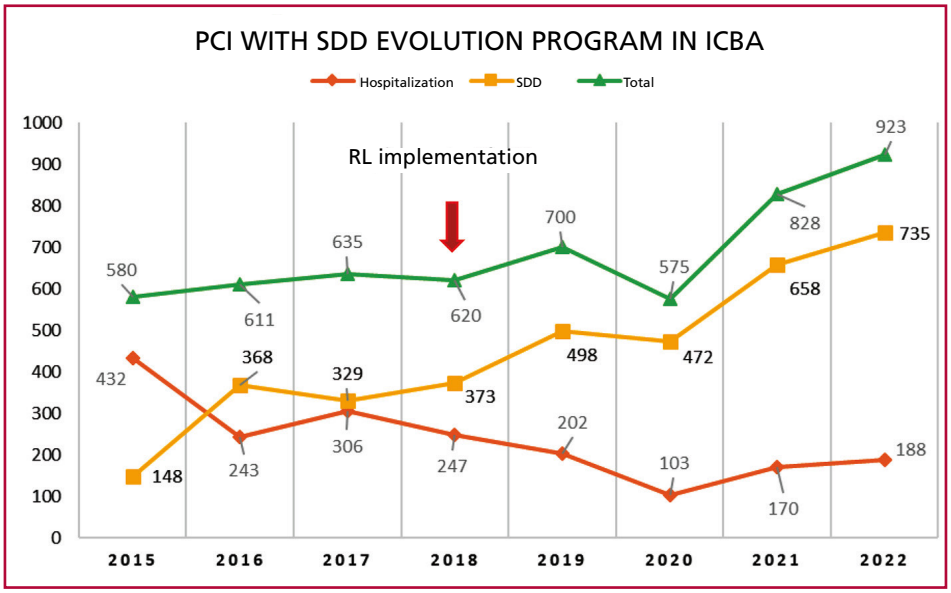

Fig. 1. Evolution of the elective percutaneous coronary intervention (PCI) program from 2015 to 2022. Implementation of the Radial Lounge (RL) model in 2018.

ICBA: Instituto Cardiovascular de Buenos Aires. SDD: same-day discharge

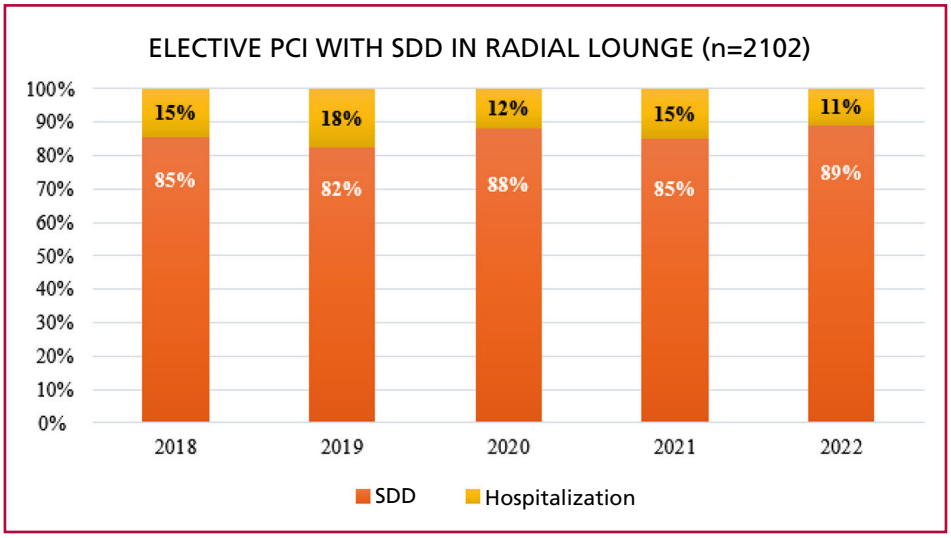

Fig. 2. Percentage of same-day discharge (SDD) vs. hospitalization for at least 24 hours in Radial Lounge.

PCI: percutaneous coronary intervention; SDD: same-day discharge

Table 2. In-hospital and 30-day events.

Major Events	Radial Lounge (n=2102)
In-hospital mortality, n (%)	2 (0.1)
Mortality at 30 days, n (%)	2 (0.1)
In-hospital reintervention, n (%)	10 (0.6)
Reintervention at 30 days, n (%)	10 (0.5)
30-day rehospitalization n, n (%)	5 (0.3)

during the 5 years analyzed, 1812 were with SDD, resulting in an average of 362 free beds per year. In a study conducted at the London Chest Hospital, similar results to those mentioned above were observed. Specifically, there was a 48.9% increase in the SDD rate following the implementation of an area specifically designed for outpatient procedures, resulting in an estimated savings of 595 bed-days due to decreased overnight admissions in this patient group. (23)

Patient experience was also assessed in a study conducted in Switzerland, where a 97% "complete satisfaction" rate was observed with the use of a five-item questionnaire after elective PCI with SDD in an LR model. (24) This demonstrates a clear improvement of patient experience by avoiding admission to a common area of the hospital for an outpatient procedure that in itself can be very stressful for the patient and family.

Finally, SDD after elective PCI has proven to be a safe strategy. Recently, the largest case series of SDD

after elective PCI was published. This study included 819 091 patients from 1716 centers, and when SDD vs. hospitalization for at least 24 hours groups were compared, 30-day mortality was identical throughout the follow-up period. (25) Multiple studies have been performed on safety in SDD, but few have been published so far performed under a different than conventional model of care. (23,26-29) As in the work published by Brewster et al., the RL model of care did not affect outcomes in terms of MACE during a 30-day follow-up. (23)

Limitations of this study include the retrospective design, which may be subject to selection bias and confounding by indication. In addition, the study was conducted in a single high-complexity center, which may limit the generalization of the findings. Finally, the satisfaction surveys were answered voluntarily by a percentage of the total number of patients, so there may be response bias .

In conclusion, the implementation of a specially designed care model such as RL proved to be safe and effective, with evidence of impact on the SDD rate. In addition, the reported patient experience was higher than 9.5/10 points in this model of care.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

2022 SONQO-CALCHAQUÍ Program: Evaluation of Cardiovascular Variables in a Mid- and High Mountain Calchaquí Population of Tucumán

Programa SONQO-CALCHAQUÍ 2022: Evaluación de variables cardiovasculares en una población Calchaquí de media y alta montaña de Tucumán

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ON BEHALF OF THE SONQO-CALCHAQUÍ 2022 PROGRAM*

ABSTRACT

Background: The community of Quilmes (Tucumán) encompasses 2400 mid- and high mountain inhabitants (1800 to 4000 meters above sea level). In 2018, a study was carried out on their cardiovascular health status (2018 SONQO-CALCHAQUÍ Program).
Objective: The aim of this study is to update and expand the survey carried out in 2018, to obtain a broader panorama of the cardiovascular health of this community.
Methods: A descriptive cross-sectional study was carried out in the Quilmes community, in people who voluntarily attended specially established clinics in September 2022. Questionnaires, laboratory tests, ECG, echocardiogram, anthropometric measurements, muscular resistance and strength tests were carried out.
Results: A total of 186 patients (119 women and 67 men) aged 45.0±1.3 years attended the study. The prevalence of cardiovascular risk factors (hypertension 17.8%, smoking 14.1%, diabetes 4.9% and dyslipidemia 30.6%) was acceptable, but a high proportion of cases had not been examined in the last year. The diet consisted mainly of flour products, with little fresh fruit and vegetables. The prevalence of overweight (34.3%) and obesity (35.4%) was high. Forty percent of respondents had secondary or higher education. Good quality of life (69.5±1.1% of the maximum possible value of satisfaction on the self-perception scale) was reported. The *Mini-mental* Test average was 15.7±0.2 points. Prehensile strength in 55.8% of cases was below the normal range.
Conclusions: The Quilmes population presents an acceptable physical condition, but with a high rate of overweight and obesity, due to the diet, a condition that should be considered in future health programs.

Key Words: Calchaquí Population - Epidemiology - Indigenous population - South America - Mid- and high mountains - Cardiovascular variables

RESUMEN

Introducción: La comunidad de Quilmes (Tucumán) consta de 2400 habitantes de media y alta montaña (1800 a 4000 metros sobre el nivel del mar). En el año 2018 se realizó un estudio sobre su estado de salud cardiovascular (Programa SONQO-CALCHAQUÍ 2018).
Objetivo: Actualizar y amplificar el relevamiento realizado en el año 2018, para obtener un panorama más completo de la salud cardiovascular de la comunidad.
Material y métodos: Se efectuó un estudio descriptivo transversal en la comunidad Quilmes, en personas que asistieron voluntariamente a consultorios especialmente establecidos, en el mes de septiembre de 2022. Se realizaron cuestionarios, dosajes de laboratorio, ECG, ecocardiograma, determinaciones antropométricas, y pruebas de resistencia y fuerza muscular.
Resultados: Concurrieron 186 pobladores (119 mujeres y 67 varones) con edad 45,0±1,3 años. La prevalencia referida de factores de riesgo cardiovascular (hipertensión 17,8%, tabaquismo 14,1%, diabetes 4,9%, dislipidemia 30,6%) fue aceptable, pero con alta proporción sin exámenes en el último año. La alimentación estaba constituida principalmente por derivados de harinas, con escasa fruta y verdura fresca. La prevalencia de sobrepeso (34,3%) y obesidad (35,4%) fue elevada. El 40% de los encuestados tenía edu-

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*ANNEX I

cación secundaria o superior. Se refirió buena calidad de vida (69,5±1,1% del valor máximo posible de satisfacción en la escala de autopercepción). El *Minimental* Test arrojó un valor promedio de 15,7±0,2 puntos. La fuerza prensil en el 55,8% de los casos estuvo por debajo del rango normal.

Conclusiones: La población Quilmes presenta un estado físico aceptable, pero con alto índice de sobrepeso y obesidad, debido al régimen alimentario. Esta situación debería ser contemplada en los programas de salud futuros.

Palabras Claves: Población Calchaquí - Población indígena - Sudamérica - Media y alta montaña - Variables cardiovasculares - Epidemiología

INTRODUCTION

The Tucumán district of the Argentine Society of Cardiology (SAC) through the SONQO-CALCHAQUÍ Program evaluated in 2018 the cardiovascular health status of the Quilmes native community (Valles Calchaquíes - Tucumán), (1) made up of scattered settlements with distinctive historical, geographic and sociocultural characteristics. (2)

In this first contact, it was observed that the inhabitants were overweight (1) and that the prevalence of cardiovascular risk factors was similar to that of urban centers. (3) This raised the hypothesis that there would be an increase in cardiovascular morbidity and mortality, as was observed in other indigenous populations. (4,5) Mandatory social isolation (quarantine) due to the COVID-19 pandemic led to a radical change in health strategies worldwide, (6) and this context not only postponed the second phase of the SONQO-CALCHAQUI program until 2022, but also further increased the historical isolation of this population. For this reason, the aim of the present study was to update and expand the survey conducted in the 2018 SONQO-CALCHAQUÍ Program, to obtain a more complete description of the cardiovascular health of the Quilmes community.

METHODS

A descriptive cross-sectional study was performed in inhabitants of the Quilmes community who voluntarily attended from September 29 to October 1, 2022, School No. 213 Cacique Martín Iquin, where 7 offices were implemented to carry out the following studies:

Office 1 (laboratory):

Assessment of thyroid-stimulating hormone (TSH; μU/mL), blood glucose (mg/dL), insulin (μU/mL), insulin resistance index (HOMA-IR), fibrinogen (mg/dL), Ultra –Sensitive C-Reactive Protein (US-CRP) (mg/L), total protein (g/L), albumin (g/L), sodium (mEq/L), potassium (mEq/L) and chloride (mEq/L).

Office 2 (surveys):

Targeted cardiovascular survey. (1)

Mini mental test, that evaluates cognitive impairment. Values up to 9 points: moderate to severe impairment; 10 to 24 points: mild to moderate impairment; 25 to 26 points: possible impairment and 27 to 30 points: no impairment. (7)

Twenty-four-hour. intake recall test. (8)

Food consumption frequency test: semi-quantitative questionnaire that includes 19 foods where the frequency (daily, weekly or monthly) with which they were consumed in the last year is indicated.

SF-12 Questionnaire: which assesses the self-perceived health status. (9)

Rosenberg 10-question self-esteem scale (Total value: 10 to 40 points) (10)

Pittsburgh Sleep Quality Index, in its Spanish version. (11)

Ten-question Frailty Test (Edmonton Scale): maximum value 20 points (not frail: 0 to 4 points; apparent vulnerability: 5 to 6 points; mild frailty: 7 to 8 points; moderate frailty: 9 to 10 points; severe frailty: 11 to 20 points). (12)

Office 3 (anthropometry, blood pressure and oximetry):

Recording of anthropometric parameters. A waist and abdominal circumference of up to 88 cm in women and 102 cm in men and a neck circumference of up to 43 cm in both sexes were considered normal.

Body mass index (BMI), expressed in kg/m2, was calculated. where participants were classified as undernourished (BMI <18.5); normo-nourished (BMI 18.5 to 24.9); overweight (BMI 25.0 to 29.9) and obese (BMI >29.9).

Blood pressure (BP) was measured with a digital sphygmomanometer (Omron ® 7120) according to the guidelines of the Argentine Consensus on Arterial Hypertension. (13)

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

Office 4 (electrocardiogram):

A digital recording of 12 simultaneous leads was performed for 3 minutes (Jotatec® TaurusTouch). The following data were evaluated: rhythm, heart rate, duration and axis of QRS complexes and heart rate variability.

Ofiice 5: (echocardiography):

A recording of dimensions (mm) and areas (cm2) of cardiac structures (Esaote® MyLab 30 Gold) was carried out, with calculation of the left ventricular ejection fraction (LVEF) using the Simpson Biplane method. (14) Cardiac and tissue color Doppler measurements were performed.

Office 6 (peripheral vascular ultrasound):

The Doppler technique was used for neck vessels (Esaote® MyLab 30 Gold). The number of atherosclerotic plaques and the presence of significant hemodynamic obstructions were recorded.

Office 7 (muscular strength and endurance test):

Resistance to stress was assessed with the Ruffier-Dickson test. (15) The Ruffier index was calculated, considering the following scale: 0: very good; 0.1 to 5: good; 5.1 to 10: average; 10.1 to 15: insufficient and 15.1 to 20: poor. (15)

The maximum prehensile strength was measured by means of a hydraulic dynamometer (Jamar®) in the dominant hand with average calculation of 3 effort trials. Values greater than or equal to those indicated in the literature were considered normal (16).

People who were not from the Quilmes community or people with sensory, cognitive or motor disabilities were excluded from the study.

Statistical analysis

Results are expressed as mean ± standard error. In each case, the range of values obtained is presented. The Chi-square test ($\chi 2$) or Student's t-test for grouped data was performed as appropriate. Statistical analysis was carried out using Prism 5.0 software.

Ethical considerations

The study was approved by the Research Ethics Committee (CEI) of the SI.PRO.SA Research Department (Opinion 34/2022). All participants granted the corresponding Informed Consent to participate.

RESULTS

A total of 186 patients attended the clinics, 119 women (63.9%) and 67 men (36.1%) with a mean age of 45.0±1.3 years (range 18 to 90 years).

Office 1

The blood sample could not be processed in 29 patients. In the 157 inhabitants in whom it was processed, the values obtained were: TSH: 2.2±0.2 μU/mL; blood glucose 63.4±2.8 mg/dL; insulin: 9.2±0.8 μU/mL; HOMA index: 2.1±0.3; fibrinogen: 267.0±11.4 mg/dL; US-CRP: 2.2±0.3 mg/L; total protein: 6.8±0.1g/L; albumin: 4.1±0.1 g/L; sodium: 127.6±1.5 mEq/L; potassium: 5.5±0.1 mEq/L and chloride: 90.8±1.1 mEq/L.

Office 2

Socioeconomic and educational data

Educational level: illiteracy was found in 9.1% of the population; 48.9% had primary education; 27.4% secondary education; 8.1% tertiary education; and 4.8% university education. A total of 1.9% participants did not answer this question.

Occupation: 23.1% answered housewife; 12.4%: unemployed; 41.5% active worker; 14.0% retired and 9.1% did not answer this question.

Mobile telephone: 83.98% owned a cell phone. Among them communication is through phone calls in 6.5% of cases, with text messages in 1.9% and through the WhatsApp application in 91.6% of cases. Regarding time of use, 9.2% use it less than one hour per day; 34.0% from 1 to 3 hours; 26.3% from 3 to 6 hours, 19.2% for more than 6 hours and 1.3% did not answer this item.

Targeted cardiovascular survey:

BP: 16.7% of respondents had not undergone a BP control in the last year; 17.8% reported hypertension (HT), of whom 12.1% were not receiving pharmacological treatment; 61.1% reported not having HT and 21.1% did not know.

Smoking: 75.7% were non-smokers; 14.1% were current smokers (with 6.6±1.5 cigarettes/day) and 10.3% were defined as former smokers. Smoking onset was at the age of 21.8±1.5 years.

Diabetes: 43.5% had not undergone blood glucose controls in the last year; 4.9% reported diabetes (among whom 66.7% were treated); 68.1% defined themselves as non-diabetic and 27.0% did not know.

Dyslipidemia: 53.2% had no cholesterol control in the last year; 30.6% had dyslipidemia (among whom 35.7% were treated); 29.2% reported not having dyslipidemia and 39.9% did not know.

Alcohol: 29.0% reported regular consumption (1.9±0.7 times per week).

Physical activity: 54.3% responded that they routinely performed physical activity (3.8±0.2 days/week).

Minimental Test

Mean impairment was 15.7±0.2 points (population with mild to moderate cognitive impairment), 91.4% knew what day and month it was and 93.1% knew the year. As for remembering 3 objects, 96% were able to do so, 1.2±0.1 repetitions being necessary; and when asked again 80.8% remembered all 3 objects. Out of 5 numbers to be retained, 3.2±0.2 numbers were remembered on average. In the activity with the paper, 89.7% took it correctly, 97.1% folded it correctly and 96.0% placed it as indicated. The drawing of pentagons was correctly done by 60.6%.

Diet

a) Twenty-four-hour reminder:

Breakfast: The most commonly consumed infusion (50.5%) was mate, followed by tea (28.5%) and milk (7.0%), in 26.3% of cases with tortillas and buns (bread made with fat) and in 7.0% with another type of bakery. The rest only took the infusion. Snack: 32.3% had drank herbal tea the previous day; 14.0% had bread made with fat and 11.8% had fruit.

Lunch: 34.9% ate some type of stew; 9.7% ate meat; 6.5% ate pasta; and 6.5% ate rice. Dessert (generally a seasonal fruit) was eaten by 36.0% of respondents.

Afternoon snack: 71.5% drank an infusion (52.5% yerba mate). 22.0% ate something between the afternoon snack and dinner (tea: 9.7%; bread: 7.5%; seasonal fruit: 5.4% and another food: 5.4%).

Dinner: 55.9% had dinner, generally the same meal as lunch, and 7% accompanied it with dessert.

b) Frequency of food consumption:

The number of servings consumed per month was: whole dairy: 10.5±1.3; semi-fat dairy: 3.9±0.8; eggs: 9.9±0.9 units; lean meats: 13.36±1.0; white meats: 8.5±0.8; white fish: 1.1±0.2; oily fish: 1.7±0.2; vegetables: 28.0±1.8; fruits: 21.1±1.6; nuts: 7.4±0.8; legumes: 5.6±1.1; olive oil: 10.3±1.1; other oils and fats: 8.6±1.3; refined cereals: 6.6±1.1; integrated cereals: 3.7±1.5; pastries: 4.5±0.6; sugars: 37.3±2.8; water: 107.7±4.7. Sixty-eight inhabitants consumed alcohol (7.3±1.7 times per month).

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

a) Questionnaire SF-12:

The mean score was 29.2±0.5 points (69.5±1.1%

of the maximum value). Figure 1 shows responses to the questionnaire.

b) Rosenberg self-esteem scale:

The average was 30.6±0.3 points out of a maximum of 40 (maximum of 4 points for each of the 10 questions). The average score for each question was: Does he/she feel a worthy person: 3.4±0.0; believes he/she has good qualities: 3.4±0.0; is a failure: 3.1±0.1; can do things just like most people: 3.3±0.1; has no reason to feel proud: 2.7±0.1; has a positive attitude towards himself: 3.4±0.1; is satisfied with him/herself: 3.4±0.1; should value him/herself more: 1.7±0.1; sometimes feels useless: 2.9±0.1 and sometimes thinks he/she is useless: 3.2±0.1.

c) Sleep scale test:

During the last month, the average bedtime was 23:00±00:06 h and the average wake-up time was 06:56±00:05 h. They allocated 07:55±00:08 hours to sleep, of which they slept 06:23±00:06 h. Regarding the quality of sleep, 30.3% indicated that it was very good; 51.7% fairly good; 15.2% fairly bad and 2.8% very bad. In 90.6% of cases, respondents reported not taking sleeping medication; 2.8% took medication less than once a week; 2.2% 1 to 2 times a week; and 4.4% more than 2 times a week. A total of 48.6% respondents reported drowsiness at some time during daily activities and 28.7% reported having problems performing daily activities because of drowsiness. Some 36.4% of respondents slept alone in the room; 7.9% with someone in another room; 9.0% with someone in the same room, but in another bed; and 46.1% with someone in the same bed.

d) Frailty Test (Edmonton scale):

The value was 3.7±0.2 points (range considered not frail). Among the population, 15.9% were apparently vulnerable; 6.0% were mildly frail; 4.6% were moderately frail; and 0.7% were markedly frail.

Office 3

Table 1 presents the results of the parameters measured. The BMI was in the range of overweight (27.9±0.4 kg/m2). Malnutrition was present in 1.7% of the population; 28.7% had adequate weight; 34.3% were overweight and 35.4% were obese. Waist circumference was elevated in 75.8% of participants; abdominal circumference was elevated in 65.6% and neck circumference in 7.0% of cases. Systolic BP was elevated in 15.1% and diastolic BP in 8.1% of respondents.

Office 4

In the ECG the average heart rate was 67.1±0.8 bpm, QRS duration was 119±10.3 msec and its axis was 38.3±4.4°. The QT interval was 442.2±18.6 msec. HR variability was 23.0±2.7. ECG alterations were found in 27 inhabitants (14.5%): 2 presented atrial fibrillation; 2 left anterior hemiblock; 2 right bundle branch block; 3 left atrial overload; 1 high density of extrasystoles with bigeminy and 17 repolarization disorders.

Office 5

Table 2 presents the echocardiographic findings. Mitral regurgitation was observed in 43 subjects (23.1%), with mild regurgitation in 40 cases. No mitral stenosis was found. Twenty subjects (10.7 %) had aortic regurgitation, mild in 17 cases. No aortic stenosis was found. Tricuspid regurgitation was observed in 39 subjects (20.9%), mild in 36 cases. One subject had mild tricuspid stenosis, and 16 (8.6%) had mild pulmonary regurgitation; 1 subject had moderate pulmonary stenosis.

Office 6

In the ultrasound study of neck vessels, no aneurysms, tumors or malformations were found in any of the inhabitants studied. Atherosclerotic plaque was found in 22 subjects (11.8%), only in 1 greater than 50%.

Office 7

In the Ruffier-Dickson test, baseline heart rate was 69.4±0.9 bpm; during exercise 100.4±1.6 bpm (46.2±2.3% increase from baseline) and after exercise 85.5±1.3 bpm (14.1±0.8% decrease with respect to exercise). The Ruffier index was within the average range (5.7±0.3). It was considered very good in 9.9% of respondents; good in 36.6%; average in 43.0%; insufficient in 7.7% and poor in 2.8%. The prehensile strength recorded with dynamometer was 23.0±1.3 kg and in 55.8% of cases it was below the normal range.

It should be noted that, due to the findings obtained, 10 patients were referred to a higher complexity care center.

DISCUSSION

In this new stage of the Program, it was possible to perform a more complete analysis of cardiovascular health in the Quilmes population than in the previous stage (2018 SONQO- CALCHAQUI Program). (1) It was also possible to integrate other areas that have a direct impact on the cardiovascular sphere, such as the psychological, physical and social state, as well as the proinflammatory state of the population. The achievement of these goals indicates the importance of having conducted a study driven from a district of the Argentine Society of Cardiology, joined by other districts, local referents, the Provincial Health System (SIPROSA) and the National University of Tucumán UNT) that allowed the development of a complete cardiological evaluation of a population usually not considered in many registries and randomized studies.

With respect to the new areas studied in this new stage of the Program, physically active people, with medium aerobic resistance to short-term effort (Ruffier Dickson Index of 5.7), were observed, but with a prehensile strength below the normal range in 55.8% of cases. These patients are poorly educated, with 10% illiteracy, not frail (according to the Edmonton Scale), but with mild to moderate cognitive impairment. They present good sleep quality and, in more than

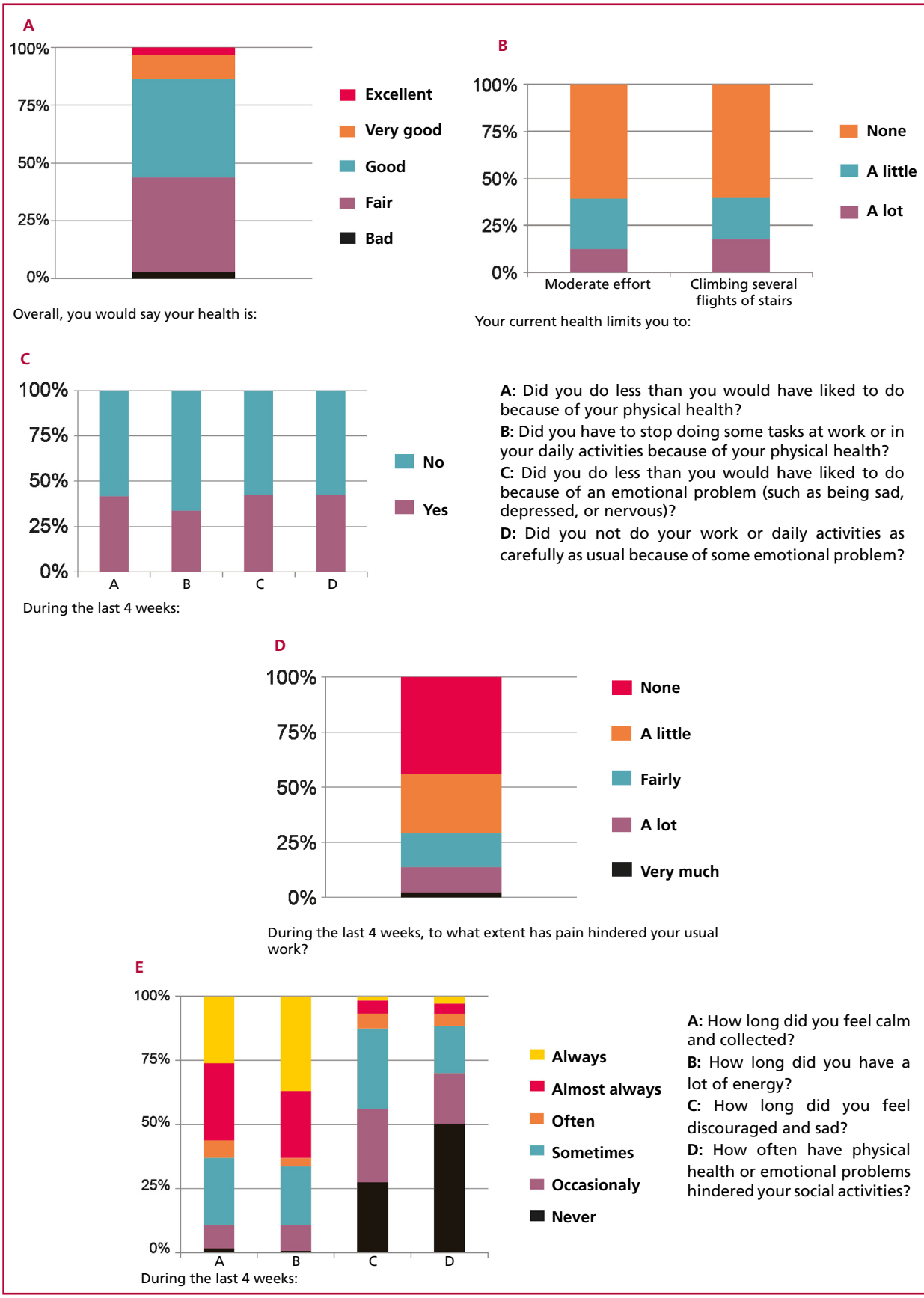

Fig. 1. Responses of the Quilmes population to the SF-12 Questionnaire (n=186).

Table 1. Anthropometric and hemodynamic variables of the population (n=186).

VARIABLE			VALUE	RANGE
Anthropometric variables	Weight (Kg)		70.3±1.1	31.0 to 104.0
	Height (cm)		159.5±0.7	13.01 to 182.0
	BMI (kg/m²)		27.9±0.4	11.1 to 43.3
	Waist circumference (cm)		103.1±0.8	76.0 to 157.0
	Abdomen circumference (cm)		95.2±1.1	35.0 to 129.5
	Neck circumference (cm)		38.0±0.4	26.0 to 69.5
	Wingspan (cm)		160.7±0.4	106.0 to 158.0
	Brachial circumference (cm)	Right	30.4±0.3	22.0 to 43.0
		Left	30.4±0.3	20.0 to 43.0
	Calf circumference (cm)	Right	36.1±0.3	28.5 to 45.5
		Left	36.0±0.3	28.0 to 47.0
Hemodynamic variables	Blood pressure (mmHg)	Systolic	122.4±1.4	83.0 to 189.0
		Diastolic	75.7±0.8	56.0 to 133.0
		Differential	46.8±1.0	16.0 to 96.0
		Mean	91.3±0.9	65.7 to 139.3
	Oxygen saturation (%)		95.9±0.2	86 to 99

Variables are expressed as mean ± standard error
BMI: body mass index

Table 2. Quantifiable echocardiogram findings.

VARIABLE			VALUE	RANGE
Parasternal long axis dimensions	LVDD (mm)		43.7±0.5	5.5 to 59.0
	LVSD (mm)		25.7±0.5	2.42 to 44.0
	LVEF (%)		55.2±0.4	42.0 to 75.0
	LVSF (%)		41.4±1.4	10.0 to 150.0
	IVS thickness (mm)		9.1±0.2	4.0 to 20.0
	PWT (mm)		8.4±0.2	4.0 to 13.0
	LVOT (mm)		19.7±0.2	4.0 to 26.0
	Ao Root (mm)		26.2±0.4	10.0 to 36.0
	Ao OD (mm)		20.8±0.5	13.0 to 37.0
	LAAPD (mm)		33.7±0.9	20,0 to 157,0
	LVM (g)		134.1±6.8	43.0 to 294.0
	LVMI (g/m)²		73.6±5.9	23.0 to 155.0
Doppler	PAAT (msec)		127.6±2.5	54.0 to 243.0
	Transmitral flow	E-wave (msec)	0.8±0.0	0.1 to 1.4
		A-Wave (msec)	0.7±0.0	0.1 to 2.4
	LVOT VTI (cm)		20.2±0.5	5.0 to 41.0
	Ao Vmax (m/sec)		1.2±0.0	0.2 to 1.8
	TR Vmax (m/sec)		2.1±0.1	0.2 to 3.0
Tissue Doppler	S-wave(cm/sec)		1.8±0.1	0.1 to 4.6
LV	e' wave (cm/sec)		1.5±0.1	0.1 to 4.4
	a' wave (cm/sec)		1.2±0.1	0.1 to 4.0
IVS	S-wave(cm/sec)		1.1±0.1	0.1 to 4.8
	e' wave (cm/sec)		1.4±0.1	0.2 to 5.0
	a' wave (cm/sec)		1.1±0.1	0.1 to 4.3

Ao: Aorta; Ao root: Ao root diameter; Ao OD: Ao opening diameter; Ao Vmax: peak aortic valve velocity; IVS: interventricular septum; LAAPD: left atrium anteroposterior diameter; LV: left ventricle; LVDD: LV diastolic diameter; LVEF: LV ejection fraction; LVM: LV mass; LVMI: LVM indexed to body surface area; LVOT: LV outflow tract diameter; LVOT VTI: LV outflow tract velocity/time integral;LVSD: LV systolic diameter; LVSF: LV shortening fraction; PAAT: pulmonary artery acceleration time; PWT: posterior wall thickness; TR Vmax: tricuspid regurgitation Vmax.
Variables are expressed as mean ± standard error.

50% of respondents, a good to excellent self-perception of their quality of life. Further studies should be carried out to assess the real weight of different variables not studied in depth in this study, such as sociocultural factors and the validation of the instruments used in an aboriginal and/or mountain population, on the results obtained. The laboratory results indicate the absence of prothrombotic and/or proinflammatory status.

A limitation that should be pointed out is that a population sampling was not carried out: the data were collected from the population that volunteered to participate, which could have influenced the number of people studied, and could have biased the responses.

Compared with the 2018 SONQO-CALCHAQUI data, (1) no significant differences are observed in the variables that were recorded in both opportunities (cardiovascular risk factors, anthropometric parameters, electrocardiogram, color Doppler echocardiogram and neck vessels and iliofemoral Doppler ultrasound). In this new stage of the SONQO-CALCHAQUI Program, new study domains were added: nutrition, cognitive status, self-perception of health status, sleep quality, frailty, endurance and muscular strength.

One of the main findings of this work is that the Quilmes community presents overweight values similar to those observed in urban centers in Argentina (3) and other parts of the world, such as the Middle East or Europe. (17,18) This data is reinforced by the fact that in a substudy of the 2018 SONQO-CALCHAQUI Program we were able to demonstrate that the prevalence of overweight in women was similar in different settings of Tucumán. (19) This could be considered as a negative finding, as no improvement in cardiovascular health was found in 4 years. One can mention, for example, the presence of obesity (36% in 2018 vs. 35.4% in 2022, p NS); BMI values (28.0±0.4 in 2018 vs. 27.9±0.4 in 2022, p NS); systolic BP (124.3±1.4 mmHg in 2018 vs. 122.4±1.4 mm Hg in 2022, p NS) and diastolic BP (77.0±0.7 mmHg in 2018 vs. 75.7±0.8 in 2022 (p NS). However, this period includes the COVID-19 pandemic, which led to a generalized increase in sedentary lifestyles and obesity, (20,21) so a more positive view might be that, despite the mandatory quarantine, there was no worsening of cardiovascular health in the Quilmes population.

The Ruffier index showed that aerobic endurance was in the average range considered despite the prevalence of overweight. However, the prehensile strength test indicated decreased muscle mass in at least half of the population. In this sense, further studies on physical fitness are needed.

Since there were still unresolved doubts in the 2018 SONQO-CALCHAQUI Program, referring to the possible westernization of the diet, already described in other aboriginal populations worldwide, (22,23) in this new stage with the 24-hour reminder and the food consumption frequency test, it could be seen that the main source of calories consists of flours and meats, with scarce consumption of vegetables and fruits. This could be due to the lack of geographical accessibility of both products, a hypothesis supported by the low consumption of ultra-processed foods and fish. The infusion mostly consumed at breakfast and at the afternoon snack is mate. It could be said, therefore, that there is a partial westernization of the diet, since they mix farinaceous products with traditional beverages.

CONCLUSIONS

Thanks to the coordinated effort of various national and provincial sectors, it was possible to obtain very valuable information on the cardiovascular health of an aboriginal population that is not usually well represented in registries and intervention studies. The Quilmes population presents an acceptable physical condition but with a high rate of overweight and obesity, which remains constant after the COVID 19 pandemic. This could be due to the diet, whose determinants and possible corrections should be considered in future health programs. No significant differences were verified with the data collected in 2018.

Conflicts of interest

None declared.

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

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To the Quilmes community in general

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ANNEX I

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ORIGINAL ARTICLE

Rapid-Deployment Valve versus Conventional Valves in Aortic Valve Replacement in Intermediate-Risk Patients

Válvulas de rápido implante versus válvulas tradicionales en reemplazo valvular aórtico en pacientes de riesgo intermedio

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ABSTRACT

Background: Aortic valve replacement (AVR) in intermediate-risk (IR) patients is particularly challenging when determining the type of prosthesis to use. Rapid-deployment valves (RD-V) are emerging as a potential alternative in this patient population.
Objectives: To compare early mortality, postoperative complications, and transvalvular hemodynamic parameters between AVR with conventional valves and RD-V in IR patients.
Methods: We conducted a retrospective observational study of consecutive IR patients (STS-Prom score 4-8) undergoing AVR with conventional prostheses and RD-V between 2007 and 2023.
Results: A total of 205 patients were included (140 AVR vs. 65 RD-V). Surgical risk was similar between both groups (STS-Prom 5.07 % vs. 5.7 % respectively, p = 0.210). The minimally invasive approach was more common in the RD-V group (32.3% vs. 0.7%, p < 0.001). The cardiopulmonary bypass time and aortic cross-clamp time was significantly shorter in the RD-V group (134.5 vs. 100 min and 104 vs. 73 min, respectively, p < 0.001). There was a trend to lower incidence of pacemaker implantation in the conventional valve group (4.3% vs. 10.8%, p = 0.075). There were no significant differences in postoperative complications, and a strong trend to lower 30-dat mortality with RD-V (0% vs. 5.7% for conventional valves, p = 0.057). The mean postoperative gradient across the prosthesis was significantly lower in the RD-V group (7.90 ± 3.3 mm Hg vs. 12.74 ± 6.07 mm Hg, p < 0.001). There were no differences in the incidence of valve thrombosis or prosthetic endocarditis.
Conclusions: Rapid deployment valves demonstrated trend to lower mortality, shorter cardiopulmonary bypass time and aortic cross-clamp time, improved hemodynamic profile, and were easier to implant via a minimally invasive approach.

Key words: Biological valves - Aortic valve replacement - Intermediate risk - Rapid deployment valves.

RESUMEN

Introducción: El reemplazo valvular aórtico (RVA) en pacientes con riesgo quirúrgico intermedio (RI) es el más desafiante al momento de decidir el tipo de prótesis a utilizar. Las válvulas de rápido implante (RD-V) serían una alternativa a considerar en este grupo específico.
Objetivos: Comparar mortalidad temprana, complicaciones postoperatorias y parámetros hemodinámicos transvalvulares en el RVA con válvulas tradicionales vs. RD-V en pacientes de RI.
Material y métodos: Estudio retrospectivo y observacional de pacientes consecutivos de RI (STS-PROM 4-8) intervenidos por RVA con prótesis tradicionales y RD-V en el período 2007-2023.
Resultados: Se incluyeron 205 pacientes (140 con prótesis tradicionales vs. 65 con RD-V). El riesgo preoperatorio fue semejante en ambos grupos (STS-PROM 5,07 % vs. 5,7 %, p = 0,210). El abordaje miniinvasivo fue más frecuente en RD-V (32,3 % vs 0,7 %, p<0,001). El tiempo de circulación extracorpórea y clampeo fue significativamente menor en RD-V (134,5 vs.100 min y 104 vs 73 min respectivamente, p<0,001). Hubo tendencia a menor implante de marcapasos con las válvulas tradicionales (4,3 % vs. 10,8 %, p = 0,075). No se observaron diferencias significativas en las complicaciones postoperatorias; hubo fuerte tendencia a menor mortalidad a los 30 días con RD-V (0 % vs. 5,7 % para válvulas tradicionales, p = 0,057). El gradiente protésico medio postoperatorio fue significativamente menor para el grupo RD-V (7,90 ± 3,3 mmHg vs. 12,74 ± 6,07 mmHg, p<0,001). No hubo diferencias respecto a incidencia de trombosis valvular o endocarditis protésica.

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Conclusiones: Las válvulas de rápido implante presentaron tendencia menor mortalidad, menor tiempo de circulación extracorpórea/clampeo, mejor perfil hemodinámico y mayor facilidad de implante por abordaje miniinvasivo.

Palabras clave: Válvulas biológicas - Reemplazo valvular aórtico - Riesgo intermedio - Válvulas de rápido implante

INTRODUCTION

The number of patients with aortic valve disease requiring aortic valve replacement (AVR) has increased in recent decades as a result of higher life expectancy in the aging population. Most patients with severe aortic stenosis are elderly patients with several comorbidities and, therefore, high preoperative risk. The development of new technologies and therapies has tried to solve this situation by reducing surgical risk. (1,2) Minimally invasive surgery (MICS) with new prosthetic valve devices has reduced the invasiveness and trauma generated by conventional AVR. Transcatheter aortic valve replacement (TAVI) has revolutionized the course of treatment of aortic valve disease and has been established as the gold standard for patients with prohibitive or very high surgical risk, defined by a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score ≥ 8. This procedure is accepted and recommended worldwide with a class I indication for this population according to European and American guidelines. (3-5) For low-risk patients (STS- PROM < 4), the indication is still conventional AVR according to these guidelines.

The current challenge is to define the best treatment for intermediate risk (IR) patients defined as those with a preoperative score between 4 to 8. This is the most interesting and difficult group to decide the best option when discussing patients in the Heart Team (a group made up of surgeons, cardiologists, interventional cardiologists and gerontologists).

Since the publication of controlled trials comparing the outcomes between AVR and TAVI in intermediate risk patients, (6,7) the guidelines have begun to consider TAVI as an alternative to surgery. These results have not been widely applied in our country due to the high cost of TAVI, which despite being accepted in IR patients, is not considered as the first option. Currently, patients in this group may be candidates for both procedures. In this context RD-Vs now play a role as one of the options that have been recently developed and have shown excellent results in terms of hemodynamic performance, versatility of use and safety. (8,9)

Our center has already published results on IR patients undergoing conventional AVR, that were consistent with those expected. (10) In 2018 we have started the RD-V program, and we observed satisfactory individual results that encouraged us to evaluate this technique as a possible better alternative to conventional valves in IR patients in terms of morbidity, mortality and hemodynamic performance.

The primary objective of this publication is to compare 30-day postoperative mortality in IR patients undergoing AVR with RD aortic valves (RD-V) versus conventional valves. The secondary objectives are to compare the incidence of intraoperative and postoperative complications within 30 days of surgery between both prostheses and the hemodynamic parameters of the device.

METHODS

We conducted an analytical retrospective cohort study of consecutive IR patients undergoing AVR at the institution between January 1, 2007, and November 1, 2023.

Patients were eligible if they presented severe aortic stenosis (with or without associated insufficiency) or aortic infective endocarditis (off-label indication for RD-V), with diagnostic criteria defined by practice guidelines and intermediate surgical risk according to STS-PROM (4%-8%). Patients with double valve replacement or associated surgeries (except myocardial revascularization surgery), ascending aorta replacement, tricuspid plastic surgery, septal myectomy or widening of the aortic annulus were excluded. The prosthesis used for the rapid implant group was only Intuity (INTUITY Elite, Edwards Lifesciences, Irvine, CA, USA) with diameters from 19 mm to 27 mm. For the traditional prostheses group, we used both biological prostheses: Hancock II and Mosaic (Medtronic, Minneapolis, MN), Perimounth and Magna Ease (Edwards Lifesciences, Irvine, CA, USA), Epic (SJM; St. Jude Medical Inc.; Minneapolis, Minn), and Mitroflow (Sorin Group Inc, Arvada, USA), as mechanical prostheses: St. Jude Regent (SJM; St. Jude Medical Inc.; Minneapolis, Minn.), Carbomedics (CarboMedics Inc.,Austin, TX), On-X (Artivion, Austin, TX, USA), and Open Pivot (Medtronic, Minneapolis, MN) in all diameters. The following variables were evaluated: a) clinical variables: age, sex, body mass index (BMI), cardiovascular history, chronic obstructive pulmonary disease (COPD), previous dialysis, presence of bicuspid aortic valve, left ventricular systolic function, usual functional class (NYHA) and STS-PROM score; b) operative variables: preoperative status, incidence, approach, valve size, prosthesis explantation, associated surgical procedures, cardiopulmonary bypass time, aortic cross-clamp time, and presence of paravalvular leak; c) perioperative complications: prolonged mechanical ventilation (MV), requirement for intra-aortic balloon pump (IABP), myocardial infarction (MI), ischemic stroke, bleeding volume within 24 hours, units of red blood cells transfused, need for reoperation due to bleeding, cardiac arrhythmias, mediastinitis, length of hospital stay and early mortality defined as death from any cause within 30 days after surgery. Finally, the values of pre- and post-implantation gradients were considered, as well as the incidence of valvular thrombosis and prosthetic endocarditis within 30 days.

Data were retrieved form the electronic medical records of the institution and administrative databases of the Department of Cardiovascular Surgery.

Statistical considerations

Continuous variables are expressed as mean and standard deviation or median and interquartile range according to

their distribution. Categorical variables are expressed as absolute and relative frequencies. Continuous variables were compared using the Student's t test or Mann-Whitney test, as appropriate. Categorical variables were compared using the chi-square test or the Fisher's exact test, as appropriate. A two-tailed value < 0.05 was considered statistically significant. All the statistical calculations were performed using STATA 13.1 software package (StataCorp LP, College Station, TX).

Ethical considerations

The study protocol was approved by the institutional review board (PRIISA Protocol N° 11721).

RESULTS

Of a total of 1437 patients, 205 (14.26%) met the eligibility criteria; with 140 patients in the conventional AVR group and 65 in the RD-V group.

The demographic and preoperative characteristics are shown in Table 1. Median age was 80.8 (76.3-84) years, and 56% were men. There were no significant differences between conventional AVR and RD-V in terms of history of cardiovascular disease except for history of MI prior to surgery (16.4% vs. 3.1%, respectively, p = 0.007) and peripheral vascular disease (34.3% vs. 7.7%, respectively; p < 0.001). Patients with active endocarditis were treated only with conventional valves (8.6%). Three patients with bicuspid aortic valve underwent AVR in both groups (2.1% vs. 4.6% respectively, p = 0.383). Patients in the conventional AVR group had worse preoperative NYHA functional class (34.3% vs.16.9% respectively, p=0.011). The STS-PROM score was 5.07 (4.4-6.01) in the conventional AVR group vs. 5.7 (4.2-6.4) in the RD-V group (p = 0.210).

The intraoperative characteristics are shown in Table 2. A minimally invasive approach was more common in the RD-V group compared with the conventional AVR group (32.3% vs. 0.7%, p < 0.001). Conversion to sternotomy was not necessary in none of the groups. There were no relevant differences regarding prosthetic valve sizes. Only one patient in the RD-V required prosthesis explantation followed by implantation of a conventional prosthetic valve (1.5%). Aortic annulus enlargement was more common in the conventional AVR group (12.9% vs. 4.6%, p = 0.084). Cardiopulmonary bypass time (CPB) and aortic cross-clamp time were lower in the RD-V group (134.5 vs. 100 min, p<0.001, and 104 vs. 73 min, p<0.001, respectively).

Table 3 shows the postoperative results. More patients in the conventional AVR group required prolonged mechanical ventilation (20.7% vs. 12.3%), although this difference was not statistically significant (p=0.174). There were no relevant differences in terms of postoperative complications, bleeding and reoperations, with a non-significant trend toward need for permanent pacemaker implantation (PPI) due to atrioventricular block in the RD-V group (10.8% vs. 4.3%).

No deaths were reported in the RD-V group while 8 patients died in the conventional AVR group (0% vs. 5.7%, p = 0.057).

In a sensitivity analysis of the postoperative outcomes excluding 12 patients with infective endocarditis (all in the conventional AVR group), there were no significant variations; mortality remained lower in the RD-V group (0% vs. 6.3%, p = 0.053).

The valvular and prosthetic hemodynamic results are detailed in Table 4. The RD-V had better hemodynamic performance after the intervention, with lower peak and mean gradients.

DISCUSSION

So far, a paucity of information exists in both the local and international literature regarding the comparison of the use of both prostheses in intermediate-risk patients. (11) Our institution has considerable experience in the use of RD-V prostheses, with 200 implants to date and favorable outcomes, which we will examine in further detail below.

Cardiopulmonary bypass time, aortic cross-clamp and minimally invasive approach

As expected, due to the technique, the RD-V group exhibited a significant decrease in CPB time (134.5 vs. 100 min; p < 0.001) and aortic cross-clamp time (104 vs. 73 min; p < 0.001) and a greater trend towards the use of a minimally invasive approach (32.3% vs. 0.7%; p < 0.001). All these factors can explain the lower morbidity and mortality rates observed in this group. (12,13)

It is notable that there were no conversions to sternotomy in patients undergoing MICS, and although the total length of hospital stay did not decrease, the improved comfort and postoperative cosmetic results in patients who underwent this approach are well-known benefits. The only case of RD-V explantation was due to paravalvular leak.

Pacemaker implantation

Undoubtedly, an unfavorable aspect reported for RD-V is the higher incidence of PPI. This was not the exception in our study (10.8% vs. 4.3%, p= 0.076). The incidence of PPI after RD-V reported in the literature ranges from 5% to approximately 13%. (14,15) Of the patients in the RD-V group who required PPI, two had first-degree atrioventricular block, one had left bundle branch block, and four had sinus rhythm. Although there are many factors related to the procedure that increase the risk of atrioventricular block, such as previous bundle branch block, hypertrophic cardiomyopathy and excessive decalcification of the annulus, (16) some are inherent to the prosthesis implant. This implantation system, requiring balloon deployment with infra-annular extension, generates direct compression of the conduction system, similar to the mechanism produced during TAVI. In a series of 700 patients, Coti et al. demonstrated that preop-

Table 1. Demographic and preoperative characteristics

	Total (n=205)	Conventional AVR (n=140)	RD-V (n=65)	p
Age, years, median (IQR)	80.8 (76.32-84)	80 (75-84)	81.3 (78.6-84)	0.072
Male sex, n (%)	115 (56.1)	82 (58.6)	33 (50.8)	0.364
BMI (Kg/m2), mean (SD)	27.66 (4.68)	27.56 (4.70)	27.87 (4.66)	0.660
Smoking habits, n (%)				
Never	139 (67.8)	90 (64.3)	49 (75.4)	0.323
Active smoker	11 (5.4)	9 (6.4)	2 (3.1)	
Former smoker	55 (26.8)	41 (29.3)	14 (21.5)	
Hypertension, n (%)	181 (88.3)	123 (87.9)	58 (89.2)	0.775
Diabetes, n (%)	53 (25.9)	39 (27.9)	14 (21.5)	0.336
Atrial fibrillation, n (%)	43 (21)	31 (22.1)	12 (18.5)	0.546
Previous MI, n (%)	25 (12.2)	23 (16.4)	2 (3.1)	0.005
Previous CABG, n (%)	29 (14.1)	19 (13.6)	10 (15.4)	0.728
Peripheral vascular disease, n (%)	53 (25.9)	48 (34.3)	5 (7.7)	<0.001
Previous stroke, n (%)	21 (10.2)	14 (10)	7 (10.8)	0.865
TIA	5 (2.4)	5 (3.6)	0 (0)	0.181
Ischemic stroke	3 (1.5)	3 (2.1)	0 (0)	0.553
COPD, n (%)	14 (6.8)	11 (7.9)	3 (4.6)	0.555
Previous dialysis, n (%)	12 (5.9)	8 (5.7)	4 (6.2)	1
Active aortic endocarditis, n (%)	12 (5.9)	12 (8.6)	0 (0)	0.010
Bicuspid aortic valve, n (%)	6 (2.9)	3 (2.1)	3 (4.6)	0.383
Moderate/severe LV dysfunction, n (%)	28 (13.7)	21 (15)	7 (10.8)	0.411
NYHA FC III/IV, n (%)	59 (28.8)	48 (34.3)	11 (16.9)	0.010
STS-PROM, median (IQR)	5.1 (4.3-6.3)	5.07 (4.4-6.01)	5.7 (4.2-6.41)	0.210

AVR: aortic valve replacement; BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary diseas:; FC: functional class; ; IQR: interquartile range; LV: left ventricular; MI: myocardial infarction; NYHA: New York Heart Association; RD-V: rapid deployment aortic vave replacement; ; SD: standard deviation; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TIA: transient ischemic attack

erative right bundle branch block (RBBB) was the only independent predictor of PPI (9.5%). (17) Therefore, we believe that candidates for RD-V implantation should be selected, and those with RBBB should be excluded. We also recommend avoiding prosthesis oversizing, and in case of uncertainty whether to implant a larger or a smaller prosthesis, the smaller size should be chosen.

Mortality

The lower postoperative mortality was one of the most outstanding findings of this study, with a strong trend favoring the RD-V (0% vs. 5.7%; p = 0.057). This result is slightly lower than that of the SURD-IR registry, (18) which analyzed mortality in all preoperative risk categories and reported a mortality rate of 0.8% in the IR group. It is noteworthy that the baseline STS-PROM score was similar in both groups.

Patients with endocarditis were also included in this series despite there were no IR patients in the RD-V group, because we have used this prosthesis in selected cases. The benefits of RD-V remained in the sensitivity analysis performed to evaluate the postoperative outcomes excluding this subgroup. Of the patients who died, the first patient underwent endarterectomy of the left anterior descending coronary artery and required extracorporeal membrane oxygenation (ECMO) after weaning from CPB. The second case was an 86-year-old patient with a history of chronic kidney failure who underwent AVR + triple bypass surgery and died of acute kidney failure and metabolic cardiopulmonary arrest. The third patient was 78 years old, had severe preoperative left ventricular dysfunction (AVR + triple bypass surgery) and presented bleeding and MI in the immediate postoperative period. The fourth case was an 82-year-old patient (AVR + single bypass surgery) who died of low cardiac output syndrome and cardiogenic shock. Finally, the fifth patient, aged 75 years (AVR + double bypass surgery) required ECMO + IABP after weaning from CPB. All of them died between postoperative days 1 and 5.

Of the remaining three patients undergoing isolated AVR, a 58-year-old patient with severe ventricular dysfunction required ECMO after weaning from CPB

Table 2. Intraoperative characteristics

	Total (n=205)	Conventional AVR (n=140)	RD-V (n=65)	p
Preoperative status, n (%)				
Elective	144 (70.2)	93 (66.4)	51 (78.5)	0.210
Urgent	57 (27.8)	44 (31.4)	13 (20)	
Emergency	4 (2)	3 (2.1)	1 (1.5)	
Incidence first surgery, n (%)	190 (92.7)	129 (92.1)	61 (93.8)	0.778
Ministernotomy, n (%)	22 (10.7)	1 (0.7)	21 (32.3)	<0.001
Mini-to-full conversion, n (%)	0 (0)	0 (0)	0(0)	
Valve size, n (%)				
19	16 (7.8)	12 (8.6)	4 (6.2)	0.260
21	81 (39.5)	58 (41.4)	23 (35.4)	
23	69 (33.7)	49 (35)	20 (30.8)	
24	1 (0.5)	1 (0.7)	0 (0)	
25	35 (17.1)	19 (13.6)	16 (24.6)	
27	3 (1.5)	1 (0.7)	2 (3.1)	
Associated procedures, n (%)	112 (54.6)	83 (59.3)	29 (44.6)	0.049
CABG, n (%)	107 (52.2)	80 (57.1)	27 (41.5)	0.038
Aortic annulus enlargement	21 (10.2)	18 (12.9)	3 (4.6)	0.084
Number of grafts, median (IQR)	1 (1-2)	1 (0-2)	2 (1-2)	0.035
CPB time, median (IQR)	125 (103-165)	134.5 (111-172)	100 (80-129)	<0.001
Aortic cross-clamp time, median (IQR)	93 (75-121)	104 (85-135)	73 (61-103)	<0.001
Paravalvular leak ≥ mild, n (%)	10 (4.9)	7 (5.0)	3 (4.6)	1

AVR: aortic valve replacement; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IQR: interquartile range; RD-V: rapid deployment valve

Table 3. Postoperative results

	Total (n=205)	Conventional AVR (n=140)	RD-V (n=65)	p
Prolonged MV, n (%)	37 (18.8)	29 (20.7)	8 (12.3)	0.145
IABP, n (%)	10 (4.9)	8 (5.7)	2 (3.1)	0.508
Postoperative MI, n (%)	2 (1)	1 (0.7)	1 (1.5)	0.534
Ischemic stroke, n (%)	13 (6.3)	9 (6.4)	4 (6.2)	1
Bleeding in ml/24 hours, median (IQR)	230 (160-340)	240 (160-365)	220 (175-315)	0.640
RBCU/48 hours, median (IQR)	2 (0-2)	2 (0-3)	2 (1-2)	0.480
Reoperation due to bleeding, n (%)	9 (4.4)	7 (5)	2 (3.1)	0.722
Postoperative atrial fibrillation, n (%)	88 (42.9)	60 (42.9)	28 (43.1)	0.976
AV block with PPI, n (%)	13 (6.3)	6 (4.3)	7 (10.8)	0.076
Mediastinitis, n (%)	4 (2)	3 (2.1)	1 (1.5)	1
LOS, median (IQR)	7 (6-13)	7.5 (6-14)	7 (5-13)	0.530
Death <30 days, n (%)	8 (3.9)	8 (5.7)	0 (0)	0.057

AV: atrioventricular; AVR: aortic valve replacement; IABP: intra-aortic balloon pump; IQR: interquartile range; LOS: hospital length of stay; MI: myocardial infarction; MV: mechanical ventilation; PPI: permanent pacemaker implantation; RBCU: red blood cell units; RD-V: rapid deployment valve.

Table 4. Valvular and prosthetic hemodynamic results

	Total (n=205)	Conventional AVR (n=140)	RD-V (n=65)	p
Peak preop aortic valve gradient (mm Hg), mean (SD)	67.04 (28.19)	63.51 (30.77)	74.26 (20.35)	0.011
Mean preop aortic valve gradient (mm Hg), mean (SD)	40.99 (17.07)	39.99 (18.77)	42.96 (12.97)	0.250
Preop aortic valve area (cm2), mean (SD)	0.75 (0.43)	0.71 (0.46)	0.83 (0.35)	0.077
Peak postop aortic valve gradient (mm Hg), mean (SD)	20.93 (9.71)	23.53 (9.89)	15.81 (6.97)	<0.001
Mean postop aortic valve gradient (mm Hg), mean (SD)	11.06 (5.76)	12.74 (6.07)	7.90 (3.35)	<0.001
Valvular thrombosis, n (%)	1 (0.5)	1 (0.7)	0 (0)	1
Prosthetic endocarditis, n (%)	5 (2.4)	4 (2.9)	1 (1.5)	1

AVR: aortic valve replacement; preop: preoperative; postop: postoperative; RD-V: rapid deployment valve; SD: standard deviation.

and died on postoperative day 5; an 88-year-old patient died on postoperative day 22 due ischemic stroke and mediastinitis, and an 82-year-old patient with cardiac tamponade who required reoperation died on postoperative day 25 due to sepsis.

Transvalvular prosthetic gradient

This analysis shows that lower postoperative gradients were obtained with the use of RD-V. This has already been published by other groups. (19,20) Although the mean diameter of the implanted prostheses was slightly larger in conventional prostheses (Table 2), the mean postoperative transvalvular gradient was statistically lower in RD-V prostheses, which demonstrates that their hemodynamic performance is better: 12.74 (6.07) mm Hg vs. 7.90 (3.35) mm Hg ($p < 0.001$). Instead, Andreas et al. (21) described the transvalvular gradients comparing both prostheses but they did not obtain a clinically relevant difference.

This would be related to the stent-based fixation system of RD-V which reshapes the left ventricular outflow tract, reduces turbulent flow and optimizes the hemodynamic performance of the valve prosthesis. Subclinical obstruction at the valve inlet may be induced by protrusion of bulky pledget material used to fixate the conventional valve. The negative effect of pledgeted mattress sutures on transvalvular gradients compared with single interrupted sutures has already been demonstrated. (22)

The RD-V used in this study (INTUITY Elite, Edwards Lifesciences, Irvine, CA, USA) is a trileaflet valve comprised of bovine pericardium based on the Carpentier-Edwards Perimount prosthesis (Edwards Lifesciences, Irvine, CA) with a balloon expandable stainless-steel frame and requires only three sutures in the annulus. This prosthesis has exceptional long-term results (freedom from reoperation due to structural damage at 15 years in patients > 70 years of 98.1% ± 0.8%), so the durability of the RD-V is also expected to be prolonged. (23) Regarding costs, they are higher than those of conventional valves, although significantly lower than those of a TAVI. This makes RD-Vs an attractive option in non-high-income countries. Although a cost-benefit analysis would be necessary to determine which prosthesis is more convenient in different scenarios.

Study limitations

The limitations of this study are those inherent to its observational and retrospective design. There may be selection bias and confusion by indication that contribute to explaining the better evolution, beyond the benefits of the valve. Furthermore, it represents to patients from a single center.

CONCLUSIONS

Our study provides relevant information on the effectiveness of rapid deployment valves compared to conventional valves in intermediate-risk patients requiring AVR. These patients benefit from shorter operative times and more favorable postoperative transvalvular gradients, with a trend towards lower mortality. Further multicenter randomized studies are needed to validate our findings.

Conflicts of interest

Dr. VK, discloses conflicts of interest with Medtronic, Edwards Lifescience, and Johnson & Johnson. The remaining authors have no conflicts of interest to declare.

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

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ORIGINAL ARTICLE

Cerebral Ischemia and Reperfusion-Induced Changes in Left Ventricular Function and Electrocardiogram in Mice

Modificaciones en la función ventricular izquierda y el electrocardiograma en ratones debidas a isquemia y reperfusión cerebral

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ABSTRACT

Background: Stroke may produce functional and electrical heart disturbances. The underlying characteristics and mechanisms have not been fully elucidated.
Objectives: To evaluate whether acute cerebral ischemia (I) and reperfusion (R) may cause cardiac dysfunction and electrocardiographic alterations in an experimental mice model.
Methods: Male mice that underwent cerebral ischemia and reperfusion (I/R) were evaluated by electrocardiography (ECG) and echocardiography. Heart rate, corrected QT (QTc) interval, T-wave peak to T-wave end (Tp-Te) interval, left ventricular ejection fraction (LVEF), shortening fraction (SF) and isovolumetric relaxation time (IVRT) were analyzed. Cerebral infarct size was calculated, and neurological deficit was assessed with the Longa scale.
Results: Twenty-four hours after R, a statistically significant decrease in LVEF (I/R: 66.5±1.5% vs. sham: 74.3±0.9%; p=0.002) and in SF (I/R: 42.9±1.7% vs sham: 52.3±1.7%; p=0.004) was observed. QTc interval prolongation was observed during I/R (baseline: 125.1±4.3 ms; 60 min after I: 143.8±5.2 ms; 24 h after R: 170.3±5.8 ms; p=0.002). Tp-Te interval was not prolonged during I (baseline: 25.9±1.3 ms vs. 60 min after I: 23.8±1.4 ms; p=0.999) but it was prolonged during R (24 h after R: 32.0±2.3 ms; p=0.049). Cerebral infarct size was 34.9±2.5% and survival in the I/R group was 43.3%.
Conclusion: Acute cerebral ischemia induces mild left ventricular dysfunction and disturbances in ventricular repolarization which intensify within the first 24 hours after reperfusion.

Key words: Cerebral ischemia - Ventricular dysfunction - Electrocardiogram - arrhythmias

RESUMEN

Introducción: El accidente cerebrovascular (ACV) puede generar perturbaciones funcionales y eléctricas del corazón. Las características y mecanismos subyacentes no están completamente elucidados.
Objetivo: Evaluar si la isquemia (I) y reperfusión (R) cerebral agudas ocasionan disfunción cardíaca y alteraciones electrocardiográficas en un modelo experimental en ratones.
Material y Métodos: Ratones macho sometidos a isquemia y reperfusión cerebral (I/R) fueron evaluados mediante electrocardiografía (ECG) y ecocardiografía. Se analizó la frecuencia cardíaca, el intervalo QT corregido (QTc) y el intervalo entre el pico de la onda T – fin de la onda T (Tp-Te), la fracción de eyección ventricular izquierda (FEVI), la fracción de acortamiento (FA) y el tiempo de relajación isovolumétrica (TRIV). Se cuantificó el tamaño del infarto cerebral (TI), y el déficit neurológico se evaluó con la escala de Longa (EL).
Resultados: Encontramos una disminución estadísticamente significativa de la FEVI a las 24 horas de R (I/R: 66,5 ± 1,5 % vs. *sham*: 74,3 ± 0,9 %; p=0,002) y la FA (I/R: 42,9 ± 1,7 % vs. *sham*: 52,3 ± 1,7 %; p=0,004). Se observó una prolongación del QTc durante la I/R (basal: 125,1 ± 4,3 ms; 60 min I: 143,8 ± 5,2 ms; 24 horas R: 170,3 ± 5,8 ms; p=0,002), sin una prolongación del Tp-Te en la I (basal: 25,9 ± 1,3 ms vs. 60 min I: 23,8 ± 1,4 ms; p=0,999) pero sí en la R (24 horas R: 32,0 ± 2,3 ms; p=0,049). El tamaño del infarto cerebral fue de 34,9 ± 2,5 % y la supervivencia del grupo I/R fue del 43,3 %.
Conclusión: La isquemia cerebral aguda induce una disfunción ventricular izquierda leve y trastornos en la repolarización ventricular que se intensifican en las primeras 24 horas de reperfusión.

Palabras clave: Isquemia cerebral - Disfunción ventricular - Electrocardiograma - Arritmias

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INTRODUCTION

Cerebrovascular disease is one the four leading causes of mortality worldwide and affects both high- and low-income countries. (1) According to recent data, it is the second leading cause of death and the leading cause of disability in Argentina. Factors worsening the prognosis of these patients include several cardiac complications collectively known as neurocardiogenic syndrome. The consequences of this syndrome, which include coronary syndromes, arrhythmias, Takotsubo syndrome and heart failure, result in more than 1.5 million deaths each year. (2, 3)

Some pathophysiological mechanisms involved in the brain-heart axis deterioration have been identified in several studies, both basic and clinical. One of the most relevant is the imbalance in the autonomic nervous system in favor of an exaggerated sympathetic discharge and parasympathetic impairment. (4, 5) Although not exclusive, research in humans and several animal species associates insular ischemic involvement with dysautonomia. (4, 6) Coincidentally, a proinflammatory state is triggered both locally and systemically, which increases cytokines and leukocyte migration that, if the stimulus persists, may induce fibrotic changes in the myocardium. (7) More recently, the role of the release of glial microvesicles with mRNA-carrying capacity, which carry distant transcriptional messages and induce myocardial injury, has been demonstrated. (8)

Although myocardial dysfunction and electrical changes, such as atrial fibrillation, atrioventricular conduction disturbances, and QT interval prolongations, have been well documented, (4, 9) their relationship and temporal evolution in acute stages have not been sufficiently studied. Thus, this work aimed to investigate cardiac functional and electrical impairment during ischemia (I) and reperfusion (R) of the right cerebral hemisphere in a male mouse model.

METHODS

Cerebral ischemia model

The experiments were carried out following the guidelines of the "Guide for the Care and Use of Laboratory Animals" of the United States National Academy of Sciences, updated by the American Physiological Society (10), and in accordance with the regulations of the Institutional Committee for the Care and Use of Laboratory Animals (CICUAL) of the School of Medicine, Universidad of Buenos Aires (Resolution CD 4081/04). The present project has been approved by CICUAL (RESCD-2023-913-E-UBA-DCT#FMED).

Eighteen FVB strain male mice aged between 8 and 12 weeks were used. Cerebral ischemia (I) and reperfusion (R) were induced using the technique described by Koizumi. (11) For this purpose, the mice were anesthetized with a ketamine-xylazine solution (100 mg/10 mg) at a dose of 4.4 μL/g intraperitoneally (IP). After cervical dissection, an intraluminal filament was inserted in the common carotid artery, advancing through the internal carotid, to obstruct the flow of the middle cerebral artery for 60 minutes. To perform reperfusion, the filament was removed. The results of this I/R mice group were compared to those of sham mice group, or surgery without cerebral ischemia. For this purpose, 5 mice underwent the same operation as the I/R mice group, except for the intraluminal filament which was not inserted in the artery and, therefore, cerebral artery occlusion did not occur. During procedure, body temperature was maintained constant at 36.5±0.5°C with a rectal thermocouple and a heat lamp.

After reperfusion, the animals recovered from anesthesia in a temperature-controlled chamber and, then, in the biotherium, they were monitored for 24 hours. Analgesics (tramadol, 5μL/g subcutaneously) and antibiotics (cefazolin, 5μL/g intramuscularly) were administered as part of postoperative care.

Neurological evaluation and mortality records

At 4 and 24 hours post-reperfusion, neurological deficits were assessed using the Longa scale. (12) On this scale, no neurological deficit was assigned 0 points; inability to flex the contralateral limbs, 1 point; circular movements toward the side of the lesion, 2 points; barreling or longitudinal axis movements, 3 points; and coma or lack of response to external stimuli, 4 points.

Survival records were carried out and plotted using Kaplan-Meier curves to analyze the temporal evolution of the mice according to neurological deficits evaluated.

Electrocardiographic recording

To obtain the electrocardiographic recordings, subcutaneous electrodes (ADinstruments®) were used together with the LabChart 8® software. Recordings were made throughout the 60 minutes of I, the first 10 minutes of R and, finally, at the end of this period. Heart rate (HR), QT interval, HR-corrected QT interval (using the Bazett formula) and the interval between the peak and end of the T wave (Tp-Te) were measured. For the statistical analysis, the values at baseline (prior to the onset of ischemia), 60 minutes after I and 24 hours after R were used.

Echocardiography

Echocardiographic studies were performed in mice under anesthesia with 290mg/kg of a 2.5% solution of 2,2,2,2 tribromoethanol (AVERTIN, Sigma Aldrich®) IP. (13) An Acuson® Sequoia C512 ultrasound machine equipped with a 14 MHz linear ultrasound transducer was used. Recordings were made 24 hours after reperfusion, during which the left ventricular ejection fraction (LVEF), shortening fraction (SF) and isovolumetric relaxation time (IVRT) were calculated.

Evaluation of cerebral infarction

To visualize the cerebral infarct area 24 hours after reperfusion, the mice were sacrificed by an overdose of ketamine and xylazine, (14) the brain was removed and frozen to obtain 2-mm-thick coronal sections. These sections were incubated in a 1% 2,3,5-triphenyltetrazolium (TTC) solution for 20 minutes at 37°C. Non-infarcted cerebral tissue was stained red, whereas the infarcted area remained white. To document the cerebral infarct area, images were acquired using an HP® scanner, and the area was subsequently quantified using ImageJ® software. Using Swanson's formula [(contralateral hemisphere - ipsilateral hemisphere/contralateral hemisphere) x 100], the value of the edema-adjusted infarct area was obtained. (15)

Statistical analysis

Graphical representations of all values were carried out using GraphPad Prism 9® software. The results were ex-

pressed as the mean ± standard error. Statistical tests were applied, including one-way analysis of variance (ANOVA), followed by Student's t-test for comparison between two groups. In addition, the log-rank test was used to analyze the Kaplan-Meier curves. A 2-tailed p-value <0.05 was considered statistically significant

RESULTS

Cerebral infarct size, neurological involvement and survival

The cerebral infarct size after 60 minutes I and 24 hours after R was 34.9±2.5% (Figure 1A and 1B). The infarct area affected territories supplied by the middle cerebral artery, including the cerebral cortex and white matter of the frontal, parietal and temporal lobes, as well as the caudate and putamen nuclei (Figure 1A).

According to the Longa scale, 67.9% of mice scored 2 and 28.6% scored 3. Only 3.6% scored 0, while no mice scored 1 or 4. At 24 hours, the survival of mice with a score of 0 was 100%, with a score of 2 was 77.8%, while only 37.5% with a score of 3 survived.

Ventricular function

Twenty-four hours after reperfusion, a statistically significant decrease in LVEF was observed in I/R group compared to the sham group (I/R: 66.5±1.5% vs. sham: 74.3±0.9%; p=0.002), as well as in the shortening fraction (SF) (I/R: 42.9±1.7% vs. sham: 52.3±1.7%; p=0.004). (Figure 2) In contrast, there were no statistically significant changes in the isovolumetric relaxation time (IVRT) between the two groups (I/R: 20.1±0.7 ms vs. sham: 19.4±0.4 ms; p=0.450) (Figure 2).

Electrocardiographic changes

During cerebral ischemia, a progressive increase in HR (baseline: 252±10 bpm, after 60 min I: 317±24 bpm; p=0.182) and a gradual prolongation of the QTc interval (baseline: 125.1±4.3 ms, after 60 min I: 143.8±5.2 ms; p=0.008) were observed (Figure 3). Twenty-four hours after reperfusion, an even more significant prolongation of the QTc interval was observed (170.3±5.8 ms; p=0.002) (Figure 3B), as well as a notable increase in HR (384± 30 bpm; p=0.034 vs. baseline).

On the contrary, the Tp-Te interval was not prolonged during ischemia (baseline: 25.9±1.3 ms, after 60 min I: 23.8±1.4 ms; p=0.999) but it was prolonged during reperfusion (32.0±2.3 ms; p=0.049 vs. after 60 min I; p=0.068 vs. baseline) (Figure 3C).

DISCUSSION

Our findings show that, in this experimental model, left ventricular dysfunction and cardiac electrical changes occur in early stages after cerebral reperfusion. Furthermore, we emphasize that the electrocardiographic changes observed during cerebral ischemia may be intensified during reperfusion. Although the aim of this work was not to make a comparative analysis with the involvement of other areas of the central nervous system, cardiac involvement is the result of a cerebral lesion that involves an extensive territory supplied by the middle cerebral artery, one of the most affected areas in ischemic stroke. (16) Right frontal cortical lesions are reflected in the type of motor dysfunction in mice, and the extent of the lesion causes different degrees of dysfunction that correlate with mortality.

We have also observed involvement of the insular cortex, which could have pathophysiological implications in this study. Previous studies have shown that insular damage produces cardiac lesions as a consequence of the autonomic imbalance. (17-19) The physiological role of this cortical area has been documented in the differential regulation of the parasympathetic nervous system associated with the left hemisphere, and the sympathetic regulation associated with the right hemisphere. (20) The greater association of the side of the insula lesion with cardiac damage is not entirely clear; while some studies associate greater involvement with right lesions, (14) others do so with contralateral lesions. (21) Although we have not yet directly or indirectly evaluated the possible association between cardiac involvement and catecholaminergic discharge, it is plausible that the increases in HR observed in our experiments show an increase in sympathetic activity, possibly due to right insular damage. This hypothesis is supported by previous research in several species, which has shown an increase in sympathetic activity during right insula ischemia. (19-23) In addition, studies on cerebral hemorrhage have shown an increase in noradrenaline, without alterations in adrenaline or plasma cortisol levels. The authors attribute this phenomenon to a response not mediated by the adrenal glands. (24) The possibility of a direct discharge of catecholamines in the sympathetic terminals of the heart was also suggested in studies in rats, where greater damage was observed at the base of the atria, an area where cardiac nerve density is higher. (4)

Interestingly, we observed a prolongation of QTc interval during cerebral ischemia, which became even greater during reperfusion, but we did not observe a prolongation of the Tp-Te interval during ischemia, which was only modified during reperfusion. This finding indicates the early onset of electrical changes suggestive of disturbances in ventricular repolarization, which became more pronounced within the first 24 h post-reperfusion. QT interval prolongation has been well documented in other neurological pathologies, such as subarachnoid hemorrhage (25) or epilepsy, (26) and in both cases, it has been associated with severe ventricular arrhythmias and sudden death. (27) These electrical disturbances have also been observed in experimental models, following selective electrical stimulation of the insular cortex, but not of surrounding areas. (19) Although we have not specifically evaluated the arrhythmias, they may be partly responsible for the mortality rate observed in mice in

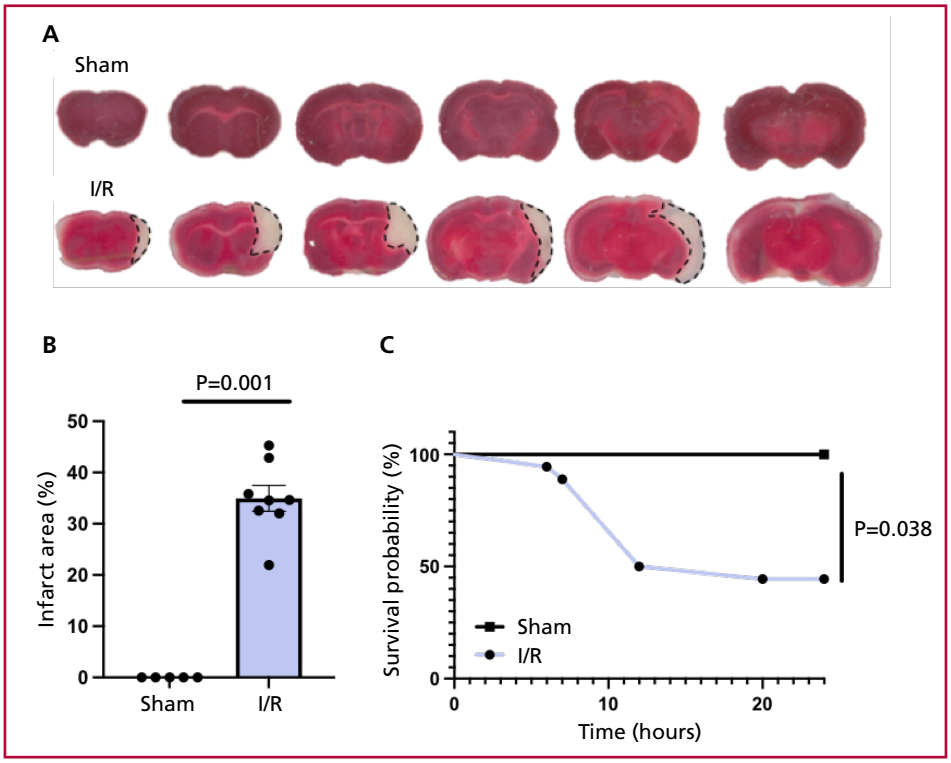

Fig. 1. A. Coronal sections of the brain stained with TTC corresponding to the sham group and ischemia and reperfusion (I/R) group are shown. The infarct area (indicated by a dotted line) is observed in the middle cerebral artery territory and affects both the cortex and the caudo-putamen. **B.** Quantification of the infarct area. Sham n=5; I/R n=8. **C.** Kaplan-Meier curve representation for survival. Survival rate at 24 hours was on average 43% for the I/R group. I/R: ischemia/reperfusion

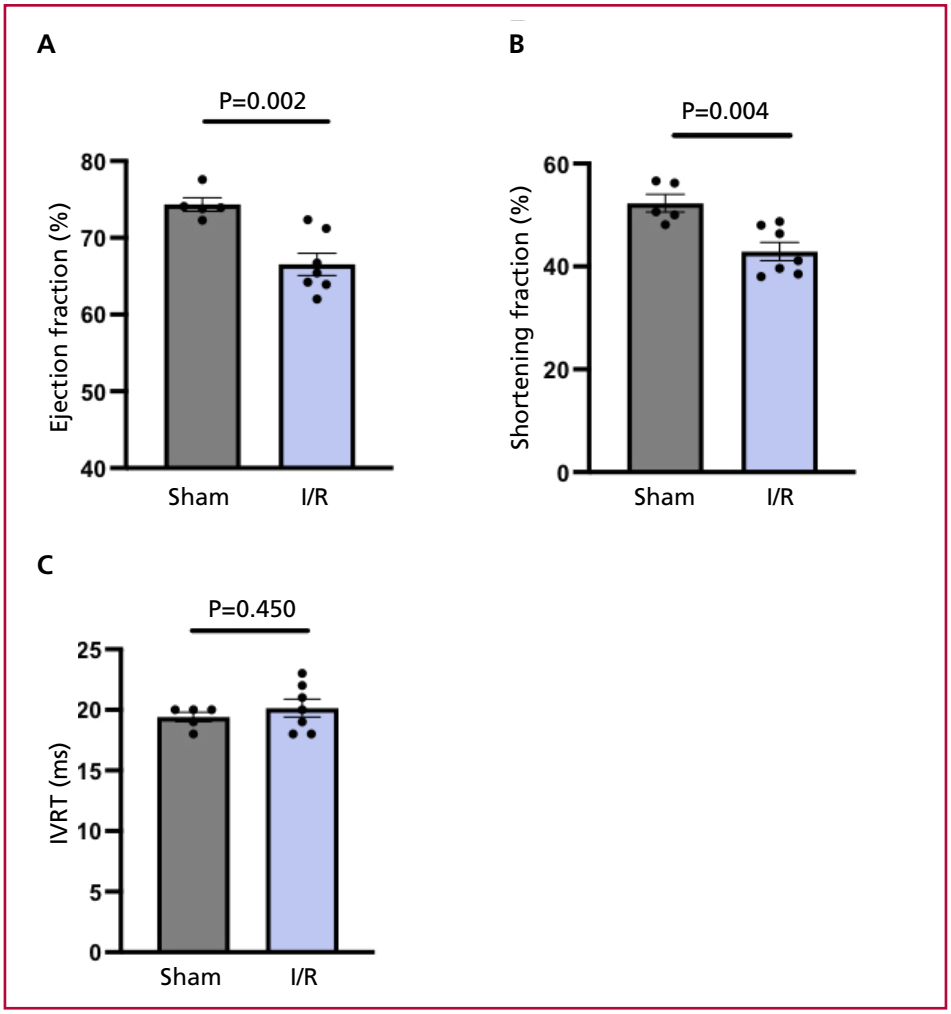

Fig. 2. Echocardiographic variables calculated 24 hours after cerebral reperfusion. Ischemia/reperfusion (I/R) group experienced a statistically significant decrease in ejection fraction (**A**) and in shortening fraction (**B**), with no changes in isovolumetric relaxation time (IVRT) (**C**). Sham n=5; I/R n=7.

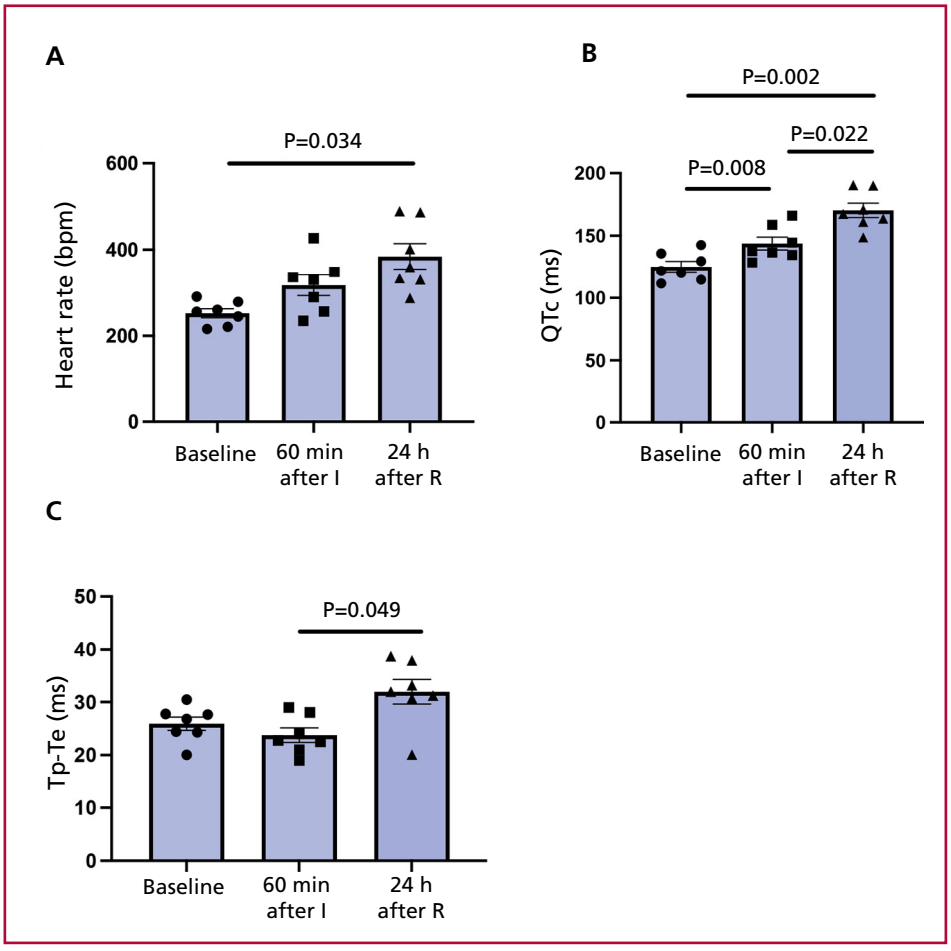

Fig. 3. Electrocardiographic changes evaluated at baseline before ischemia, at the end of ischemia and at the end of reperfusion. (**A**) Twenty-four hours after reperfusion, there is evidence of an increase in heart rate compared to baseline and 60 minutes after ischemia. (**B**) A prolongation of the QTc interval (Bazzet) is observed after 60 minutes ischemia and 24 hours after cerebral reperfusion. (**C**) There are no differences in the TpTe interval during ischemia, but there are differences at the end of reperfusion. I: ischemia; R: reperfusion; Tp-Te: interval from the peak to the end of T wave. n=7.

our study. It is known that prolongation of both intervals is an index of greater arrhythmogenicity (26) than the isolated prolongation of the QTc interval. These electrical alterations may be associated with intense sympathetic activation. This encourages us to continue studying repolarization disorders in other experimental groups.

Another potential mechanism associated with cardiac involvement in cerebral ischemia is the local and systemic inflammatory response. Inflammation plays a crucial role in the pathogenesis and progression of various cardiovascular pathologies. (28,29) The increase in proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), is linked to both myocardial functional damage and alterations in electrical potentials, thus predisposing to the appearance of arrhythmias. (28) Increased expression of these cytokines can lead to the recruitment of macrophages and fibroblasts, generating a local inflammatory environment with acute functional damage and long-term fibrotic compromise. (30) Several experimental and clinical studies have shown the increase of cytokines at local and systemic levels, as well as the mobilization of leukocytes following cerebral ischemia. (7, 14) In addition, the dynamic and bilateral association between the increase in the sympathetic response and in inflammation is recognized. (31) Therefore, it is likely that both possible mechanisms are involved in the pathophysiology of cardiac damage in our model.

CONCLUSION

In our experimental model, acute ischemia with cerebral reperfusion in the right hemisphere affecting the insular cortex induces functional and ventricular repolarization disorders that could be responsible for the increased mortality rate observed.

Conflicts of interest

None declared.

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

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BRIEF ARTICLE

Cardiac Resynchronization Therapy. Long-Term Evolution of Responder and Non-Responder Patients

Terapia de resincronización cardíaca. Evolución a largo plazo de los pacientes respondedores y no respondedores

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an effective treatment in patients with heart failure (HF), low left ventricular ejection fraction (LVEF) and wide QRS. However, there are a percentage of these patients who are non-responders, implying worse clinical outcomes.
Objectives: The aim of this study was to assess the differences in echocardiographic parameters of reverse remodeling and event rates [hospitalization for heart failure (HHF), all-cause mortality (ACM), heart transplantation (HTX) and appropriate therapies (AT)] between responder vs. non-responder patients to CRT.
Methods: A total of 343 patients with CRT, classified into responders and non-responders according to clinical and echocardiographic parameters, were included in the study. A 2-year follow-up was performed, in which reverse remodeling and the incidence of HHF, ACM, HTX and AT were evaluated.
Results: Among the 343 patients, 17% were non-responders and 83% responders. At 6 and 12 months there were no significant differences in ventricular diameters, but significant differences in LVEF ($p<0.001$), with greater increase in responders. At 24 months, responders had smaller diastolic diameter ($p=0.004$), smaller systolic diameter ($p=0.003$) and higher LVEF ($p<0.001$). Non-responders had significantly higher incidence of HHF ($p<0.001$), HTX ($p=0.001$) and AT ($p=0.002$), and an excess of ACM at the limit of statistical significance ($p= 0.056$).
Conclusions: Patients responding to CRT presented greater reverse remodeling and better clinical evolution, in accordance with the results of international observational studies.

Keywords: Cardiac Resynchronization Therapy - Heart Failure - Clinical Evolution - Hospitalization

RESUMEN

Introducción: La terapia de resincronización cardíaca (TRC) es un tratamiento eficaz en pacientes con insuficiencia cardíaca (IC), baja fracción de eyección del ventrículo izquierdo (FEVI) y QRS ancho. Sin embargo, hay un porcentaje de estos que son no respondedores, lo que implicaría peores resultados clínicos.
Objetivos: Valorar las diferencias en parámetros ecocardiográficos de remodelado reverso y tasa de eventos [hospitalización por insuficiencia cardíaca (HIC), muerte de todas las causas (MT), trasplante cardíaco (TXC) y terapias apropiadas (TA)] entre pacientes respondedores vs. no respondedores a la TRC.
Material y métodos: Se incluyeron 343 pacientes con TRC. Se los clasificó en respondedores y no respondedores según parámetros clínicos y ecocardiográficos. Se realizó seguimiento a 2 años, en que se evaluó el remodelado reverso y la incidencia de HIC, MT, TXC y TA.
Resultados: De los 343 pacientes, 17% fueron no respondedores y 83% respondedores. A los 6 meses y 12 meses no hubo diferencias significativas en cuando a diámetros ventriculares, pero si en la FEVI ($p<0,001$), que aumentó más en los respondedores. A los 24 meses los respondedores presentaron menor diámetro diastólico ($p=0,004$), menor diámetro sistólico ($p=0,003$) y mayor FEVI ($p<0,001$) Los no respondedores tuvieron significativamente mayor incidencia de HIC ($p< 0,001$), TXC ($p=0,001$) y TA ($p=0,002$)) y un exceso de MT en el límite de la significación estadística ($p= 0,056$).
Conclusiones: Los pacientes respondedores a la TRC presentaron mayor remodelado reverso y mejor evolución clínica, en forma acorde a los resultados de estudios observacionales internacionales.

Palabras clave: Terapia de resincronización cardíaca - Insuficiencia cardíaca - Evolución clínica - Hospitalización

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INTRODUCTION

The prevalence of heart failure (HF) is estimated between 1-3% in the adult population and increases to more than 10% and 30% in those over 70 and 85 years of age, respectively. (1) In recent years, advances in medical treatment have substantially improved the prognosis of these patients. (2,3) However, when optimal medical treatment is insufficient and the patient continues to deteriorate, cardiac resynchronization therapy (CRT) emerges as an effective alternative to improve quality of life, increase left ventricular ejection fraction (LVEF) and reduce mortality in patients who meet the criteria for its indication. (4,5).

The response to CRT depends on multiple factors including adequate patient selection, underlying heart disease, gender, electrode implantation in the appropriate vein of the coronary sinus, A-V and V-V interval programming, and maintenance of a biventricular pacing rate close to 100%, among others. Despite all this, there is a percentage of these patients who do not respond to CRT, which would imply worse long-term clinical outcomes.

OBJECTIVES

The aim of this study was to assess differences in echocardiographic parameters of reverse remodeling and event rates [hospitalization for heart failure (HHF), all-cause mortality (ACM), heart transplantation (HTX) and appropriate therapies (AT, including antitachycardia pacing and appropriate shocks)] between responder vs. non-responder patients to CRT at 2-year follow-up.

METHODS

A retrospective analysis was carried out of prospectively collected data from a single-center cohort of 418 patients with HF in whom CRT devices were implanted between March 2003 and December 2020. Among them, 75 patients were excluded from the analysis due to lack of complete follow-up data. Based on clinical and echocardiographic parameters, patients were classified into responders (those who reduced at least one NYHA functional class, or increased LVEF by 5% in absolute values) and non-responders (those who did not meet these criteria). A 2-year follow-up was performed, in which echocardiographic parameters of reverse remodeling were evaluated: LV diastolic diameter (LVDD), LV systolic diameter (LVSD) and LVEF, and the incidence of significant events: HHF, ACM, HTX and AT.

Statistical analysis

Continuous variables are presented as mean and standard deviation, and were compared with the t test. Categorical variables are expressed as frequencies and percentages, and were compared with the chi-square test or Fisher´s exact test, as appropriate. A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Among the 343 patients evaluated, 58 (17 %) were non-responders and 285 (83 %) were responders. Baseline population characteristics are shown in Table 1. Mean age at implantation was 64 years, and the percentage of women in the non-responder group was higher. Sixty-eight percent of responders had non-ischemic etiology, while in the non-responder group this occurred in 50%. There were no significant differences between groups in terms of cardiovascular risk factors, nor in the baseline echocardiogram. Most patients were in NYHA functional class I or II. There were differences in the baseline electrocardiogram (ECG): in the non-responder group only 31% had complete left bundle branch block (LBBB), vs. 66% of responders. Baseline QRS duration was shorter in the non-responder group.

At 6 and 12 months there were no significant differences in ventricular diameters, but there were, logically, significant differences in LVEF ($p<0.001$), since an increase in LVEF was one of the criteria for defining response to treatment. At 24 months, there were differences in the group of responders, with significantly lower LVDD ($p=0.004$) and LVSD ($p=0.003$), and higher LVEF ($p<0.001$) (Figure 1).

At the end of the 2-year follow-up, 82% of non-responders had had HHF compared with 13.6% of responders ($p<0.001$). Six non-responder patients (10.3%) died during follow-up (all were cardiovascular deaths, 5 due to HF and 1 to sudden death). Among responders, 12 (4.2%) died, 8 from cardiovascular causes (7 from HF and 1 from electrical storm) and 4 from non-cardiovascular causes. This implies a difference at the limit of statistical significance ($p= 0.056$). Heart transplantation was performed in 10.3% of non-responders vs. 2.1% of responders ($p=0.001$). The incidence of appropriate therapies was 17.2% in non-responders vs. 5.6% in responders ($p=0.002$). (Figure 2).

DISCUSSION

Cardiac resynchronization therapy is an effective treatment for HF refractory to medical therapy, in a subgroup of patients who meet criteria for its indication. This was demonstrated in large randomized studies, including the MIRACLE, COMPANION, CARE HF, REVERSE, MADIT CRT and RAFT trials, on which current clinical practice guideline recommendations are based (6-11). However, not all patients respond to CRT. According to the study analyzed, this percentage varies between 20% and 40%, which depends, in part, on the definition of response to treatment used. Although there is currently no consensus on the definition of CRT response parameters, the most commonly used are clinical parameters (functional class and quality of life), echocardiographic parameters of reverse remodeling, and rates of clinical events, such as HHF and mortality. According to the author, these are used alone or in combination to define response. For years, attempts have been made to detect the factors related to this lack of response: the first ones identified were QRS width,

Table 1. Baseline characteristics

	RESPONDERS (n= 285)	NON-RESPONDERS (n= 58)	p
Age (Years)	63.9 ± 11	64.2 ± 9	0.214
Male gender	194 (68%)	28 (48%)	0.004
Etiology			
Ischemic	90 (31%)	29 (50%)	0.007
Non-ischemic	195 (68%)	29 (50%)	
Risk Factors			
HT	177 (62%)	41 (70%)	0.215
DM	68 (23%)	15 (25%)	0.745
Baseline Medication			
Furosemide	206 (72%)	43 (74%)	0.772
Spironolactone/eplerenone	248 (87%)	47 (81%)	0.231
ACEI/ARB	267 (93%)	53 (91%)	0.522
BB	277 (97%)	57 (98%)	0.638
Prevention			
Primary	256 (89%)	47 (81%)	0.572
Secondary	16 (5.6%)	7 (12%)	0.073
CRT-P	13 (4.5%)	4 (6.8%)	0.455
Baseline FC (NYHA)			
I	11 (3.8%)	7 (12%)	0.010
II	131 (45.9%))	28 (48%)	0.747
III	139 (48.77%)	22 (37%)	0.131
IV	4 (1.4%)	1 (1.7%)	0.852
Baseline ECG			
AF	70 (24%)	21 (36%)	0.067
LBBB	189 (66%)	18 (31%)	< 0.001
QRS duration (ms)	165.3 ±26.3	156.5 ± 31.21	0.003
Echocardiogram			
LVDD (mm)	67.5 ± 9	68.4 ± 10	0.515
LVSD (mm)	54.6 ± 11	57.4 ±12	0.155
LVEF (%)	25.11 ± 6	25.5 ± 6	0.357

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; AF: atrial fibrillation; BB: beta-blockers; CRT-P: cardiac resynchronizing therapy without associated cardioverter-defibrillator; DM: diabetes mellitus; FC: Functional class; HT: hypertension; LBBB: complete left bundle branch block; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter. Qualitative variables are presented as frequency and percentage, n (%); quantitative variables as mean ± standard deviation.

LBBB and functional class, on which the indication criteria are currently based. In 2009 Mullens et al. studied 75 patients with persistent HF symptoms and lack of LV reverse remodeling 6 months after implantation. Most patients had identifiable reasons for suboptimal response: inadequate device configuration (47%), suboptimal medical therapy (32%), arrhythmias causing low percentage of CRT (32%), inadequate LV catheter position (21%), and lack of baseline dyssynchrony (9%). (12) Gender is also a factor to be taken into account; a meta-analysis showed that women had lower total mortality and higher reverse remodeling compared with men. (13) Another fundamental factor is etiology. In 2005 Gasparini et al. showed that patients with non-ischemic cardiomyopathy had greater increase in LVEF and improvement in functional class. (14) This was confirmed by subsequent studies. (15) There are now indications that some genetic variables might also be related, although much remains to be studied. (16)

In our study, to our knowledge the largest and longest follow-up study in Argentina, we used combined parameters of functional class improvement and reverse remodeling to define response. The percentage of non-responders was 17%, and the long-term evolution of these patients was worse, with a significantly higher rate of HHF, HTX, ACM and AT compared with responders. Although our work had a low rate of non-responders compared with the literature, the adverse clinical outcomes in this population encourages us to continue working in order to identify factors related with suboptimal response to CRT, to perform early interventions and try to improve their long-term prognosis.

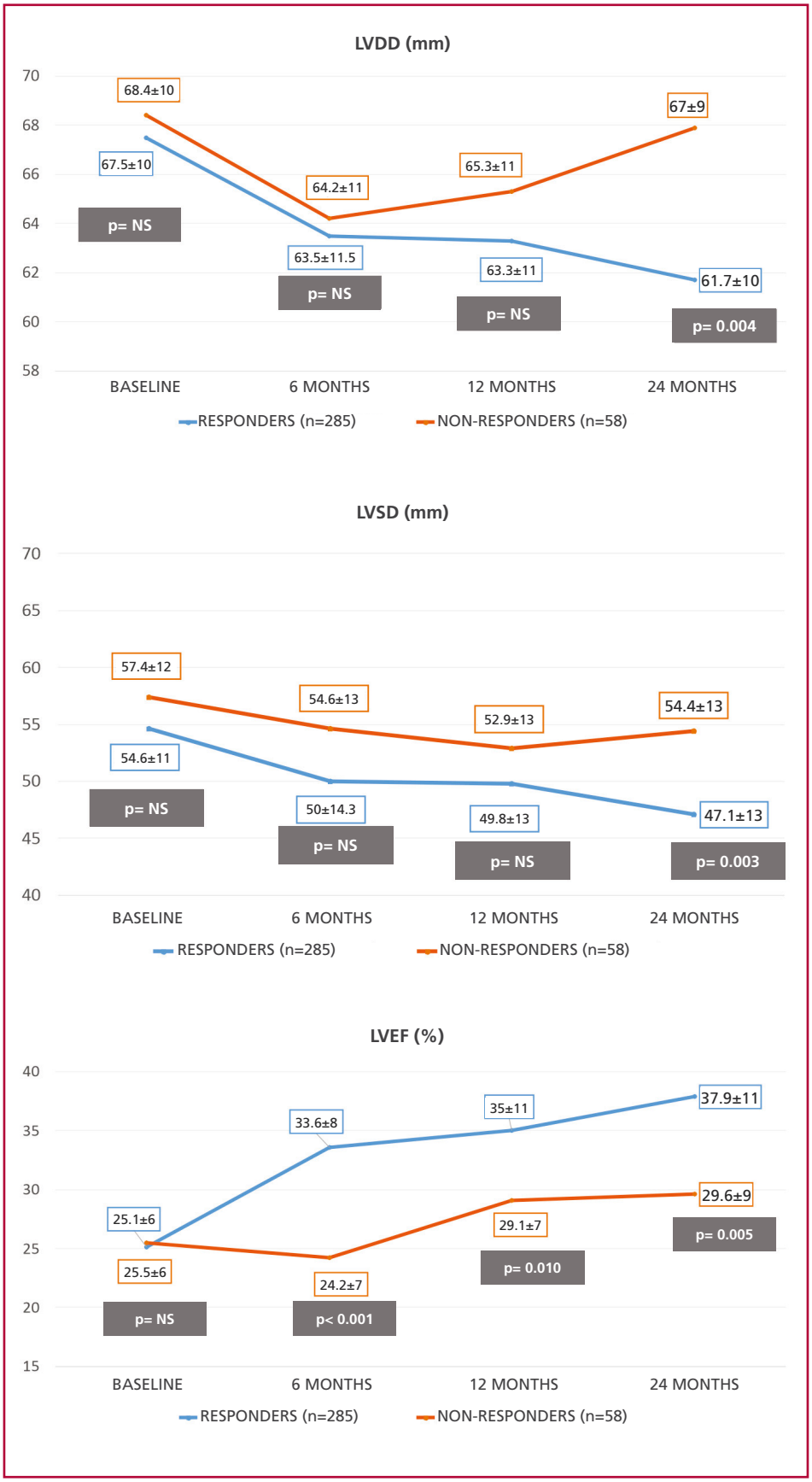

Fig. 1. Echocardiographic evolution in responders and non-responders.

LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter

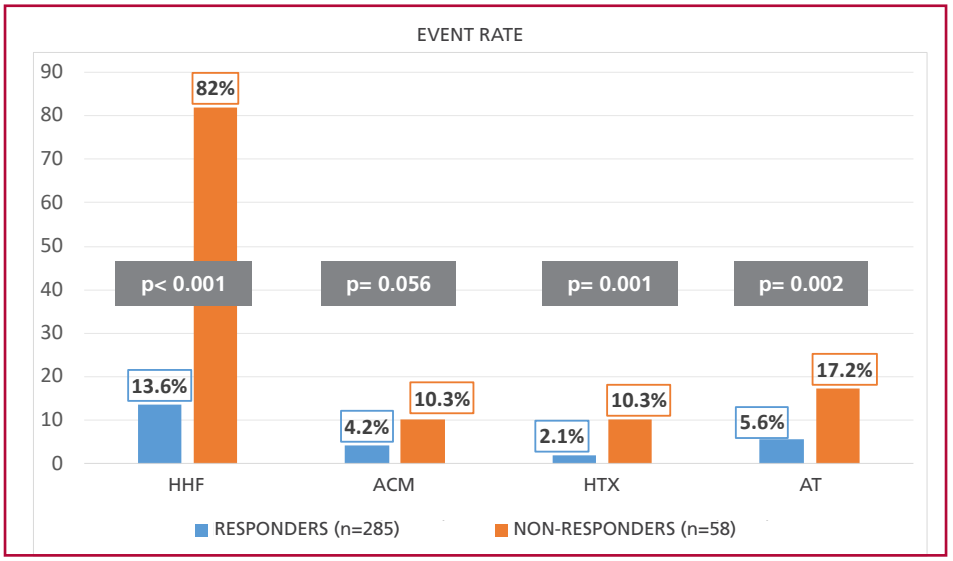

Fig. 2. Incidence of events in responders and non-responders.

ACM: all cause mortality; AT: appropriate therapies; HHF: hospitalization for heart failure; HTX: heart transplantation

CONCLUSION

In our population, responder patients had significantly better echocardiographic parameters of reverse remodeling. This may explain the significantly lower rate of HHF, ACM, HTX, and AT compared with non-responders.

Conflicts of interest

None declared.

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

Financing

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BRIEF ARTICLE

Valve-Sparing Aortic Root Replacement in Children and Adolescents: Experience and Results in a Public Institution in Argentina

Reemplazo de la raíz aórtica con preservación valvular en niños y adolescentes: experiencia y resultados en una institución pública en Argentina

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ABSTRACT

Background: Valve-sparing aortic root replacement (VSARR) with reimplantation technique is indicated in patients with aortic root aneurysm.
Objective: To evaluate the mid-term outcomes of this surgical technique in children and adolescents in our institution.
Methods: Retrospective study. Twenty-one patients who underwent VSARR surgery were included between July 2006 and July 2022. The relationship between baseline variables and progression of aortic regurgitation (AR) was assessed.
Results: The median age was 13 years. Seventeen patients had connective tissue disorders (3 with bicuspid aortic valve), 2 operated congenital heart disease, 1 isolated bicuspid aortic valve and 1 Turner syndrome. Thirteen patients had mild AR and 5 had moderate AR preoperatively.
Three patients underwent early aortic replacement, 2 due to endocarditis and 1 due to severe acute AR. The median follow-up was 4.1 years. Of 17 patients at follow-up, 2 developed mild-moderate AR, 2 moderate AR and 3 severe AR. One of them underwent Bentall surgery. No association was found between the degree of preoperative AR or the presence of bicuspid aortic valve and the progression of postoperative AR. There was no association between the type of postoperative valve coaptation and the development of AR greater than mild at follow-up.
Conclusions: VSARR with reimplantation is a feasible surgical technique with favorable mid-term outcomes and low reoperation rate in pediatric patients.

Key words: A root aneurysm - Aortic root replacement - Valve-sparing.

RESUMEN

Introducción: La cirugía de reemplazo de la raíz aórtica con preservación valvar tipo reimplante (RRAoPV) está indicada en pacientes con aneurisma de la raíz aórtica.
Objetivo: Evaluar los resultados a mediano plazo de esta técnica quirúrgica en niños y adolescentes de nuestra institución.
Material y métodos: Estudio retrospectivo. Se incluyó a 21 pacientes a quienes se realizó cirugía de RRAoPV entre julio de 2006 y julio de 2022. Se evaluó la relación entre las variables basales y la progresión de insuficiencia aórtica (IAo).
Resultados: La mediana de edad fue de 13 años. Diecisiete pacientes tenían enfermedad del tejido conectivo, (3 de ellos además con aorta bicúspide), 2 cardiopatías congénitas operadas aisladas, 1 válvula aórtica bicúspide aislada y 1 síndrome de Turner. Trece pacientes tenían IAo leve y 5 moderada en el preoperatorio.
Tres pacientes requirieron reemplazo aórtico precoz, 2 por endocarditis y uno por IAo aguda grave. La mediana de seguimiento fue de 4,1 años. De 17 pacientes en seguimiento, 2 evolucionaron con IAo leve-moderada, 2 moderada y 3 grave. Uno de ellos requirió cirugía de Bentall. No se encontró asociación del grado de IAo preoperatoria, ni de la presencia de aorta bicúspide, con la progresión de la IAo postoperatoria. No hubo asociación entre el tipo de coaptación valvular postoperatorio y el desarrollo de la IAo mayor que leve en el seguimiento.
Conclusiones: El RRAoPV tipo reimplante es una técnica quirúrgica viable en pacientes pediátricos con buenos resultados a mediano plazo y baja tasa de reoperación.

Palabras clave: Aneurisma raíz aórtico - Reemplazo raíz aórtica - Preservación valvular.

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INTRODUCTION

Aortic root aneurysms are rare in children and are generally associated with connective tissue disorders, (1,2) such as Marfan or Loeys-Dietz syndromes, or with the progression of conotruncal heart diseases. (2) These aneurysms may result in aortic rupture, aortic dissection or severe aortic regurgitation (AR). (2,3) Aortic root replacement is indicated to avoid the risk of these complications. Clinical guidelines and surgical indication are based on aortic root size, progression of dilatation (mm/year) and genetic syndrome.

The purpose of Tirone David surgery is to replace the pathological segment of the aortic (Ao) root complex while preserving the anatomical and functional integrity of the valve leaflets. (4) The advantage over Bentall surgery (aortic root replacement with a mechanically valved conduit) is that it avoids lifelong anticoagulation and its inherent risks. However, the main limitation of valve-sparing aortic root replacement (VSARR) in pediatric population is the potential need for reoperation, as during growth, the reconstructed aortic root and the aortic valve may become small for the future body surface area. (4)

This study evaluates our experience and the outcomes of VSARR with the Tirone David technique at the Hospital Nacional de Pediatría J.P. Garrahan.

METHODS

A retrospective study was performed. The medical records and echocardiographic recordings of 21 patients who underwent VSARR with the Tirone David technique between July 2006 and July 2022 were reviewed. The degree of AR, the valve morphology, the aortic root measurement and the Z-scores were assessed by transthoracic echocardiography and intraoperative transesophageal echocardiography (iTEE). Another imaging studies (cardiac tomography or resonance) were performed in 60% of patients.

Statistical data were analyzed with the STATA software. Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. The relationship between the basal variables and the progression of AR was evaluated.

RESULTS

Preoperative characteristics

The median age at surgery was 13.1 (10.5-14.4) years; the median weight was 40 (13-99) kg. The youngest patient was 2.9 years old and weighed 13 kg. Five patients were younger than 8 years. Eleven patients were female. All surgeries were scheduled and indicated based on the aortic root size and progression of aortic root dilatation (according to clinical guidelines). Seventeen patients had a diagnosis of connective tissue disease: 13 Marfan (2 associated with bicuspid aortic valve disease), 3 Loeys-Dietz (one associated with conotruncal heart defect) and 1 uncharacterized; 1 patient had Turner syndrome with bicuspid aortic valve disease; 2 isolated operated congenital heart diseases (1 conotruncal heart defect and 1 multiple ventricular septal defect cerclage), and 1 patient isolated bicuspid aortic valve disease.

The median diameter of the aortic annulus was 25 mm with a Z-score of +3.5 (+2.85-+5.7), and that of the Valsalva sinuses was 42.5 (36.5-51.5) mm with a Z-score of +6.2 (+4.6-+7.5). Regarding preoperative AR, 2 patients had no AR, 13 patients had mild AR, 1 mild-moderate AR and 5 patients had moderate AR.

Surgical data

The Tirone David technique was used in all patients. The smallest conduit size was 22 mm and the largest was 30 mm. All patients had a straight conduit. The median time of extracorporeal circulation (ECC) was 179 min and that of clamping 156 min. The longest ECC times were a consequence of associated procedures (pulmonary homograft replacement, mitral plastic surgery, transverse arch and descending aorta replacement). Only one patient (with Marfan syndrome and bicuspid aortic valve) was reoperated during the same procedure to resuspend the valve.

The iTEE performed in all patients showed trivial AR in fifteen patients and no AR in the remainder. Of 14 patients who had coaptation height assessed in relation to the conduit, 9 patients had type B coaptation and 5 had type C coaptation. (5)

Outcomes

The median stay in the intensive care unit was 7 days. Three patients underwent early aortic valve replacement. One patient with Marfan syndrome and bicuspid aortic valve, who required intraoperative aortic valve resuspension, suffered from severe acute AR 2 days after operation and underwent Bentall surgery. Two patients died in the immediate postoperative period from infectious complications (one case of mediastinitis at 28 days and one case of endocarditis at 47 days). Three patients required a pacemaker implantation because of atrioventricular block. Two patients suffered from endocarditis: one of them had endocarditis by *Klebsiella* that affected the mitral valve, which was complicated by a pseudoaneurysm of the mitral-aortic intervalvular fibrosa 61 days after operation, for which an aortic homograft was placed; the other one had endocarditis by methicillin-resistant *Staphylococcus aureus* that affected the aortic and mitral valves 47 days after operation, for which an aortic homograft was placed.

The median follow-up of 17 patients who underwent Tirone David technique was 4.1 (1.35-12) years, including one patient lost to follow-up. Of the followed-up patients, 43% developed aortic dilatation distal to the implanted conduit. One of them, who had uncharacterized genetic syndrome, underwent replacement of the ascending aorta 4 years after operation and died from dissection of the descending aorta one year after the second surgery.

Coronary button aneurysms were observed in 5 patients.

Two patients had mild-moderate AR, 3 had moderate AR and 2 had severe AR, of whom 1 underwent

Bentall procedure 9 years after VSARR. The rest had mild AR. The higher degrees of regurgitation were caused by leaflet prolapse. The median postoperative Ao annulus size was 21 mm with a Z-score of +2.4 (+1.65 to +2.8). At follow-up, one patient with bicuspid aortic valve disease developed moderate AR.

At present, 81.2% of patients under follow-up are free from reoperation.

DISCUSSION

Aortic root aneurysms are rare in children and adolescents and are mostly associated with connective tissue disorders, (1-4) especially Marfan and Loeys-Dietz syndromes, and bicuspid aortic valve disease. (2,4) Aneurysms have also been described following surgery for conotruncal heart defects. (2) The risk of aortic dissection or rupture is related to the diameter of the aortic root and the ascending aorta. (2-4) Clinical guidelines and surgical indications are based on the progression of dilatation (mm/year), (1) the size of the aortic root and the association with a genetic syndrome.

No guidelines have been established regarding surgical timing in children, so indications are extrapolated from adult recommendations. (5) The risk of these events is very low in this population, and they generally occur in late adolescence. (5,6) In children below the age of 12, the indications for surgery are even less clear, so, in addition to the above, the expression of the genetic syndrome and the degree of AR are considered. (1,4,6) Different groups define criteria for aortic root replacement in children according to their experience (Table 1). In the case of Loeys-Dietz syndrome, Lange et al. consider that Tirone David technique should be postponed until the annulus diameter reaches a value of at least 18 mm so that a prosthetic conduit ≥22 mm may be used and a subsequent reoperation may be avoided. (4)

In adults, the Svensson index is used, which considers the aortic cross-sectional area indexed to height; a value ≥10 implies greater risk of aortic dissection, (7) but this is not validated in children or adults with operated congenital heart disease. (8) Indications for surgery based on aneurysm growth rate >2-3 mm/year may be difficult in children because of the natural growth of the aorta. Davies et al. established the Aortic Size Index (ASI), which is defined as aortic diameter divided by body surface area, to assess the risk of adverse events. An ASI of 2.75-4.25 cm/m² is associated with a moderate risk of rupture (8%/year), whereas an ASI >4.25 cm/m² implies a high risk of rupture (20-25%/year). (6,8,9)

During the last two decades, various surgical techniques have been developed to manage these patients. Aortic root replacement with a mechanical valved conduit (Bentall procedure) was originally proposed, but this procedure involved lifelong anticoagulation, risk of thromboembolism and bleeding. These risks have led to the development of the VSARR procedures, which aim to preserve the aortic valve function and hemodynamics. (4) These procedures include the remodeling or Yacoub technique, and the reimplantation or Tirone David technique. (2) There are many published reports of these techniques in adults, but very few in children. (1) The largest series in this age group which included 100 consecutive cases in 20 years has been reported by Fraser et al. at John Hopkins Hospital. (2) In patients with operated conotruncal heart defects (truncus arteriosus, tetralogy of Fallot, transposition of the great arteries) and in patients who underwent the Ross procedure, who have a very low risk of dissection, aortic root replacement surgery is recommended even in the absence of AR if the diameter is greater than 50 mm and/or the Svensson index is >10 cm/m². (9) In patients with Turner syndrome with an ASI ≥2.5cm/m² and risk factors it is reasonable to perform Tirone David surgery.

Several series have shown that the remodeling technique is not recommended in children because of the high risk of mid-term failure due to the develop-

Tabla 1. Indications for surgery for aortic root replacement

	Marfan	Loeys-Dietz	Bicuspid aortic valve
Fraser et al. (2)	Diam. >5 cm Increase >0.5 cm/year >4.5 cm with family history of rupture >4-5 cm mitral valve surgery	Type I and II: >3.5-4 cm or Z-score >3 Type III: Diam. > 4-4.5cm	Diam. >5.5 cm
Lange et al. (4)	Diam. <5 cm if Z-score >5	Z-score >3	
Kluin et al. (6)	Z-score >4-4.5	Z-score >3 Diam. >3.5cm	
AHA/ACC 2022 Ao Disease Guidelines. (7)	Diam. ≥ 5cm With RF, Diam. ≥ 4.5cm Increase ≥0.3 cm/year Ao root area/height ratio ≥10	Diam. ≥ 4.5cm In at-risk patients, Diam. ≥ 4 cm	Diam. ≥5.5cm Ao root area/height ratio ≥10 With RF, Diam. >5cm

Ao: aortic; Diam: diameter; RF: risk factors

ment of AR following progressive annular dilatation. (2,3,5,6) In contrast, the reimplantation technique is low risk and provides better outcomes, since it offers efficient annular stabilization because of the conduit implantation in the ventriculoarterial junction. The main concern is the stress produced in the leaflets due to the lack of cortex formation, which physiologically occurs in the sinuses. (1) To reduce this stress, conduits with sinuses, such as Valsalva grafts, have been developed, but the smallest size is 24 mm, so they are not appropriate for small children. (4) The long-term performance of the leaflets inside the rigid conduit is still uncertain. Myers et al. have also shown better outcomes in terms of the need for reoperation in patients with operated congenital heart defects using the replacement technique. Besides, they have warned that underestimating the conduit size could result in early valve deterioration. (9)

Regarding the choice of the diameter of the prosthesis, some groups, if possible, postpone surgery until the aortic root size allows the implantation of a conduit for adults. (10) At our institution, we use a conduit diameter that is 3-4 mm larger than the optimal sinotubular junction (STJ) size, as recommended by Cameron and Vricella, to ensure the best apposition of the leaflets. (11) They use conduits that are 2-3 mm larger than the optimal STJ size in patients with Loeys-Dietz syndrome. (12) New techniques for children below the age of 3 have been described using a subannular ring and a superior ring at the STJ to minimize the late onset of AR. (13)

Contraindications for VSARR include marked valve asymmetry, large fenestrations of the leaflets, acute dissection, severe prolapse, valve calcification and ventricularization of the sinuses. (2) According to Baltimore's experience, bicuspid aortic valve is not a contraindication to valve preservation, but special care should be taken to maintain the geometry when resuspending the commissures to ensure postoperative valve competence. (2)

Forty-three percent of patients in our series developed aneurysms in other segments of the aorta distal to the conduit. One patient underwent ascending aorta replacement 4 years after operation, and another underwent arch replacement at the time of the Tirone David surgery. Lange and Fraser suggest reconsidering the management of the distal ascending aorta as well as the aortic arch in patients with severe connective tissue disorders. (2,4) Other groups discourage it because of the high risk of neurological damage (6) and to avoid additional suture lines that may increase the risk of bleeding and pseudoaneurysms.

The iTEE showed trivial residual AR in most patients. During this procedure, we evaluated the presence or absence of AR, the degree of severity, the jet direction and the coaptation height related to the conduit. (14) A patient with Marfan syndrome, bicuspid aortic valve, significant residual AR and eccentric jet underwent reoperation with ECC. Commissural resuspension was performed and his AR remained mild. Two days later, he presented with severe acute AR and underwent Bentall surgery. It has been described that the AR progression could be a consequence of the structural degeneration of the leaflets due to abnormal flow distribution during diastolic closure, or to a functional failure secondary to inadequate coaptation height (less than 11 mm/type C coaptation). (14-17) Five of our patients had moderate or greater AR in the remote postoperative period, and all of them had connective tissue disorders (Table 2). We found no association between the degree of preoperative AR or the presence of bicuspid aortic valve and the development of AR, in contrast with the risk factors described by Tirone David in adult population. (18)

There was no association between the type of postoperative valve coaptation and the development of AR greater than mild at follow-up, in contrast to the study by Hall et al., possibly due to the small sample size. Because of the short follow-up, we are not able to hypothesize whether the cause of AR progression in our patients was due to the degree of leaflet coaptation with respect to the conduit, the impact of the connective tissue disorders, or the valve degeneration. Longer follow-up would be necessary to determine the causes of progression.

In our series, 5 patients developed coronary button aneurysms, as described in the progression of the most severe forms of connective tissue disorders. (9)

At the follow-up of these patients, the recommendation is to include clinical checks and echocardiography every six months during the first postoperative year and then annually, with the addition of tomography

Table 2. Preoperative and postoperative aortic regurgitation.

Degree of AR (n=21)	Preoperative period (n=21)	Immediate postoperative period (n=21)	Remote postoperative period (n=16)
No	2	5	1
Mild	13	16	8
Mild-moderate	1	0	2
Moderate	5	0	2
Severe			3

In the immediate postoperative period, 1 patient died and 3 underwent valve replacement. One patient was lost to follow-up.

or cardiac resonance at least every 2 years. (2,4,10) In the case of Marfan and Loeys-Dietz syndromes, a stricter follow-up is recommended during the first postoperative year with echocardiography every 3 to 6 months. Prescription of beta-blockers and/or angiotensin receptor antagonists should be continued.

The limitations of our study include its retrospective design and the small sample size.

CONCLUSIONS

Children and adolescents with connective tissue disorders or operated congenital heart disease may undergone Tirone David surgery with good outcomes and low mid-term reoperation rate. Neither bicuspid aortic valve nor preoperative aortic regurgitation seems to be associated with greater aortic valve dysfunction at follow-up.

Conflicts of interest

None declared.

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

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CONTROVERSY

Percutaneous Renal Denervation Should Be Considered in Hypertension Treatment

La denervación renal percutánea debe considerarse en el tratamiento de la hipertensión arterial

AGONIST

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"Controversy is the fuel of progress; only by facing opposing ideas can we move forward". John Stuart Mill

The present controversy refers to the clinical implications of the percutaneous renal denervation (PRD) strategy in hypertensive patients. Although beforehand my role as PRD "agonist" could be termed "the dark side of the moon" (in relation to the antagonist), I will try to postulate in the following paragraphs the potential benefits and the clinical scenarios where we should not neglect considering this treatment to optimize the care of our patients.

INTRODUCTION

Hypertension (HTN) is still one of the main cardiovascular risk factors worldwide, with a prevalence of 34% according to data of the most recent review of the International Society of Hypertension, (1) and it is associated with a clear deleterious clinical effect. (2)

Even though the prevalence of HTN continues to be constant, the absolute number of people diagnosed with this disease has markedly increased, from 648 million in 1990 to 1.28 billion in 2019, representing a constant challenge for public health. (3)

Currently, the achievement of blood pressure (BP) targets in patients with HTN is still low in most regions of the world. (4) One of the main reasons is the low adherence to pharmacological treatment, identified as one of the main causes of HTN management failure. (5,6) Thus, we should consider "alternative" therapeutic strategies for HTN treatment (though from now on we could term them "additional"), among which PRD is postulated as a promising tool.

PHYSIOLOGICAL BASIS OF PRD

When considering a therapeutic strategy, it is essential to understand its mechanism of action in order to obtain the desired benefit. In the context of the complex pathophysiology of HTN, the renal sympathetic nervous system, composed of both afferent and efferent sympathetic nervous fibers, plays a crucial role in the development of this entity. (7) The activation of the sympathetic efferent nerves in the renal arteries may cause vasoconstriction of the kidney arterioles, reduced renal blood flow, increased renin secretion, and finally activation of the renin-angiotensin-aldosterone system, which leads to increased sodium and water absorption, and as a result, increased intravascular volume and the perpetuation of systemic HTN. (8) On the other hand, the activation of the sympathetic afferent nerves from the renal arteries can produce an increase in systemic sympathetic activity and the release of hypothalamic hormones, leading to increased systemic vascular resistance and, consequently, to the maintenance of HTN. (9) This is the pathophysiological basis of PRD therapy, which interrupts through the implementation of various mechanisms (radiofrequency [RF], ultrasound [US], neurolysis) the pathways of both afferent and efferent sympathetic nerves in the renal artery, thus achieving an "additional" (and not "alternative") therapeutic approach to the treatment of HTN.

SCIENTIFIC EVIDENCE

Symplicity HTN-3 Study

In our setting, PRD is still a rarely prescribed procedure. It could be assumed that this position is based on the results of the Symplicity HTN-3 study. (10) This was the first sham-controlled, randomized study to demonstrate a high safety profile of the PRD procedure using a device based on an RF-emitting monoelectrode (Symplicity renal-denervation catheter, Medtronic), but that did not succeed in demonstrating superiority in terms of 24-hour outpatient systolic BP (SBP) and office BP reduction, compared with the sham subgroup. It is worth highlighting how striking

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these negative findings are, considering that early studies in the first half of the twentieth century had demonstrated the effectiveness of surgical sympathectomy as a tool for treating severe HTN. (11)

Further analyses have identified multiple causes of negative results in the Symplicity HTN-3 study, including changes in pharmacological adherence during the course of the study, poor experience of operators with the PRD device, high variability in the results of the procedures and the inability of the first-generation device to perform simultaneous ablations, among others. (12) Identifying these points was essential to improve further studies.

SPYRAL HTN-ON MED EXPANSION AND SPYRAL HTN-OFF MED PIVOTAL STUDIES

These were the first international, randomized, sham-controlled studies that included patients with HTN evaluating the benefit of PRD in terms of reducing 24-hour SBP both in the presence of antihypertensive pharmacological treatment (SPYRAL HTN-ON MED Expansion), (13) and in its absence (SPYRAL HTN-OFF MED Pivotal). (14) With a 3-month follow-up, the SPYRAL HTN-OFF MED Pivotal study succeeded in demonstrating a statistically significant decrease in 24-hour SBP (α -4.0 [-6.2 to -1.8] mmHg), and office SBP (α6.6 [-7.9 to -1.9) mm Hg in relation to the sham subgroup; (14) whereas, conversely, SPYRAL HTN-ON MED Expansion did not identify a statistically significant difference between the two subgroups in terms of 24 hour SBP, which could be explained by an exaggerated reduction in pressure values within the sham subgroup secondary to an unbalanced prescription of pharmacological treatment and also by the impact of the SARS-CoV-2 pandemic. (13) It is also highlighted that the PRD subgroup showed a significant reduction in office SBP and diastolic BP, and a further reduction of blood pressure levels during nighttime, which represents an additional therapeutic benefit. (13) Both studies demonstrated a high safety profile, with an occurrence of adverse periprocedural events close to 1-2% and a rate of major adverse events of 0.4% at one year of the index procedure. (15)

RADIANCE-HTN STUDY

The RADIANCE-HTN study was a multicenter, randomized, sham-controlled study that identified a benefit of the US Paradise-based DRP system (ReCor Medical, Palo Alto, CA, USA) in terms of reducing BP in patients with HTN, in relation to the sham procedure, both in the subgroup with no concomitant antihypertensive treatment (RADIANCE-HTN SOLO) (16) and in those with resistant HTN treated with a fixed dose of a triple pharmacological combination. (RADIANCE-HTN TRIO). (17) It is important to note that the benefit of this therapy in terms of BP reduction remained constant for a period of 36 months since the index procedure (Table 1). (18)

PATIENT SELECTION AND RECOMMENDATION OF CLINICAL PRACTICE GUIDELINES

There are currently underrepresented subpopulations of HTN patients in which this therapeutic approach strategy is not recommended, namely: (19)

- Renal transplant recipients.
- Patients with severe renal impairment (glomerular filtration rate ≤40 ml/min/1.73 m^2).
- Patients requiring hemodialysis therapy.
- Patients diagnosed with fibromuscular dysplasia.
- Patients with untreated secondary HTN.
- Patients with a single functional kidney (functionally monorenal).

Conversely, clinical practice guidelines recommend considering PRD in patients with "resistant HTN" (defined as office BP ≥140/90 mmHg, confirmed by 24-hour outpatient pressure monitoring with SBP ≥130 mmHg or daytime SBP ≥135 mm Hg, treated with ≥3 antihypertensive drugs, including a diuretic at the highest tolerated dose) and with an estimated glomerular filtration rate of ≥40 ml/min/1.73m2 (class of recommendation [COR] II, level of evidence [LOE] B). It is also recommended in patients with "uncontrolled HTN" (under treatment with ≥4 antihypertensive drugs) and in those who have severe adverse events or quality of life impairment secondary to pharmacological treatment. It is also worth pointing out that this procedure should be carried out in specialized medical centers (COR I, LOE C), with a multidisciplinary team for decision-making and that patient preference should be considered (COR I, LOE C). (19,20) Patients not adhering to or intolerant to multiple pharmacological treatments should also be considered as candidates for PRD (Figure 1).

CONCLUDING CONSIDERATIONS

The benefit of PRD systems in patients with HTN is not negligible and has proven to be a safe and lasting strategy. In this regard, by analyzing the evidence as a whole, identifying an approximate decrease of 10 mmHg in office SBP and 6 mm Hg in 24-hour outpatient SBP monitoring could result in 20% reduction in major cardiovascular events, 28% of heart failure events, 17% of atherosclerotic coronary disease and 13% decrease of mortality. (21)

In our setting, and considering the invasive nature of the PRD strategy, the costs required by the health system and the above-mentioned "modest" benefit observed, it is clear that this strategy should not be used systematically. Despite the "invasiveness" of the method, it has been demonstrated that it is a safe procedure and does not exceed the risk of adverse events inherent in the natural evolution of the study population, while in terms of cost-effectiveness it appears to be a cost-effective strategy in selected patients. (22)

Given that the clinical benefit of PRD is equivalent to the reduction of only one antihypertensive drug, (23) it is worth noting that current evidence on PRD

Table 1. Randomized, sham-controlled clinical studies and real-world evidence supporting percutaneous renal denervation.

	SPYRAL HTN-ON MED (13)	SPYRAL HTN-OFF MED (14)	RADIANCE HTN-SOLO (16)	RADIANCE HTN-TRIO (17)	RADIANCE II (PIVOTAL) (26)	Global SYMPLICITY Registry (27)	NETROD HTN Study (28)	Iberis-HTN Trial (29)	SMART Trial (30)
Design	Multicenter, randomized, sham-controlled study.	Multicenter, randomized, sham-controlled study.	Multicenter, randomized, sham-controlled study.	Multicenter, randomized, sham-controlled study.	Multicenter, randomized, sham-controlled study.	Observational, prospective, open-label, single-arm registry.	Multicenter, randomized, sham-controlled study.	Multicenter, randomized, sham-controlled study.	Multicenter, randomized, sham-controlled study.
Sample size	337 patients	331 patients	146 patients	136 patients	224 patients	>3000 patients.	205 patients	217 patients	220 patients
Objective	Assess the efficacy of PRD in patients under antihypertensive treatment	Assess the efficacy of PRD in patients without antihypertensive treatment.	Assess the efficacy of US PRD in patients without antihypertensive treatment.	Assess the efficacy of US PRD in patients with antihypertensive treatment.	Assess the efficacy of US PRD in patients with stage 2 HTN under treatment with 0-2 antihypertensive drugs.	Assess the safety and efficacy of PRD in "real-world" patients.	Assess the safety and efficacy of PRD in hypertensive patients under treatment with two antihypertensive drugs.	Assess the safety and efficacy of PRD in hypertensive patients under treatment with triple pharmacological therapy.	Assess the safety and efficacy of a mapping system and selective PRD in hypertensive patients under dual pharmacological therapy treatment.
Primary endpoints	Change in average 24-hour ambulatory SBP with respect to baseline, at 6-month follow-up.	Change in average 24-hour ambulatory SBP with respect to baseline, at 3-month follow-up.	Change in average daytime SBP with respect to baseline, at 2-month follow-up.	Change in average daytime SBP with respect to baseline, at 2-month follow-up.	Change in average daytime SBP with respect to baseline, at 2-month follow-up.	N/A	Change in average office SBP with respect to baseline, at 6-month follow-up.	Change in average 24-hour ambulatory SBP with respect to baseline, at 6-month follow-up.	Asses the proportion of patients with office SBP ≤140/90 mmHg (non-inferiority). Difference in antihypertensive medication load
Results	Change in 24-hour ambulatory SBP: PRD -6.5 ±10.7 mmHg vs. sham -4.5±10.3 mmHg (p=0.12).	Change in 24-hour ambulatory SBP: PRD -4.7 mmHg vs. sham -0.6 mmHg (Δ -4.0 mmHg; p<0.001).	Change in daytime SBP: PRD -8.5±9.3 mmHg vs. sham -2.2±10.0 mmHg (p< 0.001).	Change in daytime SBP: PRD -8.0 (-16.4 to 0) mmHg vs. sham -3.0 (-10.3 to -1.8) mmHg (p=0.022)	Change in daytime SBP: PRD -7.9±11.6 mmHg vs. sham -1.8±9.5 mmHg (Δ -6.3 mmHg; p<0.001).	Change in office SBP: PRD -12.8 ±26.2 mmHg vs. baseline (p<0.001); 24-hour ambulatory SBP: PRD -7.2±17.8 mmHg vs. baseline (p<0.001).	Change in office SBP: PRD -25.2±13.9 mmHg vs. sham -6.2±12.5 mmHg (p<0.001).	Change in 24-hour ambulatory SBP: PRD-13.0±12.1 mmHg vs. sham -3.0±13.0 mmHg (Δ -9.4 mmHg; p<0.001).	Office SBP control percentage: PRD 95% vs. sham 93% (p=0.429, non-inferiority p <0.001). Less antihypertensive drugs (or lower dose) in the PRD subgroup vs. sham (Δ -3.3, superiority p =0.003).
Conclusions	Negative study, without significant difference in the primary endpoint.	Positive study, showing significant RF PRD benefit relative to sham.	Positive study, showing significant US PRD benefit relative to sham.	Positive study, showing significant US PRD benefit relative to sham.	Positive study, showing significant US PRD benefit relative to sham.	Positive study, showing significant RF PRD benefit sustained throughout time with high safety profile.	Positive study, showing significant RF PRD benefit relative to sham.	Positive study, showing significant RF PRD benefit relative to sham.	Positive study, showing feasibility, efficacy and safety of selective PRD.

HTN: hypertension; N/A: Not applicable; PRD: percutaneous renal denervation; RF: radiofrequency; SBP: systolic blood pressure; sham: simulated procedure; US: ultrasound

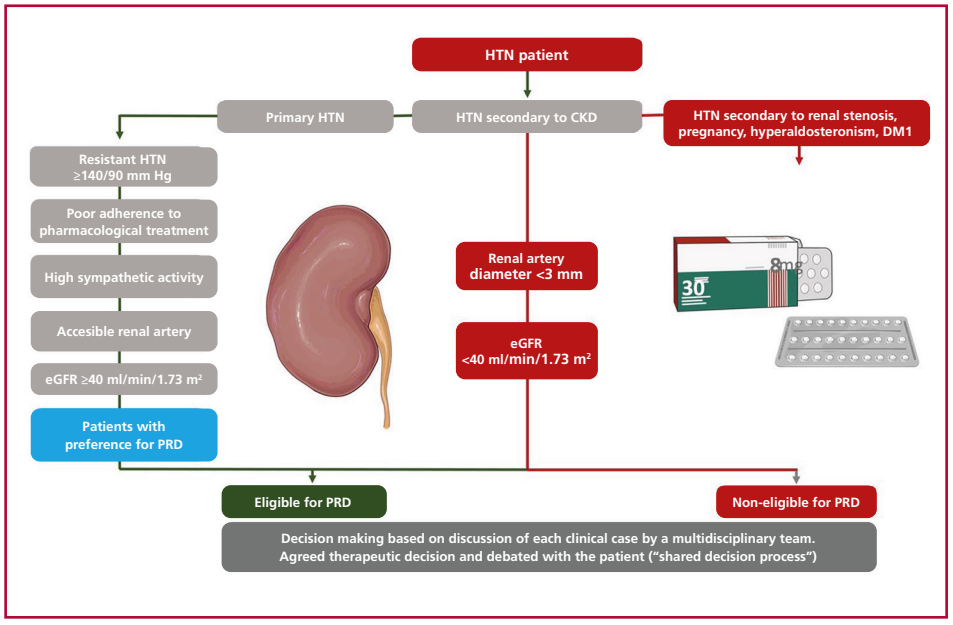

Fig. 1. Algorithm suggested algorithm for PRD indication as additional therapeutic strategy in hypertensive patients

CKD: chronic kidney disease; DM1: type 1 diabetes mellitus; eGFR: estimated glomerular filtration rate; HTN: hypertension; PRD: percutaneous renal denervation

suggests that this therapy produces a constant reduction in daytime and nighttime BP, which is known as the 'always-on' effect.(24) This contrasts with the pharmacokinetic profiles and dosage regimes of antihypertensive drugs, and also overcomes the challenges of pharmacological adherence, so their pharmacologic equivalence should not be considered a valid argument for its non-implementation.

The decision shared with the patient should not be underestimated. In both patients with intolerance to antihypertensive drugs and in those with a history of poor pharmacological adherence, PRD therapy is postulated as a valuable therapeutic option. Although this therapeutic alternative is commonly considered in our setting for patients with "refractory HTN", (25) evidence has shown that its prescription at earlier stages of the disease implies substantial clinical benefit.

CONCLUSIONS

Percutaneous renal denervation therapy is a safe and effective therapeutic strategy for selected hypertensive patients, which achieves an additional benefit to pharmacological medical treatment and reduces the number of associated adverse events, so we should consider it in our therapeutic arsenal based on the clinical judgement of a multidisciplinary team, and offer patients this option to participate in decision-making.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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ANTAGONIST

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Percutaneous renal denervation (PRD) has reemerged as a promising option for the treatment of resistant or refractory HTN. (1-3) However, beyond the efficacy that can be attributed in terms of BP reduction, better structured scenarios would be needed for its optimal indication.

In the current scenario, two main factors contribute to a still insufficient recommendation: low patient adherence to non-invasive antihypertensive treatment, and medical inertia or limited availability of resources. (4-7)

A provocative analogy that exemplifies this view might be to compare the need to prescribe parenteral feeding to a person who could eat by himself if provided with adequate food, a plate and cutlery.

Some of the main challenges that we consider to optimize the scenario and define the prominence of PRD are:

a) Challenge 1: **Pseudo-resistance**

Let us consider a possible situation: on the one hand, a patient with resistant HTN, and on the other his family doctor, who does not have the resources to rule out the causes of pseudo- resistance, such as lack of adherence to prescribed medications, secondary causes of hypertension, hemodynamic mechanisms, and dysautonomia.

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In this case, if PRD were an available treatment, would it be an appropriate option?

The answer should be negative; it would be preferable to improve access to non-invasive options with a better risk/benefit and cost/benefit equation with respect to PRD.

This is especially relevant if one takes into account that pseudo or apparent resistance may be present in 10 to 40% of patients considered resistant. (8,9)

b) Challenge 2: **The paradox of dysautonomia treatment**

A relevant and little explored aspect in the literature concerning renal denervation is simply the paradox of considering the invasive intervention of the autonomic nervous system, without having previously tried other non-invasive interventions. It is true that the treatment of dysautonomia may be less known and addressed in everyday medical practice compared with other more common conditions. (10) However, some of the causes of certain medical inertia in its diagnostic and therapeutic approach could be:

1. Low prevalence: although dysautonomia may be prevalent in certain populations (such as in people with diabetes, Parkinson's disease, or after a stroke), its frequency, compared with other more common diseases, can make it not a priority of continuous medical training and education, which gives rise to a significant low level of research, and limited centers where the diagnosis can be adequately addressed in situations such as HTN, since it is generally centralized in specialists in neurology or electrophysiology.

2. Complex diagnosis: accurate diagnosis of dysautonomia disorders can be challenging due to the variety of symptoms and the overlap with other medical conditions.

3. Lack of resources and specialization: assessment and management of dysautonomia may require specific resources, such as specialized autonomic function testing and collaboration with specialists in neurology or rehabilitation medicine.

4. Focus on specific symptoms: physicians may often focus on treating individual symptoms (such as hypertension or tachycardia) without recognizing dysautonomia as the underlying cause.

To strengthen this concept, the frequency of use of medications that affect the autonomic nervous system (for example, alpha 1 adrenergic antagonists, central alpha 2 adrenergic agonists) can be analyzed in our caseload of patients with resistant HTN. Given that PRD is an invasive treatment aimed at reducing sympathetic stimulation in HTN, it would have been logical to explore non-invasive interventions aimed at the same mechanism prior to its indication, to determine if a favorable result could be obtained with less intrusive resources when addressing this underlying mechanism in the patient's condition. (9)

Figure 1 proposes an ideal scheme for the evaluation of a patient with resistant HTN, before considering him for PRD. (11)

c) Challenge 3: **The absence of phenotyping**

In the main studies supporting the efficacy of PRD, the patient recruited for participation is stabilized for a few months with drugs that do not include direct effects on the autonomic nervous system. (12,13) This situation does not contribute to providing information about their phenotyping before and after the procedure. Patients with different degrees of dysautonomia may present significant alterations in autonomic control, which may influence BP regulation and the response to therapeutic interventions such as renal denervation. The efficacy of the procedure is different and not uniform in its magnitude or in its persistence in the follow-up among the included patients, so future studies are required on the possibility of stratifying the response, as is done in other clinical studies.

Assessing sympathetic nervous system function before renal denervation is crucial for several reasons:

1. Appropriate patient selection: allows identifying those patients whose HTN may be significantly influenced by sympathetic activity. Renal denervation may be more beneficial in these cases, since its main mechanism of action is to reduce sympathetic activity at the renal level.

2. Prediction of treatment response: evaluation of the sympathetic nervous system can help predict the probability that a patient will respond favorably to renal denervation. Those with elevated sympathetic activity may be more likely to benefit from the procedure.

3. Optimization of therapeutic management: before opting for an invasive treatment such as renal denervation, it is important to ensure that non-invasive treatments targeting the sympathetic nervous system have been exhausted and optimized. This may include medication and lifestyle changes, as well as other therapeutic interventions.

4. Reducing therapeutic inertia: identifying elevated sympathetic activity can help avoid therapeutic inertia, that is, the delay in escalating treatment when BP goals are not achieved with conventional medications.

d) Challenge 4: **Inconsistent research results**

Overall, the arguments underline the need for a critical and evidence-based evaluation of renal denervation as a treatment for resistant HTN, considering both the potential benefits and the possible risks and limitations of the intervention. The trajectory of research and the results obtained have had contradictions, but the most recent data are encouraging and bring renal denervation back into scientific analysis. (14) However, some points remain to be resolved:

1. Limited evidence of long-term efficacy.
2. Methodology and design of the studies.
3. Variability in results.
4. Therapeutic alternatives.
5. Potential risks and safety.

A design that could provide answers in the future, and be welcomed in the medical community, would

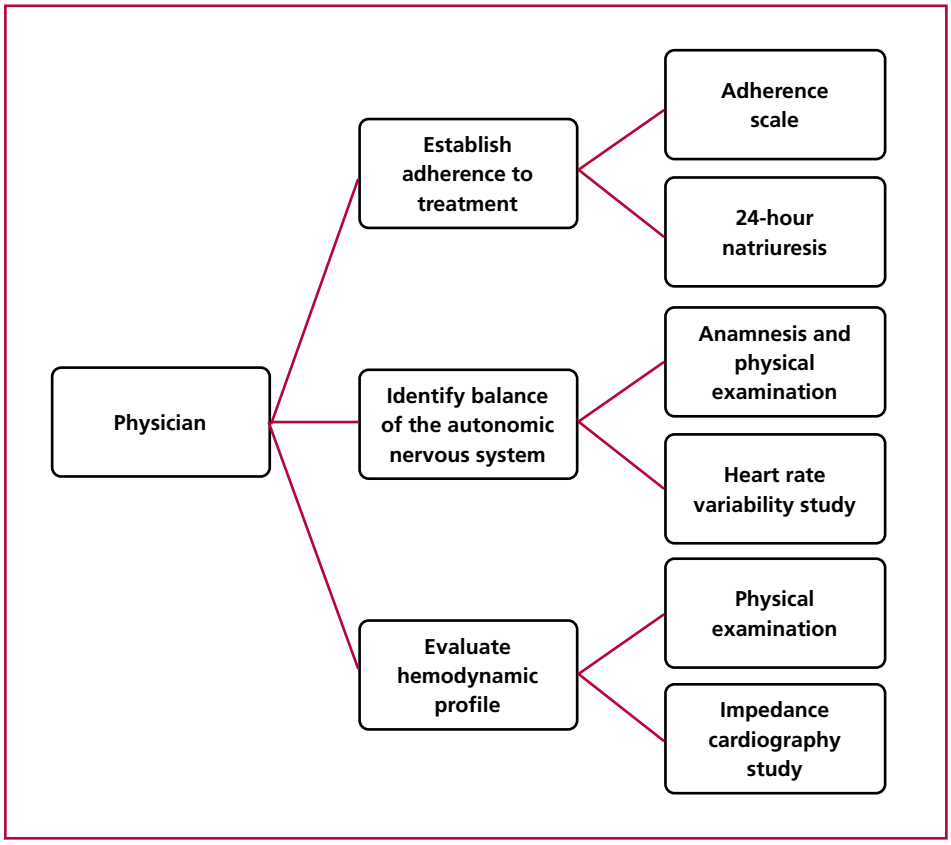

Fig. 1. Evaluation of patients with resistant arterial hypertension.

consist of randomly assigning patients with resistant HTN to compare PRD with traditional pharmacological treatment, together with drugs that directly modulate the autonomic nervous system. In addition, evaluation of PRD efficacy compared with an intensive healthy lifestyle strategy, and monitoring adherence in both groups, could be considered, among other possible options.

e) Challenge 5: **Is the expectation greater than the result?**

The average SBP reduction achieved in 24-hour ambulatory monitoring is approximately 6 mm Hg, as reported in new randomized clinical trials. This value, undoubtedly significant in terms of risk and event reduction, is equivalent to that of an antihypertensive medication.

A favorable point of view would assume that it is a curative treatment, but in fact it is not, since it is necessary to continue with pharmacological treatment after PRD, though at lower doses and perhaps fewer drugs. From a pessimistic point of view, it is still a potentially replaceable invasive intervention with better patient adherence.

Moreover, in pharmacological studies we demand evidence of event reduction, which have not yet been reported in renal denervation studies, that only have modeling of the possible decrease in events associated with a drop in BP. (15)

CONCLUSIONS

To conclude, the context on which decision-making is based regarding the efficacy and indication of PRD for the treatment of HTN is constantly evolving and shows clear potential. However, there are some relevant considerations that still need to be addressed for greater generalization of this intervention:

- Data are required on the direct impact of PRD on the reduction of cardiovascular events, as required from pharmacological studies.
- It is crucial to implement resources that allow evaluating the patient's adherence to sodium intake restriction by determining 24-hour natriuresis. Available evidence suggests that this measure can achieve a similar or even greater reduction in SBP compared with renal sympathetic denervation.
- Strategies to evaluate the patient's response to non-invasive treatments that modulate the autonomic nervous system are necessary before considering invasive treatment. This premise should be applied both in daily clinical practice and in research studies.
- Propose predictive scores for the response to PRD, allowing a more precise selection of candidate patients.

Finally, the perspective of PRD acceptance and the most recent data is still divergent. While in the

United States no PRD device has yet been authorized by the FDA (Food and Drug Administration), in Europe the strategy is gaining ground and raises the possibility of treating in a similar way patients with non-resistant HTN, unlike the original indications of the technique limited to rescue cases for those with resistant HTN. Interestingly, a study conducted in Germany with 1000 patients with HTN revealed that 25% would prefer to undergo PRD rather than use a drug. (16) These considerations are crucial to advance in the understanding and effective application of PRD in the management of HTN, ensuring more personalized and evidence-based care for patients.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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AGONIST REPLY

First of all, I congratulate Dr. Kotliar for the strength and clarity of her presentation. At the end of the reading, the concepts of "poor adherence", "medical inertia" and "dysautonomia" were prominent. I fully agree that poor adherence to pharmacological treatment is an area for improvement, but I disagree that the strategy of percutaneous renal denervation (PRD) should be considered only when others have failed, which would position it as an "alternative" rather than a "complementary" strategy. Not only does this remind me of the previously mentioned "medical inertia" (probably due to limited knowledge of the technique), but it also fails to consider the additional advantages of PRD, such as the 'always-on' phenomenon, and its potentially greater benefit when implemented at earlier stages in selected patients.

I agree that the pseudo-resistance mentioned by Dr Kotliar is a frequent phenomenon in clinical practice. However, it is important to note that there is scientific evidence to support PRD as a highly cost-effective strategy in patients with resistant hypertension, especially when implemented in early stages. In addition, I would like to point out that the global acceptance of PRD differs from that mentioned by Dr Kotliar. Currently, devices such as the Symplicity Spyral (Medtronic) and Paradise (ReCor) have been approved by the FDA (US Food and Drug Administration), and many others are CE (Conformité Européenne) marked, allowing their use in the treatment of resistant hypertension. Although more clinical evidence is still required to demonstrate a reduction in adverse clinical events associated with this therapy, there is abundant evidence on its safety profile. Therefore, we should not discard this option from our therapeutic arsenal, and it would be prudent to discuss it with our patients, considering their individual preferences.

Dr. Cristian M. Garmendia

ANTAGONIST REPLY

The agonist argumentation is certainly a valuable contribution that lists and describes the main results and trajectory of the available research. I certainly agree with the points that will hopefully be clarified in future studies.

However, in my view, I do not consider that we are in a position to consider PRD as an "additional treatment" for the management of resistant HTN. I base this on the fact that in none of the studies mentioned in the agonist position have all the necessary diagnostic requirements been fulfilled to "adequately" determine the condition of true resistance: for example, natriuresis to verify adherence to sodium intake restriction, evaluation of the correct intake of the indicated medications, among others.

On the other hand, international recommendations include non-invasive hemodynamic study in the management of resistant HTN, if available. In a study of the magnitude of those conducted to evaluate the effectiveness of different PRD catheters, it would be expected that more accurate and comprehensive information on hemodynamic and autonomic activation patterns would be available, in order to determine whether the patient's pharmacological treatment is the most appropriate before opting for invasive treatment.

Dr. Carol Kotliar

SCIENTIFIC LETTER

Dilated Cardiomyopathy and Duchenne Muscular Dystrophy

Miocardiopatía dilatada y distrofia muscular de Duchenne

MARIELA K. HUERTAS[1], PAMELA L. MORA[1], NICOLÁS A. MENICHINI[1], JUAN P. LESTARD[1]

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder that affects the expression of a protein essential for the stability of muscle fibers producing myocyte inflammation and death. Cardiac involvement is one of the main causes of morbidity and mortality in these patients. Most patients are asymptomatic or present with minimal symptoms because they self-limit their physical activity. (1,2) Cardiac involvement is characterized by progressive left ventricular dysfunction that progresses to dilated cardiomyopathy with subsequent heart failure, arrhythmias and sudden cardiac death.

We report the case of a 24-year-old male patient, with a history of muscle weakness, who visited the emergency department due to symptoms consistent with acute abdomen. The vital signs were normal. The physical examination showed a positive Murphy's sign. The ECG showed sinus rhythm, with poor R wave progression in precordial leads. The laboratory tests reported high white cell count and bilirubin levels. On abdominal ultrasound the gallbladder was distended and presented wall thickening. An 8.8 mm stone was observed in the infundibulum of the gallbladder and there was a 5.6 mm stone inside the gallbladder. The patient was admitted to the department of general surgery with a diagnosis of acute cholecystitis. He underwent laparoscopic cholecystectomy 48 hours later, with favorable outcome and was discharged 24 hours later.

Thereafter, after having visited the emergency department on two occasions due to lower extremity edema, he was admitted for diagnosis and monitoring with a clinical diagnosis of acute heart failure. A transthoracic echocardiography showed dilated cardiomyopathy with severe ventricular dysfunction, left ventricular ejection fraction (LVEF) of 29% with global hypokinesis. The patient was admitted to the coronary care unit (CCU) for further workup and treatment. During hospitalization, the patient reported a family history of Duchenne muscular dystrophy (DMD) and that he had undergone genetic diagnosis and muscle biopsy when he was 6 years old, which confirmed the diagnosis. However, the disease was irregularly followed-up and he had not been medicated.

The indications in the CCU included negative fluid balance, levosimendan pulses and complete medical treatment for advanced heart failure. During hospitalization an echocardiogram was performed with measurement of ventricular strain (-14%). There were no coronary artery lesions on coronary computed angiotomography with coronary calcium scoring. Cardiac magnetic resonance imaging (MRI) with gadolinium-based contrast agent demonstrated dilated cardiomyopathy with mid-myocardial delayed enhancement pattern involving the junction site between the right and left ventricular myocardium and anteroseptal and inferoseptal segments, and subepicardial enhancement of the anterolateral and inferolateral segments, a pattern also described in other entities such as idiopathic dilated cardiomyopathy and myocarditis. In addition, a 24-hour Holter monitoring was ordered, which only evidenced infrequent atrial premature contractions. After six days of hospitalization, the patient was discharged with indication for referral to a heart transplant center on an outpatient basis.

One month later, the patient was hospitalized in a high-complexity center. As his clinical condition worsened, he was included on the emergency waiting list for transplantation. After being hospitalized for five months, the patient required ventricular assist device and remained on the emergency waiting list. Finally, heart transplantation was successfully performed, and the patient was discharged twenty-three days later. He is currently on post-transplant care

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Fig. 1. Color Doppler echocardiogram performed during hospitalization showing a LVEF of 29% (A) and mild tricuspid regurgitation (B); coronary computed angiotomography: the left anterior descending coronary artery has no lesions (C).

Fig. 2. Cardiac magnetic resonance imaging with gadolinium-based contrast agent showing mid-myocardium delayed enhancement pattern involving the junction site between right and left ventricular myocardium and anteroseptal and inferoseptal segments, and subepicardial enhancement of the anterolateral and inferolateral segments.

and kinesiotherapy and receives genetic counseling with his family (mother and sister).

Becker muscular dystrophy and DMD are the most common muscular dystrophies in humans. They are X-linked genetic disorders with deletion, duplication and mutations of exons encoding for dystrophin, a protein that plays a role in the stabilization and signaling between myocyte membrane, extracellular matrix and cytoskeleton. While the genetic abnormality in Becker dystrophy consists of decreased expression of this protein or abnormal size, dystrophin is still functional. (1, 3) In DMD, the genetic involvement leads to absence of expression, or expression of a non-functional protein, so it usually has a worse prognosis with a life expectancy of three decades. The latter variant of dystrophy is also the most common, with a prevalence of around 5 per 100 000 males and an incidence of 1 per 3800-6300 live-born males. (4)

Since the cardiac condition is due to an inherited myopathy, the therapeutic possibilities are limited. For the genetic analysis of our case we used the CTAB method, the DNA was analyzed by multiplex and simplex PCR to specifically find deletions, because of the loss of one or several exons of the dystrophin gene. Genomic deletion of exons 45 and 47 was detected, confirming the diagnosis of inconclusive muscular dystrophy: Duchenne/Becker.

Currently there are no clinical data or scientific evidence to support therapy, so each particular case should be evaluated by a Heart Team when considering heart transplantation, because although this is the standard of care for refractory heart failure, it is usually not recommended in patients with DMD because of comorbidities that limit the benefit. (1) However, there are case reports showing a favorable outcome in these patients.

DMD is a genetic, progressive, disabling and fatal disease that affects the skeletal muscle and requires early diagnosis, genetic counseling and the crea-

tion of a multidisciplinary team for treatment and comprehensive follow-up. The scope of this disease involves genetics and personalized medicine in the search of tailored treatments, although there is no definite treatment or cure yet. The clinical manifestations of heart failure occur in the end stages of the disease, therefore strict monitoring and follow-up is essential. (1,4-6)

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

(See conflicts of interest forms on the website).

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REVIEW ARTICLE

Carotid Dolichoarteriopathies: A Comprehensive Overview

Dolicoarteriopatías carotídeas: un enfoque global

PABLO A. IOMINI[1], RICARDO BEIGELMAN[2 MTSAC], GIUSEPPE AMBROSIO[3], ANDRÉS IZAGUIRRE[2, MTSAC], JOSÉ MILEI[2, MTSAC]

ABSTRACT

Carotid dolichoarteriopathies (CDA) represent a group of morphological abnormalities, with changes in the geometry and tortuosity of the carotid arteries. They were described in 1925 for the first time and were classified in three types according to the angle of torsion, in tortuosity (angle > 90°), coiling (S-shaped curve or loop) and kinking (angle < 90°). The pathophysiology of CDA is controversial and includes congenital mechanisms, genetic factors, connective tissue diseases, acquired mechanisms which can be associated with but not dependent on cardiovascular risk factors, and anomalies of the cervical spine.
CDA have been associated with different cardiovascular and cerebrovascular events secondary to hemodynamic abnormalities, thromboembolism and cerebrovascular insufficiency and ischemia. However, the evidence is limited and for some authors they are more of a curiosity than a real predictor of ischemic events. Other studies support the clinical value of the diagnosis and follow-up of CDA and their understanding not only by internists, cardiologists and neurologists, but also by surgeons and otolaryngologists. Several authors proposed different therapeutic strategies to correct CDA, including surgical procedures. However, the indications and management approaches are controversial, and further randomized, multicenter, prospective studies are required to determine the most appropriate course of action. Until then, imaging techniques remain the basis for the etiologic diagnosis of cerebrovascular adverse events when all other causes have been excluded, and close clinical monitoring and follow-up of patients remain key strategies for the prevention of secondary events.

Keywords: Dolichoarteriopathies - Tortuosity - Carotid Arteries - Vessel Abnormalities - Cerebrovascular Disease - Cardiovascular Risk Factors

RESUMEN

Las dolicoarteriopatías carotídeas (DAC) son un grupo de anomalías morfológicas, con alteración de la geometría y torsión de los vasos carotídeos. Descriptas por primera vez en 1925, las DAC fueron clasificadas en tres tipos, según el grado de torsión: tortuosidad (ángulo mayor de 90°), enrollamiento o coiling (forma de S o looping), y acodamiento o kinking (ángulo menor de 90º). La fisiopatología de las DAC es controvertida, pero se han propuesto mecanismos congénitos, genéticos, enfermedades del tejido conectivo, adquiridos, relacionados con, pero no dependientes de, factores de riesgo cardiovascular, y alteraciones de la columna cervical.
Las DAC han sido asociadas a diferentes eventos cardio y cerebrovasculares, secundarios a alteraciones hemodinámicas, tromboembolismo e insuficiencia e isquemia cerebrovascular. Pero la evidencia es limitada y, para algunos autores, son más una curiosidad que una condición clínica grave. Otros trabajos sustentan el valor clínico del diagnóstico y seguimiento de las DAC, y su reconocimiento no solo por internistas, cardiólogos y neurólogos, sino también por cirujanos y otorrinolaringólogos. Varios autores propusieron diversas estrategias terapéuticas, incluyendo procedimientos quirúrgicos para corregirlas. Sin embargo, las indicaciones y métodos de tratamiento son controvertidos, y son necesarios más estudios aleatorizados, multicéntricos y prospectivos para determinar cómo proceder. Hasta entonces, técnicas de imagen son la base para el diagnóstico etiológico de eventos adversos cerebrovasculares cuando se descartan todas las otras causas, y el control clínico cercano y seguimiento de los pacientes continúan siendo estrategias clave para la prevención de eventos secundarios.

Palabras clave: Dolicoarteriopatías - Tortuosidad - Arterias carótidas - Anomalías de los vasos - Enfermedad cerebrovascular - Factores de riesgo cardiovascular

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INTRODUCTION

Carotid artery atherosclerosis is the most common cause of extracranial carotid artery disease and is one of the leading causes of cerebrovascular disease (CVD) and death, (1,2) constituting the predominant etiology of CVD in Western countries. (3) However, other non-atheromatous causes of carotid disease are also related with CVD such as fibrodysplasia, Takayasu disease, and aortic dissection. (1, 4) Dolichoarteriopathies (from the Greek δόλιχος, dolichos, "abnormally long") have recently attracted the attention of specialists and are included within non-atheromatous carotid artery diseases. Carotid dolichoarteriopathies (CDA) have been associated with a wide range of CVD, including stroke and transient ischemic attack (TIA). (1) However, their clinical significance remains unclear. (1) This article reviews the main aspects of CDA, focusing on its pathophysiology, diagnosis, prognosis, and treatment.

METHODS

We conducted a non-systematic review and selected the most relevant papers on this topic. PubMed, Scielo, and Scholar Google electronic databases were searched using the terms "dolichoartheriopathies," "carotid dolichoartheriopathies," "arterial tortuosity," "dolichoectasia," and their equivalents in Spanish.

RESULTS

Definition, classification and epidemiology

CDA are anatomical anomalies that result in a change in the geometric arrangement of the carotid vessels along their course, that causes coiling, kinking, and tortuosity. (1, 5) Some authors include them within the group of dolichoectasias (vessel elongation, tortuosity and/or dilatation). (6) First described by Kelly in 1925, (7) CDA were classified by Weibel and Fields, (8) in three groups (Figure 1):

- Type I or tortuosity: any S-shaped or C-shaped elongation or undulation of the course of the artery with an angulation >90°.
- Type II or coiling: the internal carotid artery forms an exaggerated, redundant S-shaped curve or its longitudinal axis makes a complete circle (360°).
- Type III or kinking: Angulation of one or more segments of the artery, with an angle < 90°.

Metz et al. sub-classified kinking based on the value of the acute angle between the two segments forming the kink in group I (between 90° and 60°, Figure 2, Panel A), group II (between 60° and 30°, Figure 2, Panel B) and group III (>30°, Figure 2, Panel C). (9)

CDA are common, with a reported prevalence of 10-45%. (10) Beigelman et al. (1), and Ghilardi et al. (11) made the diagnosis of CDA in 13.3-31% of the

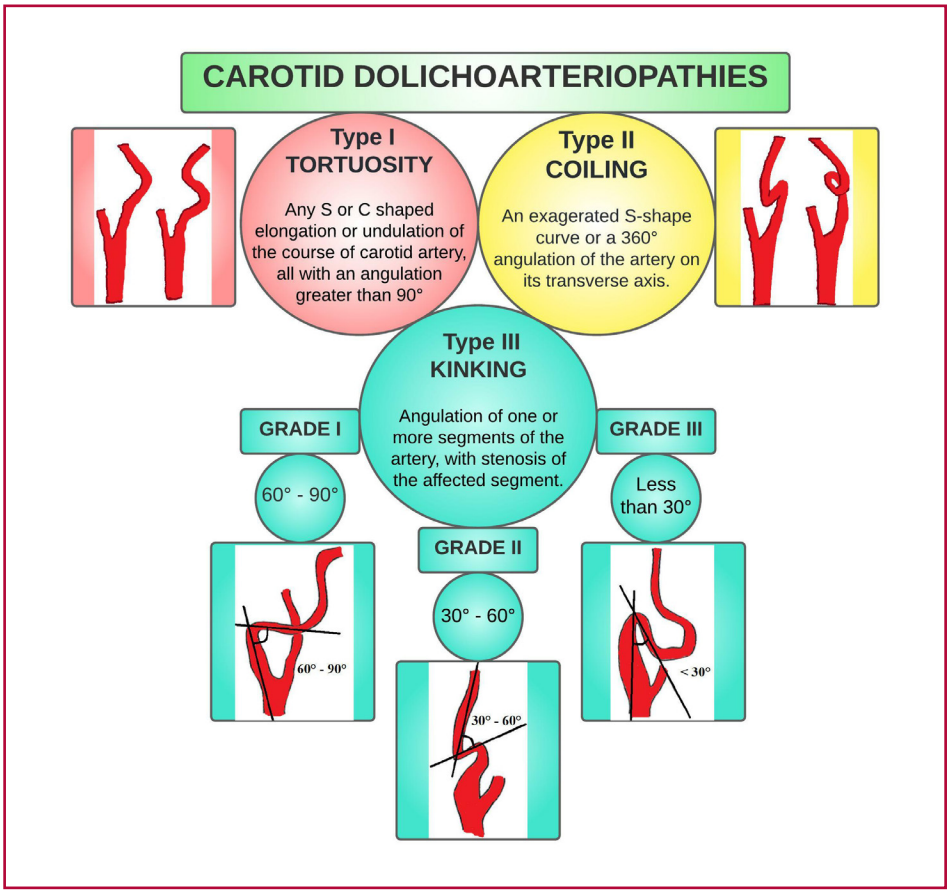

Fig. 1. Classification of carotid dolichoarteriopathies diagram combining the Weibel-Fields and Metz classifications. The Weibel-Fields classification diagram has been modified from Reference #41. The Metz classification illustration has been modified from Reference #5

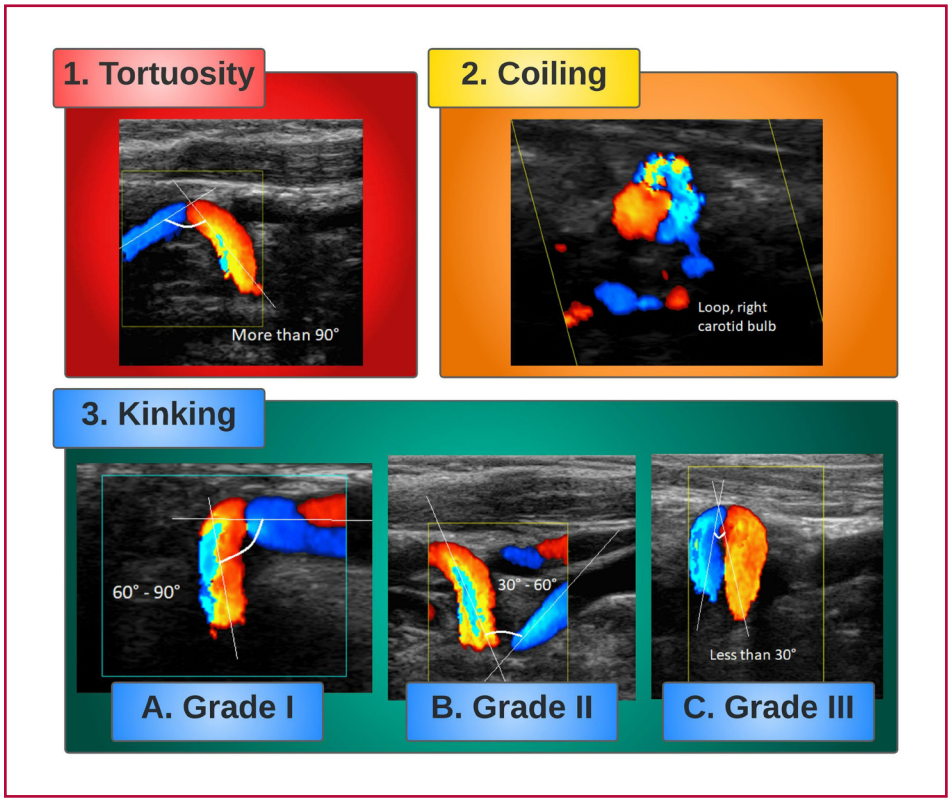

Fig. 2. Images of different types of carotid dolichoarteriopathies obtained with color Doppler ultrasound. The angle between each part of the artery is drawn with white lines and described in the corresponding image.

cases, while in studies conducted in hospitalized patients, the prevalence ranged between 13.5% and 58%. (6) They are more prevalent in women and elderly patients, especially those > 60 years, and can be unilateral or bilateral, affecting the common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA), but more commonly the ICA, especially on the left side. (12,13) Tortuosity and kinking are more common than coiling. (1, 12)

Pathophysiology

The development of CDA has been linked to several mechanisms, although there is still some debate about the exact causes. A key question is whether they are congenital or acquired and whether they are related to atherosclerosis or other cardiovascular risk factors. Some studies shed light on the subject.

A. Embryology

The cerebral vasculature begins to develop early in the embryo, during the third week of intrauterine life, with the formation of the aortic arches (AA). (13,14) There are six pairs of AA connecting the ventral aorta (VA) to the dorsal aorta (DA). (14, 15) Each AA arises from the bulbus arteriosus, and courses in its corresponding pharyngeal arch to end in the DA. (14) The first and second arches regress, and their remnants from the VA and DA persist as incipient ICA and ECA. The ICA merges bilaterally with the third AA, while the ventral aortic root between the third and fourth arches persists as the CCA. (15) There is considerable variability in the course and position of the CCA and carotid bifurcations. Elongation of the CCA and ICA results in tortuosity and kinking. (16) The position of the carotid bifurcation reflects the degree of embryologic migration of the ECA and is variable. (16) Huber et al. reported the position of the carotid bifurcation at C4 to C5 in 48% and at C3 to C4 in 34% of 658 bifurcations. (17) There are cases described of bifurcations from T3 to C2. (18) In children, bifurcation position from C2 to C3 was observed in 40% of cases and from C3 to C4 in 40% of cases. (19) Carney et al. found tortuosity in 5 of 20 fetuses of ages ranging from 5 months to full term. (20) Harrison et al. suggested that the development of carotid arteries and skeletal system might be asynchronous, causing changes and tortuosity in the course of the artery. (21) Beigelman et al. studied a population of 885 individuals ranging from newborns (4 hours 30 minutes) to 90 years. The study population was divided into two groups: a control group of 245 individuals (children and adolescents up to 15 years old) and another group of 640 individuals (16-90 years old) in whom diagnostic color Doppler ultrasonography of the neck vessels had been requested because of clinical suspicion of atherosclerotic vascular disease. The incidence of coiling and kinking was similar in both groups. The presence of atheromatous

plaques in tortuous arteries was only observed in 3 group 2 patients. The authors found a lack of correlation with other cardiovascular risk factors, and of the site of carotid artery plaques with CDA. (1)

B. Genetic and molecular disorders

Voevoda et al. examined 61 families of children with previously diagnosed ICA dolichoarteriopathy using color Duplex ultrasound. The group comprised 100 individuals with ICA dolichoarteriopathy. Control group (n=245) was formed from DNA bank based on a population approach. The authors found an association between A80807T polymorphism of the transcriptional factor Sp4 gene and CDA. (22) Zaidi et al. reported the case of a consanguineous Kurdish family whose child had severe elongation and tortuosity of the aorta, carotid and other arteries, along with other changes (loose skin, joint hypermobility, hernias, and facial features resembling Ehler-Danlos syndrome [EDS]). By homozygosity mapping, they found evidence of the involvement of the locus at chromosome 20q13 in the affected child. (23) Arslan et al. observed significantly higher matrix metalloproteinase-2 (MMP-2) levels in patients with CDA compared to the control group. The expression of MMP-12 was higher in those with atheromatous plaques than in those without atherosclerosis. (24)

C. Connective tissue diseases (CTD)

Foiadelli et al. reported the case of 7 children with EDS between 3 and 13 years of age, with CDA and variable clinical manifestations. (25) Welby et al. evaluated 286 patients divided into control group and CTD group. The presence of CDA was 44% in the second group, and 16% in controls ($p < 0.001$). Coiling was more prevalent. The prevalence of CDA was 88% in Marfan syndrome, 63% in Loeys-Dietz syndrome, 42% in neurofibromatosis type 1, and 19% in patients with both vascular and nonvascular types of EDS. (26)

D. Association with other congenital diseases

According to Paltseva et al., CDA have higher elastin levels but with fiber fragmentation, higher MMP-9 expression, and lower smooth muscle actin expression. (27) Ballotta et al. analyzed 78 carotid arteries with dolichoarteriopathy and found typical and atypical patterns of fibromuscular dysplasia (FMD). (28) Sethi et al. found a significantly higher prevalence of CDA with S-shaped curve in patients with FMD. (29)

Ballota et al. analyzed 43 patients with asymptomatic abdominal aortic aneurysm (AAA) and CDA and found degenerative dysplastic changes in the tunica media in all carotid specimens; in a few cases, nonobstructive atherosclerotic intimal lesions were superimposed. The histologic features of classic AAA (thinning of the media underlying the atherosclerotic plaque) were observed in almost all aortic wall specimens, suggesting underlying connective tissue disorders in both conditions. (30)

E. Acquired mechanisms

Harrison et al. suggest that CDA may be due to kyphosis or lordosis, which would deviate the carotid axis. (21) For Etheredge et al., inflammation of the pericarotid tissues would cause retraction of the carotid arteries and deviate them from their path, resulting in tortuosity. (31)

Ghilardi et al. and Del Corso et al. describe a high prevalence of hypertension (HTN) and atherosclerosis in patients with CDA. (11, 32) However, both studies lacked a control group of normal subjects and addressed only a population selected because of vascular disease, in which these cardiovascular risk factors are expected to predominate. For Khasiyev et al., because CDA also show dilatation, compensatory external remodeling in response to atherosclerosis may play a role in this phenotype. (6) Dilatation of the carotid arteries may also be a sign of connective tissue weakness of a non-atherosclerotic nature. Pancera et al. found a statistically significant association between kinking and HTN, and also between HTN and kinking with a greater degree of bending. (33) Oliviero et al. analyzed the prevalence of CDA in patients with HTN and diabetes. The prevalence of CDA was significantly higher in the group of hypertensive patients than in diabetics and controls and was also associated with the duration of hypertension. (34) The eccentric forces related to HTN and possibly artery aging with stiffness may play a role in ICA dilatation and, thus, in the development of CDA. (6)

Wang et al. evaluated the association between body mass index (BMI) and CDA. They analyzed 513 patients without CTD using the tortuosity index (TI) expressed as a percentage, calculated as the ratio between the actual length of the ICA (AL) and the length measured from the carotid bifurcation to the base of the skull, called the cord length (CL):

$$TI = [(AL/CL) - 1]*100$$

Male sex and BMI were significantly correlated with the TI. For each increase in BMI of 1 kg/m2, there was a 1.59-fold increase in the risk of developing CDA. (35) Dilba et al. used the same index in a population of the Plaque At RISK study and concluded that age, obesity and hypercholesterolemia were associated with higher TI. They also found higher prevalence and severity of CDA in the left ICA. Higher BMI and CDA could be due to high intra-abdominal pressure which may result in an upward shift of the diaphragm and a rise of the mediastinum. This would push up the carotid arteries, which, surrounded by lax connective tissue, can slip and become tortuous. Because the brachiocephalic artery "absorbs" part of the lifting force, the right ICA develops less severe tortuosity than the left. Thus, repeated and prolonged exposure to periods of high and low flow results in stress that affects arterial remodeling and causes tortuosity. (36)

Derubertis et al. observed a higher prevalence of

CDA in previously irradiated patients. Radiation can cause retraction and alteration of the connective tissue, resulting in tortuosity of the artery. (37) Saba et al. analyzed a population of 124 patients with ICA dissection diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) and found a statistically significant association between dissection and kinking and coiling. (38) Barbour et al. found a significant association between spontaneous ICA dissection and tortuosity, particularly if tortuosity is present bilaterally. (39) Some authors propose that changes in hemodynamics might lead to the local disruption of the endothelial integrity which trigger inflammation that can modify the structure of the vessel, and the release of inflammatory agents might predispose to carotid dissection. (6)

Diagnosis

A diagnosis of CDA can be made by many imaging tests. Ultrasound seems to be the gold standard. (1,2,6) The turbulent blood flow inside the tortuous vessels can be evaluated with Doppler scanning. (40) Di Pino et al. studied the prevalence of dolichoarteriopathies of the ICA using color Doppler ultrasound in 2856 subjects (0-96 years) and demonstrated peaks of prevalence distributed in a bimodal fashion (< 21 years and > 60 years). CDA were detected in 9.9% of participants. This study was one of the first to use ultrasound in a large cohort. (41) Uchino et al. reported a case of CDA diagnosed by computed tomography (CT) angiography and single photon emission computed tomography (SPECT). Both tests better defined the morphology of ICA tortuosity and secondary perfusion abnormalities. (42) In other studies, CT allowed the evaluation of subtle abnormalities, such as microaneurysms, and 3D reconstructions of CT appear to be more effective in classifying morphological variations of the ICA and detecting these anomalies. (43-45) Balevi et al. found a prevalence of CDA of 40.3% in the general population using contrast-enhanced magnetic resonance angiography (MRA). (12) Tomiya et al. performed MRA in 13 patients and obtained very clear images of CDA. (46) Yu et al. believe that MRA is a good option for the diagnosis of CDA. Digital subtraction angiography (DSA) remains the gold standard for the diagnosis of cervical and intracranial vascular disease, could provide hemodynamic data and show the morphology of CDA in detail, but cannot determine the pathological changes of the arterial wall of the ICA. (40) It would serve as a complementary imaging test in the study of CDA rather than a useful imaging test for diagnosis. All these techniques are valid and not mutually exclusive and should be chosen in order of increasing complexity and invasiveness to make a correct diagnosis.

Clinical implication

The clinical implication of CDA is controversial. There is limited evidence to support the association between CDA and CVD. (6) Yin et al. observed a higher incidence of white matter lesions in patients with CDA compared to controls. The severity of these lesions was directly related to the number of kinks. (47) Other authors argue that ischemic disease is more common in people with CDA and other cardiovascular risk factors. Pancera et al. found a significant association between kinking and TIA. Hypertension and CDA could be additive risk factors in the pathophysiology of TIA. (33) Oliviero et al. demonstrated that the presence of carotid kinking in hypertensive subjects may not be considered a further risk factor for ischemic events. (48) But, as Pancera et al. state, the addition of risk factors to the presence of CDA may increase the risk of vascular events. (33) Iwai-Takano et al. observed an association between CDA and aging, HTN and sex, but not with dyslipidemias, diabetes or smoking. (49)

Those who consider that CDA are harmful believe that kinking in the ICA, in addition to causing luminal narrowing and endothelial lesions, can create turbulent blood flow that can lead to a prothrombotic state. For others, as Balevi et al., CDA are more a curiosity than a real predictor of ischemic events. (12) Valvano et al. believe that there is no association between CDA and CVD. (50) CDA can cause cerebral hypoperfusion that produces encephalopathy, vertigo, diplopia, TIA or infarction. (40) The prevalence of cerebrovascular symptoms in patients with CDA varies between 15 and 23%. (51) Coiling is not considered a risk factor for ischemic events due to its weak association with symptoms, as opposed to kinking which might be associated with symptoms which most commonly appear due to transitory hypotension during sleep or sudden and extreme movement of the head and neck. (40) Other symptoms observed are visual impairment as amaurosis fugax, uveitis, retinitis and macular dystrophy. (52) Severe cases of CDA can produce mass effect, resulting in dysphagia, dyspnea, upper airway obstruction and obstructive apnea, and, more rarely, pulsatile tinnitus and hemilingual spasm. (40, 53, 54)

In the Northern Manhattan Study (NOMAS), Khasiyev et al. analyzed the relationship between CDA and biomarkers of atherosclerosis in 558 participants and found an association between CDA and diastolic blood pressure and larger aortic root diameter, but not with other markers of atherosclerosis. Determining the risks of vascular events associated with this non-atherosclerotic phenotype may help for a better risk stratification for individuals with CDA. (55)

Beigelman et al. investigated the genesis of neurological complications associated with CDA. Sixty patients with CDA without atherosclerosis underwent head rotation tests and color Doppler ultrasound of the ICAs and ophthalmic arteries with evaluation of flow velocities. The results suggested that CDA do not cause neurological abnormalities or symptoms, as no events were recorded during the test, and a significant reduction in the velocities in the ophthalmic artery was observed in only 3 of 60 cases. (56)

Wang et al. analyzed the blood pressure changes caused by CDA in 12 patients using DSA. They measured the angle of kinking by rotational angiography and calculated the blood pressure at the proximal, kinking and distal sites of the ICA using a microcatheter. These results were compared with two simulation models. A numerical simulation model was constructed with a software based on a geometric model of a tortuous ICA. An in vitro fluid simulation model was built using a silicone tube with different kinking angles. Water flowed through the silicon tube via a peristaltic pump. The software simulation showed a linear drop in blood flow pressure with decreases in the kinking angle. The pressure drop was the smallest at the kinking angle of 180° and was the largest at 30°. However, a reversal occurred between the kinking angles of 30° and 20°; the increasing kinking degree led to a smaller pressure drop. This was confirmed in the in vitro experimental system. When the flow rate was constant, the pressure drop decreased with increasing kinking angle, but the pressure drop increased when the kinking angle increased from 20° to 30°. However, these findings did not correlate with clinical observations: the clinical tests performed on patients showed greater pressure drops when the kinking angle was < 30°, and severe kinking induced an average decrease of 15.5% in blood pressure. The development of the reversal of greater pressure drops with increased kinking angles from 20° to 30° was not observed in the clinical measurements. This was attributed to excessive elongation and stenosis of the ICA in cases of severe kinking. And although the pressure drop changed gradually in the simulation models, it decreased rapidly in clinical measurements when the angle was < 45º but was more gradual with higher angles. This behavior could be caused by the characteristics of the medium (blood is a non-Newtonian fluid), and the elastic walls of the ICA. Both factors can contribute to the self-regulatory mechanism of blood flow. (57) This was one of the first studies to evaluate these aspects of CDA by comparing clinical and artificial observations with direct measurements of ICA pressures. These results show that blood pressure and blood flow abnormalities may be responsible for the interruption of cerebral perfusion, resulting in ischemia and thus cerebrovascular events.

Some authors observed an association between CDA and aneurysms in the context of CTD. (26) The positive predictive value of the combination of aortic aneurysm and CDA associated with CTD was 95.4% with a specificity of 98.6%. Increased tortuosity index in the aorta and vertebral artery is an independent predictor of aortic dissection in patients with Marfan syndrome. Thus, in patients with CTD, CDA can indicate the presence of clinically significant aneurysms. (6, 26, 40)

Dolichoarteriopathies have been associated with increased morbidity and mortality in head and neck surgery. This risk was recognized in the studies by Weibel and Fields (8) and Metz. (9) Nayak et al. emphasize the importance of evaluating the morphology of the carotid arteries prior to pharyngeal procedures, as they can be complicated by vascular injury, bleeding, and in severe cases, death due to massive hemorrhage. (58) For this reason, it is essential to thoroughly examine the carotid arteries before performing any procedure in the neck.

Treatment

Despite the controversy about the clinical implications of CDA, some indications have been developed to manage them according to the degree of hemodynamic involvement of the tortuosity, among other parameters. Gavrilenko et al. (59) proposed treating CDA under the following conditions:

1. ICA stenosis ≥ 60% with atherosclerotic plaques and any degree of cerebrovascular insufficiency; or
2. ICA stenosis < 60% with atherosclerotic plaques, a moderate to severe degree of cerebrovascular insufficiency in combination with tortuosity, a linear blood flow rate ≥ 110 cm/s and a turbulent blood flow.

Grego et al. (60) proposed specific indications for surgery:

a) TIA (hemispheric symptoms);
b) Asymptomatic patients with kink angle < 30°, with contralateral carotid artery occlusion;
c) Patients with non-hemispheric symptoms after a screening to exclude all other possible neurological or non-neurological causes with: 1) Doppler ultrasound positive for significant increase of flow velocity, 2) positive cerebral CT scan or MRA for ischemic lesions in the ipsilateral hemisphere, and 3) reversal of circulatory flow in the anterior cerebral artery and its reduction in the middle cerebral artery, in relation to rotation and cephalic flexion-extension maneuvers.

Other authors have suggested initiating treatment in cases with an ICA-to-common carotid ratio > 2 or a blood flow velocity greater than 180 cm/s. (61,62) However, the actual indication for treating CDA remains controversial. Most authors agree that symptomatic CDA should be treated after excluding other causes.

Invasive techniques have been proposed to correct CDA with successful results (fixation of the ICA to the digastric muscle, end-to-end anastomosis, end-to-side reimplantation, carotid endarterectomy with patch, bypass grafting, and carotid angioplasty with stenting). (40) However, despite the success of these techniques, the appropriate treatment remains controversial. Further studies are needed to determine the real effectiveness of the surgical approach to CDA.

CONCLUSION

CDA are a common condition with multifactorial etiology and limited, but not negligible, evidence of cerebrovascular involvement. Further studies are needed

to determine the usefulness of the therapeutic strategies to improve its prognosis. Strict monitoring and closer follow-up of patients with global assessment of thromboembolic risk are reasonable measures to prevent future events.

Conflicts of interest

None declared.

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

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OPINION ARTICLE

How Did Probability Come to Medicine?

¿Cómo llegó la probabilidad a la medicina?

JORGE TRAININI[1, MTSAC]

1. HOBBES'S SOCIAL MATHEMATICS

The mechanics established by Newton (1643-1727) enjoyed great application during the 18th and 19th centuries, to the point that it was quickly transferred to political, economic and social theories. In this way the community was analyzed through arithmetic analysis. It was assumed that politics should be converted into science through measurements, given that with quantitative measures, the irrational of human nature could be controlled.

Thomas Hobbes (1588-1679) and simultaneously his disciple William Petty (1623-1687) tried to introduce this mathematics into the human sciences. Hobbes, with his book, *Leviathan* (1651), (1) tried to develop the political theory with this mechanism. This text is written with a mechanistic vision of man's behavior and also of society. He introduced laws to rule. He tried to ensure that power was not a partial or capricious conviction but rather a logic support for political theory.

Hobbes's thought of incorporating Newtonian physics into society would produce, even long after *Leviathan* was published, a certain optimism when, for example, Kenneth Waltz (1924-2013) expressed, "[politics] *is closely related to character and training.*" (2) The historical time of science would show that mechanistic politics would succumb to the randomness of systems, such as that of human society. On the other hand, this concept of political arithmetic would enhance the sciences. In fact, physics with the development of quantum mechanics and the randomness and uncertainty of systems would permeate all science. It should also be noted that this mathematical game could be used, not only in medicine, but in all human fields; the latter being an attempt by Petty in his writing *Political Arithmetick* published shortly after "Leviathan".

It was not unintentionally that Hobbes had traveled to Florence to meet Galileo (1564-1642) and his theory about the constant motion of bodies. He understood that this notion could be extrapolated to people and organisms as a machine concept. Then he went so far as to declare: "... *reason is nothing more than calculation... Every man flees from death and does so, driven by an impulse of nature*." (1) We would later see this perception with Arthur Schopenhauer (1788-1860) in his book *The world as Will and Representation* (1819). (3) Impulse is evolutionary, with more force at each step of the living forms complexity, until it joins with human consciousness as the last force acquired by the existential entity towards its natural development.

Hobbes tried to understand the behavior of societies through postulates. Medicine later learned to fall into this concept that the disease and its therapeutic responses are not so complex that they cannot be solved from those minimum postulates. The plural man was brought to physics, but where was the singular man? The question about free will also inevitably arises here: what space is left for it?

This concept of *Leviathan* did not cease to horrify since it referred to human beings. Descartes had already anticipated this mechanism with an even more hopeless paragraph: "… *I wish you to consider that all these functions take place in this machine only by virtue of the arrangement of its organs, in a manner no less natural than the movements of a clock.*" (4)

Thus, the universe was considered as an immense clockwork mechanism. Therefore, it had to be dismantled to study it under a reductionist strategy that has seduced science ever since. This criterion of the infinite fragmentation of man in clinical study and interpretation is still more enhanced in medicine. We have gone beyond the horizon where the concept of psycho-organic-social integrity is lost with the logical consequences of falling into the coldness of a positivism in which the "human factor" is nullified.

But let's go back to Hobbes and his proposal. Was it possible to perform a social arithmetic that would help us understand social behavior? John Locke

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(1632-1704) and Jeremy Bentham (1748-1832) believed that reason was enough to achieve that alchemy of joining the benefits of society with those of each individual. Karl Marx (1818-1883) benefited from these theories for his later formulation. Hobbes had thus become a political scientist.

Physics is quantitative, mathematical. Hobbes did not really intend for the social to be a similar discipline. However, his disciple Petty introduced social arithmetic. Being an empiricist, he was not concerned with individual psychology. This development was inevitable. This is how mortality data appeared with John Grant (1624-1674) in 1662. Of course, we must realize that the conscience of the deceased no longer weighed in the observations made; therefore, sometimes an imponderable heart attack was noted as the cause of death instead of syphilis in order to avoid social scandal among the bereaved and close relations. The purpose of the exchange was achieved with a few coins requested by the tabulators. It was no longer the reality of the missing person that influenced the statistics but the honor of those who remained alive. This material did not fail to seduce those who speculated on the behavior of society. Birth and death rates were the first concerns of social mathematics. This new task sought to know the behavior of the masses that is beyond the knowledge of power. The figures of society from the Prussian Gottfried Achenwall (1719-1772), considered the father of statistics, were called "*statiskit*" since he legislated on natural states. Starting in 1769, those who manipulate data are called statisticians.

Here we must stop at some concepts about statistics and medicine. Establishing medical conduct without knowing the complexity of the patient quantitatively and qualitatively distances medicine from an individual decision regarding the patient. Physics has had influences through its mathematics on science in general. The risk in the human sciences is to extrapolate quantification to the individual man. There is no possible certainty in transferring the physics of probability to a clinical act, because the first measures the average behavior of people with numbers and the second interacts with a singular consciousness.

Statistics not only implied at that time the possibility of knowing what was happening but also what could happen. Neither more nor less than knowing about destiny. Marie Jean de Condorcet (1743-1794) foresaw the importance of this mathematical tool. He then attempted to relate social, political and economic issues to laws analogous to Newton's mechanics. His optimism led him to express: "*Everything indicates that one of the great revolutions in human history is near... the present state assures us happiness.*" (5) He believed in the human evolution from instinct to altruism and when being persecuted by the French Revolution, he decided to poison himself in his cell rather than fall under the revolutionary guillotine.

Although he did not totally share Condorcet's optimism, Thomas Malthus (1766-1834) agreed that society had the same relationship as mechanics with the movements of bodies. The Newtonian system was the dream that led him to believe that society could be governed by science and its calculations. David Hume (1711-1776) with his empiricism argued that human nature could be reduced to fundamental laws.

All this led to the prediction that human beings were doomed to happiness just as bodies and the laws of gravity were. Thomas Jefferson (1743-1826) thought so while Edmund Burke (1729-1797), for whom the complexity of people did not allow for a scientific analysis since their trajectories were random, denied it. Here emerges Auguste Comte (1798-1857) who with his *Cours de philosophie positive* maintained that natural laws would be known through the science that came from Newton. His words take Enlightenment to the highest point: "*Now that the human mind has understood terrestrial and celestial physics, mechanics and chemistry, organic, vegetable and animal physics, there still remains a science that must complete the series of observational sciences: social physics.*" (6) However, atoms would lead physics and the rest of the sciences to the freedom of the individual. Let's see.

2. IN SEARCH OF THE LAWS OF SOCIETY

The existence of atoms had been envisioned around 500 BC. by Leucippus, Democritus, Epicurus and later by Lucretius (99-55 BC). Daniel Bernoulli (1700-1782) around 1738 in his work *Hydrodynamics* took up the idea with the concept that small particles that collide are the constituents of gases. Taking advantage of this theoretical development, the Jesuit Ruder Boskovic (1711-1787) formulated the hypothesis that "*an omnipotent mind might foresee all subsequent states and movements and the phenomena that necessarily derive from them*." (7)

This concept would be revealed some time later by Pierre-Simon Laplace (1749-1827) and James Clerk Maxwell (1831-1879). The first stated: "*An intelligent being who at a given moment knew all the forces that animate Nature and the positions of the beings that form it, and that was vast enough to be able to analyze that data, could condense into a single formula the movement of the largest objects in the universe and that of the lightest atoms: nothing would be uncertain for such a being; and both the future and the past would be present before his eyes.*"(8) William Thomson (1824-1907) baptized this being with the name "demon." That is to say; the future of history could be deduced from a moment in time. The logical question arises again: what about free will? Under these concepts of being able to predict each of the

events, freedom was buried by the determinism that classical physics had achieved, transferred to political science.

Laplace, astronomer and mathematician, warned about errors in Newton's mathematical regularity. Together with his student, Dennis Poisson (1781-1840), they estimated that these errors were random and that they decreased with a greater number of observations. In this way, from astronomy, it was determined that probability had to do with the error of measurements. This distribution of data formed a figure that was called the "error curve." Later Carl Friedrich Gauss (1777-1855) gave his name to the probability distribution curve, also known as a *stochastic* curve, since each observation acts independently.

Knowledge of the works of Laplace and Poisson gave Adolphe Quetelet (1796-1874) the impression that they determined the natural order. He went to the limit. He saw the variations not as a natural process, but as deviations from an ideal. He transferred this concept to behavior, since he considered that everything about man is a physical fact. The *average behavior* of an individual was correct. This placed uniformity above singularity.

Quetelet set out to legislate scientific understanding in society. He used Hobbes's mechanical concept upon which he added statistics and the conviction that natural laws were found in the internal structure of society. Every scientific and human discipline was brought into the fold of positivism without any difference between mathematical sciences and strictly human sciences, such as medicine, psychology or politics. There were no differences between cosmic movements and that of individuals. Let us add that Quetelet was an astronomer by profession. The statistics that he used from his physical training gave him the necessary drive to tackle social studies. Astronomy positioned itself in this position and its practitioners realized that they could describe the natural laws of human behavior. They had active participation in searching for the laws that governed society.

There was controversy over these concepts. Henry Thomas Bucke (1821-1862) argued that statistics would allow history to be a science that would avoid falling into the arbitrariness of singularity. Nassau William Senior (1790-1864), English economist, went much further in this prediction: "*human will obey laws as precise as those that govern matter.*" Maxwell's judgment of Senior was to consider him an extremist of positivism. This statistical prediction obviously led to strong opposition. In relation to these mechanistic laws, even within the concept of probability, Friedrich Nietzsche (1844-1900) was sardonic: "*if history has laws, neither these laws are worth anything nor is history worth anything.*" (9) Similarly, it was later explained by Hilaire Belloc (1870-1953) in the following way: "*Statistics are the triumph of the quantitative method, and the quantitative method is the victory of sterility and death.*" (10)

Regarding this point of social arithmetic, it was believed that knowledge of a society could determine people's behavior. Here we must incorporate another postulate of quantum physics, "non-objective reality." It is substantially doubtful to continue considering the postulate of objectivity in science. It is almost impossible for observation not to be affected by the "reality" of the observer. Quantum physics has demonstrated with its development that we should not exclude the concept of "non-objective reality." In medicine, for example, the objectivity that was imposed in science faded consciousness as an essential fact in the health/disease process.

3. PROBABILITY OR INDIVIDUAL CONSCIOUSNESS

Consciousness, the fundamental and unique fact of the universe, causes all physical and human analogies to be abolished as incongruous. Consciousness cannot be reduced to a mere physical structure. And even more so when this is unique and exclusive to each individual. (11, 12) The probability used in human organic systems obeys an arithmetic tool, ignoring the role of consciousness, the true attractor of the new physics of dissipative structures, which makes each individual a unique being. To ignore consciousness in organic processes is to ignore the true mind-body integration possessed by the exclusive being that can describe the entire universe through the interpretation given to it by the conscious faculty. Each response, whether physical or spiritual, passes through the sieve of consciousness. Given this situation, how to confront it with arithmetic? Obviously, the only method for the singular analysis of a consciousness is through the singularity of another consciousness.

The application of statistics to individuals is a risky topic. This is what has happened with statistics in medicine. Evidently, the concept that gave rise to social arithmetic with Hobbes and Petty has changed, where classical physics had lorded over the behavior of individuals. Beyond the step taken from the strictly mechanical to probability, even in the sciences that have to do with the singular man, there are risks in the global interpretation through statistics. What would the behavior of a clinical trial be in an individual case? We could ask ourselves, imitating Charles Pierce (1839-1914) (13), when in relation to chance on natural diversity he asked "*what will be the natural selection in each individual case?*".

Conflicts of interest

None declared.

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

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Physical Activity and Physical Exercise: Two Different Concepts

Actividad física y ejercicio físico: dos conceptos diferentes

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"Physical activity" has been defined as any movement requiring energy expenditure, while the term "physical exercise" involves a planned, structured and repetitive routine, generally performed with a goal or purpose in mind, and of a certain duration, intensity and frequency.

Using multivariate interventions in patients diagnosed with cardiovascular disease to achieve changes in their lifestyles is a Class IA recommendation in clinical practice guidelines. (1,2) Cardiovascular rehabilitation (CVR) is an essential secondary prevention strategy, making an active contribution to comprehensive care, and supported by abundant scientific evidence in terms of benefits. One of the biggest challenges is to maintain these changes in the long term. According to data from the Fourth National Survey of Risk Factors, almost half of the population does not perform the minimum amount of physical activity required to benefit their health, and prevalence of sedentarism is higher in those over 65 years of age. (3) Early studies showing the benefits of physical activity for survival have focused mainly on healthy individuals, making no distinction between primary and secondary prevention of CV disease. (4) Subsequent studies supported exercise-based CVR in patients with coronary artery disease and chronic heart failure. (5) Current guidelines from the most relevant cardiological societies recommend 30-60 minutes of moderate aerobic exercise at least 5 days a week, in addition to muscle strengthening exercises with 1-2 stimuli a week. This suggests that the recommended level of physical activity is comparable to that of healthy adults.

Physical activity has been shown to reduce mortality in a dose-response manner. The present recommendation is 500-1000 MET-min/week of aerobic exercise, which is equivalent to 150-300 minutes of moderate physical activity or 75-150 minutes of strenuous physical activity per week. This recommendation is based on the observation that the maximum survival benefit is gained with 500-1000 MET-min/week. (6)

In the study by Jeong SW et al. (7) to compare the impact of physical activity on mortality in primary versus secondary prevention patients, it was observed that while individuals without CV disease were mostly benefited by 1 to 500 MET-min/week of physical activity, the benefit for those with CV disease continued to be above 1000 MET-min/week. In fact, the adjusted mortality risk of individuals with CV disease with a high level of physical activity was shown to be comparable to or lower than that of their counterparts with no CV disease.

Since the late 1990s, several publications have warned about poor adherence to exercise after taking part in a CVR program. The latest have included instruments, ranging from accelerometers to cell phone applications, and shown that adherence decreases over time. (8-11) Other trends suggest the importance of adapting physical activity interventions by promoting resilience resources, such as a "sense of coherence", to improve both the ability to consistently adopt a physically active lifestyle over time, and the patients' quality of life after an acute coronary event. (12)

In our experience, in a CVR population of two groups, a group under in-person intervention twice a week, and a group under hybrid intervention consisting of in-person phase II intervention and distance phase III intervention, all included in the same physiotherapists-coordinated WhatsApp group, where exercise routines, motivational messages, experiences, fears, doubts and achievements were shared, adherence to physical exercise was defined as ≥1000 MET-min/week, and a questionnaire was used one year after completion of phase III. Energy expenditure (MET-min/week) was calculated as the sum of exercise

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intensity, frequency and duration. (13) We had a level of physical exercise ranging from 120 to 3240 MET-min/week, with a median of 945 MET-min/week. Only three patients (17.64%) failed to achieve the minimum level of physical exercise (500 MET-min/week) recommended for the general population. In a preliminary analysis, physical exercise equivalent to ≥1000 MET-min/week was associated with a younger age, and a higher intensity and longer duration of exercises. It is also noteworthy that muscle strengthening exercises ranked second among the types of exercise chosen by patients one year after completing phase III of the CVR program. As a result, and consistently with recent published data from the CardioRACE trial, (14) a high percentage of our patients with coronary artery disease perform muscle strengthening exercises plus aerobic exercises, as we have been able to convey that this combination improves the CV risk profile.

Therefore, keeping in mind that a switch to healthy habits and maintaining exercise is very likely to be associated with the individual's own characteristics, such as self-efficacy, balanced decision making, and use of behavioral processes, we should focus on these concepts as early as in the anamnesis, with CVR being favorable for this exchange. It is inevitable to address these concepts, historically associated to mental health, as identifying the aforementioned individual characteristics and motivating candidates will provide information on engagement in and long-term maintenance of exercise. (15,16)

In addition, a distinction should be made between the expressions "physical activity" and "physical exercise". While the impact of any energy expenditure or physical activity on survival is well-recognized, patients with coronary artery disease gain more benefit from structure and planning, and they should also achieve a goal (objective) in terms of secondary CV prevention. The amount of exercise is relevant for these patients, thus the need to consider frequency, intensity and duration. Adequate prescription of physical exercise, unexplored by most healthcare professionals, would then become part of our practice.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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Pathophysiology of Hyperacute T Waves in Acute Ischemia

High-peaked hyperacute T waves in transmural myocardial infarction are the last bastion in ischemic storm

Fisiopatogenia de las ondas T acuminadas en la isquemia aguda

Las ondas T altas y acuminadas en infartos transmurales son el último baluarte de defensa en la tormenta isquémica

SAMUEL SCLAROVSKY[1]

I would like to express my gratitude to my friend and academic master, Marcelo V. Elizari, for his assistance in writing and critiquing this work. This work is dedicated to our unforgotten master, Mauricio B. Rosenbaum (RIP), with whom it all began.

To the editor:

The first manifestations of acute ischemia are high-peaked hyperacute T waves attributed to a sudden increase in potassium (K^+) in the epicardium. It has been suggested that this phenomenon protects against the development of necrosis in this region of the myocardium caused by ischemia. (1)

The relationship between T wave voltage and extracellular K^+ has been known for several decades. Hyperkalemia between 5.5 and 6.5 mEq/L generates high-peaked hyperacute T waves in precordial leads. Experiments have shown that blockade of K^+ channels or knockout of the genes encoding K^+ channels prevent the development of high-peaked hyperacute T waves in myocardial ischemia. (2,3) K^+ influx produces taller and more narrow T waves in the epicardium, and this effect is less evident in the endocardium. (4) Notably, these T waves are present in sudden segmental, regional, transmural and subendocardial ischemia (Figures 1 and 2). (5) In the obstructive phase of anteroseptal myocardial infarctions, well protected by a good collateral circulation, only high-peaked hyperacute T waves are recorded in the electrocardiogram. (6) An experimental study in canine hearts reproduced changes similar to those observed in clinical practice with balloon occlusion of the left anterior descending coronary artery. Occlusion of the artery for 2 minutes produced a typical pattern of anteroseptal ischemia with ST-segment elevation of 9 mm and high-peaked hyperacute T waves of 15 mm (Figure 3). This experiment demonstrates the effect of diazoxide in increasing adenosine-triphosphate (ATP) dependent K^+ levels in the epicardium. (7)

Biological processes that reduce the effects of the ischemic storm

Mitochondria are independent organisms within the cells that have their own membranes and exhibit DNA similar to that of bacteria. (8) Their main function is to provide energy to cells. They produce ATP from fatty acids, glucose and oxygen via a complex enzyme system. (9) Phosphorus is released through a fission process and generates heat and energy. This is how mitochondria produce energy in all normally functioning cells. (10) The mechanism is similar to the one used by nuclear energy plants where uranium undergoes a fission process that produces heat and energy. Phosphorus is the second most abundant element in organisms and has been used as the main source of energy during evolution. (11) Consequently, it can be reasonably assumed that this source of energy is the most effective and cost-efficient option. The myocyte requires large amounts of energy to function and contains large numbers of mitochondria. During exercise, mitochondria in myocytes replicate into thousands, like bacterial binary fission, to provide the energy needed. (12) After mitochondrial fission, adenosine diphosphate (ADP) is formed, which apparently has no biological function. Part of it returns to the mitochondria to synthetize ATP, and another part loses phosphates. In acute ischemia, another phosphate is lost due to lack of oxygen and forms adenosine monophosphate (AMP). (13) This process plays an essential role in cellular biology by facilitating the influx of calcium through calcium channels into the sarcoplasmic reticulum (a calcium reservoir within the myocyte).Following phosphorus degradation, adenosine is released. The latter plays a

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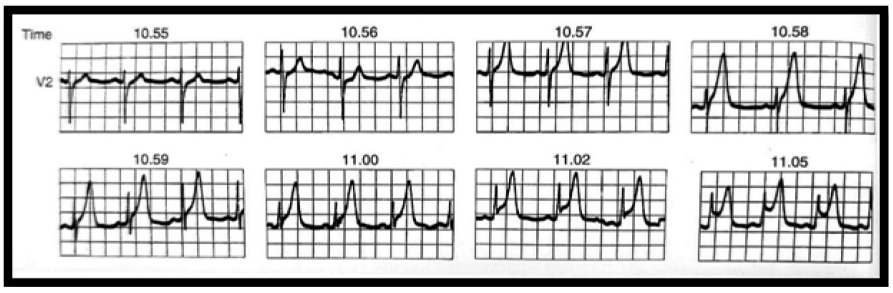

Fig. 1. Electrocardiographic changes of a sudden total occlusion of the left anterior descending coronary artery. The T wave changes between 10:55 and 10:58, becoming high-peaked hyperacute (13 mm wave) as the first manifestation of the ATP-dependent K^+ influx to protect the epicardium until ST-segment elevation develops. High-peaked hyperacute T waves are due to the sudden influx of K^+ into the epicardium. ST-segment elevation is related to calcium, which acts as a buffer in the center of ischemia with very low pH

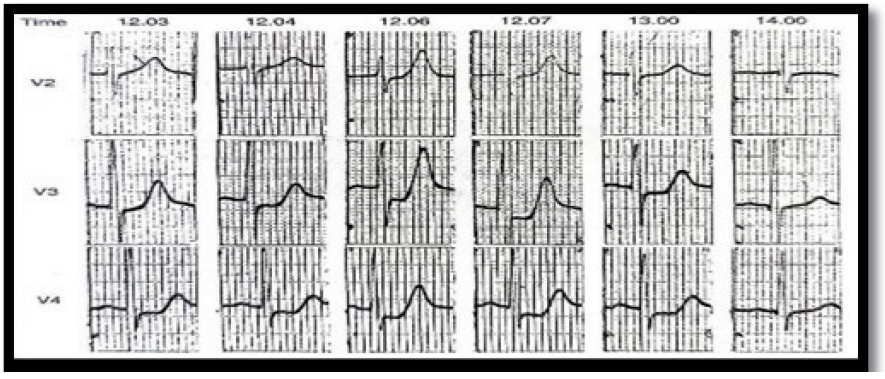

Fig. 2. Electrocardiographic changes of a sudden subtotal occlusion of left the anterior descending coronary artery, expressed with high-peaked hyperacute T waves and ST-segment-depression, suggesting acute subendocardial ischemia. See how the 15-mm high hyperacute T wave evolves. Although ischemia is subendocardial, the ATP-dependent K^+ influx protects the epicardium. (5) Two hours after the onset of ischemia, a minimal subendocardial Q wave develops

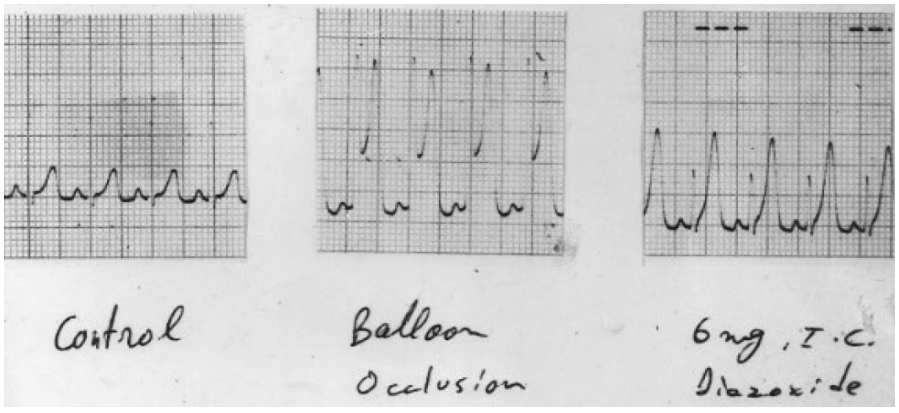

Fig. 3. Canine experiment. Left image: baseline recording. Central image: introduction of a balloon catheter and sudden occlusion of the left anterior descending coronary artery for 2 minutes. The typical 15-mm high T wave is observed. Right image: intracoronary injection of 5 mg of diazoxide. A T wave similar to an ischemic T wave is recorded. Diazoxide stimulates adenosine release, which increases epicardial K+ concentration

crucial role in myocardial protection during ischemic storm. (14) Adenosine 1 blocks the effects of adrenaline on the sinus node preventing sinus tachycardia, which is a negative factor in acute ischemia. (15) An increase in energy demands during tachycardia is a high-risk factor in the event of a sudden reduction in coronary flow. Adenosine 1 is responsible for maintaining, sinus rhythm in acute ischemia at a rate of 55 to 70 beats per minute despite the patient's anxiety and suffering.

In patients with acute myocardial infarction who did not receive medical care within the first 72 hours, sinus tachycardia may occur and is typically related to adenosine depletion. Adenosine 2 is present in the left ventricle and plays a vital role in the epicardium, as it increases K^+ concentration. (16) This invasion of K^+ in the epicardium is expressed by high-peaked (> 15 mm) hyperacute T waves in the anterior epicardial leads in anteroseptal myocardial infarctions and in some pos-

teroinferior infarctions. These ischemic T waves are the expression of a shorter phase 2 of the epicardial action potential, during which calcium enters the myocyte. The decrease in calcium influx reduces epicardial contraction and thus decreases oxygen uptake (preconditioning). (16)

Anteroseptal transmural infarction involves necrosis of 2/3 of the myocardial wall (17-19). The third corresponding to the epicardium is protected by the increase in K^+ concentration facilitated by adenosine 2. Anteroseptal infarctions complicated with cardiac rupture present T waves of approximately 5 mm or less, along with a reduced ST-T gradient. This suggests that the epicardium may not be protected by the mechanism of adenosine 2 and increased K^+ concentrations. (20) Adenosine A2A has also an effect on the brain that is different from that of caffeine, suggesting that patients with acute infarction avoid moving to reduce the cardiac demands for energy, another effect to protect myocardial infarction in the obstructive stage. (21)

At the beginning of this century, several studies have been published on the mitochondrial function and dysfunction, especially in heart failure and hypertrophy. (22)

But we have not found publications in the medical literature addressing the importance of mitochondria and the biological cascade that begins with ATP and continues with adenosine upregulation and ATP-dependent K^+ influx to protect the anteroseptal epicardium. In case of cardiac rupture in the context of acute myocardial infarction, we may speculate that it is a manifestation of mitochondrial dysfunction. Figure 3 shows the effect of intracoronary diazoxide injection in a canine experiment, stimulating adenosine production and inducing ATP-dependent K^+ influx into the epicardium. The T wave obtained in the experiment is very similar to the T wave in occlusion of the left anterior descending artery (both waves measure 15 mm).

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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Acute Myocardial Infarction: Questions and Decisions

Infarto agudo de miocardio: sobre interrogantes y decisiones

ARTURO CAGIDE[1]

Two recent communications challenged concepts widely accepted by the cardiology community. The first questions whether interventions with proven efficacy in heart failure with reduced ejection fraction (HFrEF) should necessarily be effective in ventricular dysfunction after acute myocardial infarction (AMI). The second raises the question about the usefulness of indicating beta-blockers (BBs) to all patients after AMI in the absence if HF and, by extension, in ischemic heart disease in the absence of angina.

Discussing how these results impact on clinical practice is as interesting as answering certain questions that may or may not justify the findings.

EMPACT-MI trial

The EMPACT-MI (1) trial evaluated the effect of empagliflozin in post-AMI patients with rEF or signs of HF.

The trial included 6522 post-AMI patients within 14 days after hospitalization (follow-up of 18 months) who were randomized to placebo or empagliflozin. The study showed no difference in the composite end point of readmission for HF or death from any cause.

Several questions arise from this finding.

Why was there no effect despite the unquestionable efficacy of effective interventions in ventricular dysfunction following myocardial infarction?

One might conclude that the question is inappropriate, because there was an effect on rehospitalizations, and that, although gliflozins demonstrated a reduction in mortality in chronic HF, it was a secondary endpoint. However, several meta-analyses have confirmed the reduction in cardiovascular mortality and all-cause mortality. (2)

Is the lack of effect due to having selected a low-risk population?

The low risk is apparent from two considerations:

- In the original sample size calculation, the authors estimated that 3313 patients were needed to be included, a number that had to be increased to 5000, based on the low event rate (6.6%/year for death from any cause or HF rehospitalization).
- When the endpoints of this study are compared with those of gliflozins in chronic HF, (3-4) (Table 1), again it becomes evident that the post-AMI study included a much lower risk population.

Were the inclusion criteria incorrect?

This does not seem to be the case: 60% had EF < 45% and associated congestion, 20% had only EF <45%, and the rest had signs of congestion requiring treatment.

In addition, other risk criteria (Table 2) associated with poor outcomes after AMI were included.

Why did these risk criteria not translate into worse clinical outcomes with a higher event rate?

It is likely that the initially calculated risk was high, but that it could include transient conditions that later resolved spontaneously with treatment.

- The probable involved mechanisms include recovery of myocardium at risk (stunning), associated with the high rate of reperfusion.
- ventricular remodeling
- resolution of the inflammatory state characteristic of the acute phase.

Is there another intervention whose benefit, applicable only to the distant post-AMI period, suggests recovery of myocardial function?

In patients with previously normal EF, and EF < 40% after AMI, the indication for implantable cardioverter-defibrillator should be postponed until day 40 after the acute episode, and only after persistent dysfunction has been proven.

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	EMPACT-MI (1)	DAPA-HF (3)	EMPEROR-Reduced (4)
CV death / HFH (%)	5.7	15.6	21
HFH (%)	3.4	9.8	15.5
Overall mortality (%)	3.8	9.5	10.7

AMI: acute myocardial infarction; CV: cardiovascular; HFH: heart failure hospitalization

Table 1. Annual incidence rate of major events in the placebo group of the empagliflozin trial after AMI (EMPACT-MI) and gliflozin studies in chronic heart failure (DAPA-HF and EMPEROR-Reduced). (1,3,4)

Inclusion criteria

- AMI within 14 days after admission
- recent EF < 45 % or symptoms of congestion (requiring treatment)
- Additional factors (at least one of the following) :
  - >65 years
  - recent EF<35%
  - history of AMI, atrial fibrillation or diabetes
  - glomerular filtration rate < 60 mL/min/1.73 m^2
  - elevated BNP / uric acid levels
  - elevated pulmonary artery pressure
  - three-vessel coronary artery disease
  - peripheral artery disease
  - absence of reperfusion strategy

AMI: acute myocardial infarction; BNP: brain natriuretic peptide; EF: ejection fraction

Table 2. Inclusion criteria in the EMPACT-MI trial (1)

Why did these presumably transient conditions not affect the beneficial effect of other interventions such as neurohormonal blockade with BBs or converting enzyme inhibitors?

These interventions evaluated against placebo might have generated a favorable scenario facilitating the recovery of the hemodynamic condition.

For example, the rate and success of reperfusion strategy is likely to be significantly higher today than when these studies were conducted, resulting in a larger area of potentially salvageable peri-infarct ischemic myocardium.

Does the result of the EMPACT-MI trial in post-AMI patients call into question the effect of gliflozins in chronic HF?

Clearly not. The clinical trials are compelling in terms of reducing the rate of the composite endpoint of death/rehospitalization for HF in patients with reduced or preserved EF with signs of congestion.

In AMI patients with EF < 40%, should gliflozins be indicated at discharge or during outpatient care?

Administration at discharge is probably associated with higher compliance. After discharge, the indication is a feasible option after confirming that the EF is < 40%. In this case, outpatient visits must be systematically scheduled for the following two weeks. This proposal has demonstrated a benefit that extends beyond the indication of gliflozins, resulting also in a global strategy that reduces rehospitalizations.

REDUCE-AMI trial

This open-label, pragmatic randomized study (5) nested in an observational cohort in 3 countries compared treatment with BBs (bisoprolol, 5 mg or metoprolol, 100 mg) versus no treatment with BBs in 5020 AMI patients with preserved EF (≥ 50%) within 7 days after hospitalization, during a mean follow-up of 3.5 years.

There was no difference in the incidence of the primary endpoint, a composite of death from any cause or new AMI.

The following clinically relevant questions may affect decision-making:

Is the result of the study sufficiently definitive to rule out the use of BB in patients with AMI and an EF ≥ 50%?

The open design, the diagnosis of AMI obtained directly from the population-based registry database, and crossovers (18% of patients discontinued BB and 14% of patients who were untreated received them) are limiting factors that may affect the interpretation of the negative result.

Again, is the lack of effect due to the inclusion of a low-risk population?

The trial design initially estimated an endpoint incidence (death from any cause or AMI) of 7.2%/year. During the study, as the actual incidence was less than 3%/year, the sample size was recalculated to 5000 patients. Death from any cause was approximately 1.2 %/year, clearly very low. The study was underpowered.

Is preserved EF a sufficient criterion to select a low-risk population not amenable to BB treatment?

Other factors beyond EF affect the outcome after AMI. In the REDUCE-AMI, age (65 years), diabetes in only 13% of the patients, previous AMI in 7%, atrial fibrillation in <1%, ST-segment elevation in only 33% of the cases and one-vessel disease in 55% of patients are low-risk variables. Under other conditions, AMI patients may be at higher risk even when EF is > 50%.

How can the results of this trial be put into practice?

In AMI patients with reduced EF, the indication for BB is well-established. In those with preserved EF, and until new information becomes available, the decision to indicate BB is based on the associated conditions that determine the patient's overall risk.

Has this study solved the problem of indicating BB in AMI patients with preserved ventricular function?

Definitely not. Further ongoing studies will bring the definitive answer.

Conflicts of interest

None declared.

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

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Hypertrophic Cardiomyopathy in Non-specialized Centers in Argentina.

Miocardiopatía hipertrófica en centros no especializados en Argentina

MARÍA MILAGROS LEZCANO[1], JORGE MARÍA CASAS[1, MTSAC, FSISIAC]

The article by Dr. Cáceres et al. published in Revista Argentina de Cardiología with preliminary data from the registry of hypertrophic cardiomyopathy (HCM) in non-specialized centers in Argentina is a retrospective, observational multicenter study that describes the assessment of this disease in non-specialized and outpatient centers of our country. (1)

A total of 95 patients with diagnosis of HCM, assessed by each professional without establishing the diagnostic criteria used, were included in the study.

Conventional studies (electrocardiogram and echocardiogram) were performed in most of the patients, but more complex practices such as cardiac magnetic resonance imaging were not. Thirty-two percent of patients were not evaluated by this technique despite it being a class I indication in cardiomyopathy management guidelines, (2) in addition to being a highly specific study to define wall thickness, detect possible phenocopies and provide useful information in risk prediction, such as the presence of late gadolinium enhancement.

Genetic tests were performed in 37% of cases. Lack of medical coverage or lack of availability in the hospital setting, were among the main reasons for not performing the tests. The high yield obtained in genotyped patients should be highlighted, exceeding that described in the literature (detection of pathogenic variants in sarcomeric mutations in 52% of requested tests).

Family screening was performed in only 44% of the cases, despite being a hereditary/familial pathology.

Clinical data (dyspnea as the most frequent symptom) and pharmacological treatment, with the use of beta-blockers and calcium channel blockers, did not differ from large international registries.

The assessment of left ventricular outflow tract obstruction was performed in resting and Valsalva conditions, and it would be useful to add its evaluation in standing position. (2)

Only 13% of the patients were studied under stress conditions by means of stress echo. A more accessible and cost-effective strategy, such as ergometry, could have been chosen to assess the behavior of intra-stress blood pressure and identify conditions of greater risk. (3)

Regarding the indication for implantable cardioverter-defibrillator (ICD), no mention is made of the risk stratification criteria used, with no clear information on family history, which is very relevant at this point. Along the same lines, Holter ECG was only performed in 66% of the cases; taking into account that the presence of ventricular arrhythmia, possibly detected with this study, is an independent predictor of sudden death. (4)

Finally, 9% of patients had or were indicated to have ICDs at follow-up, a lower number than that reported in international multicenter registries. (5)

We can conclude that this interesting registry with local data reflects the lack of access to more specialized systems for patients with this not infrequent disease, in which a multidisciplinary group that also includes specialists in genetics and advanced cardiac imaging can be counted on to improve, above all, diagnosis, risk stratification and family screening.

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 Drs Lezcano and Casas,

We appreciate your comments on our article "Preliminary data from the registry of hypertrophic cardiomyopathy in non-specialized centers in Argentina: exploring behind the veils of everyday practice". We are pleased to see the interest and attention to detail you have devoted to our study.

As you have pointed out, the work presented is a preliminary, observational study with initial data. We especially appreciate your observations regarding functional testing, the importance of family screening, and the indication for implantable cardioverter-defibrillator (ICD). In this preliminary phase, our aim was to provide a preview of the most significant registry data. We also mentioned that, despite the "natural ambitious inertia" of trying to collect as much data as possible, we chose to prioritize certain relevant data to ensure a high participation rate and data completeness, which we consider fundamental to the success of any clinical registry.

We hope that, in the final phase of the study, with more data and more detailed analysis, we will be able to address these areas more comprehensively. We again thank you for your valuable input and wish that the final results of the study will provide a more complete picture of the management of hypertrophic cardiomyopathy. We hope that our work will inspire new proposals to improve the care of our patients.

Sincerely.

Leonardo Cáceres, Rodrigo Cano, Camila Correa Sadouet, Adrián Mahl, Gisela Streintenberger, Guillermo Mazo, Maribel Kanchi, Heraldo D' Imperio
SAC Research Area

High-density Lipoproteins and SARS-CoV-2 Infection

Lipoproteínas de alta densidad e infección por SARS-CoV-2

PABLO DANIEL CUTINE[1]

The association between infectious diseases and development of cardiovascular (CV) disease is a phenomenon of growing importance, underscored in recent years by the observation of a marked increase in the incidence of CV events among COVID-19 patients within one year after having the infection.

An inverse relationship between the levels of high-density lipoprotein (HDL)-cholesterol and atherosclerosis development has been described in observational studies (within a certain range of values). Several mechanisms have been proposed to explain this observation, such as reverse cholesterol transport and antioxidant activity, among others. (2)

The research conducted by Davico et al. (3) highlights the frequently unaddressed complexities of the pathophysiological analysis of lipoprotein metabolism

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and its relationship with both COVID-19 and atherosclerosis.

The authors evaluated the cardioprotective effect of HDL in 18 asymptomatic patients after 4 weeks of SARS-CoV-2 infection, 9 patients with post-COVID syndrome (with a consistently worse performance in the 6-minute walk test), and 10 healthy controls. They particularly focused on their antioxidant capacity, mainly as a result of paraoxonase-1 (PON1), and reverse cholesterol transport, evaluating cellular cholesterol efflux, free cholesterol esterification by lecithin-cholesterol acyltransferase (LCAT), and the exchange of triglyceride-esterified cholesterol between HDL and Apo B-containing lipoproteins by means of the cholesterol ester transfer protein (CETP).

No significant differences were found in the lipoprotein profile, tested inflammatory markers, or evaluated parameters of reverse cholesterol transport among the groups under analysis. However, asymptomatic patients showed a higher PON1 enzymatic activity versus the asymptomatic and post COVID-19 syndrome groups. HDL antioxidant activity could therefore be a defense mechanism against SARS-CoV-2 infection.

They also observed a negative correlation between the steps in reverse cholesterol transport and inflammatory markers, which supports the theory that inflammation may affect HDL functionality. This finding, consistent with previous publications (4), might shed light on a mechanism by which persistent inflammation, in this case related to SARS-CoV-2 infection, is associated with a higher incidence of cardiovascular events in the medium term. This promising hypothesis needs to be confirmed by subsequent studies on atherosclerosis that reproduce the results in a larger population.

Large clinical trials of specific therapies targeting HDL cholesterol have failed to show any relevant clinical benefit. The reason may be that HDL consists of heterogeneous particles with multiple and complex mechanisms affecting various body functions. (5) The findings of this study emphasize the need for further research on lipoprotein metabolism.

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 are deeply grateful for your interest in our article, as well as your analysis, which highlights the importance of evaluating the functional aspects of high-density lipoproteins (HDL), with their well-known cardioprotective capacity, rather than just their cholesterol content. Clinical trials focused on therapies aimed at increasing HDL-cholesterol levels have failed to demonstrate the expected clinical benefits with respect to morbidity and mortality due to cardiovascular disease, suggesting that the therapeutic target should be some of the antiatherogenic functions of HDL. Our work confirms that persistent inflammation and oxidative stress, in this case as a result of SARS-CoV-2 infection and known to be associated with atherosclerosis, are related to impaired reverse cholesterol transport, as well as HDL antioxidant function. These pathophysiological mechanisms would be important not only for SARS-CoV-2 infection and similar viruses, but also for all conditions involving chronic inflammation and oxidative stress. Therefore, they could at least partly explain the residual cardiovascular risk after the implementation of therapies targeting traditional lipid profile markers such as HDL-cholesterol.

Belén Davico

Hemodynamic Parameters and Prognosis in Pulmonary Hypertension

Parámetros hemodinámicos y pronóstico en hipertensión pulmonar

NICOLAS D'AMELIO[1]

Pulmonary hypertension (PH) is a hemodynamic condition associated with numerous diseases, classified into different subgroups according to the latest 2022 ESC/ERS clinical practice guidelines. (1) The presence of this condition increases the morbidity and mortality of patients suffering from it, and, left to its natural evolution it ends up affecting right ventricular function, conditioning ventricular arterial uncoupling, the onset of heart failure and death.

Risk stratification of patients with PH is a fundamental step at the time of diagnosis and during follow-up, since it is the basis for decision-making on the amount and type of vasodilator drugs to be used. (1) As highlighted by the authors of the study Usefulness of various hemodynamic parameters as prognostic markers in pulmonary hypertension, (2) from the time of diagnosis, throughout the performance of right heart catheterization (RHC), we can acquire hemodynamic data validated in the risk calculators recommended by the 2022 ESC/ERS, where right atrial pressure, indexed systolic volume, pulmonary artery oxygen saturation and cardiac index stand out. Regardless of the recommendations, those of us who dedicate our daily work to this disease understand that there are numerous alternative variables to those proposed, with a strong prognostic impact, though with the problem of not being validated in the large registries of this disease. The hemodynamic evaluation of afterload is equivalent in cardiac mechanics to the resistance imposed on the ventricle during contraction and represents the ventricular wall tension that must be overcome to eject blood and generate cardiac output. Afterload is represented by two components, pulmonary vascular resistance (PVR) and capacitance (PC). Pulmonary vascular resistance constitutes the stationary element and is found mainly in small arteries and arterioles, since it is highly dependent on vessel diameter. Pulmonary compliance represents the pulsatile component, which is the storage capacity of all arteries and arterioles as a whole, and is related to arterial elasticity and the geometric characteristics of the vessel given by its thickness and radius. (3,4)

Our colleagues were able to show, in an impressive number of patients for this disease and for our country, the prognostic validity of two key hemodynamic variables in the pathophysiology of afterload in patients with PH, justifying and ratifying the use of alternative variables in addition to those established in prognostic scores recommended by clinical practice guidelines but not validated in our population. I consider promising and challenging the upcoming time in which the Argentine Registry of Pulmonary Hypertension (ARGEN-HP), which is currently in the recruitment phase, can be used as an opportunity to validate the strategies recommended to date by the 2022 ESC/ERS, as well as alternative variables that allow stratification of the prognosis of this entity using data from our own 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

Dear Dr. D'Amelio,

On behalf of the authors of the study, I thank you for your comments and share your opinion on the importance of prioritizing the assessment of ventriculoarterial coupling when estimating the prognosis of patients with pulmonary hypertension, regardless of its etiology.

At present, there are many randomized studies in pulmonary arterial hypertension that use pulmonary vascular resistance as the endpoint, probably assuming it as a surrogate for events. We will see if future national and international recommendations include these variables in the prognostic score of patients.

Sincerely yours faithfully.

Dr. Nicolas Caruso

Prof. Dr. Eduardo Fernández Rostello

It is difficult to define a master in simple words. It is a person who is fully committed to their work and derives satisfaction from it. An individual who consistently supports and celebrates the achievements of students — from the youngest to the oldest —, even when they are already spreading their own wings. There is no better representative of a master than Professor Doctor Eduardo Fernández Rostello, who recently passed away, but whose legacy will remain forever.

He had the wisdom to simplify complex concepts. One could identify cases of transposition of the great arteries, single ventricle or scimitar syndrome in daily practice thanks to his explanations in class. We are indebted to him for his famous phrases such as: "Doctor, that is not a large atrium, but rather an *auriculón*", or his motivational phrase: "I know you can do it, doctor," and his unforgettable funny descriptions: "Watch doctor, that is a *valvulón*". All of this will remain forever in the memories of the hundreds of students who attended his classes in the UBA, SAC, AMA and *Hospital Rivadavia*, as well as in all other places where he gave his utmost in his master classes.

He held the most senior roles in the organizations where he worked. Professor at the UBA, Doctor of Medicine, Director of Hospital, Director of the UBA SAC Echocardiography Update Course, President of the Scientific Committee of the SAC Imaging Congress, Director of the ECO-SAC journal, and numerous other positions. However, it is likely that we will all remember him most of all for his most distinguished title: "the best friend".

We cannot deny the profound sadness we feel at his physical departure. His absence will be irreplaceable. However, his imprint will endure among all of us who knew him, within the beloved Argentine Society of Cardiology, to which he gave so much, and in the loving family he built with his wife.

We will always remember him and honor his memory by striving to follow in his footsteps. Farewell, dear Eduardo!

Members of the "Dr. Oscar Orías" Council of Echocardiography and Vascular Ultrasound and authorities of the SAC Echocardiography Courses.

To our friend Eduardo Fernández Rostello

"When a friend leaves..." The verse from Alberto Cortes' song that continues with ..." an empty space is left behind" has never been so real and true.

I met Dr. Eduardo Fernandez Rostello in the SAC, mainly in the Council of Doppler Echocardiography during the late 1990s. I was fortunate to share with him many moments, both in our professional lives and in everyday settings. But I do not want to refer to his well-known professional merits and achievements, but rather to his profile as a human being and friend. He was an endearing, affectionate, and respectful person with excellent common sense and a special sense of humor that strengthened our mutual affinity. He was the eternal presenter of my Normal Echo classes at the SAC course, and he always ended with a friendly and funny joke that involved both of us. Despite the limitations of distance and differing work schedules, we maintained a beautiful and cordial friendship. Our common interests included medicine, teaching, and, undoubtedly, humor.

I would like to remember Eduardo for his exceptional personal qualities. He was an excellent person, a great friend, a solid professional, and a loved one who will remain in my memory and surely in the memory of many others. My respectful and sincere condolences to all his family.

Today, an empty space is left behind… May you rest in peace, Eduardo!

Rubén Horacio Álvarez[MTSAC]

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The SAC. The Human Resource that We Must Look After...

La SAC. El recurso humano que debemos cuidar...

Dear Colleagues,

The current year is marked by a high level of activity in our society. More than 700 residents began the two-year course. For the first time in the history of our course, 65 residents from Uruguay and Paraguay are sharing our training program. Our online courses are being attended by 1280 colleagues. Six interdistric conferences have been organized by *SAC País*. Ten webinars were held with 2700 attendees. Twelve podcasts were uploaded by CARDIO SAC. Fifteen consensus statements and position papers on different cardiology topics are under development. The SAC Manual of Practical Cardiology is being created by our Councils and Areas. Two new registries are being conducted: 1. The MEDITAAR registry, which will determine the diameters and cut-off points of the proximal, mid, and distal abdominal aorta in a cohort of healthy patients in our country, and 2. The REGESTAR registry, a collaborative and intersociety registry on the treatment of aortic stenosis in Argentina. The Argentine Journal of Cardiology has its own web page and an updated, documentary structure. We have released of our new SAC logo and our web page will be more dynamic in the near future, in line with our current timeline. We had a highly active presence in the country's leading media with articles for the community together with the Argentine Foundation of Cardiology and Health Policies. The Instructional Resources Area (ARI) has been disseminating our academic activities through social media. Our members have made notable contributions at international congresses and events, including the ACC, SIAC, and those held by the Uruguayan, Colombian, Ecuadorian, and Venezuelan Societies. Please accept my apologies if I have omitted any other details.

I would like to make a special mention to the Diagnostic Imaging Congress which was organized by our Councils of Diagnostic Imaging, Technicians, Pediatric Cardiology and Congenital Heart Diseases. This year, the Congress was held in a new venue and had a record attendance of 1600 registered participants. The program was of the highest quality and the Congress has become one of the most important events in the specialty in America.

On Thursday morning, the first day of the congress, I was discussing with a colleague the positive atmosphere and energy of the attendees as they moved from room to room. I observed young cardiologists who were perhaps presenting their first e-poster, or friends or fellow workers chatting casually in the rest area while drinking a coffee. We concurred that, with this universe of women and men, with so much desire to learn, work and progress, we Argentines do not deserve to have a country in this situation. Or rather we do not deserve a political leadership that has contributed to a serious structural decline over the past few decades.

The current economic situation has resulted in an impoverishment of our country. We are world champions of inflation. Our country is placed 66th out of 67 countries in the global competitiveness index. Our healthcare system is broken, and it has never been a political priority for any government. We demand access to first-world medicine that nobody wants to pay. Indeed, we, the SAC (along with 35 other scientific societies), have been sued for cartelization by a consumer association for attempting to defend a fair consultation fee. It is our intention to continue working towards this goal. We are experiencing a number of different simultaneous inflationary processes, which are affecting all the spheres of our daily lives. People speak of winners and losers in these economic processes. **Strange, isn't it?** I certainly know two losers: patients and workers...including healthcare workers... that is, all of us. From the SAC, we have been working with the group *Cardiología Unida*, which brings together the country's leading scientific societies and colleges, as well as 57 other scientific societies that make up *Sociedades Médicas Unidas*, a group focused on producing changes. It is a challenging undertaking in a country where there is a lack of intermediaries. We have made some progress. The scientific societies are among the few institutions that can still be relied upon in our country. We want all cardiologists to engage in policy-making wherever they are, implementing actions that will benefit the common good. And from the SAC, we are pleased to offer you a platform for a constructive struggle, with a focus on consensus-building and the multiplication of efforts that will allow us to provide tools that will help to build new solutions after so many years of decline.

Víctor Mauro MTSAC
President of the Argentine Society of Cardiology

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