Argentine Journal of Cardiology
Revista Argentina de Cardiología

OCTOBER 2022 - Vol 90 Nº 5 ISSN 2314-2278 www.sac.org.ar

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

Argentine Journal of Cardiology / Revista Argentina de Cardiología

The Argentine Journal of Cardiology / Revista Argentina de Cardiología (AJC/RAC) is a peer-reviewed bimonthly journal published by the Argentine Society of Cardiology. AJC/RAC was founded in 1934 by a group of scientists headed by Blas Moia and Eduardo Braun Menéndez. Its main objective is to disseminate original research articles in cardiology in Latin American countries, keeping cardiologists updated on advances in the diagnosis and treatment of cardiovascular diseases. Initially in Spanish, nowadays AJC/RAC is published bimonthly also in English, both in paper and in electronic versions (http://ppct.caicyt.gov.ar/index.php/rac and http://www.sac.org.ar/web/es/revista-argentina-de-cardiologia). The AJC/RAC also provides immediate full open access to its contents based on the principle of supplying free investigation material to the readers and encouraging greater sharing of knowledge.

The AJC/RAC publishes original articles on basic, clinical or epidemiological research on different areas of cardiology. It also includes editorials, brief and case reports, controversies, reviews, images in cardiology, consensus and letters to the editor. The front pages of the AJC/RAC include Argentine artwork from local artists, in order to show the close relationship between art and science.

AJC/RAC plays a dynamic role in the encouragement and diffusion of local scientific and intellectual production throughout the region. Its local Editorial Board is formed by a group of specialists, independent from the political authorities of the Argentine Society of Cardiology, as well as from the pharmaceutical, medical equipment and device industries. The International Editorial Board comprises distinguished cardiologists mainly from Europe and America who help with the continuous improvement of the journal quality.

The AJC/RAC is included, under its abbreviated Spanish title only (Rev Argent Cardiol), in LILACS database (Literatura Latino-Americana e do Caribe em Ciências da Saúde), SCOPUS, EMBASE, LATINDEX; SciELO, Dialnet, DOAJ (Directory of Open Access Journals) Redalyc and U.S. National Library of Medicine (NLM). The "Information for Authors and Guidelines for Manuscript Submission" can be viewed in English and Spanish on the AJC/RAC website (http://ppct.caicyt.gov.ar/index.php/rac and http://www.sac.org.ar/web/es/revista-argentina-de-cardiologia) and in all February issues of the journal.

ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 90 N° 5 OCTOBER 2022
Scientific and administrative address
Azcuénaga 980 - (1115) Buenos Aires - Argentina / Tel.: +54-11-4961-6027/8/9 / Fax: +54-11-4961-6020 / e-mail: revista@sac.org.ar
web site: www.sac.org.ar / http://ppct.caicyt.gov.ar/index.php/rac
Editorial and graphic production
CF Brand Design & Communication- e-mail: estanislao@cfdisenografico.com.ar / www.cfdisenografico.com.ar
Printing: Pymedia - Gandolfo 1106, Victoria, San Fernando - www.pymedia.com.ar
This paper meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper)

VOL 90 Nº 5
OCTOBER 2022

Summary

EDITORIAL

The Importance of Volumetric Stress Echocardiography: the Contractile Reserve in the Stress Echo Lab

La importancia de la ecocardiografía volumétrica de estrés: la reserva contráctil en el laboratorio de Eco Estrés

LAURO CORTIGIANI[1]

LEFT VENTRICULAR VOLUMES: TOO BORING TO MEASURE?

Quantitative measurements of left ventricular (LV) end-diastolic volume (EDV) and end-systolic volume (ESV) are not routinely employed in many laboratories since they are time-consuming and not so reproducible for image degradation during stress. Ejection fraction (EF) is usually accurately estimated by eyeballing but the measurement of LV volumes requires a quantitative assessment with endocardial border delineation of LV planimetry by hand (1). Yet, good pathophysiological reasons and recent technological innovations make such measurements simpler and more reliable.

LV CONTRACTILE RESERVE: THE PATHOPHYSIOLOGICAL RATIONALE

LV contractile reserve can be obtained as the increase from rest to stress in load-dependent EF, or a geometry-independent, quantitative, global longitudinal strain which is however limited by high heart rate during stress. According to Marwick 2022, "*perhaps the best way to integrate the role of loading in the evaluation of LV function is to ensure that the measurement of blood pressure should be included in imaging studies that could be used clinically to estimate contractility*" (2). Elastance (also known as Force) does that (3, 4). Similar information can be obtained with other indices assessing the global contractile reserve independently of regional function, from stroke volume to cardiac output to cardiac power. There is more information in the assessment of global LV performance that can be detected simply with regional wall motion abnormalities. From a pathophysiological perspective, this is not surprising. The perfusion of the subendocardial layer is linked to regional wall thickening and regional wall motion abnormality, but a scar, necrosis, or subepicardial layer damage do not affect changes in regional wall motion. The subendocardial layer develops intracavitary and systolic blood pressure (SBP), and the subepicardial layer has an anti-remodeling, volume-reducing, effect. Therefore, myocardial damage or ischemia can be missed by regional wall motion abnormality and detected as a lower force reserve since a diseased myocardium develops less force (SBP/ESV). Subendocardial damage develops lower SBP. Subepicardial damage is associated with a higher ESV for each level of SBP. This is true even at rest, and we know for 50 years that for every level of EF, higher ESV and lower SBP at rest correspond to a worse prognosis. The same happens during stress.

LV CONTRACTILE RESERVE: THE TECHNOLOGY PUSH

EDV, ESV, and EF are part of the minimum data set recommended during Stress Echo for the detection of coronary artery disease, and outside coronary artery disease. However, analysis is usually qualitative with side-by-side comparison, without measurement. As a result, mostly qualitative patterns have been identified, with the normal response characterized by an increase in EDV and a decrease in ESV during stress, with an increase in EF. The identification of the endocardial contour of the left ventricle can be easier, faster, and more precise with ultrasound-enhancing agents, real-time 3-dimensional echocardiography, and artificial intelligence. The time for automated, precise, reproducible, click-free calculation of LV volumes has come. No more boring, time-consuming, imprecise planimetric calculations. Without tedious effort, we have real-time calculations of EDV (an index of preload reserve), ESV (an index of contractile reserve), and cardiac output (an index of cardiac reserve). The reduction of the cardiac reserve is a common condition, can occur in the absence of regional wall motion abnormalities, and recognizes 3 different hemodynamic phenotypes: chronotropic insufficiency (reduction of heart rate reserve by 1-lead electrocardiogram), preload insufficiency (lack of increase in EDV at intermediate stages of stress), inotropic insufficien-

Rev Argent Cardiol 2022;90:319-320. http://dx.doi.org/10.7775/rac.v90.i5.20563

SEE RELATED ARTICLE: Rev Argent Cardiol 2022;90:239-335. http://dx.doi.org/10.7775/rac.v90.i5.20560

Address for reprints: Lauro Cortigiani. San Luca Hospitalm Via Guglielmo Lippi Francesconi. 55100 Lucca – Italy. E-mail: lacortig@tin.it

[1] Cardiovascular Unit, San Luca Hospital, Lucca, Italy

cy (blunted force reserve with lack of ESV reduction). This parameter is universal (does not require proprietary technology), omnivorous (important for all patients, from chronic coronary syndromes to heart failure), and ecumenic (applied to all stresses, from exercise to dobutamine to vasodilators, obviously with different stress-specific cutoff values) (5, 6).

STRESS ECHO 2.0: ANOTHER BRICK IN THE WALL

The Argentinian echocardiographic community is at the leading edge of innovation for decades. The regional wall motion abnormality is the cornerstone of stress echocardiography and was upgraded 20 years ago by the addition of coronary flow velocity reserve in the left anterior descending coronary arteries. After decades from the 2003 pioneering experience of the group of Jorge Lowenstein (7), coronary flow velocity reserve of the left anterior descending with transthoracic Doppler echocardiography is recommended (class 2b) by the 2021 American College Cardiology/American Heart Association guidelines in INOCA patients (8). After 20 years, the same Lowenstein group identifies another game-changer, the global LV contractile reserve, beyond EF. The elastance reserve during exercise identifies troublemakers missed by regional wall motion abnormalities and EF, allows better phenotyping of the patient, and improves risk stratification. The fourth wave of innovation improves the versatility and performance of stress echo: after regional wall motion abnormality, coronary flow velocity reserve, B-lines, now LV contractile reserve with automated volumetric Stress Echo. The required images are the same acquired and stored for analysis in regional wall motion, and there is no increase in imaging and analysis time with the automated approach. Stress Echo is able to capture the many aspects of the prognostic vulnerability of the contemporary patient and does it with a technique run by cardiologists living an imaging experience, with affordable costs, ionizing radiation-free, near zero environmental impact, and unique versatility and sustainability (9). Once again, the group of Jorge Lowenstein from Buenos Aires showed to the entire scientific community that this conceptual and clinical upgrade can take place in a clinically oriented, busy environment, and simple pathophysiological concepts coupled with state-of-the-art technology can bring surprising dividends to the patient (10). Hopefully, the uptake of this important concept by mainstream cardiology will take less than 20 years.

Conflicts of interest

None declared.

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

REFERENCES

1. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, et al. Guidelines for Performance, Interpretation, and Application of SE in Ischemic Heart Disease: From the American Society of Echocardiography. J Am Soc Echocardiogr 2020;33:1-41. https://doi.org/10.1016/j.echo.2019.07.001

2. Marwick T, Negishi K. Global LV systolic function: EF versus strain. American Society of Echocardiography's Comprehensive echocardiography. Editors: Lang RM, Goldstein SA, Kronzon I, Khanderia BK, Mor-Avi V. Elsevier, Philadelphia; 2022. Chapter 24, pp 146-9.

3. Ginzton LE, Laks MM, Brizendine M, Conant R, Mena I. Noninvasive measurement of the rest and exercise peak systolic pressure/ESV ratio: a sensitive two-dimensional echocardiographic indicator of LV function. J Am Coll Cardiol 1984;4:509-16. https://doi.org/10.1016/S0735-1097(84)80094-7

4. Bombardini T, Correia MJ, Cicerone C, Agricola E, Ripoli A, Picano E. Force-frequency relationship in the echocardiography laboratory: a noninvasive assessment of Bowditch treppe? J Am Soc Echocardiogr 2003;16:646-55. https://doi.org/10.1016/S0894-7317(03)00221-9

5. Cortigiani L, Huqi A, Ciampi Q, Bombardini T, Bovenzi F, Picano E. Integration of Wall Motion, Coronary Flow Velocity, and LV Contractile Reserve in a Single Test: Prognostic Value of Vasodilator SE in Patients with Diabetes. J Am Soc Echocardiogr 2018;31:692-701. https://doi.org/10.1016/j.echo.2017.11.019

6. Cortigiani L, Sorbo S, Miccoli M, Scali MC, Simioniuc A, Morrone D, et al. Prognostic value of cardiac power output to LV mass in patients with LV dysfunction and dobutamine stress echo negative by wall motion criteria. Eur Heart J Cardiovasc Imaging 2017;18:153-8. https://doi.org/10.1093/ehjci/jew073

7. Lowenstein J, Tiano C, Marquez G, Presti C, Quiroz C. Simultaneous analysis of wall motion and CFR of the left anterior descending coronary artery by transthoracic Doppler echocardiography during dipyridamole stress. J Am Soc Echocardiogr 2003;17:735-44. https://doi.org/10.1016/S0894-7317(03)00281-5

8. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021;78:e187–e285. https://doi.org/10.1161/CIR.0000000000001029

9. Picano E. Sustainability of medical imaging. Education and debate. BMJ J 2004;328:578-80. https://doi.org/10.1136/bmj.328.7439.578

10. Lowenstein Haber D M, Arbucci R, Merlo P, Martinex L, Gastaldello N, Saad AK, et al. Contractile reserve by left ventricular EF alone or considering elastance. Which is the best predictor of events after a stress echo without ischemia? Rev Argent Cardiol 2022;90:329-335 https://doi.org/10.7775/rac.v90.i5.20502

EDITORIAL

Cardiovascular risk factors, violence and inequities affect us all

Los factores de riesgo cardiovascular, la violencia y las inequidades nos afectan a todos

ANA SALVATI[MTSAC]

The practice of Cardiology has undergone unprecedented changes in recent decades, which undoubtedly have an impact on professionals in various spheres, and affect their physical well-being and quality of life. The growing increase in the female presence in healthcare activities and in academic life has introduced changes in the way of practicing medicine. Cardiology was historically a specialty dominated by men, but progressively we are witnessing its feminization. This year, for the first time, in the residences that are undergoing their theoretical training at the Argentine Society of Cardiology, the number of women exceeds the number of men.

The American College of Cardiology conducts the Professional Life Survey among cardiologists approximately every 10 years to learn demographic characteristics, job preferences, and level of satisfaction in the specialty. (1) Having this information allows us to know the reality that health professionals live and introduce changes to improve the level of satisfaction and quality of life.

In Argentina, due to the lack of our own information, we frequently extrapolate data from other countries, which may have characteristics that are different from ours. The survey carried out by Dr. Verónica Crosa et al., from the Heart and Women Area , opens a window for us to begin to learn about our reality, simultaneously addressing two very important aspects: on the one hand, it tries to define the prevalence of cardiovascular risk factors in a specific population group, and on the other hand, it inquires about professional well-being, violence and labor equity among doctors belonging to the registry of members of the Argentine Society of Cardiology who voluntarily and anonymously agreed to complete the questionnaire.

Approximately 10% of the professionals contacted answered the survey. Female representation was high, as women made up more than 40% of those surveyed. The women belonged to a younger age group than men, probably because the majority of women have entered entering the practice of Cardiology more recently.

One of the aspects investigated in this survey is related to cardiovascular risk factors. If we compare the results with those reported in the last National Survey of Risk Factors (ENFR), (2) conducted in Argentina during 2018, the prevalence of obesity, sedentary lifestyle, and smoking was lower among female cardiologists than what was observed in the general population, and compared to their male colleagues, women had fewer risk factors than men. Arterial hypertension and diabetes were also less prevalent among professionals than in the ENFR population.

Consultation for periodic cardiology evaluation was more frequent in men, and this should make us reflect on very internalized attitudes in women, of assuming a role of caretaker and leaving aside their own care on many occasions.

It is interesting to observe how certain patterns referring specifically to the professional sphere are repeated in different countries. (1) The workload in this survey was considered excessive by both sexes. The pandemic exacerbated this feeling, but it had a greater impact on women. In a paper published jointly by the ACC, AHA, ESC, and WHF in 2021 on physician well-being, the burnout rate in cardiology was found to affect 25% of physicians, with another 50% reporting feeling stress, both entities being more common among women, (3) comparable to the survey observations.

Dissatisfaction with financial remuneration did not follow the same parallelism as workload. Three out of four women considered that their remuneration was not adequate for their academic training and dedication, while in men this relationship was 6 out of 10, showing once again that the premise of equal remuneration for similar tasks performed is not respected.

The profession also determines family planning more frequently in women than in men, resulting in fewer female cardiologists being married, with a partner or with children. And caring for children impacts professional development much more in women than in men. It continues to be frequently reported that

Rev Argent Cardiol 2022;90:321-322. http://dx.doi.org/10.7775/rac.v90.i5.20567

SEE RELATED ARTICLE: Rev Argent Cardiol 2022;90:323-328. http://dx.doi.org/10.7775/rac.v90.i5.20562

[1] Expresident of Sociedad Argentina de Cardiología
[2] President of Fundación Cardiológica Argentina
[3] Medical consultant of Coronary Unit of Hospital de Clínicas - UBA

in job interviews women are questioned about their expectations regarding future pregnancies, this response often being taken into account with the same hierarchy as professional aptitude to define incorporation. (4)

In the United States, women less frequently occupy the place of first or last author in scientific publications, a fact that negatively conditions the possibility of promotion to hierarchical academic positions. (5) This reality is replicated in Argentina.

Women are also underrepresented in management and responsibility positions in Cardiology societies in our country, and in specialty congresses the number of exhibitors clearly leans towards the male sex.

The results related to violence are very impressive. The fact that 58% of women report having suffered situations of gender violence in their work environment challenges us as a society and should make us reflect on behaviors that are unacceptable among professionals. These levels of violence are infinitely lower in the case of men.

Reviewing our own information helps us understand local realities and plan strategies to modify them. We should think about more flexible forms of work activity and continuous medical training to facilitate the incorporation of women, especially during periods of pregnancy or during the first years of their children's lives, and thus avoid expulsion from the system. Undoubtedly, there is still a long way to go towards a more equitable practice of the profession and associated with a level of satisfaction that makes it possible to eliminate an additional stressor that impacts the emotional and cardiovascular health of those who take care of the population.

Conflicts of interest
None declared.

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

REFERENCES

1. Lewis SJ, Mehta LS, Douglas PS, Gulati M, Limacher MC, Poppas A, et al; American College of Cardiology Women in Cardiology Leadership Council. Changes in the Professional Lives of Cardiologists Over 2 Decades. J Am Coll Cardiol 2017;69:452-62. https://doi.org/10.1016/j.jacc.2016.11.027

2. Encuesta Nacional de Factores de Riesgo (4ta edición) Ministerio de Salud de la Nación, 2018. https://biblioteca.indec.gob.ar/bases/minde/enfr_2018_resultados_definitivos.pdf

3. Mehta LS, Elkind MSV, Achenbach S, Pinto FJ, Poppas A. Clinician Well-Being-Addressing Global Needs for Improvements in the Health Care Field: A Joint Opinion From the American College of Cardiology, American Heart Association, European Society of Cardiology, and the World Heart Federation. Circulation 2021;144(7):e151-e155. https://doi.org/10.1161/CIRCULATIONAHA.121.055748.

4. Sarma AA, Nkonde-Price C, Gulati M, Duvernoy CS, Lewis SJ, Wood MJ; American College of Cardiology Women in Cardiology Leadership Council. Cardiovascular Medicine and Society: The Pregnant Cardiologist. J Am Coll Cardio. 2017;69:92-101. https://doi.org/10.1016/j.jacc.2016.09.978.

5. Sharma G, Sarma AA, Walsh MN, Hayes SN, Sahni S, Brown SA, et al; American College of Cardiology Women in Cardiology Leadership Council and Diversity and Inclusion Task Force. 10 Recommendations to Enhance Recruitment, Retention, and Career Advancement of Women Cardiologists. J Am Coll Cardiol 2019;74:1839-42. https://doi.org/10.1016/j.jacc.2019.08.016.

ORIGINAL ARTICLE

Labor Equity, Gender Violence and Cardiovascular Risk Factors in Cardiology Specialists

Equidad laboral, violencia de género y factores de riesgo cardiovascular en especialistas en cardiología argentinos

VERÓNICA LÍA CROSA[1], ALEJANDRA AVALOS ODDI[1], SILVINA VERDUGO[1], YANINA CASTILLO COSTA[2, MTSAC], LEONARDO CÁCERES[2, MTSAC], BIBIANA RUBILAR[1, MTSAC]

ABSTRACT

Background: Cardiology specialists may suffer from stressors that affect their health, such as labor inequity and gender violence, in addition to traditional cardiovascular risk factors (RF) for cardiovascular disease (CVD).
Objective: The aim of this study was to detect the level of well-being, labor equity and gender violence and to establish the prevalence of CRF in cardiology specialists in Argentina.
Methods: This was an observational, cross-sectional study through an anonymous survey conducted in September 2021 among specialists included in the Argentine Society of Cardiology registry. Data on labor equity, labor and domestic violence and CRF were collected.
Results: Six hundred and eleven professionals (40.5% women) participated in the survey: 63% worked more than 44 hours per week; 3 out of 10 were on duty for 12 or 24 hours (38.5% women vs. 28% men, p<0.01). Seventy-two percent of respondents considered the workload excessive while 70% thought their payment was not in accordance with the academic training. Half of female cardiologists surveyed considered that motherhood limited professional development in the specialty. Work-related violence was more frequent in female cardiologists (58% vs. 10% p <0.01), as was domestic violence (16% vs. 6% p <0.01). Men were more overweight (67% men vs. 34% women, p <0.01) and obese (16% vs. 11%, p <0.01) and women were more sedentary (53% vs. 45%, p <0.01).
Conclusion: The disconformity in working conditions experienced by both genders was evident, as was the evidence of higher workplace and domestic gender violence in the female specialists surveyed. Despite having knowledge about CVD and cardiovascular RF, the surveyed specialists have a high prevalence of RF.

Keywords: Cardiologists - Gender Equity - Heart Disease Risk Factors - Gender-Based Violence - Workplace Violence - Argentina.

RESUMEN

Los especialistas en cardiología pueden sufrir estresores que afecten su salud, como inequidad laboral y violencia de género, además de padecer factores de riesgo (FR) tradicionales para enfermedad cardiovascular (ECV)
Objetivo: detectar el nivel de bienestar, equidad laboral y violencia de género y conocer la prevalencia de los FR en especialistas en cardiología en Argentina
Método: Estudio observacional, de corte transversal a través de una encuesta anónima realizada en septiembre de 2021 a los especialistas del padrón de la Sociedad Argentina de Cardiología. Se recabaron datos sobre equidad laboral, violencia laboral y doméstica y FR.
Resultados: Participaron 611 profesionales (40,5% mujeres). El 63% trabajaba más de 44 horas semanales; 3 de cada 10 cumplían guardias de 12 o 24 horas (38,5% mujeres vs 28% varones, p<0,01). El 72% consideró excesiva la carga laboral, con remuneración no acorde a su formación académica (70%). La mitad de las cardiólogas encuestadas consideró que la maternidad limitó el desarrollo profesional en la especialidad. La violencia de género laboral fue más frecuente en las cardiólogas (58% vs 10% p< 0,01) al igual que la violencia doméstica (16% vs 6% p< 0,01). Los varones tenían más sobrepeso (67% vs 34% las mujeres, p<0,01) y obesidad (16% vs 11%, p<0.01) y las mujeres resultaron ser más sedentarias (53% vs 45%, p< 0,01).
Conclusión: resultó evidente la disconformidad en las condiciones laborales en ambos genderos y la mayor prevalencia de violencia de género laboral y doméstica en las especialistas mujeres encuestadas. A pesar de contar con el conocimiento sobre ECV y FR los especialistas encuestados tienen una alta prevalencia de FR.

Palabras claves: Cardiólogos - Equidad de Género - Factores de Riesgo de Enfermedad Cardíaca - Violencia de Género - Violencia Laboral - Argentina

Rev Argent Cardiol 2022;90:323-328. http://dx.doi.org/10.7775/rac.v90.i5.20562

SEE RELATED ARTICLE: Rev Argent Cardiol 2022;90:321-322.. http://dx.doi.org/10.7775/rac.v90.i5.20567

Received: 07/10/2022 – *Accepted:* 09/02/2022

[1] Dr. Liliana Grinfeld Heart and Woman Area of the Argentine Society of Cardiology, Buenos Aires, Argentina.
[2] Research Area of the Argentine Society of Cardiology, Buenos Aires, Argentina.

INTRODUCTION

The practice of healthcare can operate as a stressor, and it is very likely that in the face of the health emergency generated by the COVID-19 pandemic, situations of work overload and labor inequity were exacerbated. Undoubtedly, the COVID-19 pandemic had a strong impact on the professional, personal and emotional lives of health professionals. (1,2) In the case of women, the effort to adapt to this new reality was aggravated by the historical caring role of their family environment.

In addition, evidence shows that women face more professional limitations, discrimination, gender harassment, inadequate remuneration and lack of opportunities in hierarchical positions. (3-5)

Recently, certain under-recognized conditions have been described that affect cardiovascular health in both genders, but which have a greater impact on the female gender, such as gender violence, low socioeconomic status, literacy level and environmental factors (6). These psychosocial and socioeconomic determinants can affect health, predisposing to the development of cardiovascular disease (CVD) and/or accelerating the progression of preexisting disease, adding their impact to that of traditional cardiovascular risk factors (CRF).

Cardiovascular disease is the leading cause of morbidity and mortality today. Cardiology specialists strive every day to control the CRF for CVD in their patients with the aim of reducing it. (7,8)

The impact of classic CRF such as hypertension (HTN), hypercholesterolemia, cigarette smoking, overweight, and sedentary lifestyle is widely known in both genders. In the case of women, gender-specific factors are added (early menarche, early menopause, and pregnancy complications, among others). (9-13)

Health professionals are not exempt from suffering from these CRF for CVD and, in the current conditions of health emergency it is very likely that they have postponed self-care and control of these CRF. Moreover, despite understanding the risks, cardiology specialists do not always put into practice the recommendations they give to their patients.

OBJECTIVE

We conducted a survey with the aim of detecting the level of well-being, work equity and gender violence and to assess the prevalence of CRF in cardiology specialists in Argentina.

METHODS

This was an observational, cross-sectional study, carried out through an on-line digital form survey with 49 closed, self-referential, anonymous and voluntary questions. The RedCap platform was used.

The survey was sent during the month of September 2021 by e-mail and Whatsapp inviting cardiology specialists belonging to the member registry of the Argentine Society of Cardiology (SAC) to participate.

Data on age, weight, height and waist circumference, traditional CRF, and personal and family history of CVD were collected.

Information was obtained on the profession, years of specialty, scope of work activity, population density and region of the site where they practice, weekly workload in hours, 12- or 24-hour medical shifts, and travel time to workplace. Questions were also asked about professional well-being. Both genders were interrogated about labor and domestic gender violence (physical, psychological, sexual and institutional violence based on sexual orientation and/or gender identity, UN) (14), as well as on their emotional sphere and personal life data, such as marital status and cohabitation situation.

Women were also asked about professional growth in relation to motherhood; in addition to questions about gender-related CRF such as obstetric history and menopause.

In both genders, information was collected on behaviors and habits (exercise, alcohol consumption, type of diet, sleep quality), and health controls as well as other non-conventional CRF (cancer and autoimmune diseases).

Statistical analysis

Qualitative variables are presented as frequencies and percentages with their confidence intervals. Mean ± standard deviation (SD) or median and interquartile range (IQR 25-75) were used to describe quantitative variables, according to their distribution.

The analysis of discrete variables was performed using the chi-square test or Fisher's test, as appropriate, and that of continuous variables with the t test or Mann Whitney test, and in the case of 3 or more groups with ANOVA or Kruskall Wallis tests, as appropriate. A p value <0.05 was considered significant.

The analysis was performed using Epi Info 7.2.2.6.

Ethical considerations

Given that it was an anonymous, self-referential and voluntary participation survey, the SAC ethics committee waived an informed consent.

RESULTS

A total of 611 cardiology specialists participated. Among them, 59.5% were men, 40.5% women and 75% were between 30 and 60 years of age. Women were younger than men (age between 30 and 60 years, 87% vs. 67%, $p<0.01$).

Forty-four per cent of the specialists surveyed reported more than 20 years of professional experience and the majority (71%) resided in Buenos Aires (Autonomous City or province).

There were no differences by gender in the number of hours worked, with 63% of them working over 44 hours per week. Medical shifts of 12 or 24 hours prevailed in female specialists (38% vs. 28% $p<0.01$).

Regarding the perception of well-being and labor equity, 66% of specialists considered that the workload was excessive, with no differences by gender.

Eighty-four per cent of those surveyed considered that the COVID-19 pandemic had generated an overload in the working or personal sphere, and this perception was higher among women (88% vs. 80%, $p<0.01$).

More than half (66%) of specialists considered that

their remuneration was not in line with their professional and academic training, (75% women vs 60% men, p<0.01), but despite this, 72% would choose the same specialty again and only 18% would choose another non-medical profession.

Sixty-two per cent of female specialists considered that motherhood limited their professional development.

Married status was higher among men (70% vs. 46%, p <0.01).

Regarding exposure to gender violence, this reality was significantly more frequent in women, both in the workplace (58% vs. 10%, p<0.01) (Figure 1) and at home (16% vs. 10%, p<0.01) (Figure 2).

Regarding the conventional CRF surveyed, 19% admitted having HTN, which was more frequent in men (26% vs. 18%, p <0.01). There were no gender differences in the occurrence of diabetes (4%), current (3%) or former (28%) cigarette smoking, and family history of CVD (50%). Men had more frequently history of CVD (6% vs. 1% p=0.03). Autoimmune disease was more frequent in women (16% vs. 5%, p<0.01) and there were no differences in the history of oncological disease (Table 1).

Overweight and obesity were more frequent in men. A total of 54% of respondents, mainly men, presented a body mass index (BMI) >25 (67% vs. 34%, p <0.01). A BMI >30, in the obesity range, was recorded in 14% of all the specialists surveyed (16% vs. 11%, p=0.04).

Women were more sedentary (47% vs. 55%, p=0.03). In 78% of cases, specialists considered that they followed a healthy diet; 6% reported regular alcohol consumption, which was more frequent in men (7% vs. 3% p <0.01). In 9% of cases, respondents reported sleeping difficulties which was a more frequent disorder in women (11% vs. 8%, p<0.01) and 5% reported disinterest, negative thoughts or unhappiness, again more frequent in women (7% vs. 3%, p=0.02) (Table 1).

Regarding health controls, men and women had the same blood pressure assessments (94%); however, men had a more frequent cardiological check-up (81% vs. 73%, p <0.01). Median total cholesterol was 180 mg/dL, LDL cholesterol 101 mg/dL and HDL cholesterol 51 mg/dL, the latter higher in women (56 mg/dL vs. 48 mg/dL, p <0.01). In the case of triglycerides, the median value was 112 mg/dL, significantly higher in men (125 mg/dL vs. 96 mg/dL, p <0.01). (Table 2)

In 57% of cases, respondents reported consuming some type of medication on a regular basis, with no differences by gender. Among the most used drugs

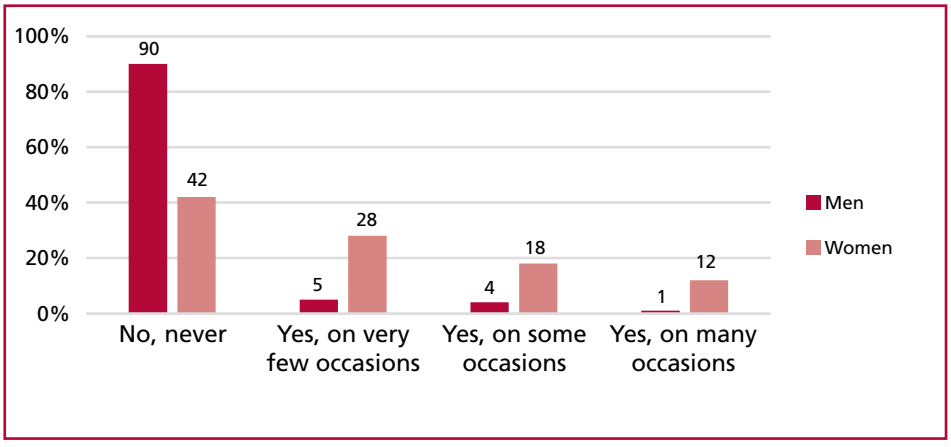


Fig. 1. Exposure to gender-based violence in the workplace

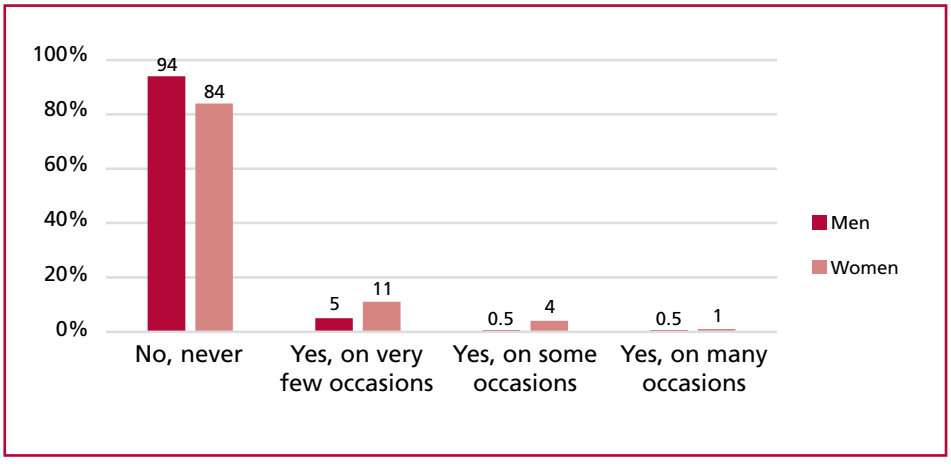


Fig. 2. Exposure to gender-based violence at home

were antihypertensives (27%) and lipid-lowering drugs (26%), both more frequently in men (26% vs. 8%, p<0.01 and 36% vs. 11%, p <0.01) and no differences by gender were encountered for anxiolytics (11%), aspirin (3%) and antidepressants (2%).

DISCUSSION

This survey was unbiased in terms of gender, since the participation of women was 40.5%.

Most specialists fulfill a workload that they perceive as excessive, and show some disagreement regarding the remuneration received based on their academic training. Labor inequity operates as a chronic stress factor for workers and healthcare professionals, and the enormous work and emotional burden of the pandemic has been added to this condition. (15)

More than half of females considered that motherhood limited their professional development to some extent, given the inequality faced by women to fulfill their work and the assignment of the role of care in the family environment. In countries of the European Union and the United States, gender differences among cardiology specialists have been documented for years, but in Latin America it still is a relatively unexplored field. (16). Globally, a trend towards the feminization of medical work has been detected and some authors propose that women have qualities that allow a different medical practice from that of men. Women can improve doctor-patient relationship and promote teamwork due to personality characteristics attributable to the female gender such as compassion, empathy, responsiveness to patient needs, and com-

Table 1. Characteristics of the population surveyed

	Global n= 611	Women n=247	Men n=364	p
Age between 30 and 60 years (n,%)	460 (75)	217 (88)	243 (67)	<0.01
HTN (n,%)	114 (19)	21 (18)	93 (26)	<0.01
Diabetes (n,%)	22 (4)	9 (4)	13 (4)	NS
Smoking (n,%)	21 (3)	11(4)	10 (3)	NS
Former smoking (n,%)	171 (28)	67 (27)	104 (28)	NS
Total cholesterol (median and IQR)	180 (160-202)	183 (160-201)	180 (162-203)	NS
LDL cholesterol (median and IQR)	101 (85-121)	106 (86-122)	100 (85-121)	NS
HDL cholesterol (median and IQR)	51 (45-60)	56 (50-68)	48 (44-56)	<0.01
TG (median and IQR)	112 (90-144)	96 (73-120)	125 (100-154)	<0.01
Exercise >150 min/week	315 (52)	116 (47)	199 (55)	0.03
Waist >88 cm (n,%)	-	73 (30)	-	-
Waist >102 cm (n,%)	-	-	91 (26)	-
BMI >25 (n,%)	329 (54)	84 (34)	245 (67)	<0.01
BMI >30 (n,%)	87 (14)	28 (11)	59 (16)	0.04
Family history. (n,%)	306 (50)	133 (54)	173 (47)	NS
CVD (n,%)	27 (6)	3 (1)	24 (6)	0.03
Cancer (n,%)	36 (6)	15 (6)	21 (6)	NS
Autoimmune disease (n,%)	59 (10)	39 (16)	20 (5)	<0.01
Alcohol >4 times/week (n,%)	36 (6)	9(3)	27 (7)	<0.01
Healthy diet <4 times/week (n,%)	194 (32)	73 (29)	121 (33)	NS
Sleep disturbances >4 times/week (n,%)	58 (9)	27 (11)	31 (8)	<0.01
Disinterest >4 times/week (n,%)	31 (5)	18 (7)	13 (3)	0.02
Irritability >4 times/week (n,%)	40 (6)	17 (7)	23 (6)	NS

CVD: Cardiovascular disease. HTN: Hypertension. TG: Triglycerides. BMI: Body mass index. IQR: Interquartile range

Table 2. Controls of the population surveyed. BP: Blood pressure.

	Global n= 611	Women n=247	Men n=364	p
BP control <1 year (n,%)	572 (94)	231 (94)	341 (94)	<0.01
Laboratory control <1 year (n,%)	469 (77)	201 (82)	268 (75)	NS
Dietary-hygienic measures (n,%)	475 (78)	195 (78)	280 (77)	NS
Any cardiological check-up (n,%)	472 (78)	179 (73)	293 (81)	<0.01

munication skills. Despite these qualities, there is an ambivalent view on the growing number of women in medicine, both in the healthcare role and in the scientific and academic fields. (17) In this sense, they are greatly underrepresented in the positions of author, reviewer and editor in scientific and medical journals. (18) There are many determinants that prevent the full participation and contribution of women in these spheres, the result of which is their unjustified invisibility. (19-21) Differences in lifestyle and the responsibilities of motherhood have been proposed as possible factors; however, the American College of Cardiology "Women in Cardiology" Professional Life Survey found that women are significantly less likely to interrupt their medical practice for a year or more as mothers. (22,23)

In the surveyed population, gender violence was significantly higher in women, both in the workplace and at home. This type of violence has serious consequences by preventing women from participating fully and on an equal footing in society. (24-26) The emotional effect associated with gender violence has been widely demonstrated as a CRF associated with CVD, with alterations in platelet reactivity and increased risk of coronary heart disease, in addition to a higher incidence of depression and suicide. (27-30)

When analyzing the conventional CRF in the surveyed population compared with the data obtained from the general Argentine population in the National Risk Factors Survey (NRFS) carried out in 2018 (31), it is observed that specialists in cardiology are a healthier group since their HTN prevalence is lower (19% vs. 34.7%), there is a lower prevalence of diabetes (4% vs. 12.7%) and they smoke less (3% vs. 22.2%). Undoubtedly, the sanction of the anti-tobacco law 26 687 generated a strong impact on the health of the Argentine population, (32) and among the specialists surveyed the condition of ex-smoker was higher than in the NRFS (28% vs. 17.6%), which suggests a greater awareness about this important modifiable RF. Questions about the level of knowledge of one's own health were also included, showing a high perception of health control and knowledge of cholesterol levels. The overweight detected was higher than in the NRFS (54% vs. 36.3%) and, like obesity, both were more frequent in men.

The conditions and workloads of cardiology specialists in Argentina could explain the lack of regular adherence to healthy habits, resulting in overweight and a sedentary lifestyle.

Similarly to other countries, women continue to represent the group with the greatest labor demand regarding labor gender equity and the excess claim to fulfill different roles. (33)

CONCLUSION

The disconformity in working conditions in both genders was evident and the greater exposure to labor and domestic gender violence in the women surveyed was alarming.

Despite having knowledge about CVD and CRF, cardiology specialists are unable to internalize and transfer to themselves the recommendations they make to their patients.

Limitations

By having a non-probabilistic sampling, it is difficult to accurately establish the prevalence of CRF in the target population. There is also a disproportion, with a high participation of doctors from Buenos Aires, and low representation from the rest of the country. The information collected was reported by the participants, without corroborating the answers.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

REFERENCES

1. Murat M, Köse S, Savaşer S. Determination of stress, depression, and burnout levels of front-line nurses during the COVID-19 pandemic. Int J Ment Health Nurs 2021;30:533-43. https://doi.org/10.1111/inm.12818

2. García-Iglesias JJ, Gómez-Salgado J, Martín-Pereira J, Fagundo-Rivera J, Ayuso-Murillo D, Martínez-Riera JR, et al. [Impact of SARS-CoV-2 (Covid-19) on the mental health of healthcare professionals: a systematic review.]. Rev Esp Salud Publica 2020;94:e202007088.

3. Raymundo-Martínez GIM, Alanis-Estrada GP, Araiza-Garaygordobil D, Delgado-Cruz IV, Gopar-Nieto R, Cabello-López A, et al. Gender differences in cardiology professionals: A Latin American Survey. Arch Cardiol Mex 2022;92:11-8. https://doi.org/10.24875/ACM.200001591

4. Kang SK, Kaplan S. Working toward gender diversity and inclusion in medicine: myths and solutions. Lancet 2019;393:579–86. https://doi.org/10.1016/S0140-6736(18)33138-6.

5. Khan MS, Usman MS, Siddiqi TJ, Ayub MT, Fatima K, Acob C, et al. Women in Leadership Positions in Academic Cardiology: A Study of Program Directors and Division Chiefs. J Womens Health (Larchmt) 2019;28:225-32. https://doi.org/10.1089/jwh.2018.7135

6. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet 2021;397:2385-438. https://doi.org/10.1016/S0140-6736(21)00684-X

7. Norris CM, Yip CYY, Nerenberg KA, Clavel M, Pacheco C, Foulds HJA, et al. State of the Science in Women's Cardiovascular Disease: A Canadian Perspective on the Influence of Sex and Gender. J Am Heart Assoc 2020 18;9:e015634. https://doi.org/10.1161/JAHA.119.015634

8. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2020;141:e59. https://doi.org/10.1161/CIR.0000000000000754.

9. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, et al. Adverse Pregnancy Outcomes and Cardiovascular Disease Risk: Unique Opportunities for Cardiovascular Disease Prevention in Women: A Scientific Statement From the American Heart Association. Circulation 2021;143:e902-e916. https://doi.org/10.1161/CIR.0000000000000961

10. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, Michos ED, Minissian M, Pepine C, Vaccarino V, Volgman AS; ACC CVD Womens Committee Members. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women:

JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:2602-18. https://doi.org/10.1016/j.jacc.2020.03.060

11. Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS. The Use of Sex-Specific Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS. The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk. Circulation 2020;141:592-9. https://doi.org/10.1161/CIRCULATIONAHA.119.043429.

12. Young L, Cho L. Unique cardiovascular risk factors in women. Heart 2019;105:1656-60. https://doi.org/10.1136/heartjnl-2018-314268

13. Maas AHEM, Rosano G, Cifkova R, Chieffo A, van Dijken D, Hamoda H, et al. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. Eur Heart J 2021;42:967-84. https://doi.org/10.1093/eurheartj/ehaa1044

14. ONU Mujeres. Preguntas frecuentes: Tipos de violencia contra las mujeres y las niñas [Internet]. ONU Mujeres. Available from: https://www.unwomen.org/es/what-we-do/ending-violence-against-women/faqs/types-of-violence

15. Shanafelt TD, West CP, Sinsky C, Trockel M, Tutty M, Satele DV, et al. Changes in Burnout and Satisfaction With Work-Life Integration in Physicians and the General US Working Population Between 2011 and 2017. Mayo Clin Proc 2019;94:1681-94. https://doi.org/10.1016/j.mayocp.2018.10.023..

16. Kang SK, Kaplan S. Working towards gender diversity and inclusion in medicine: Myths and solutions. Lancet 2019;393:579-86. https://doi.org/10.1016/S0140-6736(18)33138-6.

17. Borracci RA, Salazar AI, Arribalzaga EB. El futuro de la feminización de la medicina en Argentina. Revista de la Fundación Educación Médica. 2018;21(3):113.

18. Lundine J, Bourgeault IL, Clark J, Heidari S, Balabanova D. The gendered system of academic publishing. Lancet 2018; 391:1754–6. https://doi.org/10.1016/S0140-6736(18)30950-4

19. Blumenthal DM, Olenski AR, Yeh RW, DeFaria Yeh D, Sarma A, Stefanescu Schmidt AC, et al. Sex Differences in Faculty Rank Among Academic Cardiologists in the United States. Circulation 2017;135:506–17. https://doi.org/10.1161/CIRCULATIONAHA.116.023520

20. Khan MS, Usman MS, Siddiqi TJ, Ayub MT, Fatima K, Acob C, et al. Women in Leadership Positions in Academic Cardiology: A Study of Program Directors and Division Chiefs. J Womens Health (Larchmt). 2019;28:225-32.

21. Asghar M, Usman MS, Aibani R, Ansari HT, Siddiqi TJ, Fatima K, et al.Sex Differences in Authorship of Academic Cardiology Literature Over the Last 2 Decades. J Am Coll Cardiol 2018;72:681-5. https://doi.org/10.1016/j.jacc.2018.05.047

22. Yeung C, Baranchuk A. Gender Equity Trends in Academic Productivity and Influence by Subspecialties of Cardiology. J Am Coll Cardiol 2018; 72:3228–9. https://doi.org/10.1016/j.jacc.2018.08.2203

23. Jagsi R, Fuentes-Afflick E, Higginbotham E. Promoting Equity for Women in Medicine - Seizing a Disruptive Opportunity. N Engl J Med 2021;384:2265-7. https://doi.org/10.1056/NEJMp2104228.

24. Qué hacemos: Poner fin a la violencia contra las mujeres [Internet]. ONU Mujeres. 2019. Available from: https://www.unwomen.org/es/what-we-do/ending-violence-against-women.

25. World Health Organization. World Health Organization [Internet]. Who.int. World Health Organization; 2022. Available from: https://www.who.int/

26. UK Government. Guidance: Domestic Violence and Abuse. UK Gov; 2016. Available at: https://www.gov.uk/government/news/new-definition-of-dome stic-violence.

27. Chandan JS, Thomas T, Bradbury-Jones C, Taylor J, Bandyopadhyay S, Nirantharakumar K. Risk of Cardiometabolic Disease and All-Cause Mortality in Female Survivors of Domestic Abuse. J Am Heart Assoc 2020;9: e014580. https://doi.org/10.1161/JAHA.119.014580.

28. Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, et al. Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease. Circulation 2015;132:965–86. https://doi.org/10.1161/CIR.0000000000000229

29. Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Arch Intern Med 2004;164:289-98. https://doi.org/10.1001/archinte.164.3.289

30. Samad Z, Boyle S, Ersboll M, Vora AN, Zhang Y, Becker RC, et al. Sex Differences in Platelet Reactivity and Cardiovascular and Psychological Response to Mental Stress in Patients With Stable Ischemic Heart Disease. J Am Coll Cardiol 2014;64:1669-78. https://doi.org/10.1016/j.jacc.2014.04.087.

31. 4° Encuesta Nacional de Factores de Riesgo [Internet]. [Cited 2022 Aug 19]. Available from: https://biblioteca.indec.gob.ar/bases/minde/enfr_2018_resultados_definitivos.pdf

32. Infoleg.gob.ar. 2022 [cited 2022 Aug 19]. Available from: http://servicios.infoleg.gob.ar/infolegInternet/anexos/180000-184999/183207/norma.htm

33. Linzer M, Harwood E. Gendered Expectations: Do They Contribute to High Burnout Among Female Physicians? J Gen Intern Med. 2018 Jun;33(6):963-965. https://doi.org/10.1007/s11606-018-4330-0

ORIGINAL ARTICLE

Contractile reserve by left ventricular ejection fraction alone, or considering elastance. ¿Which is the best predictor of events after a Stress Echo without ischemia?

Reserva contráctil por fracción de eyección sola, o con elastancia. ¿Cuál es el mejor predictor de eventos luego de un ecoestrés sin isquemia?

DIEGO M. LOWENSTEIN HABER[1, MTSAC], ROSINA ARBUCCI[1, MTSAC], PABLO MERLO[1, MTSAC], LILIANA MARTINEZ[1], NATALIO GASTALDELLO[1], ARIEL K. SAAD[1, MTSAC], GUSTAVO F. ZAMBRANA[1], JORGE A. LOWENSTEIN

ABSTRACT

Background: The behavior of left ventricular ejection fraction (LVEF) during exercise is used to measure contractile reserve (CR). CR measured by elastance could have greater prognostic value.
Objective: To establish whether the measurement of CR by elastance adds long-term prognostic value to CR measured by LVEF in patients with a Stress Echo without myocardial ischemia.
Material and methods: Retrospective study, carried out in 904 patients with an exercise Stress Echo without ischemia. CR was assessed by LVEF and by elastance. Patients were divided into 2 groups: Group 1: presence of CR by LVEF (in turn this group was divided into 2 subgroups: Group 1A, CR with elastance present, and Group 1B: absence of CR by elastance), and Group 2: patients with absence of CR by LVEF. The follow-up was 17,7 ± 5,4 months. Outcomes considered were death, acute myocardial infarction (AMI), stroke, and cardiovascular hospitalization.
Results: 536 patients were included in Group 1, 200 (37,3 %) in Group 1A and 336 (62,7%) in Group 1B. In Group 2, 368 patients were included. At follow-up, patients in Group 2 had more events, 30 (8.1%) vs. 22 (2.6 %) (HR 3.14, 95% CI 1.95-5.9, log rank test p<0.001). Within G1, patients in Group 1B presented more events: 18(5.3%) vs 4 (2%) (HR 2.46 CI 95% 1.06-7.3, log rank test p<0.05). In the regression model, CR assessed by LVEF and additionally by elastance was the only significant outcome predictor (HR 3.2, 95% CI 1.83-5.6, p<0.001).
Conclusions: In an exercise Stress Echo negative for ischemia, CR behavior evaluated by elastance allowed us to identify a subgroup with a worse long-term prognosis in patients with normal LVEF response.

Keywords: Echocardiography, Stress - Myocardial Contraction - Ventricular Function, Left / physiology

RESUMEN

Introducción: El comportamiento de la fracción de eyección del ventrículo izquierdo (FEVI) durante el ejercicio se utiliza para medir la reserva contráctil (RC). La RC medida por elastancia podría tener mayor valor pronóstico.
Objetivo: Establecer si la medición de la RC por elastancia añade valor pronóstico a largo plazo en relación al comportamiento aislado de la FEVI en pacientes con un eco estrés sin isquemia miocárdica.
Material y métodos: Estudio retrospectivo, realizado en 904 pacientes con Eco Estrés con ejercicio sin isquemia. Se valoró la RC por FEVI y por elastancia. Se dividieron en 2 grupos: Grupo 1: RC por FEVI presente (a su vez este grupo se dividió en 2 subgrupos: Grupo 1 A, RC con elastancia presente y Grupo 1B: ausencia de RC por elastancia), y Grupo 2: pacientes con ausencia de RC por FEVI. El seguimiento fue de 17,7 ± 5,4 meses. Se consideraron como eventos: muerte, infarto agudo de miocardio (IAM), accidente cerebrovascular (ACV) y/o internación de causa cardiovascular.
Resultados: Del total del Grupo 1 (536 pacientes), 200 (37,3%) se incluyeron en el Grupo 1A y 336 (62,7%) en el Grupo 1B. En el Grupo 2, se incluyeron 368 pacientes. En el seguimiento, los pacientes del Grupo 2 tuvieron más eventos, 30 (8,1%) vs. 22 (2,6 %) (HR 3,14, IC95% 1,95-5,9, log rank test p<0,001). Dentro del G1, los pacientes del Grupo 1B presentaron más eventos: 18 (5,3%) vs 4 eventos (2%) (HR 2,46 IC95% 1,06-7,3, log rank test p<0,05). En el modelo de regresión, la elastancia fue la única variable predictora de eventos (HR 3.2, IC95% 1,83-5,6, p<0,001).
Conclusiones: En el Eco Estrés ejercicio negativo para isquemia, el comportamiento de la RC evaluada por elastancia permitió identificar un subgrupo de peor pronóstico a largo plazo en pacientes con comportamiento normal de la FEVI.

Palabras clave: Ecocardiografía de Estrés - Contracción Miocárdica - Función Ventricular Izquierda/fisiología

Rev Argent Cardiol 2022;90:329-335. http://dx.doi.org/10.7775/rac.v90.i5.20560

SEE RELATED ARTICLE: Rev Argent Cardiol 2022;90:319-320. http://dx.doi.org/10.7775/rac.v90.i5.20563

Received: 05/12/2022 – *Accepted:* 08/24/2022

Address for reprints: Diego Maximiliano Lowenstein Haber. Humboldt 2045 CP 1414 CABA. E-mail: lowediego@hotmail.com

[1] Cardiodiagnostic Service. Medical Research. Buenos Aires, Argentina.
[MTSAC] Full Member of Argentine Society of Cardiology

INTRODUCTION

The concept of Contractile Reserve (CR), defined as the ability of the myocardium to increase its pump function in response to an inotropic stimulus, is universally known as a prognostic key for multiple pathologies. For its assessment, one of the most used parameter is the behavior of the left ventricular ejection fraction (LVEF) during exercise.

Its measurement is widely used to diagnose diseases, determine their severity, establish prognosis and guide therapy. However, its usefulness in assessing systolic function is limited, not only due to difficulties inherent in the quality of the images or ventricular geometry, but,also because it depends on various factors in addition to contractility , such as pre and afterload, heart rate, and ventricular synchrony. These variables are substantially modified during exercise, which limits the capacity of the LVEF as a specific surrogate of the contractile function. On many occasions, LVEF can be increased during exercise, even though the contractility decreases, for example due to the development of significant mitral regurgitation with the consequent afterload decrease. Conversely, LVEF can decrease in the presence of preserved contractility, secondary to an exaggerated hypertensive response with increased afterload, or by increased heart rate with decreased ventricular filling, especially in small and stiff ventricles, or in the presence of dyssynchrony; a typical example is the appearance of left bundle branch block during exertion. The most important factor is the ventricular afterload. (1)

Among the reference publications in systolic function study, we can mention the group of Suga et al, who since 1969 (2) have studied ventricular contraction and left ventricular performance in canine hearts through instant measurement of the pressure/volume ratio throughout the cardiac cycle. Their findings demonstrated that the pressure/volume curve is independent of load conditions, although it varies with changes in contractility, (3) constituting one of the most representative parameters in the evaluation of ventricular systolic function. This index, called Ventricular Elastance (elastance), is defined as the ratio between systolic blood pressure and left ventricular end-systolic volume. It has the advantages of having greater sensitivity than other parameters, and being able to globally assess systolic function both at rest and with effort. (4-6) As observed by the group of Picano et al, their behavior with exercise can show 3 responses: normal ascending (exertion values that double the baseline, related to high systolic blood pressure values with decreased end-systolic volume), abnormal biphasic (initial slight increase followed by a return to baseline), and abnormal flat (both pressure and volume remain unchanged during stress) (7)

Considering the findings of these previous investigations, we can infer that the evaluation of CR by elastance during stress with exercise could have a higher prognostic value than the isolated measurement of the CR reserve by LVEF in patients with negative Stress Echo for ischemia (8, 9), and even in early stages of cardiomyopathies.

OBJECTIVE

The objective of this study was to establish whether the measurement of CR by elastance adds long-term prognostic value to isolated LVEF behavior in patients with Stress Echo without myocardial ischemia.

METHODS

Population

In a retrospective, descriptive, comparative, single-center study, we included 904 patients, studied in our center, with an exercise Stress Echo during a 2 years period (January 2018 to December 2019). The average age of the patients was 61.92 ± 12.59 years; 509 patients (56.3%) were men.

Patients had to be older than 18 years, with Stress Echo eco negative for ischemia; patients with history of known myocardial disease, structural heart disease of another etiology (for example, valvular patients), complete left bundle branch block, with atrial fibrillation or inadequate ultrasound window, were excluded.

All patients underwent exercise Stress Echo, with reported normal global and regional function at rest, and dyssynergy absence during stress. Previously, all signed the informed consent accepting the performance of the test and the use of the data for scientific purposes.

Echocardiogram Stress

The patients remained fasting for at least 4 hours. To carry out the study, a stretcher with a Schiller brand supine bicycle was used. The exercise was performed according to the Astrand protocol.

A Vivid E9 or E95 echocardiograph (GE Healthcare) was used, with a 5 MHz Matrix transducer, with two-dimensional image acquisition at a rate of 60-70 frames/second. The evaluation of the usual ultrasound parameters was performed according to American Society of Echocardiography (ASE) guidelines

Contractile Reserve Estimation by Ejection Fraction and Ventricular Elastance

LVEF was defined as the percentage that represents the stroke volume, defined as the difference between left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) related to the EDV. LVEF= [(EDV - ESV) / EDV] x 100.

Left ventricular elastance was defined as the ratio between systolic blood pressure (SBP) and left ventricular end-systolic volume (SBP/ESV).

LVEF and estimation of ventricular volumes were obtained automatically with manual corrections when warranted by endocardial visual monitoring. The final values resulted from the average of at least 2 measurements.

At each stage of the study protocol, blood pressure was recorded using an Omron automatic sphygmomanometer.

Contractile reserve valuation

Contractile Reserve (CR) was assessed by LVEF and by elastance. CR assessed by LVEF was considered present when the absolute increase in LVEF during exercise was at least 5 points, and CR assessed by elastance was considered when the stress/rest elastance ratio was equal to or greater than 2.

The operator who performed all the studies is certified as highly experienced in reading ventricular volumes as required for entry into the 2020 project led by Eugenio Picano . (10)

Major Events – Final Points

Major cardiovascular outcomes were death, acute myocardial infarction (AMI), cerebrovascular accident (CVA) and/or need for hospitalization due to cardiovascular causes, in the average follow-up of 17.7 ± 5.44 months.

Statistical analysis

Quantitative variables were presented as mean and standard deviation or median and interquartile range depending on whether the distribution was parametric or not. For the comparison of two groups, the Student's t test or Wilcoxon's test was used depending on whether the distribution was parametric or not, respectively. Qualitative variables were expressed as percentages and statistical significance was determined using the chi square test. All comparisons were bilateral, considering statistically significant values of $p < 0.05$. The variables that in the univariate analysis showed a relationship with a value of $p < 0.1$ were entered into a multivariate analysis using logistic regression. Data processing was performed with the statistical package SPSS 10.0 (SPSS Inc. Chicago, USA).

Ethical Considerations

The study was evaluated and approved by an institutional Research Committee. Informed consent was required, authorized by a relative or guardian of each patient included in the study.

Ethical considerations

Given that it was an anonymous, self-referential and voluntary participation survey, the SAC ethics committee waived an informed consent.

RESULTS

The 904 patients included in the study were divided into 2 groups. Group 1 included those patients who presented CR assessed by LVEF. This group in turn was divided into 2 subgroups: Group 1A: CR assessed by elastance present, and Group 1B: CR assessed by elastance absent. Group 2 included those patients with no CR according to LVEF. Coincidentally, in this group all patients had no CR according to elastance.

Of the total, 536 patients (59.29%) were included in Group 1, 200 (37.32%) in Group 1A and 336 (62.68%) in Group 1B; 368 patients (40.71%) were included in Group 2.

Group 2 patients were significantly older (63.58 ± 11.2 years vs. 60.78 ± 13. 3 years in group 1, $p < 0.001$). There were no baseline clinical differences between the patients in Group 1A and 1B. (Table 1 and Table 2).

Stress Echo Results

All patients had no myocardial ischemia at the double product achieved, in motility analysis and longitudinal strain behavior by speckle tracking.

There were differences in ventricular volumes changes with exercise between the different groups. Group 2 patients had a higher increment of delta indexed EDV (stress-rest) to Group 1: 3.22 ± 11.1 mL vs -1.10 ± 11.1 mL in Group 1, $p<0$,001; and less decrease in delta indexed ESV: -0.86±5.6 mL vs -3.83± 3.75 mL, respectively; $p< 0.001$.

G1A patients had a greater decrease in indexed ESV than G1B: delta stress-rest indexed ESV: -5.12 ± 3.3 mL vs -2.54±3.68 mL, respectively; $p<0.001$, as can be seen in Table 2.

Table 1. General baseline and stress characteristics. Group 1 vs. Group 2.

Variables	Group 1 (CR by LVEF+)	Group 2 (CR by LVEF -)	p
Age (years)	60.78 ± 13 .3	63.58 ± 11.2	0 .001
BMI (kg/m^2)	28.92 ± 5 .2	28.73 ± 4.9	NS
HBP (%)	44.7	55.3	0.1
DM (%)	20.1	18.3	NS
SBP at rest (mmHg)	125.49 ± 21.8	128.20 ± 21.4	NS
LVEF rest %	59.59 ± 8.4	58.79 ± 10.5	NS
EDVi (ml/m^2)	43.28 ± 12.85	45.53 ± 15.36	NS
ESVi at rest (ml/m^2)	17.5 ± 9.73	19.62 ± 2.3	NS
Stress SBP (mmHg)	188.12 ± 31.4	185.49 ± 30.1	NS
LVEF stress %	66.85 ± 8.4	60.6 ± 64	0.001
Stress HR (bpm)	131 ± 20	128 ± 19	NS
EDVi stress (ml/m^2)	42.18 ± 10.9	48.5 ± 11.2	0.001
ESVi stress (ml/m^2)	13.98 ± 3.2	18.76 ± 12.02	0.001
LVEF Variation	7.26 ± 1.22	1.81 ± 1.28	0.001
Elastance	1.88 ± 0.53	1.51 ± 0.41	0.05
Delta EDVi stress/rest	-1.10 ± 11.1	3.22 ± 11.1	0.001
Delta ESVi stress/rest	-3.83 .± 3.75	-0.86 ± 3.6	0.001

CR: Contractile Reserve; BMI: body mass index; HBP: high blood pressure; DM: diabetes mellitus; SBP: systolic blood pressure; EDVi: indexed end-diastolic volume; ESVi: indexed end-systolic volume; HR: heart rate; LVEF: left ventricular ejection fraction; NS: not significant

Follow -up Outcomes

Mean follow-up was 17.7 ± 5.44 months. Patients without CR (Group 2), presented a greater number of major events compared to those in Group 1: 30 (8.15%) vs 22 (2.59%) (HR 3.14, 95% CI 1.95-5.9; log Rank test p < 0.008). (Figure 1).

Subgroup 1A patients had 4 major events (2%) vs. 18 (5.35%) in Subgroup 1B (HR 2.46, 95% CI 1.06-7.3; log Rank test p < 0.05). (Figure 2).

Finally, a Cox Regression model was carried out in which all the variables with significance p < 0.10 were included. CR assessed by LVEF and additionally by elastance was the only significant outcome predictor (HR 3.22, CI 95% 1. 83-5.6), p < 0 .001),

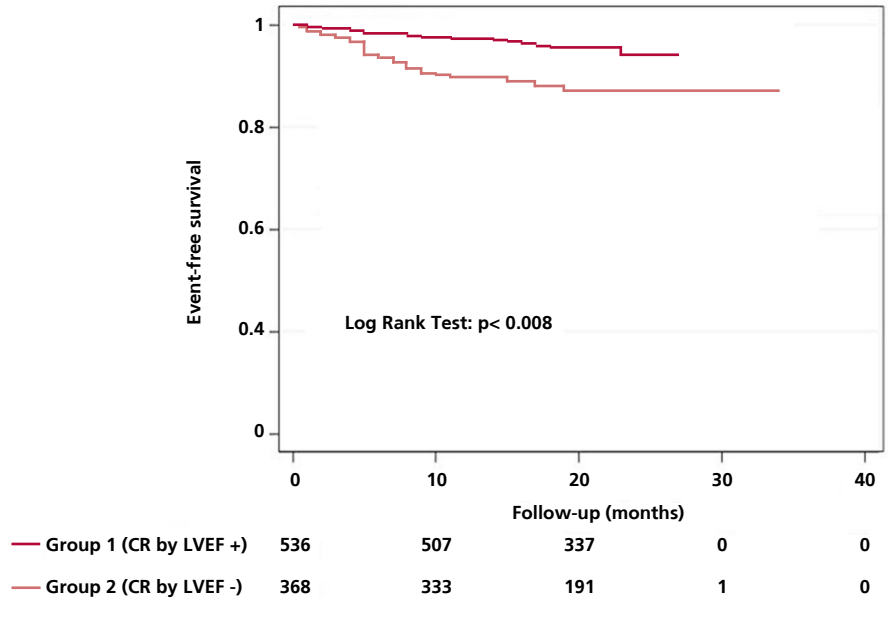
DISCUSSION

In the present study, two methods were compared to assess CR in a group of patients with exercise Stress Echo without inducible ischemia assessed by visual motility analysis and longitudinal strain by speckle tracking. CR was quantified in the usual way, and the ratio between systolic blood pressure and LV end-systolic volume, that is, ventricular elastance, at stress relative to rest, was measured.

Variables	Group 1A (CR by LVEF + and Elastance +)	Group 1B (CR by LVEF + and Elastance -)	p
Age (years)	59.41 ± 13.1	62.15 ± 13.5	NS
BMI	28.39 ± 4.9	29.45 ± 5.5	NS
HBP (%)	43.4	46.0	NS
DBT (%)	20.03	20.13	NS
SBP rest (mmHg)	126.79 ± 23.2	124.01 ± 20.51	0.1
LVEF rest %	60.23 ± 8.2	58.95 ± 8.6	NS
ESVi at rest(ml/m²)	16.4 ± 9.35	18.6 ± 10.11	NS
Stress SBP (mmHg)	194.22 ± 34.4	182.02 ± 28.4	0.001
Stress LVEF %	67.89 ± 8.6	65.81 ± 8.2	NS
Stress HR (bpm)	130±20	132 ± 20	NS
LVEF Variation	7.66 ± 1.1	6.86 ± 1.02	0.1
Elastance	2.21 ± 0.11	1.59 ± 0.11	0.001
Stress ESVi (ml/m²)	11.28 ± 6.2	16.06 ± 2.3	0.001
Delta ESVi stress/rest	-5.12 ± 3.3	-2.54 ± 6.5	0.001

CR: Contractile Reserve; BMI: body mass index; HBP: high blood pressure; DM: diabetes mellitus; SBP: systolic blood pressure; ESVi: indexed end-systolic volume; HR: heart rate; LVEF: left ventricular ejection fraction; NS: not significant.

Table 2. General baseline and stress characteristics. Group 1A vs. Group 1B.



CR: Contractile reserve; LVEF: Left ventricular ejection fraction.

Fig. 1. Contractile Reserve and Event Free Survival. Group 1 vs. Group 2.

As expected, patients with decreased CR assessed by LVEF had a worse prognosis. But within the group with LVEF still-preserved CR, the assessment of CR by elastance made it possible to identify two groups with different evolution, worse in those with decreased CR by elastance assessment.

The ABCD protocol proposed by Picano et al (10,11) integrates several parameters to be evaluated during the performance of a Stress Echo, through physical or pharmacological stress. The analysis of segmental motility or Asinergies (A) is only one of the variables to consider, to which is added the evaluation of B lines by means of lung echo (B), the evaluation of CR (C), and coronary reserve by measuring the behavior of the velocities in the distal anterior descending artery with pulsed Doppler (D). All these aspects are important for a comprehensive evaluation of cardiovascular function, not only in ischemic heart disease but also in other pathologies (12)

In an exhaustive patient assessment, CR measurement is one of the main parameters that we must take into account when analyzing the Stress Echo results. Although traditionally analyzed by the LVEF increase during the stress phase, this method has two important limitations: its strong dependence on loading conditions and the high intra- and inter- observer variability. Another method of measurement proposed is through the behavior of elastance, which has been validated in previous studies. (13,14) Normally, during stress, an increase in SBP is observed together with a decrease in indexed ESV, so that the relationship between the two doubles during the Stress Echo. It should be noted that other cut-off values are used in studies with vasodilators (a value >1.1 is considered normal), since the behavior of SBP and ESV is different.

Elastance reflects the intrinsic contractile state of the left ventricle, less dependent on loads. This measurement incorporates 2 recognized prognostic markers, a low increase in SBP during exercise and/or a smaller decrease in indexed ESV, which are associated with a worse prognosis and higher mortality. Previous studies suggest that this measurement could have greater sensitivity than the one assessed by LVEF, and could detect a group of patients at higher risk. (15,16)

In our study, we found 62.8% of patients with preserved LVEF and low elastance, a figure slightly higher than that described by T Bombardini et al. which refers this discrepancy in about 40% of patients. (5)

Under normal conditions, the end-diastolic volume of the ventricle has a slight increase at low exercise load, and then decreases at maximum effort to similar levels to those at rest, so that the increase in LVEF occurs fundamentally at the expense of the decrease in ESV. It is known that the EDV has no real influence on the calculation of the ventricular elastance, although it does on the LVEF. (17)

Experimental data suggest that ESV is less affected by loading conditions, especially preload, and its correlates with both resting and exercise systolic blood pressure. (18)

A study by Turakhia et al described in 934 patients with known coronary artery disease that those who had a reverse behavior of the left ventricle ESV with exercise had a higher incidence of cardiovascular events during follow-up, even in patients without ischemic behavior, like was observed in our work. (19)

We consider that the evaluation of ventricular volumes behavior should be done in all constraints (pharmacological and exercise), either by measuring the ventricular diameters or direct estimation through

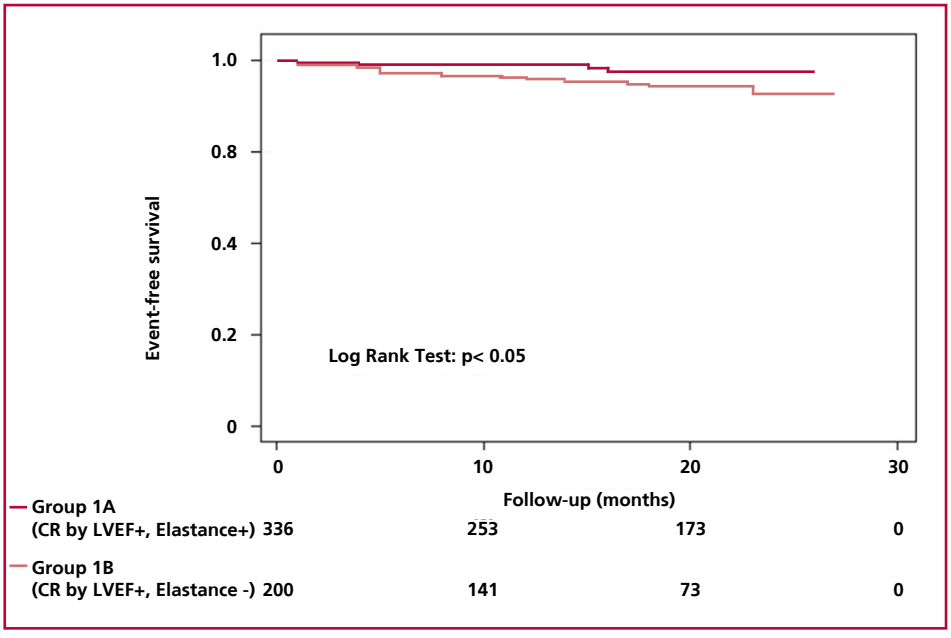


Fig. 2. Contractile Reserve and Event Free Survival. Group 1A vs. Group 1B.

CR: Contractile reserve; LVEF: Left ventricular ejection fraction.

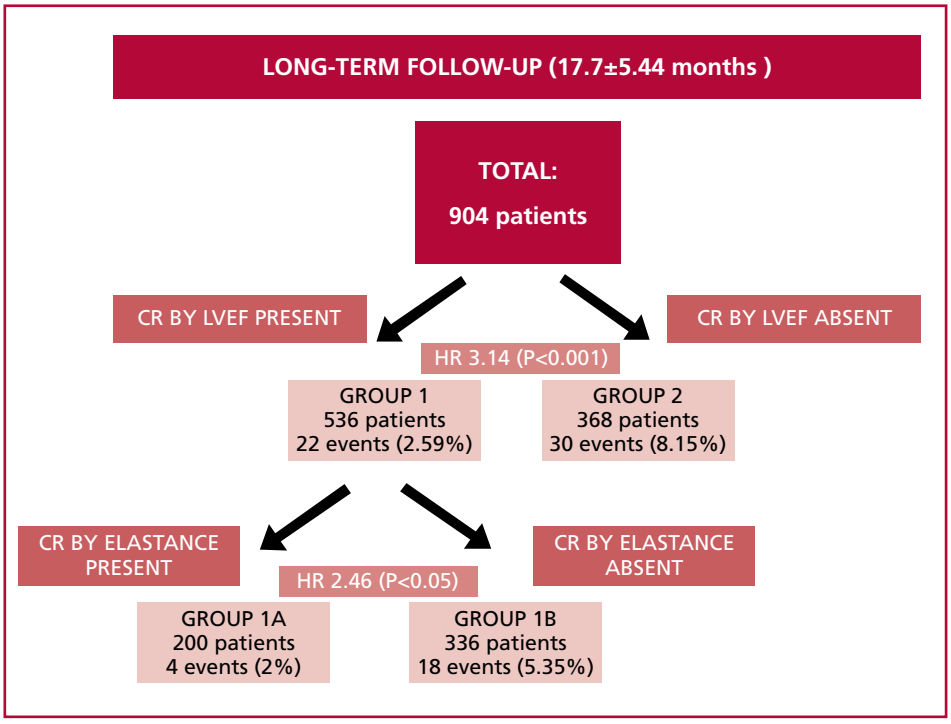


Fig. 3. Long term outcomes.

CR: Contractile reserve; LVEF: Left ventricular ejection fraction.

the Simpson method. It must be considered that an increase of 10 ml in ESV at maximum effort is associated with a 15% increase in the probability of serious events during follow-up. (19)

The determination of ESV is simpler than measuring LVEF, which needs to add the measure of EDV, so the error probability increases.

It is noteworthy that in an analysis carried out by our group, which has a lot of experience in measuring ventricular volumes semi-automatically, CR evaluated by elastance was not associated with the sufficiency of the ergometric test, so it is a useful parameter even in patients with poor exercise capacity or treated with beta blockers. (20)

We can conclude that a stress study can be defined as negative for myocardial ischemia when performing segmental motion analysis, but another parameters, such as ventricular elastance, allow adding additional prognostic information of great value.

Clinical Implications

Compared with the isolated measurement of CR by LVEF, ventricular elastance may be a more sensitive and accurate indicator of contractile reserve, less affected by load conditions and heart rate (Bowditch Treppe effect), reflecting the intrinsic contractility of the left ventricle during the exercise.

Our work shows that in addition to these pathophysiological advantages, its determination, which is very simple and does not require extra study time, has an impact on outcomes during patient follow-up; so its routine evaluation is suggested during Stress Echo studies. (Figure 3).

Limitations

The study was retrospective and single center.

We did not obtain, in the follow-up, the anatomical correlation by coronary angiography or computed tomography angiography, in those patients who had clinical events.

Finally, a small group of patients were evaluated under anti-ischemic medication, which can reduce the presence of contractile abnormalities during stress.

CONCLUSIONS

Decreased CR evaluated by ventricular elastance during a Stress Echo negative for myocardial ischemia and adequate behavior of the LVEF during exercise, allowed to identify a subgroup of patients with worse long-term prognosis.

Conflicts of interest

None declared.

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

REFERENCES

1. Takeuchi M, Bombardini T, Picano E. Rational Basis of Stress Echocardiography. En: Stress Echocardiography. 6th ed. Springer, Cham, 2015. pp 53-68. https://doi.org/10.1007/978-3-319-20958-6_4

2. Suga H. Time course of left ventricular pressure volume relationship under various end-diastolic volume. Jpn Heart J 1969;10:509-15. https://doi.org/10.1536/ihj.10.509

3. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res. 1973;32:314-22. https://doi.org/10.1161/01.res.32.3.314.

4. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-Systolic Pressure/Volume Ratio: A New Index of Ventricular Contractil-

ity. Am J Cardiol 1977;40:748-53. https://doi.org/10.1016/0002-9149(77)90192-8.
5. Bombardini T, Zoppè M, Ciampi Q, Cortigiani L, Agricola E, Salvadori S, et al. Myocardial contractility in the stress echo lab: from pathophysiological toy to clinical tool. Cardiovasc Ultrasound 2013;11:41. https://doi.org/10.1186/1476-7120-11-41
6. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501-12. https://doi.org/10.1152/ajpheart.00138.2005
7. Picano E, Bombardini T, Kovačevit Preradović T, Cortigiani L, Wierzbowska-Drabik K, Ciampi Q. Left ventricular contractile reserve in stress echocardiography: the bright side of the force. Kardiol Pol 2019;77:164-172 https://doi.org/10.5603/KP.a2019.0002
8. Bombardini T, Mulieri LA, Salvadori S, Costantino MF, Scali MC, Marzilli M, et al. Pressure-volume Relationship in the Stress-echocardiography Laboratory: Does (Left Ventricular End-diastolic) Size Matter? Rev Esp Cardiol (Engl Ed). 2017;70:96-104. https://doi.org/10.1016/j.rec.2016.04.047
9. Grosu A, Bombardini T, Senni M, Duino V, Gori M, Picano E. End-systolic pressure/volume relationship during dobutamine stress echo: a prognostically useful non-invasive index of left ventricular contractility. Eur Heart J 2005;26:2404-12. https://doi.org/10.1093/eurheartj/ehi444.
10. Picano E, Ciampi Q, Wierzbowska-Drabik K, Urluescu ML, Morrone D, Carpeggiani C. The new clinical standard of integrated quadruple stress echocardiography with ABCD protocol. Cardiovasc Ultrasound 2018;16:22. https://doi.org/10.1186/s12947-018-0141-z
11. Ciampi Q, Zagatina A, Cortigiani L, Wierzbowska-Drabik K, Kasprzak JD, Haberka M, et al. Prognostic Value of stress echocardiography assessed by the ABCDE protocol. Eur Heart J 2021;42:3869-78.
12. Daros CB, Ciampi Q, Cortigiani L, Gaibazzi N, Rigo F, Wierzbowska-Drabik K, et al, On Behalf Of The Stress Echo Study Group Of The Italian Society Of Echocardiography And Cardiovascular Imaging. Coronary Flow, Left Ventricular Contractile and Heart Rate Reserve in Non-Ischemic Heart Failure. J Clin Med 2021;10:3405. https://doi.org/10.3390/jcm10153405
13. Sekido M, Uemura R, Takayama M, Kiuchi K, Nejima J, Takano T. Left ventricular peak systolic pressure/end-systolic volume ratio change after dobutamine infusion for predicting left ventricular contractile reserve: comparison with Emax. J Cardiol 2002;39:75-84.
14. Bombardini T, Correia M. J, Cicerone C, Agricola E, Ripoli A, Picano E. Force-frequency relationship in the echo lab: a non invasive assessment of Bowditch Treppe? J Am Soc Echocardiogr 2003;17:832-41.
15. Cortigiani L, Bombardini T, Corbisiero A., Mazzoni A, Bovenzi F, Picano E. The additive prognostic value of end-systolic pressure-volume relation in patients with diabetes mellitus having negative dobutamine stress echocardiography by wall motion criteria. Heart 2009;95:1429-35. https://doi.org/10.1136/hrt.2008.161752.
16. Bombardini T, Costantino MF, Sicari R, Ciampi Q, Pratali L, Picano E. End-systolic elastance and ventricular-arterial coupling reserve predict cardiac events in patients with negative stress echocardiography. Biomed Res Int 2013;235194. https://doi.org/10.1155/2013/235194
17. Torres MA, Texeira TF, Camarozano AC, Bellagamba CCA, Quevedo NM, Junior AI, et al; Stress Echo 2020 study group of the Italian Society of Cardiovascular Imaging. The value of a simplified approach to end-systolic volume measurement for assessment of left ventricular contractile reserve during stress-echocardiography. .Int J Cardiovasc Imaging 2019;35:1019-26. https://doi.org/10.1007/s10554-019-01599-5
18. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44-51. https://doi.org/10.1161/01.cir.76.1.44. 10.1161/01.cir.76.1.44.
19. Turakhia MP, McManus DD, Whooley MA, Schiller NB. Increase in end-systolic volume after exercise independently predicts mortality in patients with coronary heart disease: data from the Heart and Soul Study.Eur Heart J 2009;30:2478-84. https://doi.org/10.1093/eurheartj/ehp270
20. Merlo P, Arbucci R, Sevilla D, Martinez L, Lowenstein, JA. Efecto de la frecuencia cardíaca sobre la reserva contráctil evaluada por elastancia ventricular en el Eco Estrés Ejercicio.. Congreso Argentino de Cardiología SAC 2018. (resumen 0377).

BRIEF ARTICLE

Follow-up of Specialist in Cardiology Graduates at University of Buenos Aires. Cosme Argerich Hospital Experience

Seguimiento de graduados de la Carrera de Médico Especialista en cardiología de la Universidad de Buenos Aires. Experiencia del Hospital Cosme Argerich

LUCÍA R. KAZELIAN[1, MTSAC], LEANDRO A. BONO[1], MARIELA E. TOLUSSO[1], HORACIO G. CESTARI[1], RODRIGO I. BLANCO[*, 1], JUAN A. GAGLIARDI[1, MTSAC]

ABSTRACT

Background: Follow-up of graduates in a career is an indicator of educational quality, and their professional and academic work allows evaluating the results of long-term instituted programs Objective: The aim of this study was to explore the perception of graduates from the postgraduate specialist course (PSC) in cardiology at University of Buenos Aires (UBA) Hospital Argerich venue on the quality of training received, how they insert in the professional world, and their engagement in subspecialties.
Methods: A descriptive, cross-sectional study was carried out from January 1 to 31, 2020. A self-administered opinion survey was designed using surveymonkey.com and submitted to 28 graduates of the PSC in cardiology UBA-Hospital Argerich, corresponding to 7 consecutive promotions (2010-2016 years of admission).
Results: The survey was answered by 25 graduates (89.2%). Mean age was 34 years and 14 (56%) were men. The questions explored the global assessment, the evaluation of the scientific and academic activity at the hospital venue as well as that of the Argentine Society of Cardiology Biennial Course of Cardiology. Most of the answers were favorable. All the graduates continue practicing the profession and 76% have received advanced training in a subspecialty.
Conclusions: Graduates from the PSC in cardiology at Hospital Argerich perceive that their training has been very good or excellent and has been essential for their professional development. All the data collected are a source of information to provide feedback and optimize teaching in the training institution.

Keywords: Surveys and Questionnaires - Education, Medical, Graduate - Educational Measurement - Cardiologists - Follow up

RESUMEN

El seguimiento de los graduados es un indicador de calidad educativa y su labor profesional y académica podría ser un indicador para evaluar los resultados de los programas instituidos a largo plazo.
Objetivo: explorar la percepción de los egresados de la Carrera de Médico Especialista en cardiología (CME) de la Universidad de Buenos Aires (UBA) sede Hospital Argerich sobre la calidad de la formación recibida durante la carrera. Conocer su inserción laboral en el mundo profesional, y la realización de subespecialidades.
Material y métodos: estudio descriptivo, de corte transversal, realizado del 1° al 31 de enero de 2020. Se diseñó una encuesta de opinión autoadministrada a través de surveymonkey.com. El universo encuestado fueron 28 egresados de 7 promociones consecutivas (año de admisión 2010-2016) de la CME en cardiología UBA-sede Argerich.
Resultados: Del total de egresados contestaron 25 (89,2%); La edad promedio fue 34 años, sexo masculino 14 (56%). Se realizaron preguntas para la evaluación global, valoración de la actividad científica y académica en la Sede del Hospital, al igual que la valoración del Curso Bianual de Cardiología en la Sociedad Argentina de Cardiología. Las respuestas en su mayoría fueron favorables Los egresados continúan ejerciendo la profesión en un 100%, el 76% se perfeccionó en una subespecialidad.
Conclusiones: Los egresados de la CME en cardiología sede Hospital Argerich perciben que su formación ha sido muy buena o excelente y ha contribuido a su desarrollo profesional de manera esencial. Toda la información recabada genera una fuente de información para retroalimentar y optimizar la enseñanza en la institución formadora.

Palabras clave: Encuestas y cuestionarios - Educación de Postgrado en Medicina - Evaluación Educacional - Cardiólogos - Seguimiento

Abbreviations

PSC	Postgraduate specialist course	**CONEAU**	Decentralized organism under the Ministry of Education jurisdiction
UBA	University of Buenos Aires		

Rev Argent Cardiol 2022;90:336-340. http://dx.doi.org/10.7775/rac.v90.i5.20552

Received: 05/09/2022 – *Accepted:* 09/14/2022

Address for reprints: Lucía R. Kazelian. Pi y Margall 750 (C1155AHD) CABA, Argentina - E-mail: kazelian@gmail.com

[1] Division of Cardiology, Hospital General de Agudos Dr. Cosme Argerich.
Specialist course in cardiology at the Buenos Aires University School of Medicine, Hospital Argerich venue.
[MTSAC] Full Member of the Argentine Society of Cardiology
*to apply as full member

INTRODUCTION

"Dr. Cosme Argerich" hospital is a historical reference center of cardiology training. The medical cardiology residency created in 1996 by Dr. Carlos Bertolasi was one of the first cardiology residencies of the country. This residency depends on the City of Buenos Aires Government which grants the specialist certificate after its completion, allowing professional practice in the Autonomous City of Buenos Aires. (1)

Training of specialty physicians through university courses has the purpose of improving the healthcare of the population. Within this context, the University of Buenos Aires (UBA) created the postgraduate specialty course (PSC) in 1988, through the Superior Council Resolution N° 3334/88. (2)

The PSC at the Hospital Argerich Cardiology Division was under the direction of Professor Dr. Alberto Ramos from its beginning until 2003, continued by Dr. Ricardo A. Sarmiento and is currently directed by Dr. Lucía R. Kazelian since 2016. (3)

This venue was accredited by the National Commission for University Evaluation and Accreditation (CONEAU), a decentralized organism under the National Ministry of Education jurisdiction through resolution N° 119/99 and 048/11. (4,5)

More than 30 promotions of university cardiologists have been trained since the beginning of the PSC in cardiology at Hospital Argerich, which grants a university license to practice the specialty both within and outside the country. In our case, the PSC articulates with the cardiology residency.

The objective of monitoring graduates is to improve the processes of institutional effectiveness of the university or higher education institution, through the analysis of information on the professional and personal performance of graduates. (6). The monitoring of graduates is an indicator of educational quality, according to national and international program accreditation organisms. (7)

Graduate professional and academic work could be an indicator to evaluate the long-term outcomes of the educational programs. (8)

The graduate survey is an appropriate instrument to assess satisfaction with the training they are receiving, and find areas for improvement. It does not measure the training quality, but it is a means to improve it (9)

OBJECTIVE

The aim of the study was to explore the perception of UBA PSC in cardiology graduates at Hospital Argerich on the quality of training received and the impact of its theoretical aspects: scientific and academic activity, classes, monography writing, insertion in the professional world, and training in subspecialties.

METHODS

This was a descriptive, cross-sectional study carried out from January 1 to 31, 2020.

A graduate was defined as any professional who had completed the PSC in cardiology at Hospital Argerich, obtaining the title of UBA university cardiologist.

The PSC is inserted in the medical, teaching and research activity of Hospital Argerich Cardiology Division. It lasts three years and is ruled by the last resolution N°6159/16. (3)

CME students carry out healthcare activities at our venue, with the corresponding rotations in the different subspecialties. In addition, they participate in theoretical classes, bibliographic seminars, central seminars of the service and courses taught by professionals belonging to the Cardiology Division, such as semiology, Doppler echocardiography, electrocardiography, hemodynamics, nuclear magnetic resonance, coronary heart disease in women, research methodology and statistical analysis, primary prevention, etc.

As part of the PSC theoretical aspect, they also assist to the Argentine Society of Cardiology Biennial Course of Cardiology. (10)

The surveyed universe consisted of seven promotions of UBA PSC in cardiology graduates at hospital Argerich who started the course from 2010 to 2016.

A self-administered survey was designed through www.surveymonkey.com. For the assessment, a scale was used where they could answer: a lot, quite a bit, little and not at all. Messages were sent to all graduates via e-mail and WhatsApp with the link to the survey, which was available during the previously indicated period.

The questionnaire included 44 questions grouped in six sections:

1. General data
2. Global assessment
3. Evaluation of the scientific activity at the Hospital Venue
4. Evaluation of the academic activity at the Hospital Venue
5. Evaluation of the Argentine Society of Cardiology Biennial Course of Cardiology
6. Venue recommendation. Observations and suggestions (free field)
7. Current professional activity

RESULTS

A total of 28 graduates from 7 consecutive promotions between 2010 and 2016 were invited to participate, and 25 (89.2%) answered the survey.

Table 1 shows general data of graduates.

Mean age was 34 years (range 30 to 41 years). Fourteen (56%) respondents were men, 11 (44%) were married, and among this last group, 9 were men. Ten (40%) graduates had children, and among them only 3 were women. In 52% of cases, graduates came from other provinces for the PSC and 28% returned to their place of origin.

Two Argentine graduates are currently in Spain (both in Barcelona), one doing the subspecialty and the other a doctorate in basic clinical cardiology.

The 22 Argentine graduates obtained their medical title in Argentina, and the foreign graduates studied medicine in their country of origin (Table 1).

Seven of the surveyed respondents were chiefs of residents (one for each promotion).

Table 2 shows the questions and the results of the global evaluation, assessment of the scientific and

academic activity at the Hospital Argerich venue, as well as that of the Argentine Society of Cardiology Biennial Course of Cardiology expressed as percentages.

They were also asked if they would recommend the Hospital Argerich site to a doctor in training in cardiology, and 100% answered that they would, based on the quality of the training, specifically on topics such as ischemic heart disease and heart failure, the competence of the professionals, with references in all areas, the number of academic activities and the updating of the bibliography, the diversity of pathologies and the emphasis on clinical judgment by teachers.

All respondents (100%) actively continue in their profession, and among them, 70 % followed a subspecialty: 13 in Doppler echocardiography (all trained at Hospital Argerich), 4 in hemodynamics [2 at Hospital Argerich, 1 at Hospital El Cruce (Buenos Aires province) and 1 at a hospital in Barcelona, Spain], 1 in diagnostic imaging in Madrid, Spain and 1 in Sportology at Universidad Católica Argentina. A graduate is doing his doctorate in Spain.

Regarding the total number of graduates surveyed who attended patients, 84% developed their care activity in several public and private institutions.

It is interesting to observe that 40% are still associated to Hospital Argerich as staff physicians, some as emergency room cardiologists, and others doing their subspecialty.

Table 1. Graduate characteristics

	N
Graduate profile	25
Age (years)-(range)	34 (30-41)
Male gender	14
Married status	11
Children	10
Country of origin/ current residence	
Argentina	22/20
Spain	0/2
Ecuador	2/2
Bolivia	1/1
Medical Degree	
Argentina	22
UBA	13
UNT	4
USAL	3
UCES	1
Fundación Barceló	1
Ecuador	2
Universidad de Guayaquil	1
Universidad Católica Santiago de Guayaquil	1
Bolivia	1
Universidad Privada del Valle	1

UBA: Universidad de Buenos Aires, UNT: Universidad Nacional de Tucumán USAL: Universidad del Salvador, UCES: Universidad de Ciencias Empresariales y Sociales

DISCUSSION

Graduates' follow-up is the way that universities have to assess educational quality and analyze their insertion in the labor market to improve their teaching and training offer, and surveys are the instrument to carry it out. That's why it's so important to conduct adequate surveys.

All graduates from the study period were contacted and the survey response rate was high. (8)

A similar gender distribution was found, with slight male predominance in accordance with the growing feminization of enrollment in medicine both at a national and international level. (11)

At the time of the survey, all participants were young adults. Less than half were married and had children, but with a clear dominance of men in this condition. This situation probably agrees with current statistical data of our country and the Western world showing a lower proportion of marriages and parenthood postponement related to the feminization of the medical career and the difficulty to exert the profession for women with a family and children. (12,13)

It is interesting to observe how the foreign students returned to their country, while very few of those from other cities of Argentina returned to their place of origin. Perhaps the decision to remain in Buenos Aires is due to a greater working opportunity, greater complexity of healthcare centers, the possibility of following a subspecialty, as well as the difficult inclusion in the medical colleges of the different provinces of our country.

All surveyed graduates considered very highly the training received in the PSC in cardiology at Hospital Argerich. The medical care and teaching areas were the ones in which they perceived greater development. This could be justified by the fact that one of the central tasks of medicine is patient care, so it is expected that medical care has been the one in which the greatest influence and the character of the service was perceived, where training of new cardiologists has always been a priority.

Some respondents requested greater participation in research projects. We consider it an interesting demand as our service is a center with constant development of research studies and PSC students are always invited to participate, each year with greater response.

When consulted about the professional activity at the time of the survey, we observed that 40% of graduates are associated to our hospital through their professional activity. Moreover, 76% has done some subspecialty, and remarkably, 14 out of 19 who did a subspecialty, followed it at our PSC venue.

Both the academic activity at our venue and the Argentine Society of Cardiology Biennial Course of Cardiology were highly valued.

The analysis of monography preparation revealed dissimilar results. Although 20 out of 25 answered

Table 2. Questionnaire and answers expressed in percentages

	Very much	Enough	Little	Nothing
GLOBAL ASSESSMENT				
How much has the PSC satisfied your expectations?	24	68	8	0
How much has the PSC been an important complement in your training during your residency/in training attendance?	40	48	12	0
How much has the PSC been an opportunity to interact with colleagues?	40	44	16	0
How much has the PSC been a stimulus to search for different sources of information?	40	48	12	0
How much has the PSC been a stimulus for the review/ analysis of conducts applied in your center?	40	11	16	0
Activity at the Hospital Argerich venue				
Was it useful to attend bibliographic seminars?	68	32	0	0
Was it useful to prepare and present bibliographic seminars?	76	24	0	0
Was it useful to attend central seminars?	92	8	0	0
Was it useful to prepare and present central seminars?	84	16	0	0
Were you encouraged to perform any scientific study?	20	36	40	4
Were you encouraged to present any scientific study or case report in meetings, congresses?	24	36	40	0
Were you encouraged to publish any case report or scientific study?	12	48	40	0
Were the classes useful?	60	36	4	0
Were classes preparation and presentation useful to incorporate knowledge?	64	32	4	0
Were the courses (semiology, diagnostic imaging, statistics) imparted by the teaching staff useful?	24	64	12	0
Was the monography preparation useful?	32	48	12	8
How much did the residency train you to develop clinical criteria in your medical practice?	84	16	0	0
Theoretical biennial course of cardiology (Argentine Society of Cardiology)				
Quality of the theoretical teaching program. Interest of the topics developed in the 8 modules	24	72	4	0
The proposed exercises/activities (bibliographic seminars, case report presentations) were interesting, related with the professional activity, contributed to affix the main concepts	32	40	28	0
Recommended literature (updated and available)	16	64	20	0
The exams at the end of each module helped to affix concepts.	12	60	28	0
Would you recommend this PSC venue to a colleague?	100	0	0	0

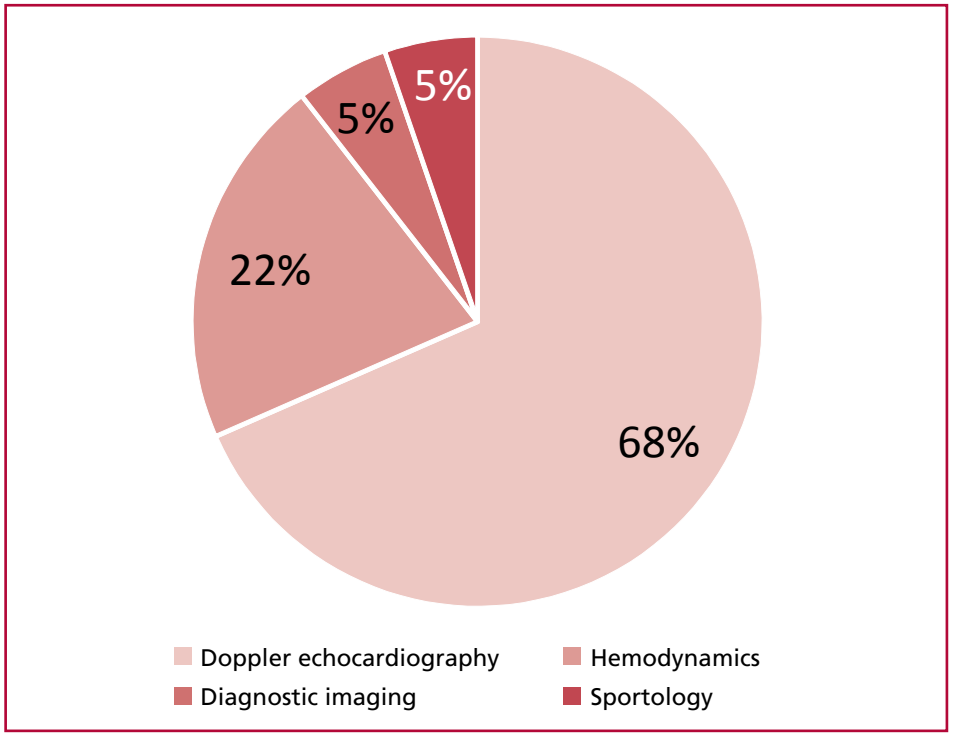


Fig. 1. Distribution of subspecialties followed by graduates

that it was quite useful or very useful, different from other items consulted, 5 responded the scarce usefulness derived from it, despite they chose the subject to be developed, which is not imposed by the course authorities.

Use of social networks, a new tool incorporated in the last decade, allows the permanent contact with the graduates both personally and institutionally, as academic activities carried out in the service are published daily, allowing their continuous remote participation.

CONCLUSIONS

Graduates from the PSC in cardiology at the Hospital Argerich venue perceive that their training has been good or excellent and has essentially contributed to their professional development. All the information collected about graduate satisfaction regarding training quality and their subsequent professional performance generates a source of information to feedback and optimize teaching in the training institution. This survey generated a bond between the graduates and the Service which persists and grows through the social networks.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

Acknowledgement

To Amanda Gally, BA, for critical reading of the manuscript.

REFERENCES

1. Ley 23.873/90. Habilitación para la obtención del certificado de especialista con residencia completa. En Infoleg. Disponible en línea: http://www.infoleg.gob.ar/infolegInternet/verNorma.do;jsessionid=E 2A3E5D456AD2C5ACD34B59081231195?id=273 Acceso: 22 de diciembre.
2. https://www.uba.ar/posgrados/medicina/medicina_ad/CS%201988%203334.pdf
3. https://www.fmed.uba.ar/carreras-de-especialistas/ofertas-de-carreras-de-especializacion
4. https://www.coneau.gob.ar/archivos/resoluciones/Res119-99c2077.pdf
5. https://www.coneau.gob.ar/archivos/resoluciones/Res048-11C20250.pdf
6. Manual de instrumentos y recomendaciones sobre el seguimiento de egresados. Red GRADUA2/Asociación Columbus. 2006
7. Eyman A, Carrio S, Durante E. Rev. Hosp. Ital. B.Aires Vol. 29 Nº 1, junio 2009. Seguimiento de Graduados de las Residencias del Hospital Italiano https://www.hospitalitaliano.org.ar/docencia/biblioteca/attachs/7-educacion-eymann.pdf
8. Moreno, SM. Diseñando una encuesta para residentes de formación sanitaria especializada sobre la satisfacción con la docencia. Experiencia en la Comunidad Autónoma del País Vasco (2009-2018). Educación Médica 2021;22:163-71
https://doi.org/10.1016/j.edumed.2020.09.002
9. Katz FM. Pautas para la evaluación de programas de personal de salud. Washington: Organización panamericana de la Salud; 1981.
10. Curso Bianual de Cardiología de la Sociedad Argentina de Cardiología. https://www.sac.org.ar/curso/bianual/
11. Bickel J. Women in academic medicine. J Am Med Womens Assoc. 2000;55:10-2, 19.
12. https://www.telam.com.ar/notas/202006/475776-casamiento-union-civil-divorcios-provincias-argentina-ley-vincular.html
13. Gulati M, Korn R, Wood M, Sarma A, Douglas PS, Singh Toniya, et al. Childbearing Among Women Cardiologists. J Am Coll Cardiol 2022;79:1076-87. https://doi.org/10.1016/j.jacc.2021.12.034

BRIEF ARTICLE

Usefulness of Cardiac Magnetic Resonance Imaging in Patients with Neuromuscular Dystrophies (Duchenne/Becker Muscular Dystrophy)

Utilidad de la resonancia magnética cardíaca en pacientes con distrofias neuromusculares (distrofia neuromuscular de Duchenne/Becker)

MARIO A. BURGOS[1, 2], ÁLVARO D. CARRIZO[1, 2], VÍCTOR D. CARRIZO[1], FRANCO L. SORIA[2], MARTIN V. GAYA[1], JULIO R. FERNÁNDEZ[2]

ABSTRACT

Background: Cardiac magnetic resonance imaging (CMR) is commonly used in patients with Duchene (DMD) and Becker (DMB) Neuromuscular Dystrophies. Late gadolinium enhancement (LGE) identifies areas of middle, subepicardial, or subendocardial wall fibrosis, and volumetric left ventricular ejection fraction (LVEF) is considered the gold standard in the diagnosis and prognosis of these dystrophies. Myocardial fibrosis occurs in patients with neuromuscular dystrophies.
Objectives: The purposes of our study were to determine the presence of cardiac fibrosis using CMR, to determine neuromuscular and cardiac involvement, and to evaluate the cardiovascular outcomes of these patients.
Material y métodos: A descriptive cross-sectional study of 16 consecutive patients was conducted from March 2021 to July 2022 in the Cardiac Imaging Service of Diagnóstico Médico and CEMET- Tucumán.
Results: A total of 16 patients were evaluated, 100% of them with confirmed diagnosis of DMD/DMB by laboratory, enzymes and genetic tests. Mean age was 19 years. All patients had severe stage of the Vignos Scale and were under neurological treatment. All patients were also treated with beta-blockers or angiotensin-converting enzyme inhibitors.
CMR revealed severe LVEF impairment <35% in 4 patients, segmental or global left ventricular (LV) wall motion disorders in 8 patients, and variable distribution pattern (diffuse, mesocardial, subendocardial and subepicardial patterns) of LGE in 12 patients. Non-compacted myocardium was observed in 6, and mild pericardial effusions in 2 patients.
Conclusion: CMR should be included as a screening method in patients with neuromuscular dystrophies. Its contribution to clinical, echocardiographic and therapeutic staging is of utmost importance.

Key words: Muscular Dystrophy, Duchenne - Neuromuscular Diseases - Muscular Dystrophies - Imaging Magnetic Resonance Imaging - Pronóstico

RESUMEN

Introducción: La Resonancia Magnética Cardíaca (RMC) es cada vez más frecuentemente utilizada en pacientes con Distrofia Neuromuscular de Duchenne y Becker (DMD y DMB). Por la capacidad de demostrar realce tardío con gadolinio (RTG), que identifica zonas de fibrosis de la pared media y subepicárdica, subendocárdica o global, y el cálculo de la fracción de eyección ventricular izquierda (FEVI), se considera el patrón oro en el diagnóstico y pronóstico de la afección cardíaca de estas distrofias.
Objetivos: Fueron nuestros objetivos determinar por medio de RMC la presencia de fibrosis cardiaca en pacientes con distrofia neuromuscular. Determinar el compromiso neuromuscular y cardiaco. Definir la evolución cardiovascular de estos pacientes
Material y métodos: Se realizó un estudio descriptivo de corte transversal de 16 pacientes consecutivos desde marzo de 2021 a julio de 2022 en el Área de imagen cardíaca de 2 centros de Tucumán.
Resultados: Se evaluaron 16 pacientes, todos con diagnóstico confirmado de DMD/DMB por laboratorio, enzimas, y test genéticos. La edad promedio fue 19 años. Todos tenían estadio grave de la Escala de Vignos y tratamiento neurológico. Todos tenían tratamiento con betabloqueantes o inhibidores de la enzima de conversión de la angiotensina. La RMC evidenció que 4 pacientes tenían deterioro grave de la FEVI (<35%); 8 pacientes tenían trastornos segmentarios o globales de la motilidad parietal del VI y en 12 se observó RTG, de distribución variable: difusa, mesocárdica, subendocárdica y subepicárdica. En 6 pacientes se observó miocardio no compacto y en 2 derrame pericárdico leve.
Conclusión: La RMC debe ser incluida como método de cribaje para pacientes con distrofias neuromusculares. Su aporte para la estadificación clínica y terapéutica es de suma importancia.

Palabras clave: Distrofia Muscular de Duchenne -Enfermedades Neuromusculares - Distrofias Musculares - Imagen por Resonancia Magnética - Prognosis

Rev Argent Cardiol 2022;90:341-344. http://dx.doi.org/10.7775/rac.v90.i5.20559

Received: 05/04/2022 – *Accepted:* 07/13/2022

Address for reprints: Mario Alejandro Burgos. Email: marioburgos1977@gmail.com

Source of funding: Part of the studies were funded by PTC Therapeutics.

[1] Department of Cardiac Imaging. (Cardio RM) Diagnóstico Médico Martin Gaya. Concepción, Tucumán, Argentina.
[2] Department of Cardiac Imaging. (Cardio RM) CEMET (Centro Médico Tafí Viejo). Tafí Viejo, Tucumán, Argentina.

INTRODUCTION

Many of the neuromuscular dystrophies (NMD) affect the heart, in some cases with clinical relevance. Both Duchenne (DMD) and Becker (BMD) dystrophies are forms of muscular dystrophinopathies with cardiac implications. (1) From a pathologic viewpoint, NMD can lead to alternating areas of myocyte hypertrophy, atrophy/necrosis and fibrosis with replacement of myocardium by connective tissue and fat, as well as generalized replacement of the entire ventricular myocardium. Cardiac involvement is present in approximately 90% DMD and BMD patients but is the cause of death in about 20% of the DMD and 50% of the BMD patients. (2, 3)

Until recently, patients with DMD often died at 15 to 20 years of age from respiratory complications, congestive heart failure, or arrhythmias. However, many patients with DMD now live into their late 20s and older. Death from cardiac or respiratory failure typically occurs in the fifth decade in BMD. This increased longevity has made cardiac function and cardiovascular health an increasingly important part of evaluating and treating NMD. (4, 5)

As part of the assessment of NMD patients, we performed cardiac magnetic resonance (CMR) imaging to complete cardiac evaluation. Our purposes in this study were to determine the presence of myocardial fibrosis, identify cardiac involvement, help define treatment, and assess cardiovascular outcomes.

METHODS

We conducted a descriptive cross-sectional study in the Department of Cardiac Imaging from the Cardiac Imaging Service of Diagnostico Medico and CEMET- Tucuman, between March 2021 and July 2022. Patients diagnosed with neuromuscular dystrophies (DMD, DMB and DMD/DMB) were included. There were no exclusion criteria based on age, sex, ethnicity or sociocultural level, but any NMD other than those mentioned above, as well as patients with peripheral neuropathies, were excluded. Neurological variables by Vignos Scale (6) (Table 1), specific neurological treatment (corticosteroids or deflazacort), cardiovascular signs and symptoms, and treatment with beta-blockers or renin angiotensin system inhibitors were considered. CMR evaluated left ventricular ejection fraction (LVEF), distribution of late gadolinium enhancement (LGE), segmental motility, the presence of non-compacted myocardium and pericardial effusion.

RESULTS

A total of 16 patients were performed contrast-enhanced CMR (11 with DMD, 2 with BMD and 3 with DMD/BMD). All the patients had confirmed diagnosis by lab tests, CPK > 100 IU/L and genetic testing.

Mean age was 19 years. All were male patients with severe stage on the Vignos Scale and under neurological treatment; 100% were treated with beta-blockers or angiotensin-converting enzyme inhibitors. Seven patients were asymptomatic, and the rest presented with a variety of symptoms. Table 2 shows CMR results. Mean LVEF was 50%. LGE was found in 13 patients, and segmental motility abnormalities in 8. LGE distribution was diffuse ventricular (4 patients), mesocardial septal (1 patient), inferior and lateral subepicardial (7 patients) and subendocardial (1 patient). Non-compacted myocardium was detected in 6 patients, and mild pericardial effusion in 2.

DISCUSSION

Dystrophies are primary muscle diseases with a mutation of more than 50 genes, causing a series of pathologic changes. (7-9) Duchenne (DMD) and Becker (BMD) are described among the most common muscular dystrophies.

DMD is the most lethal type, and occurs in 1 in 3500 to 6000 live births; inheritance is sex-linked, and there is no cure for this disease. (10)

Given that the common symptom of exercise intol-

Table 1. Vignos Scale (6)

Parameters	Value
1-Walks and climbs stairs without assistance	1
2-Walks and climbs stairs with aid of railing	2
3-Walks and climbs stairs slowly with aid of railing	3
4-Walks unassisted and rises from chair but cannot climb stairs	4
5-Walks unassisted but cannot rise from chair or climb stairs	5
6-Walks only with assistance or walks independently with long leg braces	6
7-Walks in long leg braces but requires assistance for balance	7
8-Stands in long leg braces but unable to walk even with assistance	8
9-Is in a wheelchair. Can flex the elbows against gravity	9
10-Is in a wheelchair or confined to a bed. Cannot flex the elbows against gravity	10
Total	
1: Minor involvement. 10: Major involvement.	
Stage of deterioration	
minor: 1 mild: 2 to 4 moderate: 5 to 7 severe: 8 to 10	

Table 2. Findings in cardiac magnetic resonance imaging.

Results	n=16
Average LVEF 50%	
< 35%	4
> 35% -45%	1
45-55%	3
> 55%	8
Late gadolinium enhancement	13
Segmental wall motion disorders	8
Segmental disorder location	
Global hypokinesis	4
Lateral	3
Mid and basal inferior	1
Late enhancement distribution	
Ventricular diffuse	4
Mesocardial septal	1
Inferior, lateral subepicardial	7
Inferior subendocardial	1
Non-compacted myocardium	6
Pericardial effusion	2

erance is often unnoticed by DMD and BMD patients, vague symptoms such as sleep disorders, loss of appetite, nausea, abdominal pain or fullness, increased cough or secretions, and weight loss should be taken into account. Patients may experience more typical cardiac symptoms, including chest pain, trepidation, dizziness and syncope, which are often associated with arrhythmias rather than with heart failure. (11, 12)

Therefore, it is very important that cardiac function in patients with DMD be monitored regularly with electrocardiography (ECG), Doppler echocardiography (DE), and mainly with CMR. (7)

Cardiac magnetic resonance (CMR) imaging is the gold standard technique to assess biventricular function. CMR non-invasively provides important additional information on tissue characterization through late gadolinium enhancement (LGE) sequences, allowing to evaluate the risk of sudden death and choose the best therapeutic strategy. (13)

LGE is present in about 30% of NMD patients. However, the relationship between its presence, location and characteristics with prognosis is not well determined. Intramyocardial linear enhancement at the septal level is the most common finding, but other patterns such as subepicardial enhancement in the left ventricular free wall, focal enhancement or mixed patterns can also be found. (14)

CMR can provide clinically useful information even without contrast dyes. (15)

The usefulness of CMR in different dystrophies is key to describe the pathophysiology of these entities, discuss their clinical presentation and expected evolution. (16)

Echocardiography-based ventricular functional assessment has weak correlation with CMR parameters in children and young adults with DMD. While this correlation improves in the subset of subjects with adequate echocardiographic image quality, it remains modest and potentially suboptimal for clinical management. Accordingly, we conclude that CMR should be performed routinely and early in children with DMD, not only for LGE imaging but also for functional assessment. (17, 18)

CMR has a better diagnostic field for the identification of fibrosis than other imaging methods; it should be associated with other routine complementary diagnostic methods such as ECG, Doppler echocardiography and speckle tracking strain in order to decide on preventive measures. It is the technique of choice to assess LVEF, left and right ventricular volumes and LV mass. CMR offers excellent spatial and temporal resolution, and, unlike echocardiography, there is no bad ultrasound window. It must be remembered that these patients present a barrel chest or a chest with increased subcutaneous cellular tissue, making echo screening more difficult. Undoubtedly, tissue characterization capability through late gadolinium enhancement is the most important contribution of CMR, allowing early detection of fibrosis even in preclinical (both neurological and cardiac) stages of the disease, as evidenced in our patients. This finding —even at an early age— can totally change the medical approach.

A drawback worth mentioning is the medical community's lack of knowledge of the common cardiac involvement in patients with NMD. NMD is a rare disease, and initial evaluation by cardiologists is rare. Another important problem is the cost of CMR, and the limited access to this technique. In Tucumán, our province, CMR is unavailable in the public sector and partially available in the private sector. To carry out this study, funding had to be requested from foundations and the pharmaceutical Industry. Our goal is to increase the number of CMRs for NMD patients in the future. We follow up more than 70 patients of different ages and stages of the disease; there is still a lot to do and learn.

In conclusion, we consider that CMR should be included as a screening method for patients with NMD; its contribution to clinical and therapeutic staging is of utmost importance.

REFERENCES

1. Posada Rodríguez IJ, Gutiérrez-Rivas E, Cabello A. Repercusión Cardiaca de las enfermedades neuromusculares. Rev Esp Cardiol 1997;50:882-901. https://doi.org/10.1016/S0300-8932(97)74695-5

2. D'Orsogna L, O'Shea JP, Miller G. Cardiomyopathy of Duchenne muscular dystrophy. Pediatr Cardiol 1988;9:205-13. https://doi.org/10.1007/BF02078410.

3. Finsterer J, Stöllberger C. The heart in human dystrophinopathies. Cardiology 2003;99:1-19. https://doi.org/10.1159/000068446.

4. Barona P, Narbona J, Álvarez MJ, Fidalgo ML, Sáenz J, Villa I.Estudio cronológico de los signos de miocardiopatía en las distrofias musculares progresivas. An Esp Pediatr 1993;38:173-7.

5. American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. Cardiovascular health supervision for individuals affected by

Duchenne or Becker muscular dystrophy. Pediatrics 2005;116:1569- 73. https://doi.org/10.1542/peds.2005-2448.

6. Bérard C, Payan C, Fermanian J, Girardot F; Groupe d'Etude MFM. Servicio de Rééducation Pédiatrique l'Escale, hospicios Civille de Lyon, Centro Hospitalario Lyon-Sud, Pierre Bénite. La medida función motora -Escala para enfermedades neuromusculares –Descripción y estudio de validación Revista de Neurología (Paris) 2006;162:485-93.

7. Bhattacharyya KB, Basu N, Ray TN, Maity B. Profile of electrocardiographic changes in Duchenne muscular dystrophy. J Indian Med Assoc 1997;95:40-2, 47.

8. Luce L, Carcione M, Mazzanti C, Buonfiglio PI, Dalamón V, Mesa L. Theragnosis for Duchenne Muscular Dystrophy. Front Pharmacol 2021;12:648390. https://doi.org/10.3389/fphar.2021.648390.

9. Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 1987;51:919-28. https://doi.org/10.1016/0092-8674(87)90579-4.

10. Dra-Isabel-Lorda-Sanchez-Consejo-genético-DMD.pdf 2009-11

11. Nigro G, Comi LI, Politano L, Bain RJ. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. Int J Cardiol 1990;26:271-7. https://doi.org/10.1016/0167-5273(90)90082-g.

12. Spurney F. Cardiomiopatía en Distrofia Muscular Duchenne: Actual Entendimiento y Futuras Direcciones. Muscle Nerve 2011;44:19

13. Power LC, Gusso S, Hornung TS, Jefferies C, Derraik JGB, Hofman PL. Exercise Cardiac Magnetic Resonance Imaging in Boys With Duchenne Muscular Dystrophy Without Cardiac Disease. Pediatr Neurol 2021;117:35-43. https://doi.org/10.1016/j.pediatrneurol. 2020.12.011

14. Panovský R, Pešl M, Holeček T, Máchal J, Feitová V, Mrázová L, et al. Cardiac profile of the Czech population of Duchenne muscular dystrophy patients: a cardiovascular magnetic resonance study with T1 mapping. Orphanet J Rare Dis 2019;14:10. https://doi.org/10.1186/s13023-018-0986-0

15. Sanchez F, Weitz C, Gutierrez JM, Mestroni L, Hanneman K, Vargas D. Cardiac MR Imaging of Muscular Dystrophies. Curr Probl Diagn Radiol 2022;51:225-34. https://doi.org/10.1067/j.cpradiol. 2020.12.010.

16. Siegel B, Olivieri L, Gordish-Dressman H, Spurney CF. Myocardial Strain Using Cardiac MR Feature Tracking and Speckle Tracking Echocardiography in Duchenne Muscular Dystrophy Patients. Pediatr Cardiol 2018;39:478-483. https://doi.org/10.1007/s00246-017-1777-4.

17. Prakash N, Suthar R, Sihag BK, Debi U, Kumar RM, Sankhyan N. Cardiac MRI and Echocardiography for Early Diagnosis of Cardiomyopathy Among Boys With Duchenne Muscular Dystrophy:A Cross-Sectional Study. Front Pediatr 2022;10:818608. https://doi.org/10.3389/fped.2022.818608.

18. Buddhe S, Lewin M, Olson A, Ferguson M, Soriano BD. Comparison of left ventricular functionassessment between echocardiography and MRI in Duchenne muscular dystrophy. Pediatr Radiol 2016;46:1399-408. https://doi.org/10.1007/s00247-016-3622-y

OPINION ARTICLE

The Doctor of the Future

HERNÁN DOVAL

Should doctors of the future continue to interact occasionally with the patient in their offices, or should they be part of a healthcare team responsible for the community, with the continuity and health promotion in their homes?

INTRODUCTION

Fewer and fewer people believe that medical progress depends entirely on technological innovations, when at the same time current worldwide healthcare —with different nuances— is fragmented, without continuous care physicians who thoroughly know their patients, and are ultimately responsible for making decisions about their health. However, Hunter has recently stated that "*As studies have shown, most patients and the public didn't really want choice—rather, they wanted accessible services provided locally where possible that they could trust and which were safe and of good quality.*" (1)

This leads us to ask ourselves: What are the factors for poor health in today's society?

In A New Engl J Med Perspective on the role of clinicians in health care reform, Darzi writes: "*Lifestyle-related health problems, like obesity, smoking, or diabetes, will not be solved by high-tech robotics and larger hospitals, but rather by access to family doctors, innovations in public health, and lessons from the emerging discipline of behavioral economics.*

The best results can be achieved only when the system itself is healthy and based on true "partnership" between patients and clinicians". (2)

Instead, …."*it is called for "partnership" with the private sector, notwithstanding the mounting evidence of the commercial determinants of ill-health such as alcohol, tobacco, ultra-processed foods, and industrial and automobile pollution*", (3) and we could add the catastrophic climate change due to global warming from non-renewable fossil energy industries.

These commercial determinants are not due to small businesses or even national companies, but to the fact that "*The power of transnational corporations, the main vectors of the commercial determinants of health, transcends national boundaries and requires strong and decisive global action both by global civil society and international institutions. In 2018, for example, of the 100 entities with the highest annual revenues, 69 were corporations and 31 were governments*". (3)

Therefore, as has been well stated: "*Most noncommunicable diseases require a personal as well as a population approach to affecting risk-enhancing lifestyles and customs. This is a core component of primary health care*". (4)

However, health risks are different, and can actually vary in the different communities. Therefore, the first essential step is to identify the risk determinants in the communities where we work, in order to adapt health care to the specific requirements of our population and monitor the outcomes.

We will attempt to demonstrate that some populations are "invisible" to their specific determinants.

"INVISIBLE" RISK FACTORS IN INFORMAL SETTLEMENTS

Argentina in general (5) and the City of Buenos Aires in particular (6) are contexts with profound health inequalities. Likelihood of premature death —dying before the age of 74— is determined by socioeconomic factors. In the highest quintile of unmet basic needs, total mortality increases by > 30% and cardiovascular mortality by > 33% in Argentina as a whole; and the difference is even more significant in the capital city, with more than double the number of deaths. (5-7)

This fact is also confirmed and repeatedly published internationally. (8-10) Therefore, health policy planning for disease prevention requires proper data availability on disease burden and risks in the population. In Argentina, National Survey of Risk Factors (NSRF) has been carried out to identify the distribution of risk factors in large population groups.

However, huge social groups are left out of those estimates, because surveys of the so-called "unsafe areas", or dismissively referred to as "marginal areas" —which technicians aseptically call "informal settlements" and people accurately call "slums"—, representing about 10% of the inhabitants of Argentina, are excluded.

The purpose of our survey was to characterize the prevalence of risk determinants among the inhabitants of the slum "Villa 31", in Retiro neighborhood, Buenos Aires, and compare it with data from the NSRF. (11)

The Argentinian group of health users and workers, *Corriente Nacional de Salud Salvador Mazza*, together with the *Pichón Riviére School of Social Psychology,* conducted a baseline field survey of the Villa 31 and 31 bis in the City of Buenos Aires. During a period of 27 months, personal interviews were car-

ried out on Saturdays using the convenience sampling method to people living in different areas of Villa 31 and 31 bis slums in Retiro neighborhood, in the City of Buenos Aires (Survey of Villa 31, EV31). The interview was conducted on those who agreed to be surveyed. A probabilistic sampling was not carried out due to lack of housing map. The interviews were conducted using a structured questionnaire of more than 100 questions that included demography, employment, risk factors, addictions, and reproductive health. All participants had their blood pressure, weight and height measured. A total of 406 people were interviewed and their data were compared with data from 32,365 people in the NSRF. All comparisons were made on the basis of age group.

Demographics

The average age within each age group was similar between the NSRF and that of EV31. The proportion of women interviewed was significantly higher in Villa 31 (67.9% vs 52.6%). People from the slums tended to have less schooling; only 35% completed high school education compared with 51.9% in the NSRF.

As expected, housing characteristics were significantly different among the people in Villa 31 compared with NSRF, including flooring materials, proportion of lack of bathrooms or any other indicator of housing structure. The average number of family members was similar in EV31 and NSRF (almost 4).

People living in the slums lacked health insurance (mandatory or voluntary) in 78.3% of cases vs 29.1% in the NSRF. Unemployment rates were also significantly different between the two populations in all age groups: more than five times more common among people in the slums.

Declared health

Fair to poor self-rated health, the presence of pain and of moderate to severe anxiety and depression were significantly higher in all age groups of the slum residents (3 to 5 times). In addition, the prevalence of self-reported hypertension was higher among slum residents (26% higher), especially in young groups; for example, in people aged 25-34 years, it was almost 3 times higher. Prevalence of overweight (26%) and obesity (72%) was significantly higher for Villa 31 residents, especially among young people. The incidence of diabetes was 12.1% for EV31 and 9.8% for NSRF (26% more); however, this incidence was three times the national average among people aged 18 to 24. Compared to NSRF, Villa 31 residents were always significantly undertreated for all the conditions evaluated. That was the case with antihypertensive and lipid-lowering treatments, with 7 times more patients treated in the city, and with antidiabetic treatment, which increased 17 times.

The decrease in daily smokers was much more significant among people in Villa 31 (less than half) in all age groups. Daily alcohol consumption was 10 times more prevalent in the slums, with hazardous use in 35% and alcohol addiction in 10% of the residents. Illegal drug use was determined using validated Drug Abuse Screening Test-10 (DAST-10), showing hazardous use in 5% and addiction in 3%; but since all addicts were men, it rose to 13% in this group.

As evidenced, the prevalence of risk factors shows a particular distribution that differs from that reported in the NSRF of the city. Those data suggest the need to further survey these population groups to establish specific policies.

Comments

This huge conglomerate of people lives in extremely precarious housing in overcrowded conditions, and they are insufficiently represented in daily life and health planning. The NSRF, by sample design, represents 25.7 million Argentines living in cities. However, the inhabitants of the so-called *villas de emergencia* (slums) are not part of these represented Argentines, because slums have not been identified as distinct residential areas within the cities.

This is confirmed, because the number of people in the NSRF who lived in a location not suitable for housing or in a space of precarious structure represents only 0.5% of the sample.

Nevertheless, self-rated health —a deliberately, subjective, simply structured question— is a strong predictor of early mortality in the general population. (12) At any age, the perception of fair to poor health was two to three times more frequent among slum residents. This finding correlates with three times as many unemployed people as Argentinians who do not live in the slums, and most of them (75%) without health insurance (public or private health insurance plan) making this population dependent on public healthcare to find solutions to their many health problems.

In line with these findings are the high rates of depression and anxiety reported, as well as the greater presence of moderate to severe pain. The rate of hazardous alcohol use among slums residents is alarming (35%). Illegal drug consumption is a real problem, hazardous use 5%, with an addiction rate of 3% (13% in men).

A series of associated risk factors —especially among young people— cause deep concern. Both overweight and obesity double the national rates, and increase diabetes, cholesterol and hypertension. Despite these higher rates, the inhabitants of the slums had their blood glucose, cholesterol and blood pressure measured much less often in the last year; in addition, treatment rate among those with diabetes, hypercholesterolemia and hypertension was very low for all age groups, reaching up to 10 times less than in city residents of the NSRF.

The poor in general —and, in this case, the poorest of the poor— cannot choose freely what to eat or when to exercise. Claiming them a “lifestyle” with a

smart diet and exercise is simplistic, and places disease as the responsibility of the individual subject, rather than their "way of life" in which "smart" eating and exercising often require them time and money they do not have. In Argentina, the price of fruits and vegetables is often high, which explains their low consumption in the diet of slum residents. Moreover, the lower incidence of smoking among slum people may not be due to prudence or intelligent decisions, but rather to the cost of cigarettes, as is probably the case in the rest of the world. It is not enough to recommend prudence and hygiene: it is necessary to understand how to reach people who will have to make complex decisions in a unique environment full of challenges.

TRAINING FOR COMMUNITY SOCIAL WORKERS (CSWS) AND HOME CARE BY PRIMARY HEALTHCARE TEAMS

The availability of consultations for this population is affected by the few outpatient care centers with few health workers, and therefore limited opening hours, among other reasons. At the same time, preventing asymptomatic entities at an early age is not fostered in a population with vital urgencies, such as being unemployed and surviving its demographic indicators. Therefore, implementing a completely different healthcare system is mandatory.

With this idea in mind, we have concluded a first theoretical-practical course and evaluation to train "*community social workers*" *(CSWs) with the slum residents themselves*, for them to help and form a care team with primary care physicians and nurses that can address health risk factors and monitor treatment in the patient's own home, including scheduled and frequent visits to maintain continuity of treatment. COVID-19 pandemic prevented us from evaluating its effectiveness with a pragmatic controlled trial; we hope to carry it out in more favorable accessibility conditions.

EXPERIENCE IN OTHER LATIN AMERICAN COUNTRIES

A similar system, in which the same care team prioritizes the relationship with the community's public health, was systematically initiated in Costa Rica in 1994, when it passed unanimously in the Legislative Assembly. It would merge the public-health services of the Ministry of Health with the Caja's system of hospitals and clinics, and every Costa Rican would be assigned to a local primary-health-care team, called Basic Integrated Health Care Team (EBAIS, *Equipo Básico de Atención Integral en Salud*). This allowed public officials to combine living conditions and health needs as a whole, and to define and monitor the objectives to be achieved.

The EBAIS includes a physician, a nurse, and a trained community-health worker known as Technical Assistant in Primary Healthcare (ATAP, *Asistente Técnico en Atención Primaria*). An ATAPS is responsible for visiting 1400 homes preventively. The homes are grouped into three categories:

Priority 1 homes have an elderly person living alone or an individual with a severe disability, an uncontrolled chronic disease, or a high-risk condition; they average three preventive visits a year.

Priority 2 homes have occupants with more moderate risk and get two visits a year.

The rest are Priority 3 homes and get one visit a year.

The effectiveness of this system is evidenced in that Costa Rica's life expectancy became the longest in Latin America.

"*The results are enviable. Since the development of the EBAIS system, deaths from communicable diseases have fallen by ninety-four per cent, and decisive progress has been made against non-communicable diseases as well. It's not just that Costa Rica has surpassed America's life expectancy while spending less on health care as a percentage of income; it actually spends less than the world average. The biggest gain these days is in the middle years of life. For people between 15 and 60 years of age, the mortality rate in Costa Rica is 8.7 per cent, versus 11.2 per cent in the U.S.—a 30% difference. But older people do better, too: in Costa Rica, the average sixty-year-old survives another 24.2 years, compared with 23.6 years in the U.S.*" (13)

PEER SUPPORT GROUPS

In turn, taking advantage of the "neighborhood effect", peer support groups could be created for the management of different risk factors, guided by an ATAP to clarify doubts, but even more importantly, to demonstrate in concrete action how to exercise, quit smoking, reduce obesity, treat diabetes and hypertension, reduce alcoholism, and stop drug use. (14, 15)

The "neighborhood effect" was described by engineers Madiz and Risom, members of the Danish Gehl team, advising on the redevelopment of Villa 31. The interviewer says: "*The main surprise of the researchers was to detect that in Villa 31 streets there are a greater number of people walking, biking, socializing, playing and watching other people pass by than in the rest of the six neighborhoods they studied..., they state and assert that the families of Villa 31 deal with severe deprivation in many aspects, and yet, in the midst of scarcity, the neighborhood offers characteristics that some of the most privileged cities aspire to*." (16)

As shown, in the first place there is the invisibility of this population, since the distribution of medical conditions found in the "general population" cannot be automatically transferred to the population of the informal settlements of the City of Buenos Aires. Neither diabetes nor hypertension, depression or access to consultation and treatment are similar to those of "the city" residents. Therefore, the "city" health planning is not applicable to slum residents, since they are not part of the city as perceived by those who measure,

plan and execute. A policy that includes these subjects —their needs, perspectives, abilities and disabilities— is essential in implementing health policies.

Secondly, articulation of this health policy should be discussed. In the light of these results, the "passive offer" of services dealing with slum residents as mere "consumers" is far from a good approach.

As Tudor Hart put it in 1994, we should speak of patients not as clients but as collaborators or co-producers, together with the healthcare system: "*recognition of patients as co-producers rather than consumers would begin to solve several problems which are otherwise only likely to get worse. As co-producers, patients must share much more actively both in defining their problems and in devising feasible solutions than they have in the past.*" (1)

There is no place in co-production (citizens - group) for outmoded notions of professional dominance or paternalism, but instead a focus on combining the respective strengths of the public and professions.

Because it is not only about implementing a containment policy for "spontaneous demands" but about promoting "partnership" and "empowering" them to discuss how to promote and reverse a burden of disease and risk among the young population, who will have a significant number of events, suffering and disabilities in the near future. This enormous challenge demands an institutional, demographic and cultural revolution.

ECONOMY OF CHANGES IN RISK BEHAVIORS AND SOCIAL DETERMINANTS. DOES THE HEALTHCARE SYSTEM HAVE ANYTHING TO SAY TO STATE POLICIES?

Since 2015, the County Health Rankings (CHR) provides data for nearly every county in the U.S. on four modifiable groups of health factors, including healthy behaviors, clinical care, physical environment, and socioeconomic conditions, and on health outcomes such as length and quality of life. The relative contributions in the validated regression modeling for each of those determinants of health were 47% socioeconomic conditions, 34% healthy behaviors, 16% clinical care, and 3% physical environment.

The combination of socioeconomic conditions and healthy behavior account for 81% of life expectancy and quality of life, compared to a meager 16% for clinical care. Realizing the greatest improvements in population health will require addressing the social (healthy behaviors) and economic determinants of health. These are State Policies, in which those of us who provide clinical care decide on what to do and, most importantly, create a strong line of opinion in the population so that it can become a reality. (17)

Preventing ill health requires a focus on the behaviors that contribute most to chronic diseases, including smoking, unhealthy diets, alcohol consumption and physical inactivity, and which also follow a socioeconomic pattern.

Interventions to these risk factors —that largely target non-conscious processes— are those aimed at whole populations and include fiscal and economic interventions, marketing approaches, and interventions altering the availability of products that harm health.

As Marteau points out, "*Achieving effective policy action requires strong political and public support to overcome powerful lobbying from commercial organizations that profit at the expense of population health. Tackling behavioral and social causes together is particularly important for price based interventions.*" (18)

We will show the evidence for these policies.

School cafeterias: Availability is evidenced in purchases made in cafeterias by more than 20,000 children and adolescents from 54 private schools in Brazil. Only 11.6% of the products offered in the school cafeterias were of high nutritional value (HNV); an increase of one HNV beverage was associated with a 19% increase, but also with an 18% decrease in subsequent expenditure on low nutritional value (LNV) beverages. (19) In other words, improvements to menu quality have the potential to increase the consumption of healthier products and decrease the consumption of unhealthy ones.

Salt consumption: An excellent open-label, cluster-randomized trial involving persons from 600 villages in rural China (almost 21,000 subjects with a history of stroke and/or high blood pressure) was conducted in 3 different places in China. The intervention group used a salt substitute (sodium chloride 75% and potassium chloride 25%), while the control group continued to use regular salt, with a follow-up of 4.7 years, significantly decreased stroke (14%), major cardiovascular events (13%), and death (12%), with no adverse effects attributed to hyperkalemia. (20) Certainly, salt should have 25% potassium chloride to produce a decrease in the damage of cerebral and cardiovascular events in the overall population.

Alcohol: There is little evidence of a decrease in alcohol sales by setting a minimum price, except in Canada. In interrupted time series regression analyses of the impact of minimum unit pricing (MUP) on Scottish household purchases, with the 1 May 2018 imposition of a MUP of 0.64 pounds per gram of alcohol, there was an immediate decrease in weekly purchasing of 9.5 grams of alcohol per adult per household, almost half of the previous one. The reduction in purchased grams of alcohol was greater in lower income households and in those that purchased the greatest amount of alcohol. If this policy were widespread, it would reduce the seventh leading risk factor for ill health and premature death in the world. (21)

Smoking: Smoking tobacco use accounted for 7·69 million deaths per year (87% were smokers at that time) and 200 million disability-adjusted life-years. (22)

"*Price is the key determinant of smoking uptake and cessation. Worldwide, a reduction of about a third*

could be achieved by doubling the inflation-adjusted price of cigarettes, which in many low- and middle-income countries could be achieved by tripling the specific excise tax on tobacco. [...] Higher taxes are particularly effective in poorer or less educated groups, and help prevent young people who are experimenting with smoking from becoming regular smokers." (23)

Surprisingly —or not so—, excise tax is frankly lower in low- and middle-income countries than in high-income countries, preventing the decrease of tobacco consumption. The same effect of the price-consumption ratio is observed in Latin American countries. (24)

Sugary drinks: In a review of sugary drink consumption in children and adolescents, price increases are associated with a decrease in consumption. "*In the case of sugary drinks, a systematic review revealed that each 10% increase in price, such as a tax, reduced sugary drink consumption by 7%*." (25)

A study on price elasticity of sugary drinks in Mexico found that a 10% price increase was associated with a decrease in quantity consumed of soft drinks by 11.6% and 10.6% for sugar-sweetened beverages. Higher elasticities were found among households living in rural areas, in more marginalized areas and with lower income. (26)

In the Monthly Surveys of the Manufacturing Industry in Mexico from 2007 to 2015, an excise tax of 1 Mexican peso was implemented to sugary drink consumption, starting on January 1, 2014. The pre-tax period (2007-2014) was compared to the post-tax period (2014-2015), showing a 7.3% decline in sugary drink sales per capita, and a 5.2% increase in per capita sales of water, in that first year. (27) At 2-year follow-up, the decrease was 8.2% on average, being even greater in the second year. For taxed beverages, the three different income groups experienced significant declines but reductions in absolute and relative terms were larger among the lowest socioeconomic group. (28)

Childhood obesity: Childhood overweight and obesity have become such a serious problem in our society that a whole city is working against obesity in children, as is the case in Amsterdam, where trained volunteers visit schools, community centers and homes to to spread messages such as to drink water rather than sugary drinks, ban unhealthy food advertisements in subways, create an exercise-friendly city, and urge private business to promote healthy products (such as selling whole-grain bread instead of white bread). Community care nurses check weight and height of school children at least annually.

Childhood overweight decreased from 21% in 2012 to 18.5% in 2015 (12% drop, despite the increase in child population in those 3 years). (29)

A cluster randomized clinical trial was conducted in 24 schools in China. A total of 1392 children aged 8 to 10 years were allocated to multifaceted intervention, (targeting both the children and their environment —engaging the school and families in supporting children's behavioral changes, for one school year) or usual follow-up. Body Mass Index (BMI) decreased significantly by -0.46 kg/m2, as well as obesity by 27% and other common signs of adiposity, with no adverse events. (30)

Poor-quality diet: Adolescence is a pivotal point to induce healthy diets that can persist into later life. While there are still many countries with malnutrition or food insecurity, there is a rapid emergence of the obesity pandemic that occurs at that age.

"*A combination of taxes, regulation, and public education campaigns seems to maximize the impact. [...] Local governments can influence planning rules, such as restrictions on fast-food restaurants near schools* or *street food vendors licensing. For instance, exposure to fast food restaurants is strongly associated with junk food consumption, in a study on Canadian adolescents*." (31)

WHAT TO DO?

If agreement is reached on these proposals in a group discussion among health users and workers (*Corriente Nacional de Salud*), it would be necessary to move on to a concrete Health Program for each specific point. Different groups could deal with each topic; for example, how to set primary care groups, goals and forms of care developed together with the community, how to intervene in schools and train teachers, check weight and height of all school children more than once a year, what foods to ban or reduce availability with taxes —or facilitate their purchase with grants or tax abolition—, as well as other goals that may be set.

In a general meeting, each topic could be discussed and agreed upon, in order to achieve a specific and detailed Health Program; with the presentation and discussion of the entire population, it could have the required impetus to put it into practice.

CONCLUSION

William Beveridge, the economist whose 1942 report led to the founding of Britain's National Health Service (NHS), famously said that "*a revolutionary moment in the world's history is a time for revolutions, not for patching*." "*Given the combination of the global downturn and the time bomb that is health insurance costs, there is no denying that health care in the United States has reached such a moment. This matter is too important to be left to the politicians and policymakers; there is an urgent requirement for professional clinicians to step up and lead the debate*". (2)

We must begin to discuss it not only with health workers but also with the entire population, creating a large social movement so as not to repeat the same mistakes, as we are already on the brink of the abyss.

While it is a difficult endeavor, we can at least claim the honor of having tried.

REFERENCES

1. Hunter DJ. The future doctor and the future patient – reaching a true partnership. Br Med J 2021;375:n3121. https://doi.org/10.1136/bmj.n3121

2. Darzi A. A Time for Revolutions – The Role of Clinicians in health Care Reform. N Engl J Med. 2009:361(6)e8. https://doi.org/10.1056/NEJMp0905707

3. Sanders D, Nandi S, Laborité R, Vance C, Van Damme W. From primary health care to universal health coverage – one step forward and two steps back. Lancet 2019;394:619-21. https://doi.org/10.1016/S0140-6736(19)31831-8

4. Goodyear-Smith F, Van Wheel C. Account for primary health care when indexing access and quality. Lancet. 2017;390:205-06. https://doi.org/10.1016/S0140-6736(17)31289-8

5. Macchia A, Mariani J, Ferrante D, Nul D, Grancelli H, Doval HC. Muerte cardiovascular prematura y condición socioeconómica en la Argentina. Acerca de las oportunidades y desafíos de representar a poblaciones vulnerables. Rev Argent Cardiol 2015;83:516-21.

6. Macchia A, Mariani J, Nul D, Grancelli H, Doval HC. Inequidad social, lugar de residencia y muerte prematura por cualquier causa en la Argentina. Rev Argent Cardiol 2016;84:114-9. https://doi.org/10.7775/rac.es.v84.i2.8267

7. Mariani J, Monsalvo M, Fernández Prieto A, Macchia A. Muerte prematura por accidente cerebrovascular y condición socioeconómica en la Argentina. Rev Argent Cardiol 2016;84:120-5. https://doi.org/10.7775/rac.es.v84.i2.8021

8. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, Ricceri F y col. LIFEPATH consortium. Socioeconomic status and the 25×25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. Lancet 2017;389:1229-37. https://doi.org/10.1016/S0140-6736(16)32380-7

9. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med 2008;358:2468-81. https://doi.org/10.1056/NEJMsa0707519

10. Hosseinpoor AR, Bergen N, Mendis S, Harper S, Verdes E, Kunst A, et al. Socioeconomic inequality in the prevalence of noncommunicable diseases in low- and middle-income countries: results from the World Health Survey. BMC Public Health 2012;12:474. https://doi.org/10.1186/1471-2458-12-474

11. Doval HC, Mariani J, Gomez GC, Vulcano L, Parlanti L, Gavranovic MA, et al. Cardiovascular and other risk factors among people who live in slums in Buenos Aires, Argentina. Public Health 2019;170:38-44. https://doi.org/10.1016/j.puhe.2019.02.014

12. Idler EL, Benyamini Y. Self-Rated Health and Mortality: A Review of Twenty-Seven Community Studies. J Health Soc Behav 1997;38:21-37. https://doi.org/10.2307/2955359

13. Gawande A. Costa Ricans liver longer than we do. What´s the secrets? The New Yorker. 23 August 2021.

14. Jain Y, Jain P. Communitisation of health care: peer support groups for chronic disease care in rural India. BMJ 2018;360:k85. https://doi.org/10.1136/bmj.k85

15. Lilford RJ, Oyebode O, Satterthwaite D, Melendez-Torres GJ, Chen YF, Mberu B, et al. Improving the health and welfare of people who live in slums. Lancet 2017;389:559-70. https://doi.org/10.1016/S0140-6736(16)31848-7

16. Jurado M. diario Clarin 21 febrero 2018 página 55.

17. Hood CM, Gennuso KP, Swain GR, Catlin BB. County Health Rankings: Relationships Between Determinants Factors and Health Outcomes. Am J Prev Med 2016;50:129-35. https://doi.org/10.1016/j.amepre.2015.08.024

18. Marteau TM, Rutter H, Marmot M. Changing behaviour: an essential component of tackling health inequalities. BMJ 2021.372n332. https://doi.org/10.1136/bmj.n332

19. Andretti B, Goldszmidt RB, Andrade EB. How changes in menu quality associate with subsequent expenditure on (un)healthy foods and beverages in school cafeterias. Prev Med 2021;146:106456. https://doi.org/10.1016/j.ypmed.2021.106456

20. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, et al. Effect of Salt Substitution on Cardiovasculat Events and Death. New Engl J Med 2021;385:1067-77. https://doi.org/10.1056/NEJMoa2105675

21. O´Donnell A, Anderson P, Jané-Llopis E, Manthey J, Kaner E, Rehm J. Inmediate impact of minimum unit pricing on alcohol purchases in Scotland. BMJ 2019;366:15274. https://doi.org/10.1136/bmj.l5274

22. GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019. Lancet 2021;397:2337-360.

23. Jha P, Phil D, Peto R. Global Effects of Smoking, of Quitting, and of Taxing Tobacco. New Engl J Med 2014;370:60-8. https://doi.org/10.1056/NEJMra1308383

24. Guindon GE, Paraje GR, Chaloupka FJ. The Impact of Prices and Taxes on the Use of Tobacco Products in Latin America and the Caribbean. Am J Public Health 2015;105(3):e9-e19. https://doi.org/10.2105/AJPH.2014.302396

25. Muth ND, Dietz WH, Magge SN, Johnson RK. Public Policies to Reduce Sugary Drink Consumption in Children and Adolescents. Pediatrics 2019;145:e20190282. https://doi.org/10.1542/peds.2019-0282

26. Colchero MA, Salgado JC, Unar-Munguia M, Hernández-Ávila M, Rivera-Dommarco JA. Price elasticity of the demand for sugar sweetened beverages and soft drinks in Mexico. Economics and Human Biology 2015;19:129-37. https://doi.org/10.1016/j.ehb.2015.08.007

27. Colchero MA, Guerrero-López CM, Molina M, Rivera JA. Beverages Sales in Mexico before and after Implementation of a Sugar Sweetened Beverage Tax. Plos One 2016;11(9):e0163463. https://doi.org/10.1371/journal.pone.0163463

28. Colchero MA, Rivera JA, Popkin BM, Wen Ng S. Sustained consumer response: evidence from two-years after implementing de sugar sweetened beverage tax in Mexico.Health Aff (Millwood) 2017;36:564-71. https://doi.org/10.1377/hlthaff.2016.1231

29. Sheldon T. Whole city working against childhood obesity. BMJ 2018;361:k2534. https://doi.org/10.1136/bmj.k2534

30. Liu Z, Gao P, Gao AY, Lin Y, Feng XX, Zhang F, y col. Effectiveness of a Mulifaceted Intervention for Prevention of Obesity in Primary School Chidren in China. JAMA Pediatrics 2022;176:e214375. https://doi.org/10.1001/jamapediatrics.2021.4375

31. Hargreaves D, Mates E, Menon P, Alderman H, Devakumar D, Fawzi W, y col. Strategies and interventions for healthy adolescent growth, nutrition, and development. Lancet 2022;399:198-210. https://doi.org/10.1016/S0140-6736(21)01593-2

REVIEW ARTICLE

Arrhythmogenic Cardiomyopathy. Genes and Desmosomal Proteins

Miocardiopatía arritmogénica. Genes y proteínas desmosómicas

HERNÁN PANTERE[1], MARIANO TUMARKIN[1], FRANCISCO AZZATO[1], JOSÉ MILEI[1, MTSAC]

ABSTRACT

In 1996 this disease was introduced into the WHO classification of cardiomyopathies with the term “arrhythmogenic cardiomyopathy”. By the end of the 70s the right ventricle (RV) was identified as a substrate for the development of arrhythmias. The replacement of the myocardium by fibrofatty tissue and the hereditary nature of this condition were described in the 1980s. Later findings led to the identification of several genes involved in the production of desmosomal proteins participating in intercellular coupling, which led to defining arrhythmogenic cardiomyopathy as a desmosomal disease. Electrocardiography and echocardiography are fundamental tools, and invasive angiocardiography was used to detect dyskinesia-akinesia and right ventricular aneurysms. Endomyocardial biopsy was established as the gold standard for the diagnosis due to its ability to detect transmural replacement by fibrofatty tissue. The advent of cardiac magnetic resonance imaging (CMRI) with late gadolinium enhancement reveals morphological and functional abnormalities and tissue damage. The understanding of intercalated disc structure involved in intercellular coupling has made it possible to determine that, apart from desmosomes, several desmosomal proteins, as adherens junctions, gap junctions and ion channels are integrated into a unit known as the " area composita". The area composita constitutes an amalgam between supporting elements and ion channels that participate in action potential propagation, which has led to develop the concept that intercalated discs are constituted by "adhesion/excitability nodes". The clinical implications in the development of malignant arrhythmias are obvious.

Key words: Arrhythmogenic Right Ventricular Dysplasia - Desmosomes - Ventricular Fibrillation

RESUMEN

Desde 1996 esta enfermedad figura en la clasificación de las miocardiopatías de la OMS con el nombre de “miocardiopatía arritmogénica”. A fines de la década del 70 se estableció que el ventrículo derecho (VD) puede ser el sustrato para el desarrollo de arritmias. En la década del 80 se describió el reemplazo del miocardio por tejido fibroadiposo y su naturaleza hereditaria. Posteriores descubrimientos permitieron la identificación de varios genes implicados en la producción de proteínas desmosómicas que participan en el acoplamiento intercelular lo cual llevó a definir a la miocardiopatía arritmogénica como una enfermedad desmosómica. El electrocardiograma y el ecocardiograma resultaron fundamentales y la angiocardiografía invasiva se utilizó para detectar disquinesia-aquinesia y aneurismas del VD. La biopsia endomiocárdica se perfiló como el gold standard para el diagnóstico, debido a su capacidad para detectar el reemplazo transmural por tejido fibroadiposo. El advenimiento de la resonancia magnética cardíaca (RMC) con realce tardío de gadolinio ha permitido revelar no solamente anomalías morfológico-funcionales sino también daño tisular. El conocimiento de la estructura del disco intercalar, involucrado en el acoplamiento intercelular ha permitido determinar que no solamente los desmosomas estarían comprometidos, sino que habría varias proteínas constituyentes tanto de los desmosomas, como de las uniones adherentes, las uniones gap, y los canales iónicos, integradas en una unidad conocida como “área composita”. Ésta constituye una amalgama entre elementos de sostén y canales iónicos que participan en la propagación del potencial de acción, lo que ha permitido desarrollar el concepto de disco intercalar compuesto por los llamados “nodos excitoadhesivos”. Las implicancias clínicas en el desarrollo de arritmias malignas son obvias.

Palabras clave: Displasia Ventricular Derecha Arritmogénica - Desmosomas - Fibrilación ventricular

In 1996 a new disease was introduced into the WHO classification of cardiomyopathies, (1) leaving aside the concept of this entity as a congenital defect. The identification of the left ventricular variant led to coin the term “arrhythmogenic cardiomyopathy” (ACM). (2) The adjective arrhythmogenic defines the pathognomonic characteristic of this non-ischemic heart muscle disease.

In the last century, towards the end of the 70s, Fontaine et al. noticed that the right ventricle (RV) could constitute the substrate for the development of arrhythmias with left bundle branch block morphology. (3,4) In 1982, Frank Marcus et al. published a series of patients with a new syndrome characterized by RV remodeling with aneurysms localized in the inflow tract, apex and outflow tract (triangle of dysplasia) (Figure 1) because the myocardium was replaced by fibrofatty tissue. (5) Nava et al. described the hereditary nature of ACM. (6) In Italy, Nava described a dominant inherited form, later named the "Veneto disease", (7) which

Rev Argent Cardiol 2022;90:351-354. http://dx.doi.org/10.7775/rac.v90.i5.20557

Received: 05/17/2022 – *Accepted:* 07/21/2022

Address for reprints: Dr. José Milei. CONICET, University of Buenos Aires, Instituto Alberto C. Taquini de Investigaciones en Medicina Traslacional (IATIMET), School of Medicine. Marcelo T. Alvear 2270, CABA..

Sources of funding: This study was partially supported by grants from the University of Buenos Aires (UBACYT 20020150100027BA).

[1] CONICET, University of Buenos Aires, Instituto Alberto C. Taquini de Investigaciones en Medicina Traslacional (IATIMET), School of Medicine, Buenos Aires, Argentina.

[MTSAC] Full Member of the Argentine Society of Cardiology

consisted of a genetically determined cardiomyopathy since its clinical manifestations were absent at birth and became evident between 10 and 12 years of age.

Sports activity increases five times the risk of sudden death in carriers. (8) In Italy, the incidence of sudden death due to ACM is 27% among athletes, with a significant reduction since ECG has been implemented as a screening tool in the evaluation of candidates for sports. (9)

Arrhythmogenic cardiomyopathy involves an acquired loss of myocardial tissue followed by fibrofatty replacement in the setting of a myocyte death and repair process (10) due to apoptosis. (11) Although myocardial inflammation is a common finding, its characterization as a consequence of necrosis or as a primary immunological phenomenon is still controversial. (12) Moreover, adipocytes have a mesenchymal origin. (13)

In the Greek island of Naxus, a recessive form of the disease was discovered, with palmoplantar keratosis and woolly hair. (14) In 1996 Ruiz et al. studied junction plakoglobin (JUP) in knockout mice and demonstrated that the absence of JUP affects the development of desmosomes in the heart. The human plakoglobin gene is located on chromosome 17q21. (15)

In Ecuador, the dermatologist Carvajal-Huerta found a recessive mutation in the gene encoding desmoplakin (DSP) in a similar familial syndrome with dilated cardiomyopathy. (16) The gene encoding DSP also became a candidate for the dominant form of ACM. Subsequently, other mutations were identified in the dominant form of ACM: plakophilin-2, desmoglein-2, desmocollin-2 and plakoglobin, confirming it is a desmosomal disease. (17) Multiple compound or heterozygote mutations imply a more severe prognosis, but the productivity of genetic testing does not exceed 50%. (18)

Thus, ACM was definitely linked to genes encoding for desmosomal proteins. Electron microscopy demonstrated disruption of the intercalated discs as a common final pathway for cell death. (19)

The diagnostic criteria were defined in 1994 and updated in 2010. (20,21) Electrocardiography and echocardiography resulted fundamental diagnostic tools. Invasive angiocardiography was used to detect dyskinesia-akinesia and RV aneurysms. (22)

Endomyocardial biopsy was established as the gold standard for diagnosis due to its ability to detect transmural replacement by fibrofatty tissue. (23) This test plays a critical role in the differential diagnosis with diseases that mimic ACM, as myocarditis, sarcoidosis, and idiopathic RV tachycardia. The advent of cardiac magnetic resonance imaging (CMRI) with late gadolinium enhancement reveals morphological and functional abnormalities and tissue damage; it also plays a fundamental role in the diagnosis of isolated left ventricular involvement. (24,25)

Genetic screening is now a routine diagnostic tool in relatives of probands with ACM who have at least one mutation, to search for relatives who are mutation carriers, and is an effective bridge between the laboratory and the patient. State-of-the-art genetic sequencing has enabled rapid and accurate screening and generates index cases either by clinical identification or in postmortem molecular investigation. (26)

Advice against physical activity is one of the most effective measures to prevent sudden death in ACM. (27) Implantable cardioverter defibrillator (ICD) also saves lives in patients with this disease. The indication for implantation depends on the prognosis; it is mandatory in patients with syncope, sustained ventricular tachycardia or previous heart attacks. (28,29)

Drug therapy is routinely used, either isolated or associated with ICD. (30). Ablation is also included among the treatment options, although it is considered a palliative procedure due to the recurrence of arrhythmias. (31) Heart transplantation is the last

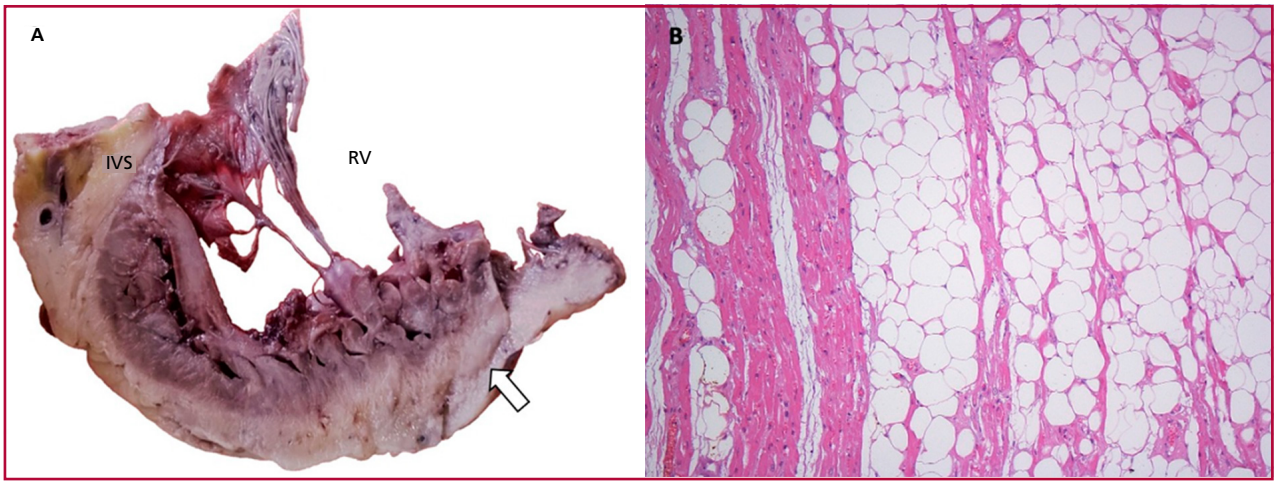


Fig. 1. 29-year-old, otherwise healthy man, with no personal or family history, with unwitnessed sudden death. **A.** Right ventricle (RV) with thin free wall and lard-like tissue (arrow) replacing the myocardium and extending to the interventricular septum (IVS) and left ventricle. **B.** Histological examination showing extensive replacement of the myocardium by fatty tissue, scarce atrophic bundles and residual myocardial fibers separated in small fascicles. HE 200x.

option reserved for end-stage congestive heart failure or unbearable electrical storm.

MOLECULAR MECHANISMS

Among the research perspectives, curative therapy should focus on the molecular mechanism involved in the pathogenesis of the disease. (32) Intercalated discs are highly organized complex structures which connect cardiomyocytes to one another and consist of gap junctions bridging the cytoplasm of the cells, adherens junctions that interconnect the cell cytoskeletons, and desmosomes that connect with the intermediate filament of the cells. Finally, ion channels are also present in the intercalated discs. The genetic abnormalities involving the components of the intercalated discs are responsible for the development of arrhythmias.

The characteristics of the intercalated disc are mainly determined by the properties of its multifunctional proteins within an integrated unit, called the "area composita" which includes adherens junctions, gap junctions, desmosomes and ion channels. Ion channels and gap junctions generate and propagate the action potential.

Deficiencies in these proteins can lead to contractility abnormalities and arrhythmias, demonstrating the interdependence between the intercalated disc components. The lateral membrane has a different composition. Its structural functional component is the costamere and includes focal adhesions linking sarcomeres to the extracellular matrix. Despite the differences, the intercalated disc and lateral membrane have several proteins in common, such as vinculin and α-actinin, and ion channels.

The adherens junction connects actin filaments from adjacent cells and is involved in transducing mechanical signals. The transmembrane protein N-cadherin is the main constituent of adherens junctions. It homodimerizes with N-cadherins from adjacent cells as an intercellular zipper, while calcium ions ensure the rod shape of this junction. N-cadherin also possesses regulatory functions and a mechanosensing role.

β-catenin directly interacts with the C-terminal cytoplasmic domain of N-cadherin. By associating with α-catenin and vinculin, it connects adherens junctions to the actin cytoskeleton. Also, β-catenin plays a central role in cadherin-mediated signaling and can activate the canonical Wnt signaling pathway. The canonical Wnt pathway is crucial in cardiac development but has also been proposed as the key mechanism in certain cardiomyopathies.

While adherens junctions transmit mechanical forces to the cytoskeleton, desmosomes are more robust thanks to their connection to mechanically resilient intermediate filaments. The intercellular part of the cardiac desmosome is built up by the cadherins desmoglein-2 (DSG2) and desmocollin-2 (DSC2). The plaque proteins plakoglobin (JUP) and plakophilin-2 (PKP2), and desmoplakin (DSP) connect desmin to the desmosome. The hyperadhesive state of the desmosome, when DSC2 and DSG2 are bound, depends on the presence of calcium ions.

PKP2 is the main protein, associated with gap junctions and necessary for the organization of the intercalated disc and desmosomal function. Together with JUP, PKP2 mediates attachment to intermediate filaments. PKP2 knockdown causes a decrease in conduction velocity and an increased propensity to develop re-entry arrhythmias.

PKP2 mutations are most common in hereditary ACM. Plakoglobin is present in both desmosomes and adherens junctions. Desmoplakin connects the desmosomes to the type III intermediate filament protein desmin. The main mutations in genes encoding desmosomal proteins in ACM include PKP2 and DSP, along with cadherins DSG2 and DSC2; mutations in JUP are less common. CDH2 encodes N-cadherin and belongs to a superfamily of proteins that mediate cell–cell adhesion in a calcium-dependent manner.

The fact that cadherin-2, like its desmosomal cadherin counterparts, plays a major role in the structure of the intercalated disc is based on the CDH2 cardiac-specific mouse model with deletion of N-cadherin in the adult mouse heart causing dissolution of the intercalated disc structure, including loss of both desmosomes and adherens junctions, demonstrating that desmosome integrity is N-cadherin or cadherin-2 dependent. These mice present atypical forms of dilated cardiomyopathy and ventricular arrhythmia that resulted in sudden death.

Arrhythmic propensity is probably due to a reduced and heterogeneously distributed connexin-43, causing loss of functional gap junctions and partial cardiomyocyte uncoupling, and highlighting the prominent role of cadherin-2 in the intercalated disc. This remodeling with concomitant reduction of desmosomal proteins, connexin-43, and cadherins has also been demonstrated in ventricular tissues of patients with ACM.

The loss of PKP2 expression has been shown to alter the amplitude and kinetics of the sodium current. This evidence suggests a model in which the intercalated disc would be constituted by “adhesion/excitability” nodes formed by aggregates of sodium channels and N-cadherins. (33)

Finally, in view of the important investigations described in the present study, we have recently indicated that the absence of routine clinical and cardiological examinations hinders the correct characterization of the potentially lethal nature of ACM. (34)
Meanwhile, the study of the disease continues.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

REFERENCES

1. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 1996;93:841-2.

2. Basso C, Nava A, Thiene G. Cardiomiopatia aritmogena. Milano: Ed. Arti Grafiche Color Black, 2001.

3. Fontaine G, Frank R, Vedel J, Grosgogeat Y, Cabrol C, Facquet J. Stimulation studies and epicardial mapping in ventricular tachycardia: study of mechanisms and selection for surgery. In: Kulbertus HE (ed). Reentrant Arrhythmias, PA: MTP Publishing. 1977;334-50

4. Fontaine G, Frank R, Gallais-Hamonno F, Allali I, Phan-Thuc H, Grosgogeat Y. Electrocardiographie des potentiels tardifs du syndrome de post-excitation [Electrocardiography of delayed potentials in post-excitation syndrome]. Arch Mal Coeur Vaiss. 1978;71:854-64.

5. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384-98. https://doi.org/10.1161/01.CIR.65.2.384

6. Nava A, Thiene G, Canciani B, Scognamiglio R, Daliento L, Buja G, et al. Familial occurrence of right ventricular dysplasia: a study involving nine families. J Am Coll Cardiol 1988;12:1222-8. https://doi.org/10.1016/0735-1097(88)92603-4

7. Nava A, Bauce B, Basso C, Muriago M, Rampazzo A, Villanova C, et al. Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2000;36:2226-33. https://doi.org/10.1016/S0735-1097(00)00997-9

8. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults?. J Am Coll Cardiol 2003;42:1959-63. https://doi.org/10.1016/j.jacc.2003.03.002

9. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA 2006;296:1593-601. https://doi.org/10.1001/jama.296.13.1593

10. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis?. Circulation 1996;94:983-91. https://doi.org/10.1161/01.CIR.94.5.983

11. Valente M, Calabrese F, Thiene G, Angelini A, Basso C, Nava A, et al. In vivo evidence of apoptosis in arrhythmogenic right ventricular cardiomyopathy. Am J Pathol 1998;152:479-84. https://doi.org/10.1007/978-88-470-2288-1_40

12. Chelko SP, Asimaki A, Lowenthal J, Bueno-Beti C, Bedja D, Scalco A, et al. Therapeutic Modulation of the Immune Response in Arrhythmogenic Cardiomyopathy. Circulation 2019;140:1491-505. https://doi.org/10.1161/CIRCULATIONAHA.119.040676

13. Sommariva E, Brambilla S, Carbucicchio C, Gambini E, Meraviglia V, Dello Russo A, et al. Cardiac mesenchymal stromal cells are a source of adipocytes in arrhythmogenic cardiomyopathy. Eur Heart J 2016;37:1835-46. https://doi.org/10.1093/eurheartj/ehv579

14. Protonotarios N, Tsatsopoulou A, Patsourakos P, Alexopoulos D, Gezerlis P, Simitsis S, et al. Cardiac abnormalities in familial palmoplantar keratosis. Br Heart J 1986;56:321-6. https://doi.org/10.1136/hrt.56.4.321

15. Ruiz P, Brinkmann V, Ledermann B, Behrend M, Grund C, Thalhammer C, et al. Targeted mutation of plakoglobin in mice reveals essential functions of desmosomes in the embryonic heart. J Cell Biol 1996;135:215-25. https://doi.org/10.1083/jcb.135.1.215

16. Kaplan SR, Gard JJ, Carvajal-Huerta L, Ruiz-Cabezas JC, Thiene G, Saffitz JE. Structural and molecular pathology of the heart in Carvajal syndrome. Cardiovasc Pathol 2004;13:26-32. https://doi.org/10.1016/S1054-8807(03)00107-8

17. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 2004;36:1162-4. https://doi.org/10.1038/ng1461

18. Rigato I, Bauce B, Rampazzo A, Zorzi A, Pilichou K, Mazzotti E, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. Circ Cardiovasc Genet 2013;6:533-42. https://doi.org/10.1161/CIRCGENETICS.113.000288

19. Basso C, Czarnowska E, Della Barbera M, Bauce B, Beffagna G, Wlodarska EK, et al. Ultrastructural evidence of intercalated disc remodelling in arrhythmogenic right ventricular cardiomyopathy: an electron microscopy investigation on endomyocardial biopsies. Eur Heart J 2006;27:1847-54. https://doi.org/10.1093/eurheartj/ehl095

20. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994;71:215-8. https://doi.org/10.1136/hrt.71.3.215

21. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533-41. https://doi.org/10.1161/CIRCULATIONAHA.108.840827

22. Daliento L, Rizzoli G, Thiene G, Nava A, Rinuncini M, Chioin R, et al. Diagnostic accuracy of right ventriculography in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 1990;66:741-5. https://doi.org/10.1016/0002-9149(90)91141-R

23. Basso C, Ronco F, Marcus F, Abudureheman A, Rizzo S, Frigo AC, et al. Quantitative assessment of endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy/dysplasia: an in vitro validation of diagnostic criteria. Eur Heart J 2008;29:2760-71. https://doi.org/10.1093/eurheartj/ehn415

24. Norman M, Simpson M, Mogensen J, Shaw A, Hughes S, Syrris P, et al. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation 2005;112:636-42. https://doi.org/10.1161/CIRCULATIONAHA.104.532234

25. Zorzi A, Perazzolo Marra M, Rigato I, De Lazzari M, Susana A, Niero A, et al. Nonischemic Left Ventricular Scar as a Substrate of Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death in Competitive Athletes. Circ Arrhythm Electrophysiol 2016;9:e004229. https://doi.org/10.1161/CIRCEP.116.004229

26. Marschall C, Moscu-Gregor A, Klein HG. Variant panorama in 1,385 index patients and sensitivity of expanded next-generation sequencing panels in arrhythmogenic disorders. Cardiovasc Diagn Ther 2019;9 (Suppl 2):S292-8. https://doi.org/10.21037/cdt.2019.06.06

27. Mirowski M, Mower MM, Staewen WS, Denniston RH, Mendeloff AI. The development of the tranvenous automatic defibrillator. Arch Intern Med 1972;129:773–9. https://doi.org/10.1001/archinte.1972.00320050097010

28. Corrado D, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2003;108:3084-91. https://doi.org/10.1161/01.CIR.0000103130.33451.D2

29. Corrado D, Basso C, Pilichou K, Thiene G. Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart 2011;97:530-9. https://doi.org/10.1136/hrt.2010.193276

30. Wichter T, Paul TM, Eckardt L, Gerdes P, Kirchhof P, Böcker D, et al. Arrhythmogenic right ventricular cardiomyopathy. Antiarrhythmic drugs, catheter ablation, or ICD? Herz 2005;30:91-101. https://doi.org/10.1007/s00059-005-2677-6

31. Philips B, Madhavan S, James C, et al. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Arrhythm Electrophysiol 2012;5:499-505. https://doi.org/10.1161/CIRCEP.111.968677

32. Denegri M, Bongianino R, Lodola F, Boncompagni S, De Giusti VC, Avelino-Cruz JE, et al. Single delivery of an adeno-associated viral construct to transfer the CASQ2 gene to knock-in mice affected by catecholaminergic polymorphic ventricular tachycardia is able to cure the disease from birth to advanced age. Circulation 2014;129:2673-81. https://doi.org/10.1161/CIRCULATIONAHA.113.006901

33. Towbin J, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS Expert consensus statement on evaluation, risk stratification and management or arrhythmogenic cardiomyopathy. Heart Rhythm 2019;16:e334-7. https://doi.org/10.1016/j.hrthm.2019.09.019

34. Pantere H, Azzato F, Milei J. Dos casos de muerte súbita. Primera manifestación por miocardiopatía arritmogénica del ventrículo derecho, tabique interventricular y ventrículo izquierdo. Rev Argent Cardiol 2021;89:363-5.https://doi.org/10.7775/rac.es.v89.i4.20422

REVIEW ARTICLE

Use of Benzodiazepines in Hypertension Treatment

Uso de benzodiazepinas en tratamiento de hipertensión

MIGUEL JAVIER SCHIAVONE [1,MTSAC], PABLO RICHLY[2], VICTORIA PRONOTTI[1], MARIANA PÉREZ[1], ANALÍA AQUIERI[1,MTSAC], HORACIO AVACA[3], JORGE E. TARTAGLIONE[4, MTSAC]

ABSTRACT

Hypertension is a worldwide prevalent disease and one of the main cardiovascular risk factors. Today we live in a society dominated by stress, depression and anxiety, disorders generating a high sympathetic discharge which is damaging for the cardiovascular health. It is usual that as physician we meet patients who in the office and/or emergency departments present some degree of anxiety associated with elevated blood pressure, and in these cases, the treatment chosen to decrease blood pressure is frequently anxiolytics, specially benzodiazepines. As currently no guidelines support the use of anxiolytics for blood pressure management, we decided to carry out a bibliographic review to assess the evidences of their indication to treat hypertension.

Key words: Hypertension - Blood Pressure - Benzodiazepines

RESUMEN

La hipertensión arterial es una enfermedad de alta prevalencia mundial y es uno de los principales factores de riesgo cardiovascular. Hoy en día vivimos como sociedad en una época donde predomina el estrés, la depresión y la ansiedad: trastornos que generan una alta descarga simpática, lo cual resulta perjudicial para la salud cardiovascular. Es habitual que como médicos nos encontremos frente a pacientes que en consultorio y/o en salas de emergencias presentan algún grado de ansiedad asociado a registros elevados de presión arterial, y es frecuente que en estos casos el tratamiento elegido para la disminución de la presión arterial sean los ansiolíticos, y específicamente las benzodiazepinas. Actualmente no existen guías que avalen el uso de drogas ansiolíticas para el manejo de la hipertensión arterial, por lo que decidimos realizar una revisión bibliográfica para evaluar las evidencias sobre su indicación en el manejo de la hipertensión arterial.

Palabras clave: Hipertensión arterial - Presión sanguínea - Benzodiazepinas

INTRODUCTION

There is growing evidence on the relationship between anxiety disorders and cardiovascular disease (CVD) (1,2), but a positive association has also been shown between anxiety disorders and arterial hypertension (HTN). (3,4) Among CVD, HTN is a highly prevalent disorder affecting more than 1 in 3 adults in our country. (5) Despite the guidelines for the management of HTN developed by different Scientific Societies recommend hygienic-dietary measures and the use of antihypertensive agents as the main tools for its control, the use of benzodiazepines (BZD) associated with this condition is remarkably frequent.

There is evidence of an association between high blood pressure (BP) and conditions linked to anxiety, which would explain the more regular use of BZD in cases of severe HTN. (6,7)

Since anxiety-related disorders are common pathologies, with a global prevalence of 7.3% (8) and a very extended use of BZD, (9) we believe it is important to emphasize the correct use of these drugs in situations in which there is evidence for their use. The main reasons are that these drugs, due to their muscle relaxing and sedative effects, are associated with greater risk of falls and car accidents, and are often involved in overdose deaths. Regarding short-term amnesic effects, there is evidence of a mid-term and long-term impact in cognition, with a strong growing association with dementia, (10) though this last point should be evaluated in future investigations, as a meta-analysis published this year reports that the association observed with BZD did not persist after adjusting for confounders. (11)

Mechanism of benzodiazepine action

All the clinically used BZD facilitate the binding of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at GABA A subtype receptors.

Although BZD have qualitatively similar clinical effects, there are important quantitative differences

Rev Argent Cardiol 2022;90:355-359. http://dx.doi.org/10.7775/rac.v90.i5.20558

Received: 05/26/2022 – *Accepted:* 08/18/2022

Address for reprints: Miguel Javier Schiavone - E-mail: mschiavone@hbritanico.com.ar - Solis 2184 - C1134ADT - CABA

[1] faltan los datos.
[MTSAC] Full Member of the Argentine Society of Cardiology
This work obtained the Raúl Borracci Award at the 48th Argentine Congress of Cardiology

in their pharmacodynamic spectrum and pharmacokinetic properties, which have determined diverse therapeutic indications. Different mechanisms of action contribute to the sedative-hypnotic, muscle relaxant, anxiolytic and anticonvulsant effects of BZD.

Practically all the BZD effects result from their action on the central nervous system (CNS), the most significant being sedation, hypnosis, reduction of anxiety, muscle relaxation, antegrade amnesia and anticonvulsant activity. Only two BZD effects are the result of peripheral actions: coronary vasodilation, observed after intravenous administration of therapeutic doses of certain BZD and neuromuscular blockade, only found at very high doses. As the BZD dose increases, sedation progresses to hypnosis and then stupor.

The physicochemical and pharmacokinetic properties of BZD greatly affect their clinical utility. They all have high lipid-water partition coefficients in the non-ionized form; however, the lipophilic activity varies >50 times according to the polarity and electronegativity of several substitutes.

All BZD are completely absorbed, except clorazepate, which is rapidly decarboxylated in the gastric juice to N-desmethyldiazepam (nordiazepam) and is then completely absorbed. Active drugs in the benzodiazepine receptor can be divided into four categories based on their half-life:

- Ultrashort-acting BZD
- Short-acting agents (half-life 6 hours), including triazolam, the nonbenzodiazepine zolpidem (half-life ~ 2 hours) and eszopiclone (half-life 5-6 hours)
- Intermediate-acting agents (half-life 6-24 hours), as alprazolam, clonazepam, lorazepam, estazolam and temazepam
- Long-acting agents (half-life >24 hours), including flurazepam, diazepam and quazepam.

The BZD volumes of distribution are large and in many cases are increased in elderly patients, requiring special attention in this population. They are also drugs which cross through the placenta and are excreted in the breast milk.

Benzodiazepines are largely metabolized by the hepatic cytochromes (CYP), mainly CYP3A4 and 2C19. Because the active metabolites of some BZD are biotransformed more slowly than the original components, the duration of action of many BZD has scant relationship with the elimination half-time of the original drug administered, as in the case of flurazepam. Conversely, the biotransformation rate of agents which are inactivated by the initial reaction is an important determinant of their duration of action, including oxazepam, lorazepam, temazepam, triazolam and midazolam. (12-16)

Hypertensive crisis and use of benzodiazepines

Consultations for severe HTN in the emergency departments are frequent. A recent meta-analysis found that in this context, the prevalence of hypertensive emergencies (in which BP elevation is associated with acute target organ damage (TOD) is 0.3%, while the so-called hypertensive emergencies (BP elevation not associated with TOD) are even more frequent and estimated at 0.9% (17) The REHASE study, carried out in Argentina, showed that the prevalence of severe hypertension without TOD was 9% of all emergency services consultations; an episode of stress was recognized in 46% of the population within the 48 hours prior to developing severe hypertension (18).

It is important to recall that many acute BP elevations can be reactive or transient due to sympathetic stimulation (stress, pain, urinary retention), a poor assessment technique or manifestation of white coat HTN. (19)

The challenge for the physician in the emergency ward is to decide which is the best therapeutic plan. This determines that some patients receive oral antihypertensive treatment associated or not to a BZD and others only rest and are discharged with alarm recommendations.

To date, several studies have evaluated different therapeutic strategies in patients presenting with high BP without TOD, but most have scarce statistical power.

In 2005, a double blind, randomized clinical trial was published in Brazil, including 100 patients who attended the emergency department at Hospital Universitario Oswaldo Crus with symptoms associated to systolic blood pressure (SBP) between 180 and 220 mmHg and/or diastolic blood pressure (DBP) between 110 and 120 mmHg. Patients were randomly assigned to receive symptomatic medication (dipyrone or diazepam) or antihypertensive medication (captopril). The proportion of patients treated with symptomatic medication who achieved BP reduction and returned home was like that of patients treated with antihypertensive medication. (20) On the same year, another research group obtained similar results in a double blind, randomized clinical trial, evaluating 36 60-year-old patients admitted to the emergency department with elevated BP (over 190/100 mmHg), who were divided into two groups randomly assigned to oral diazepam 5 mg or sublingual captopril 25 mg. The results demonstrated that both treatments were equally tolerated and in both groups the BP reduction was similar. (21)

A research team led by Dr. Sun Keun Park published in 2017 a prospective, randomized, controlled study evaluating the effect of BP reduction using rest alone versus oral antihypertensive treatment in patients admitted to the emergency department due to a hypertensive urgency. Patients were randomized into two groups; one received 40 mg telmisartan and the other placebo. Both groups had to remain at rest in a room for 2 hours. In this study, the BP reduction of patients at rest was similar to that of the group receiving the antihypertensive medication. (22) In the same sense, the previously mentioned REHASE study showed that among the 816 patients attending an

emergency department without EOD, 32% responded to rest [with 20% reduction of the initial mean blood pressure (MBP)] without need of antihypertensive agents.

In a prospective, single blind, randomized, controlled study, Yilmaz et al. compared oral treatment with alprazolam versus captopril in 53 patients admitted to the emergency department with diagnosis of hypertensive urgency. Different from other works, this study not only considered evaluating BP measurements by an oscillometric method but also used validated scales, to define those patients who in addition to HTN presented some sign/symptom of anxiety. It was noteworthy that in this group of patients, 92% of participants presented, according to the cited scales, some trait of anxiety. In both groups, BP was similarly reduced with the intervention, but the reduction of anxiety was more effective in the groups receiving alprazolam. (23)

The evidence is clearer in those situations in which the patient is suspected to present symptoms associated with autonomic hyperactivity by amphetamine, methamphetamine or cocaine intoxication. The clinical condition is characterized by HTN, tremors, agitation, and convulsions, and can lead to a stroke, acute myocardial infarction (AMI) or aortic dissection. In this case, BZD treatment should be indicated from the onset, with drugs such as intramuscular lorazepam or midazolam, and once the intravenous access is achieved, initiate diazepam. (24) Phentolamine, a competitive alfa blocking agent for intravenous administration, is recommended in case of additional need for antihypertensive treatment, and when this is not available, use nicardipine or nitroprusside. (25) Alternatively, clonidine can be used, which in addition to its sympatholytic actions has sedative effects. In the event of accompanying coronary ischemia associated to cocaine consumption, aspirin added to BZD is recommended in nitroglycerine treatment.(26)

Chronic use of benzodiazepines and long-term effects on blood pressure

Small studies and reviews have been carried on the chronic use of BZD as antihypertensive treatment, with dissimilar results.

A double blind, randomized study published in 2018, evaluated 25 healthy participants between 65 and 74 years of age, treated with diazepam 5 mg or placebo, administered at night. At the end of 4 weeks, office BP and ambulatory BP monitoring (ABPM) values did not differ. Blood pressure values during the night were higher in the diazepam group than in the one treated with placebo: higher SBP (7.6%, $p<0.01$) and DBP (5.8%, $p<0.05$), and similar results were obtained for heart rate (HR): 6.6% higher in the diazepam group ($p<0.05$). The HR in the group receiving diazepam remained high during the morning, while during the afternoon and the first hours of the night, the values of SBP, DBP and HR were similar in both groups. The authors concluded that these effects probably depend of an increase in the sympathetic impulse mediated by diazepam and a decrease in the vagal tone that could have clinical relevance due to the role of BP and HR increase as independent predictors of cardiovascular morbidity and mortality. (27)

In the same year, a retrospective article of 4629 patients studied the association between chronic BZD consumption (3 months) and ABPM values. Patients were divided into a group of 524 individuals receiving anxiolytics and a control group consisting of the rest of the patients. Eighty-one percent of patients in the BZD group were over 60 years of age, more frequently female, presented diabetes and consumed a higher number of antihypertensive agents. After adjusting for sex, age, number of antihypertensive drugs and comorbidities, a greater BP reduction (both systolic and diastolic) was demonstrated during 24 hours in the group consuming BZD. The reduction was similar for short and long half-life drugs. However, total mortality and cardiovascular events (secondary objective at 42-month follow-up) were similar between both groups. In addition to the different number of individuals between both groups, another weakness of this study was that it did nor evaluate the adverse effects of BZD. (28)

Costa et al. published in 2019 a study evaluating the effect on ABPM and HR in 37 patients receiving bromazepam 3 mg alone, in combination with propranolol 40 mg or placebo for 2 weeks. The nighttime SBP and DBP values were not affected by bromazepam alone compared with placebo, but were significantly reduced with propranolol alone and associated with bromazepam. On the other hand, nighttime HR reduction was significantly greater in patients receiving propranolol, while it increased in those taking bromazepam alone or together with propranolol. The authors considered that the increase in HR observed with bromazepam depends on a reduction in the vagal tone mediated by this psychotropic drug, which could have clinical relevance, particularly in already at-risk hypertensive subjects. (29)

In 2021, the same authors published another study evaluating cardiovascular parameters (24-hour SBP, DBP and HR) after 2-week alprazolam and lorazepam consumption (used as hypnotics) in mild hypertensive patients. The study included 32 individuals, between 40 and 65 years of age, with SBP between 140 and 160 mmHg and/or DBP between 90 and 99 mmHg, with no medical treatment, without other comorbidities and with normal values in depressive and anxiety disorder scales. Alprazolam versus placebo, lorazepam versus placebo and placebo versus placebo consumption were compared for a period of 2 weeks each. Each group underwent ABPM after each period. There were no 24-hour SBP, DBP and HR changes among patients, except nighttime DBP, which was significantly higher in patients receiving lorazepam. (30)

Mendelson et al. retrospectively analyzed 4938

ABPM studies evaluating the use of BZD in the previous 3 months. Results showed that in patients ≥60 years, the regular consumption of BZD was significantly associated with lower SBP and DBP, while in younger patients BZD did not have a significant association with BP. The investigators point out that despite no increase in mortality was found with BZD, caution is required in their prescription in elderly patients due to a greater risk of falls, fractures, or syncope. (31)

A retrospective analysis was published in 2020 on this topic in 538 patients ≥60 years, 6% of which were regularly receiving BZD. Use of these drugs was associated with greater SBP reduction 10 seconds after standing up, independently of sex, age, concomitant antihypertensive drugs and level of frailty, leading to the conclusion that elderly persons taking BZD can be at greater risk or orthostatic hypotension, perhaps due to an exaggerated immediate fall of BP. Therefore, use of BZD should be avoided in persons at greater risk of falls. (32)

CONCLUSION

Benzodiazepines are among the more frequently prescribed psychotropic drugs

It is a growing health care problem in several countries around the world, especially related to an increased number of deaths for overdose associated with BZD consumption and to the need for consultations in the emergency department due to disorders linked with their use. These increases have been produced simultaneously with the elevated rate of BZD prescription. (33)

Thus, this extensive bibliographic review on BZD use in HTN, clearly reveals that they are drugs that should be used in the treatment of anxiety disorders and under medical supervision. Their use as antihypertensive agents would only be relegated to cases in which BP elevation were the consequence of sympathomimetic drug consumption, or in cases in which BP elevation is not associated with TOD and is the product of an anxiety condition, for example, a panic attack. In these cases, the physician will use them with this criterion and under no concept the patient should continue the prescription as antihypertensive treatment.

We should recall that they are not harmless drugs. The American Geriatrics Society (AGS) placed BZD in a list of drugs that should be avoided in patients over 65 years, (34) since they could be associated with higher increase of mortality. Although there is no concluding evidence, it is clear that they are related to an enhanced risk of fractures, with the elevated morbidity and mortality this fact entails in the geriatric population.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

REFERENCES

1. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol 2010;56:38-46. https://doi.org/10.1016/j.jacc.2010.03.034

2. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens 2015;28:1295-302. https://doi.org/10.1093/ajh/hpv047

3. Pan Y, Cai W, Cheng Q, Dong W, An T, Yan J. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. Neuropsychiatr Dis Treat 2015;11:1121–30. https://doi.org/10.2147/NDT.S77710

4. Johnson HM. Anxiety and Hypertension: Is There a Link? A Literature Review of the Comorbidity Relationship Between Anxiety and Hypertension. Curr Hypertens Rep 2019;21:66. https://doi.org/10.1007/s11906-019-0972-5

5. Delucchi AM, Majul CR, Vicario A, Cerezo GH, Fábregues G. Registro Nacional de Hipertensión Arterial. Características epidemiológicas de la hipertensión arterial en la Argentina. Estudio RENATA 2. Rev Argent Cardiol 2017;85:354-60. http://dx.doi.org/10.7775/rac.es.v85.i4.11061

6. Yilmaz S, Pekdemir M, Tural U, Uygun M. Comparison of alprazolam versus captopril in high blood pressure: a randomized controlled trial. Blood Press 2011;20:239-43. https://doi.org/10.3109/08037051.2011.553934

7. Grossman E, Nadler M, Sharabi Y, Thaler M, Shachar A, Shamiss A. Antianxiety treatment in patients with excessive hypertension. Am J Hypertens. 2005;18:1174-7. https://doi.org/10.1016/j.amjhyper.2005.03.728

8. Craske MG, Stein MB. Anxiety. Lancet 2016;388:3048-59. https://doi.org/10.1016/S0140-6736(16)30381-6

9. Estudio Nacional Informe de Resultados N° 1 en población de 12 a 65 años, sobre Consumo de Sustancias Psicoactivas Argentina 2017. SEDRONAR

10. Hayhoe Benedict, Lee-Davey James. Tackling Benzodiazepine Misuse Bmj 2018; 362:K3208. https://doi.org/10.1136/bmj.k3208

11. AlDawsari A, Bushell TJ, Abutheraa N, Sakata S, Al Hussain S, Kurdi A. Use of sedative-hypnotic medications and risk of dementia: A systematic review and meta-analysis. Br J Cln Pharmacol. 2022;88:1567-89. https://doi.org/10.1111/bcp.15113

12. Goodman & Gilman. Las Bases Farmacológicas De La Terapéutica (12a Edición). Laurence Brunton, Bruce A. Chabner.

13. Fernández García A, González Viña A, Peña Machado MA. Bases científicas para el uso de las benzodiazepinas. Rev Cubana Med Gen Integr 2003;19

14. Sigel E, Ernst M. The Benzodiazepine Binding Sites of GABAA Receptors. Trends Pharmacol Sci 2018;39:659-71. https://doi.org/10.1016/j.tips.2018.03.006

15. Balon R, Starcevic V. Role of Benzodiazepines in Anxiety Disorders. Adv Exp Med Biol 2020;1191:367-88. https://doi.org/10.1007/978-981-32-9705-0_20

16. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J 2013;13:214-23.

17. Astarita A, Covella M, Vallelonga F, Cesareo M, Totaro S, Ventre L, et al. Hypertensive emergencies and urgencies in emergency departments: a systematic review and meta-analysis .J Hypertens. 2020;38:1203-10. https://doi.org/10.1097/HJH.0000000000002372

18. Rodríguez P, Flaherty MO, Forcada P, Grassi D, Díaz M, Ferrante D, y cols . Estudio REHASE. Rev Argent Cardiol 2006;74:102-8.

19. Marín M, Bendersky M, Paéz O, Obregon S, Rodríguez P, Cerezo G, y col. Consenso Argentino de Hipertensión Arterial. Rev Argent Cardiol 2018;86(Supl 2):1-53.

20. Goncalves De Lima S, Simoes Do Nascimento L, Nobre Dos Santos Filho C, Militao De Albuquerque MFP; Guimaraes EV. Hipertensión Arterial Sistémica En Urgencias. El Uso De Fármacos Sintomáticos Como Tratamiento Alternativo. Arq Bras Cardiol 2005;85. https://doi.org/10.1590/S0066-782X2005001500008

21. Grossman E, Nadler M, Sharabi Y, Thaler M, Shacar A, Shamiss A. Antianxiety Treatment In Patients With Excessive Hypertension.

Ajh 2005;18:1174-7. https://doi.org/10.1097/HJH.0000000000001340
22. Park SK, Kim WJ, Lee DY, Lee SY, Park HS, Kim HW, et al. Comparing The Clinical Efficacy Of Resting And Antihypertensive Medication In Patiens Of Hypertensive Urgency: A Randomized, Control Trial. J Hypertens 2017;35:1474-80. https://doi.org/10.1097/HJH.0000000000001340
23. Yilmaz S, Pekdemir M, Tural U, Uygun M. Comparison of alprazolam versus captopril in high blood pressure: a randomized controlled trial. Blood Press. 2011;20:239-43. https://doi.org/10.3109/08037051.2011.553934.
24. Kotliar C, Redón I Mas J, Brandani L, Obregón S. Manual de Hipertensión arterial secundaria. Claves y Algoritmos. 1º ed. 2019.
25. Van den Born BH, Lip GYH, Brguljan-Hitij J, Cremer A, Segura J, Morales E, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. Eur Heart J Cardiovasc Pharmacother 2019;5:37-46. https://doi.org/10.1093/ehjcvp/pvy032
26. McCord J, Jneid H, Hollander JE, de Lemos JA, Cercek B, Hsue P, et al; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation 2008;117:1897-907. https://doi.org/10.1161/CIRCULATIONAHA.107.188950
27. Fogari R, Costa A, Zoppi A, D'Angelo A, Ghiotto N, Battaglia D, et al. Diazepam as an oral hypnotic increases nocturnal blood pressure in the elderly. Aging Clin Exp Res 2019;31:463-8. https://doi.org/10.1007/s40520-018-0991-0
28. Mendelson N, Gontmacher B, Vodonos A, Novack V, Abuajaj M, Wolak A, et al. Benzodiazepine Consumption Is Associated with Lower Blood Pressure in Ambulatory Blood Pressure Monitoring (Abpm): Retrospective Analysis of 4938 Abpms. Am J Hypertens 2018;31:431-7. https://doi.org/10.1093/ajh/hpx188
29. Costa A, Bosone D, Cotta Ramusino M, Perini G, Ghiotto N, Zoppi A, et al. Effect of Evening Bromazepam Administration on Blood Pressure and Heart Rate in Mild Hypertensive Patients. Pharmacology 2019;10:1-6. https://doi.org/10.1159/000499371
30. Costa A, D'angelo A, Cotta Ramusino M, Perini G, Bosone D, Derosa G, et al. Effects of Oral Administration of Alprazolam and Lorazepam as Hypnotics on Cardiovascular Parameters In Hypertensive patients. J Clin Psychopharmacol 2021;41. https://doi.org/10.1097/JCP.0000000000001362
31. Mendelson N, Gontmacher B, Vodonos A, Novack V, Abu-AjAj M, Wolak A, et al. Benzodiazepine Consumption is Associated with Lower Blood Pressure in Ambulatory Blood Pressure Monitoring (ABPM): Retrospective Analysis of 4938 ABPMs. Am J Hypertens 2018;31:431-7. https://doi.org/10.1093/ajh/hpx188
32. Rivasi G, Kenny RA, Ungar A, Romero-Ortuno R. Effects of benzodiazepines on orthostatic blood pressure in older people. Eur J Intern Med. 2020;72:73-8. https://doi.org/10.1016/j.ejim.2019.10.032
33. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. Drug Alcohol Depend. 2019;200:95-114. https://doi.org/10.1016/j.drugalcdep.2019.02.033
34. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015;63:2227-46. https://doi.org/10.1111/jgs.13702

Michael Servetus. Pulmonary circulation at the stake

Miguel Serveto. La circulación pulmonar a la hoguera

JORGE C. TRAININI[MTSAC]

After the discovery of **Ibn an-Nafís**, around the year 1245, the author of the first print that developed the concept of minor circulation in the western world was **Michael Servetus (Miguel Serveto y Revés)**, since the text of the Arab doctor was only known in 1924. **Servetus** was born in Villanueva de Sijena (Huesca) in 1511. The circumstance of belonging to a noble and wealthy family allowed him to attain a solid culture and to treasure at an early age a classical humanistic training linked to the spirit of the Renaissance, which -as we will see later- made him the martyr of a new way of life: freedom of thought.

Servetus lived in a time imbued, from a philosophical point of view, with the anti-dogmatism of **Desiderius Erasmus** (Dutch, 1467-1536), who favored in his theology the return of faith to the first word of God. Tireless traveler, he was a doctor, astrologer, mathematician, philosopher, but fundamentally his field was theology. He studied law in Toulouse (France), the site of initiation of his reformist religious thought, when he came into contact with new religious ideas promoted by **Philip Melanchthon** (German, 1497-1560) and **Raymond of Sabunde** or **Sibiuda** (Spanish, who died in 1436), authors of "*Loci Communes*" and "*Theologia Naturalis*" or "*Liber Creaturárum*" respectively. In this atmosphere **Servetus** was an isolated researcher, since the new paradigm of modernity was propelled primarily in personalities and in academies. Instead, the universities showed a scholastic continuity, a much more pronounced Galenic profile.

In Bologna he was secretary to **Fray Juan de Quintana**, attending in 1530 the coronation of **Charles V**, of whom **Quintana** was confessor. This historical fact of lavish court was the starting point of his dissatisfaction with the traditional church. Later in Geneva, Basel and Strasbourg, he connected with reform theologians such as **Martin Bucer** (German, 1491-1551), **Ulrich Zwingli** (Swiss, 1484-1531) and **John Ecolampadius** (Swiss, 1482-1531), culminating his position with the first in bitter dispute. From that moment on, his life became a permanent pilgrimage, trying to avoid the persecution and surveillance to which he was subjected.

In 1531 he published "*De trinitratis errobirus libri septum*" (Basel) dealing with the Trinity, holding that "*Jesus was the son of the eternal God, but not the eternal son of God.*" This text gained the disapproval of both Catholics and reformers. The following year he publishes "*Dialogorum de Trinitrati*" ("T*wo dialogues on the Trinity*"), with an equidistant position with respect to the religious personalities mentioned above, derived from his studies on sacred texts. Then he went to Paris, where he came into contact for the first time with **John Calvin** (French, 1509-1564), a relationship evidencing a deep dispute from the start. Fleeing from the Inquisition of Zaragoza, he moved to Lyon, where he changed his name to **Miguel Villanueva**, editing with important corrections the Ptolemy Geography in 1535 and "*In Leonardum Fuchsium Apología*" (1536), of medical-theological character.

His only text of a medical nature, "*Syruporum universa ratio*", published in Paris in 1537, evidences the classical knowledge of medicine of **Hippocrates** and **Galen**, although always ready to accept the modifications that observation could provide. Thus, he does not hesitate to attack the use of syrups in humorally based febrile affections. Written under the pseudonym of **Villanueva**, he declared himself in favor of "*a happily Renaissance*" science, condemning the "*Saracen phalanges*", demonstrating a high humanistic content, with a return to the concept of "*vis medicatrix naturae*". In this same year he enrolled at the University of Medicine of Paris, on the advice of the physician and botanist **Symphorien Champier**, with whom he had been related in Lyon. There, together with **Andreas Vesalius**, he is a disciple of **Jean Fernel** (French, 1497-1558), **Jacob Dubois** "*Silvio*" (French, 1475-1555) and **Günther von Andernach** (1505-1574).

The practice of dissection on corpses allowed his fundamentally theological studies to add the anatomical knowledge necessary for his sensational medical discovery, made by the author as a means to carry out his religious reasoning. Predecessors of his practice in dissection can be found in the text by **Günther von Andernach** "*Institutiones anatomicae*" (Basel, 1539), who states: "*After [referring to Vesalius], Miguel Villanovanus who was my friendly assistant in dissections -a person who honors in any branch of the letters-, does not lag behind anyone in knowledge of the galenic doctrine*".

While taking a course on astrology in Paris, he is put on trial from which he emerges with a benevolent sentence. Therefore, in 1540 he goes to Charien

(Loire), and then to Lyon where he reviews and edits the "B*ible*" of **Santes Pagnini** (1542), the "*Summa*" of **Saint Thomas** and the "*Biblia sacra cum glossis*" (1545). Established in Dauphiné Vienna, he dedicated himself to the practice of medicine, reprinting the "*Syruporum*" on several occasions.

From approximately 1536, **Servetus** had in mind to write the "*Christianismi Restitutio*", which only saw the light in 1553 in printed form, in an edition of 800 copies, with 734 pages, without the author's signature or place of printing. A manuscript of the text, dated 1546, had been sent to **Calvin**, causing him a great astonishment, to the point of expressing "*no matter how little authority I have, I will not tolerate him staying alive*". This explains the circumstance that when the publication became effective, he was prosecuted in Vienna on April 4, 1553 for heresy, managing to flee from the city. On June 17, the sentence was handed down to be burned alive. **Servetus** remained hidden, until he was apprehended again on August 13 in Geneva by order of **Calvin** and sentenced to death at the stake, which was carried out on October 27, 1553. The edition had previously been incinerated, thus preventing its disclosure. Only two complete texts (currently in Vienna and Paris) and one incomplete (Edinburgh) with 16 missing pages were saved.

The work "Christianismi Restitutio" is theological, but in its Book V, between pages 168 and 173, mention is made of the minor circulation, in a clear and precise way. How does such a physiological finding emerge from a religious work? **Augustus Teulon** expresses that the event occurred "*when trying to find the existing correlation between the two great books: the one of the word of God, the Bible, and the one of Nature*". In order to correlate the "physis" with the "deidos", it was necessary to merge in **Servetus** the position on faith and his medical training, in an era, that of the Renaissance, which allowed him the verification "*ob oculo*" of the human anatomy. In essence "*Christianismi Restitutio*" is a compendium that deals with the Trinity, makes an apology of **Philip Melanchthon** and contains the correspondence with **Calvin**. According to **Servetus**, from the analysis of the Genesis, Leviticus and Deuteronomy it follows that blood is the means for God to communicate with man. This concept was the fundamental reason that led him to the description of the pulmonary circulation.

Servetus, despite his description, as **Ibn an-Nafís** had done before, did not depart from **Galen's** physiology. He only advanced on the cardiopulmonary functional complexity, by truly describing the minor circulation. Through doubt he develops the reasoning, wondering if the size of the "*vena arterialis*" (pulmonary artery) was justified only for the function of nourishing the lung. That leads him to the following explanation: "*The remarkable size of the pulmonary artery confirms that it was not made of such size, nor does it emit such a large and important volume of blood from the heart to the lungs, simply for its nutrition.*" He also tries an explanation of the pulmonary oxygenation, considering the left ventricle very narrow, so as to carry out in it the total pneumatization of the blood with the vital spirit, which was the element admitted at that time to mix with the fluid. In his own words, he explains the pulmonary oxygenation in the following way: "*In the same way, not only air, but air mixed with blood is sent from the lungs to the heart through the venous artery. Therefore, mixing takes place in the lungs. The red color given to the blood has been in the lungs, not in the heart. In the left ventricle there is not enough space for such a copious mixture or for the elaboration to imprint the red color*".

It follows from the text that Servetus annuls Galen's description of the passage of blood from the right heart to the left through the pores of the septum, by saying "*... this communication is not made through the heart's midwall, as is commonly believed, but by some grand artifice the subtle blood is propelled forward from the right ventricle by a long circuit through the lungs,*" and further on he states: "*Finally, the interventricular septum, since it lacks vessels and mechanisms, is not suitable for that communication and elaboration, although something may filter*".

Incinerated, Servetus' work was just going to be rediscovered and placed in its just primacy by **G. Woton** in 1694 in his book "*Reflections upon ancient and modern learning*" (London). Had he abjured his claims, **Servetus** would have saved his life, but he preferred the value of his ideals over physical death. This alternative, in total accordance with his lifestyle and thought, is an attitude that lays bare a personality dedicated to the objectivity of knowledge, the seed of future achievements. The story of **Guilhem Farel, Calvin's** second, speaks to us about his moral value, expressed in the text of **J. Calvini**, "Opera" (Strasbourg, 1870): "*he never wanted to make an authentic confession. Several times he prayed and asked his companions to pray for him. But we could not get him to openly consider his error and acknowledge Christ as the eternal Son of God.*"

Unilateral Absence of the Left Pulmonary Artery in a Patient with Acute Pulmonary Embolism

We report the case of a 49-year-old male patient, former smoker and living a sedentary lifestyle, with a history of prolonged travel in the last week and treatment with beta-blockers for an unspecified arrhythmia.

He was admitted to the coronary care unit with a diagnosis of non-ST segment elevation acute coronary syndrome, typical angina and FC III-IV dyspnea (NYHA).

On physical examination, he weighted 76 kg and was 1.72 m tall; blood pressure was 120/70 mm Hg and heart rate was 70 bpm. He had no fever, the respiratory rate was 17 bpm and the arterial oxygen saturation was 94%.

The electrocardiogram showed sinus rhythm, heart rate of 65 bpm, vertical electric axis and abnormal ventricular repolarization in the anteroseptal wall, corresponding to the right ventricle (Figure 1A). The anteroposterior chest X-ray showed absent hiliar shadow and mediastinal shift to the left side with left hemidiaphragm elevation, and hyperinflation of the contralateral lung (Figure 1 B).

The remarkable results of the laboratory were high-sensitivity troponin of 213/176/90 pg/mL (normal value: ≤ 34) D-dimer of 3427 ng/mL (normal value: ≤ 198) and BNP of 73 pg/mL (normal ≤100).

On transthoracic echocardiography, left ventricular function was preserved and wall motion was normal. The right cardiac chambers and the main pulmonary artery diameters were in the upper normal limit.

The patient underwent coronary angiography. There were no signs of obstructive coronary artery disease; pulmonary sequestration of the right coronary artery (RCA). A right aortic arch was present. (Figure 2A)

The computed pulmonary angio tomography showed absence of the main left pulmonary artery with ipsilateral shift of the mediastinum and great vessels, and right aortic arch (Figure 1B). There was

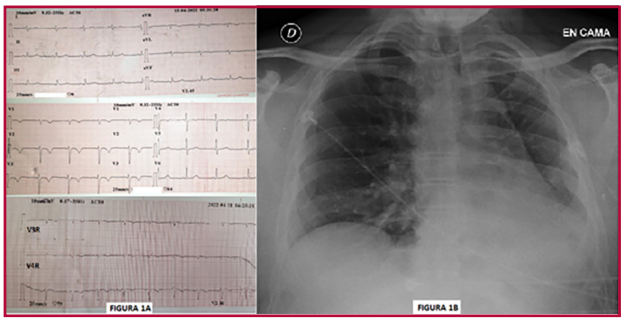


Fig. 1. A. Electrocardiogram with right-sided leads. **B.** Chest X-ray

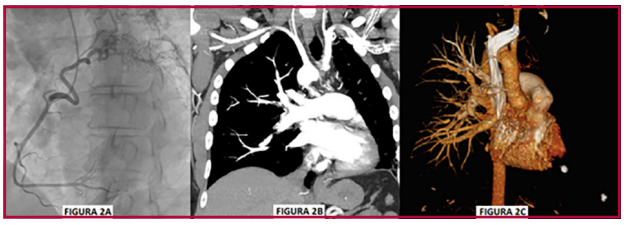


Fig. 1. A. Coronary angiography. **B.** Computed tomography pulmonary angiogram. C. 3D reconstruction

a filling defect in the lobar segmental and subsegmental right pulmonary artery branches consistent with acute pulmonary embolism (PE). The left lung was hypoplastic and the right main pulmonary artery and right cardiac chambers were enlarged. (Figure 2B-2C).

The lower limb ultrasound revealed deep venous thrombosis in the popliteal vein and left tibioperoneal trunk.

The final diagnosis was venous thromboembolism and high-risk pulmonary embolism with right ventricular infarction in the context of absence of the left main pulmonary artery. The patient received medical treatment with anticoagulation and had favorable outcome.

Unilateral absence of a pulmonary artery (UAPA) is a rare congenital abnormality, with a prevalence of 1 in 200,000. It occurs equally in both sexes. Most of the cases have associated cardiovascular anomalies, as coarctation of the aorta (isolated or associated with interventricular septal defects), subvavular aortic stenosis, transposition of the great vessels, patent ductus arteriosus, tetralogy of Fallot and right aortic arch. (1)

The pulmonary arteries develop in week 16 of gestation from the sixth proximal aortic arch. Absence of pulmonary artery occurs due to failure of the sixth aortic arch to connect with the main pulmonary trunk, hypothetically secondary to low blood flow. (2) Absence of the left or right pulmonary arteries may present with ipsilateral pulmonar aplasia or hypoplasia. The hypoplastic lung is perfused by remnants of the aortic arches persisting as embryonic arteries, collaterals of the bronchial arteries, subclavian arteries, intercostal arteries, diaphragmatic arteries and even by coronary arteries, which could cause steal phenomenon with coronary hypoperfusion and ischemia. (3)

Although few patients with UAPA remain asymptomatic until adulthood (15%), the diagnosis is usually made early due to clinical manifestations such as recurrent pulmonary infections, decreased exercise tolerance and exercise-induced dyspnea (40%). Twenty percent of cases present with hemoptysis due to extensive collateral circulation and 25% develop pulmonary hypertension secondary to increased blood flow to the contralateral lung, with implications for long-term survival. (1, 3, 4).

Other form of presentation is dyspnea in the context of pregnancy or at high altitude, as a manifestation of silent pulmonary hypertension. (5)

The diagnostic workup includes chest X-ray with the findings previously described. Doppler-echocardiography may confirm the diagnosis and suggest the presence of pulmonary arterial hypertension. Computed tomography pulmonary angiogram allows visualization of the entire pulmonary vascular tree, including the distal beds, detection of hilar pulmonary arteries by pulmonary vein wedge angiography and the presence of bronchiectasis. (5- 6)

The association between UAPA and pulmonary embolism has rarely been reported in the literature. The differential diagnosis with chronic PE should be made when amputation of the main branches occurs due to thrombotic obstruction.

A small group of patients with UAPA remain asymptomatic during their lifetime. This condition should be suspected in the presence of recurrent respiratory infections, hemoptysis or pulmonary arterial hypertension. In the presence of angiographic evidence of extensive or enlarged collateral arteries, as a potential cause of pulmonary hypertension or bleeding, embolization may be beneficial. The early diagnosis of this disease and treatment of its complications can reduce the associated morbidity and mortality. The differential diagnosis with chronic pulmonary thromboembolism is important due to the therapeutic implications.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

Paula Boggio[1], Franco Mátar[1], Valentina Rodriguez[1], Andrea Astesiano[1], Nicolás Renna[1], Alfredo Astesiano[1]

[1] Hospital Español de Mendoza. Coronary Care Unit.

Paula Boggio - Hospital Español de Mendoza. Unidad Coronaria - Av. San Martín 965 - 5501 - Mendoza - E-mail: boggiopaula@gmail.com

REFERENCES

1. Mohan V, Mohan B, Tandon R, Kumbkarni S, Chhabra ST, Aslam N, et al. Case report of isolated congenital absence of right pulmonary artery with collaterals from coronary circulation. Indian Heart J 2014;66:220-2. https://doi.org/10.1016/j.ihj.2013.12.032

2. Zylak CJ, Eyler WR, Spizarny DL, Stone CH. Developmental lung anomalies in the adult: radiologic-pathologic correlation. Radiographics 2002;22:25-43. https://doi.org/10.1148/radiographics.22.suppl_1.g02oc26s25.

3. Soliman A, Jelani A, Eid A, AlQaseer M. Myocardial infarction due to coronary steal caused by a congenital unilateral absence of the right pulmonary artery: A rare case. BMJ Case Rep. 2012;2012:bcr0420114108. https://doi.org/10.1136/bcr.04.2011.4108.

4. Pool PE, Vogel JH, Blount SG Jr. Congenital unilateral absence of a pulmonary artery. Am J Cardiol 1962;10:706–32. https://doi.org/10.1016/0002-9149(62)90248-5

5. Ten Harkel AD, Blom NA, Ottenkamp J. Isolated unilateral absence of a pulmonary artery: a case report and review of the literature. Chest 2002;122:1471-7. https://doi.org/10.1378/chest.122.4.1471

6. Choe KO, Hong YK, Kim HJ, Joo SH, Cho BK, Chang BC, et al. The use of high-resolution computed tomography in the evaluation of pulmonary hemodynamics in patients with congenital heart disease: in pulmonary vessels larger than 1 mm in diameter. Pediatr Cardiol 2000;21:202–10. https://doi.org/10.1007/s002460010040

Rev Argent Cardiol 2022;90:362-363.
http://dx.doi.org/10.7775/rac.v90.i5.20551

Papillary Fibroelastoma: A Benign Tumor with Potentially Devastating Consequences

We report the case of a 69-year-old woman with hypertension, hypothyroidism and rheumatoid arthritis, under treatment with methotrexate.

The patient was transferred from the Emergency Department to the Interventional Cardiology Section for acute myocardial infarction with anterolateral ST-segment elevation (Killip-Kimball IV).

The patient persisted with an oppressive central chest pain radiating to both arms. She was hypotensive (Blood Pressure; 90/60 mmHg), with poor peripheral perfusion despite continuous dobutamine infusion at 5 mcg/kg/min. In addition, arterial oxygen saturation was around 90% despite the use of a reservoir mask at 15 L/min, and pulmonary auscultation revealed crepitations up to mid-zones.

Catheterization revealed good-sized left main coronary artery with a convex thrombus occluding the distal portion (Figure 1). After bypassing the occlusion

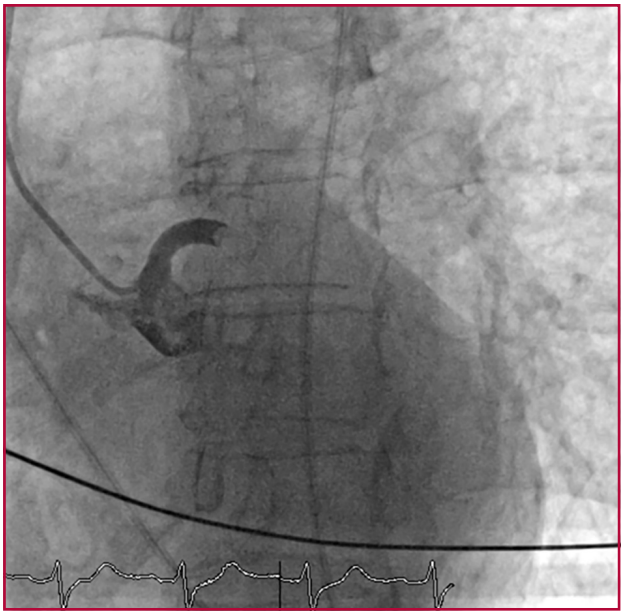


Fig. 1. Cardiac catheterization, left anterior oblique projection (28°). Image showing a good-sized left main coronary artery with a convex thrombus occluding the distal portion; no visualization of the anterior descending artery or the circumflex artery.

with a guidewire and locating it in the left anterior descending artery (LAD), the vessel did not recover flow and manual thromboaspiration was performed, resulting in LAD flow recovery and macroscopic material collection.

Due to thrombus migration to the first obtuse marginal artery, a bolus was started, followed by continuous tirofiban infusion, together with aspirin and prasugrel loading. However, final TIMI 1 flow and abundant thrombotic burden remained.

Since thrombotic etiology was initially suspected, intracoronary imaging with optical coherence tomography (OCT) was performed, showing no endothelial lesion at any level.

The patient was transferred to the Coronary Care Unit, hemodynamically unstable but with improved peripheral perfusion, no chest pain and good respiratory progression.

Laboratory findings included glomerular filtration rate of 57 ml/min/1.73 m^2, normal electrolyte panel, blood count and coagulation tests, and ultrasensitive troponin T that initially was 23 ng/L, reaching a peak of 28041 ng/L. Further evaluation with a transthoracic echocardiography (TTE) revealed severely depressed left ventricular function due to apical akinesia extending to the mid-septal segments and almost all the anterior and lateral walls.

Despite the absence of significant valve diseases, a 9 x 6 mm sessile nodular image was targeted on the ventricular side of the non-coronary cusp of the aortic valve (Figure 2).

Agitated saline was also administered, confirming the absence of right-to left bubble passage.

Given the poor hemodynamic response —requiring higher doses of vasoactive drugs and balloon counterpulsation—, the transplant referral center in our area was contacted to evaluate the case.

Coronary embolism is considered a rare phenomenon, likely under-diagnosed, with an incidence to be around 0.06%. (1) The most frequently documented etiology is infective endocarditis (IE), followed by atrial fibrillation and prosthetic heart valve thrombosis.

Fig. 2. Transthoracic echocardiography. **A.** Long axis parasternal view showing a 9 x 6 mm sessile nodular image on the ventricular side of the non-coronary cusp of the aortic valve. **B.** Zoom-in on the nodular image

Other etiologies include iatrogenic embolism, paradoxical embolism, atrial myxoma, and papillary fibroelastoma. (1) IE seemed unlikely in our patient, who was afebrile, with no stigmata of endocarditis on physical examination, and infectious parameters were not significantly elevated on admission. The patient had no history of trepidation, did not have a prosthetic valve, or had not undergone a recent medical intervention that could account for iatrogenic embolism.

TTE showed no right-to-left bubble passage, and given the mass characteristics and location, papillary fibroelastoma (PF) seemed to be the most likely etiology of coronary embolism.

Primary cardiac tumors are very rare, with a documented prevalence at autopsy of 0.01%. (2)

Myxoma is the most frequent primary cardiac tumor, but PF is the most common valvular tumor of the heart, accounting for 15% of all primary cardiac tumors. (2) In most series, it occurs predominantly in adult men (mean age of detection 60 years). While tumors may occur on any cardiac structure, around 77% are located on the valvular surface, the aortic valve being the most commonly involved valve. (3) Most of PFs are discovered incidentally, but may present with a broad range of symptoms, depending on their location, size, rate of tumor growth and possible embolization of the tumor. Cerebral embolism is the most common presentation; however, myocardial infarction and sudden death often occur when PF is located in the aortic valve. (3) These major events are mainly attributed to two mechanisms: occlusion of the coronary ostium during valve movement or embolization of the tumor fragments to the coronary arteries. (4)

TTE is a useful tool in a first evaluation, but it may fail to detect up to one third of the PFs, which are evident in the transesophageal echocardiography (TEE); (5) therefore, TEE should be performed in cases of high diagnostic suspicion, as it can also locate the anchor site to design the surgical treatment. (2) The typical echocardiographic image appears as a pedunculated, mobile, homogeneous, small mass (typically < 20 mm), with a characteristic stippling along its edges. (2)

The decision on management of PF is difficult as there have been no randomized controlled trials. (2) Literature published to date suggests that surgical excision in symptomatic patients is curative with an excellent long-term prognosis and no documented postoperative recurrences. (3, 5) Surgery is also recommended if the tumor is mobile, since tumor mobility is considered a predictor of mortality and risk of embolism. (2) However, in asymptomatic patients with nonmobile tumors, close follow-up is recommended. (3) Although papillary fibroelastoma is a benign tumor, given its potential to cause both cardiac and noncardiac fatal complications and the curative treatment available, PF is a differential diagnosis that should be considered in myocardial infarctions with normal coronary arteries.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

Uxue Idiazabal Rodríguez[1], Iñigo Pereiro Lili[1], Ane Elorriaga Madariaga[1], Rafael Martínez de Bourio Uriarte[1], Paula María Mendoza Cuartero[1], Jesús Roberto Sáez Moreno[1]

[1] Hospital Universitario Basurto. Department of Cardiology. Coronary Care Unit. Osakidetza

Uxue Idiazabal Rodríguez – Hospital Universitario Basurto. Department of Cardiology. Coronary Care Unit. Osakidetza - Av. Montevideo 18 – 48013, Bilbao, España. E-mail: Uxue_278@hotmail.com

REFERENCES

1. Lacey MJ, Raza S, Rehman H, Puri R, Bhatt DL, Kalra A. Coronary Embolism: A Systematic Review. Cardiovasc Revasc Med 2020;21:367-74. https://doi.org/10.1016/j.carrev.2019.05.012

2. Logan N, Islam MS, Chughthai JZ, Murphy NF. An atypical cause of muycardial infarction: case report of an obstructing papillary fibroelastoma of the aortic valve. Eur Heart J Case Rep 2019;3:ytz058. https://doi.org/10.1093/ehjcr/ytz058.

3. Gowda RM, Lhan IA, Nair CK, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac papillary fibroelastoma: A comprehensive analysis of 725 cases. Am Heart J 2003;146:404-10. https://doi.org/10.1016/S0002-8703(03)00249-7.

4. Takada A, Saito K, Ro A, Tokudome S, Murai T. Papillary fibroelastoma of the aortic valve: a sudden death case of coronary embolism with myocardial infarction. Forensic Sci Int 2000;113:209-14. https://doi.org/10.1016/s0379-0738(00)00207-3.

5. Yandrapalli S, Mehta B, Mondal P, Gupta T, Khattar P, Fallon J, et al. Cardiac papillary fibroelastoma: The need for a timely diagnosis. World J Clin Cases 2017; 5:9-13. https://doi.org/10.12998/wjcc.v5.i1.9

Rev Argent Cardiol 2022;90:363-365.
http://dx.doi.org/10.7775/rac.v90.i5.20555

Coronary Subclavian Steal Syndrome: A Not-So-Rare Cause of Acute Coronary Syndrome

We report the case of a 65-year-old male patient, ex-smoker, with a history of high blood pressure and dyslipidemia under medical treatment.

In June 2019, he was admitted to our center with non-ST-segment elevation acute coronary syndrome (Killip-Kimball I). Catheterization showed severe coronary artery disease involving the left main coronary artery and 3 vessels; triple coronary artery bypass (left mammary artery to middle third of anterior descending artery, right Y-graft using the mammary artery to first obtuse marginal branch, and saphenous vein to posterior descending artery) was performed. Mild left ventricular dysfunction due to mid-basal and inferoposterior akinesia persisted at discharge.

Two years later, the patient was admitted to our Coronary Care Unit with a new episode of angina at rest, changes in ECG and raised myocardial injury markers (ultrasensitive troponin T 1148ng/mL). Echocardiogram showed increased ventricular dysfunction, left ventricular ejection fraction (LVEF) 30-35%, at the expense of new-onset akinesia of the anterolateral wall. The condition was interpreted as high-risk non-ST-elevation myocardial infarction. Given the hemodynamic and clinical instability, urgent coronary catheterization was performed at 24 h (Figure 1); all the grafts were patent, without new lesions in the distal beds; however, there was occlusion of the origin of the left subclavian artery.

The computed axial tomography (CAT) (Figure 2) and Doppler ultrasound confirmed complete occlusion of the origin of the left subclavian artery, with reversal of blood flow through the left vertebral artery, suggestive of subclavian-vertebral steal syndrome, in addition to the subclavian-coronary steal causing myocardial ischemia in our patient.

The clinical benefits of using the left internal mammary to bypass the left anterior descending artery are well established, but coronary subclavian steal syndrome is an underestimated complication in these patients. (1)

The prevalence of subclavian artery stenosis is 2% in the general population, and 7% in patients with peripheral arterial disease, (2) figures that increase to 2.5 - 4.5%, (3) and 12% respectively (4) in patients with previous aortocoronary surgery.

The strongest predictors of subclavian artery stenosis include peripheral artery disease, smoking, higher levels of systolic blood pressure, or low levels of HDL cholesterol. Atherosclerosis is responsible for more than 90% of subclavian artery stenosis; less common etiologies include arteritis, inflammation, ra-

Fig. 1. Urgent coronary catheterization: Occlusion of the origin of the left subclavian artery (A & B); after the administration via left radial access, abrupt cessation of the passage of contrast from the subclavian artery to the aorta is observed. Patent bypass grafts of left internal mammary artery to the left anterior descending artery, right internal mammary artery to obtuse marginal artery (A & B), and saphenous vein to posterior interventricular artery (C) are observed. No lesions in the distal beds.

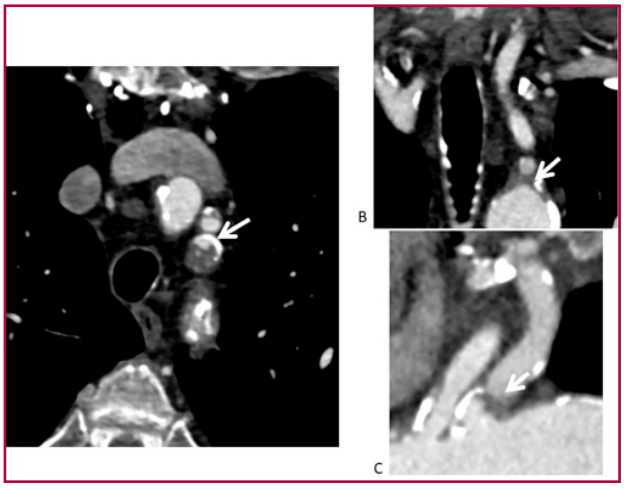


Fig. 2. CAT of supra-aortic trunks and circle of Willis: axial (**A**), coronal (**B**) and sagittal (**C**) images, showing calcified atheromatosis with occlusion of the origin of the left subclavian artery. The left internal mammary artery is patent. No occlusions in the structures of the circle of Willis or in the vertebrobasilar or carotid systems are observed.

diation exposure, compression syndromes, and fibromuscular dysplasia, with the proximal portion of the left subclavian artery being the most common location (> 75%).

While most subclavian stenosis patients remain asymptomatic, a small percentage may debut with clinical manifestations, such as stable angina, acute coronary syndrome -as was the case in our patient-, heart failure or malignant ventricular arrhythmias. (1)

However, current guidelines for coronary artery bypass grafting (5) lack recommendations for screening of subclavian artery stenosis before or after coronary surgery. Some authors recommend blood pressure measurements in both arms in the preoperative screening of these patients. (1) In patients with a differential systolic blood pressure (SBP) ≥ 15 mmHg, or in those with known or suspected peripheral artery disease (arm claudication, digital wounds, neurological symptoms), specific imaging tests are recommended to rule out subclavian stenosis. (1) Doppler ultrasound and CAT offer good sensitivity (73% and 91% respectively) and specificity (91% and 96% respectively) and are useful tools especially for the diagnosis of subclavian stenosis. However, magnetic resonance imaging (MRI) offers better results for coronary steal detection (sensitivity 90%, specificity 95%): in addition to anatomic information, it shows the directionality of retrograde flow within the mammary graft. Nevertheless, subclavian artery angiography remains the gold standard. (1)

As differential diagnosis for our patient, we could consider bypass obstruction or new lesions in the distal coronary beds, which are ruled out in the catheterization. If the patient had presented with other associated symptoms, such as ipsilateral upper extremity ischemia, aortic disease affecting the left subclavian and brachial arteries should be ruled out.

After confirming the diagnosis, our patient was evaluated by Vascular Surgery. It was decided to perform endovascular intervention, with predilatation and stent placement in the ostium of the left subclavian artery, with good angiographic outcomes.

Based on current evidence, revascularization is indicated in symptomatic (recommendation IIa C) and asymptomatic patients with bilateral subclavian stenosis (recommendation IIb C).

No clinical trials have compared the results with endovascular or surgical treatment, and the risk of major complications —including vertebrobasilar stroke— is low in both procedures (2.6% for endovascular treatment, and 0.9-2.4% for open surgery); therefore, current guidelines recommend both approaches with the same level of recommendation (IIa C) to be individualized depending on the case, (6) even though the endovascular approach is often the default strategy, as in our patient. It generally consists of stent placement, with a higher patency rate at 5 years (up to 85%). The success rate is 100% in stenosis and 80-95% in occlusions, as was the case with our patient. (6)

Open surgery, on the other hand, is limited to selected low-surgical risk patients, generally after failure of endovascular treatment. It offers good outcomes, with 1-year patency 95%, 3-year patency 86%, and 5-year patency 73-96%, (6) being the extra-anatomic bypass procedures (axillo-axillary, carotid-axillary or carotid-carotid bypass) the most used. (5, 6)

Postoperative clinical course of our patient was excellent and uneventful, and with pending follow-up in our Cardiology Department to assess the recovery of ventricular function.

In conclusion, we highlight our case because, despite left internal mammary graft is the most used in coronary revascularization surgery, subclavian artery obstruction is an underestimated entity in these patients. This entity may lead to angina recurrence or even acute coronary syndrome; therefore, we should keep it in mind in the differential diagnosis of previously operated patients debuting with angina, and include screening in the preoperative assessment of patients referred to aortocoronary surgery.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

Ana Ruiz, Ane Elorriaga, Amaia Arregi, Paula Mendoza, Abel Andrés, Roberto Sáez
Department of Cardiology.
Hospital Universitario de Basurto (Bilbao, España).
Ana Ruiz Rodríguez - Email: anarrmo@gmail.com
Phone: 619 127 425

REFERENCES

1. Cua B, Mamdani N, Halpin D, Jhamnani S, Jayasuriya S, Mena-Hurtado C. Review of coronary subclavian steal syndrome. J Cardiol 2017;70:432-7. https://doi.org/10.1016/j.jjcc.2017.02.012
2. Shadman R, Criqui MH, Bundens WP, Fronek A, Denenberg JO, Gamst AC, et al. Subclavian artery stenosis: prevalence, risk factors, and association with cardiovascular diseases. J Am Coll Cardiol 2004;44:618–23. https://doi.org/10.1016/j.jacc.2004.04.044
3. Sintek M, Coverstone E, Singh J. Coronary subclavian steal syndrome. Curr Opin Cardiol 2014;29:506. https://doi.org/10.1097/HCO.0000000000000109
4. Iglesias JF, Degrauwe S, Monney P, Glauser F,Qanadli SD, Eeckhout E, et al. Coro-nary subclavian steal syndrome and acute anterior myocardial infarction: a new treatment dilemma in the era of primary percutaneous coronary intervention. Circulation 2015;132:70–1. https://doi.org/10.1161/CIRCULATIONAHA.115.015226
5.. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascu-larization. Eur Heart J 2019;40:87-165. https://doi.org/10.1093/eurheartj/ehy394.
6. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European So-ciety for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816. https://doi.org/10.1093/eurheartj/ehx095

Rev Argent Cardiol 2022;90:365-367.
http://dx.doi.org/10.7775/rac.v90.i5.20557

Repair of Coarctation of the Aorta in Preterm Infant Weighting 1180 g

Repair of congenital heart diseases in low-weight infants has proved successful. (1) Critical coarctation of the aorta is a life-threatening lesion in newborns; two different approaches in low-weight preterm infants are adopted worldwide. Whereas some advocate delaying the timing of surgery until the baby grows up and gains weight, others favor early intervention. (2) Many centers have reported low mortality rates for coarctation in these patients. (3) However, most debate continues to focus on the question of optimal timing for surgery and the incidence of recoarctation of the aorta. Results of balloon dilation of native aortic coarctation in low-weight patients are disappointing, with recoarctation rates of 83% in neonates. (4)

We report the case of a preterm male infant with surgical repair of critical aortic coarctation, weighing 1180 grams, at the *Hospital Interzonal Especializado Materno Infantil de Mar del Plata*, with no postoperative complications or signs of recoarctation at one-year postoperative follow-up.

It is a male twin born from a controlled pregnancy, with a maternal history of insulin-requiring gestational diabetes and positive serologic test for syphilis, with inadequate treatment. After 32-week gestation, the patient was delivered by C-section due to pathological fetal Doppler and selective intrauterine growth restriction, weighting 1170 g, with an APGAR score of 9/10, not requiring resuscitation at birth. On admission to the Neonatal Intensive Care Unit, the patient presented with respiratory distress, grunting, recession and decreased saturation, requiring Mechanical Ventilatory Support (MVS) and lung surfactant 100mg/kg. Routine echocardiography revealed a 3 mm patent ductus arteriosus, with left-to-right shunt and enlargement of the left chambers, with no other structural heart disease. Physical examination showed symmetrical, peripheral pulses and signs of heart failure. Treatment with indomethacin for patent ductus arteriosus closure was started; 24 hours later, the patient decompensated hemodynamically with oligoanuria, abdominal bloating, poor peripheral perfusion and nonpalpable femoral pulses, requiring inotropic drugs. Follow-up echocardiography showed closed ductus arteriosus, coarctation of the aorta with a gradient of 27 m/sec and diastolic ramp, preserved left ventricular systolic function. Prostaglandin infusion at 0.01 micrograms/kg/min was used to open the ductus arteriosus. Ventilatory measures were taken to decrease pulmonary hyperflow. The patient showed positive diuresis and palpable pulses in lower limbs.

A multidisciplinary panel decided to perform surgical repair due to worsening of renal function, symptoms of heart failure as a result of ductus arteriosus shunt unresponsive to medical measures, increased MVS, high inspired oxygen fraction, dilatation of the left chambers, and also due to the fact that patent ductus arteriosus opening in preterm infants worsens or increases the incidence of intraventricular hemorrhage. Routine preoperative transfontanellar ultrasound revealed a grade 1 intraventricular hemorrhage.

With the patient (18 days of age, 1180 grams) in lateral decubitus position, a left posterolateral thoracotomy through the fourth intercostal space was performed; the ascending aorta, transverse aortic arch and branches, isthmus, large ductus arteriosus, and descending aorta were dissected. The image shows aortic coarctation at the level of the isthmus (Figure 1). The patent ductus arteriosus was ligated and the left carotid and left subclavian arteries were clamped at the level of the ascending aorta, allowing blood flow to the brachiocephalic trunk for cerebral perfusion; the descending aorta was also clamped. The ductus arteriosus was sectioned and the area of coarctation was resected; the incision was extended along the inferior transverse arch and over the left carotid artery. Finally, an extended end-to-end anastomosis was performed, with a clamping time of 16 min and no surgical complications (Figure 2). With good descending aortic pulse and no

palpable anastomotic thrill, the patient was transferred to the cardiac recovery room with low-dose adrenaline (stopped 12 hours post-procedure) and milrinone 0.75 micrograms/kg/min. Postoperative echocardiography reported a gradient in the area of the aortic isthmus of 4 mmHg, apical intraventricular septum of 1.7 mm without hemodynamic repercussion, left ventricular diastolic and systolic diameters of 18 mm and 11 mm respectively, and patent foramen ovale with left to right shunt. Postoperative course was uneventful (no bleeding, chylothorax, diaphragmatic paralysis or arterial hypertension); transfontanellar ultrasound showed no changes compared to the previous ultrasound. The patient was transferred to the Neonatal Intensive Care Unit, remaining in MVS due to sepsis associated with a central venous catheter, and requiring low-dose inotropic drugs. Elective extubation was performed (total MVS time, 40 days) with nasal cannula support for 48 hours, without recurrent nerve palsy. The patient remained in the pediatric ward for nutritional recovery.

At one-year postoperative follow-up, the patient has symmetrical, peripheral pulses; echocardiography shows a slight narrowing of the isthmus (gradient 15 mmHg) without diastolic runoff; preserved left ventricular systolic function, left ventricular diastolic and systolic diameters of 28 mm and 18 mm respectively, and abdominal aorta with pulsatile flow.

Repair of cardiac defects in low-birth and very low-birth weight neonates is increasingly performed in a reparative rather than palliative manner. Only a few risk factors for death after coarctation of the aorta repair in small infants have been recognized so far; however, critical preoperative clinical status and associated complex cardiac lesions have been documented to be the most common and important risk factors to influence mortality after surgery. Bacha et al. found that low-weight infants (< 1.5 kg) have a significantly higher chance of developing a recoarctation. However, Mc Elhinney et al. and Sudarshan et al. concluded that low weight at the time of repair is not a risk factor for recurrent coarctation. (2, 5)

Surgical repair in premature infants with very low birth weight (< 1500 g) and a diagnosis of coarctation of the aorta can be successfully performed. Given that surgical and interventional experience is still limited, the therapeutic decision must be individualized for each patient, and taken together with neonatologists, cardiologists and pediatric cardiac surgeons.

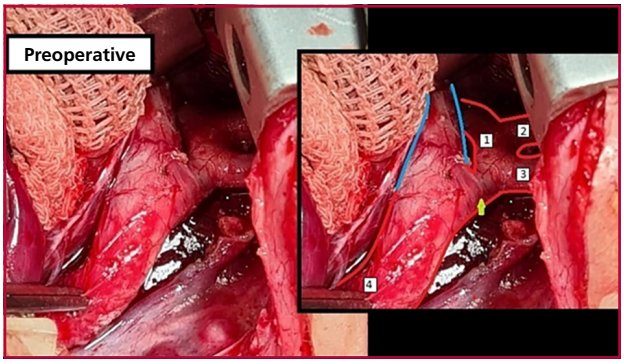


Fig. 1. CImage showing transverse arch (1), left carotid artery (2), left subclavian artery (3), descending aorta (4), patent ductus arteriosus (light-blue lines), and aortic isthmus and coarctation area (green arrow). This image does not show the brachiocephalic trunk.

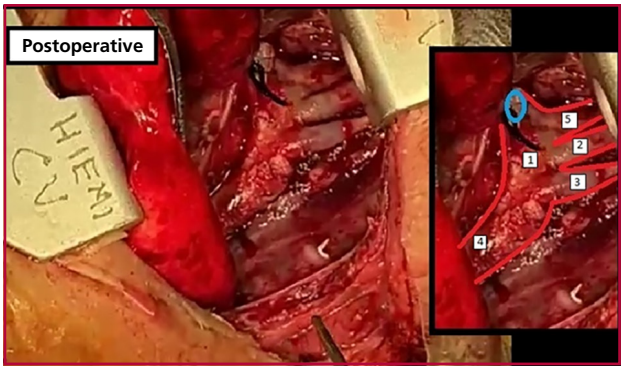


Fig. 2. Postoperative image showing ligated and sectioned ductus arteriosus (light-blue circle), resected aortic isthmus and coarctation area, and extended end-to-end anastomosis; brachiocephalic arterial trunk (5).

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

Ramiro M. Pellicciari[1], Carlos J. Vázquez[1],

[1] Department of Pediatric Cardiovascular Surgery, Hospital Interzonal Especializado Materno Infantil de Mar del Plata. Ramiro Marcos Pellicciari - Avenida Juan José Paso 867, Mar del Plata, Buenos Aires. Argentina

E-mail: ramiropellicciari@gmail.com - Phone: 11-59732992.

REFERENCES

1. Rossi AF, Seiden HS, Sadeghi AM, Nguyen KH, Quintana CS, Gross RP, et al. The outcome of cardiac operations in infants weighing two kilograms or less. J Thorac Cardiovasc Surg 1998;116:28-35. https://doi.org/10.1016/S0022-5223(98)70239-9

2. McElhinney DB, Yang SG, Hogarty AN, Rychik J, Gleason MM, Zachary CH, et al. Recurrent arch obstruction after repair of isolated coarctation of the aorta in neonates and young infants: is low weight a risk factor? J Thorac Cardiovasc Surg 2001;122:883–90. https://doi.org/10.1067/mtc.2001.116316

3. Bacha EA, Almodovar M, Wessel DL, Zurakowski D, Mayer JE Jr, Jonas RA, et al. Surgery for coarctation of the aorta in infants weighing less than 2 kg. Ann Thorac Surg 2001;71:1260–4. https://doi.org/10.1016/s0003-4975(00)02664-3

4. Rao PS, Galal O, Smith PA, Wilson AD. Five- to nine-year follow-up results of balloon angioplasty of native aortic coarctation in infants and children. J Am Coll Cardiol 1996;27:462–70. https://doi.org/10.1016/0735-1097(95)00479-3.

5. Sudarshan CD, Cochrane AD, Jun ZH, Soto R, Brizard CP. Repair of Coarctation of the Aorta in Infants Weighing Less Than 2 Kilograms. Ann Thorac Surg 2006;82:158–63. https://doi.org/10.1016/j.athoracsur.2006.03.007

Rev Argent Cardiol 2022;90:367-368.
http://dx.doi.org/10.7775/rac.v90.i5.20553

JORGE THIERER[MTSAC]

SECURE study: advantages of the administration of a polypill in secondary prevention of cardiovascular events

Castellano JM, Pocock SJ, Bhatt DL, Quesada AJ, Owen R, Fernandez -Ortiz A et al. Polypill Strategy in Secondary Cardiovascular Prevention. **N Engl J Med 2022;387:967-77. https://doi.org/10.1056/NEJMoa2208275.**

Cardiovascular disease is the leading cause of death and complications worldwide. Despite the existence of different effective pharmacological measures in the field of secondary prevention, the incidence of new ischemic events after an index event remains high. Lack of adherence to treatment is one of the most important causes, and its incidence is estimated at around 50%. Inadequate adherence to prescribed treatment is associated with worse outcomes. Among the measures proposed to overcome this problem is the adoption of a polypill, which, by bringing together the drugs indicated for prevention in a single tablet, simplifies their administration. A recent meta-analysis demonstrated the advantage of using a polypill in primary prevention. We now know the results of the SECURE study, which explored the usefulness of the strategy in secondary prevention.

SECURE was a multicenter, phase 3, randomized, controlled study in which elderly patients with a history of acute myocardial infarction (AMI) were assigned to a strategy based on the polypill, versus a usual strategy of administering the indicated therapy for secondary prevention. It was carried out in 113 centers in Spain, France, Germany, Poland, the Czech Republic and Hungary. Patients had to have a history of type 1 AMI according to the Universal Classification (plaque rupture or erosion and thrombosis, with or without ST-segment elevation) and be >75 years old, or ≥65 years old with at least one of the the following conditions: diabetes, glomerular filtration rate between 30 and 60 mL/min/1.73 m^2, or history of AMI, coronary revascularization or cerebrovascular accident (CVA). Patients receiving oral anticoagulation and those in whom a revascularization procedure was scheduled were excluded. The patients were randomly assigned to receive usual pharmacological treatment according to the practice guidelines of the European Society of Cardiology, or a polypill, AAR40, in three presentations, containing aspirin 100 mg, atorvastatin 40 mg and ramipril in doses of 2.5, 5 or 10 mg. In patients who had not previously been receiving angiotensin-converting enzyme inhibitors (ACEI), treatment was started with the polypill containing 2.5 mg of ramipril. In those who had already received prior treatment with ACEI, the polypill with the equivalent dose of ramipril was used. The goal was to reach ramipril 10 mg. If the treating physician wanted to decrease the dose of atorvastatin, he could switch to the AAR20 preparation, similar to the AAR 40 preparations, but with 20 mg of atorvastatin. Face-to-face follow-up was planned at 6, 12, and 24 months, with telephone calls at 18, 36, and 48 months. Adherence was evaluated with Morisky's 8-point scale. The study's primary endpoint was a composite of cardiovascular death, nonfatal type 1 MI, nonfatal stroke, or urgent revascularization. The main secondary end point, a composite similar to the primary, but without considering urgent revascularization. End points were also each of the components separately, and adherence at 2 years.

The study was designed for noninferiority, and the upper end of the 97.5% CI of the HR of the relationship between polypill and conventional treatment, set at a value of 1.373, was assumed as the noninferiority margin (that is, it was assumed until 37.3% excess in presentation of the primary end point, to accept non-inferiority). If non-inferiority was demonstrated, a superiority test could then be performed. If superiority was demonstrated for the primary endpoint, it could then be explored for the secondary endpoint. Considering an estimated incidence of the primary end point of 7.2% per year, it was considered that with 3206 patients with a minimum of 2 years of follow-up, there would be 90% power to reject the null hypothesis of non-inferiority, and 80% power to detect a 21% reduction in the primary endpoint, with a 5% loss to follow-up and a p-value of 0.05. The estimate was later changed to an expected incidence of the primary endpoint in the control arm of 7.7%, so that, with 2514 patients, there would be 78% power to detect superiority. An intention-to- treat analysis was proposed, and, additionally, a per-protocol analysis for the primary and primary secondary endpoints.

Between August 2016 and December 2019, 2466 patients were included in the study, 1237 in the polypill arm. The median time from AMI to inclusion was 8 days. The mean age was 76 years, 31% were women, 77.9% had hypertension, 57.4% diabetes, and 51.3% had a history of smoking. On admission, mean systolic blood pressure (SBP) was 129.1 mm Hg and mean LDL cholesterol was 89.2 mg/dL. In the polypill arm, 91.7% received the preparation with 40 mg of atorvastatin, compared to 40.4% who used a high-intensity statin in the usual treatment arm. In this arm, 98.7% received aspirin (by design, all received aspirin in the polypill arm); and a second antiplatelet agent was used in more than 90% of the cases in both arms.

Adherence was greater in the polypill group: at 6 months 70.6% vs 62.7% (RR 1.13, 95% CI 1.06-1.20) and at 2 years 74.1% vs 63.2% (RR 1.17, 95% CI 1.10-1.25). The median duration of follow-up was 3 years. During it, the incidence of the primary endpoint was 9.5% in the polypill arm versus 12.7% in the usual treatment arm (HR 0.76, 95% CI 0.60-0.96; p < 0.001 for non-inferiority and 0.02 for superiority). The incidence of the primary secondary endpoint was 8.2% vs. 11.7% respectively (HR 0.70, 95% CI 0.54-0.90; p=0.005). Although all components of the composite endpoint contributed to the results, the significant reduction in cardiovascular death stands out: 3.9% vs. 5.8%, HR 0.67, 95% CI 0.47-0.97. There was no significant reduction in death from all causes. There was no difference in the incidence of adverse events (32.7% vs. 31.6%) or non-fatal serious adverse events (19.2% vs. 18.2%).

In Rev Argent Cardiol 2021, vol 89 (5), we comment on a meta-analysis of individual data from 3 large, randomized studies that explored the use of the polypill in primary prevention (with some differences in components): PolyIran, TIPS-3, and HOPE-3. In total, it included 18 162 participants, half women, with a mean age of 63 years; 49.8% were hypertensive, 23.4% were smokers or former smokers, and 19.4% had diabetes. Mean SBP was 137.7 mm Hg and mean LDL cholesterol 121.7 mg/dL. The primary endpoint of the study was a composite of cardiovascular death, AMI, stroke, or any revascularization procedure. Compared to the control, at a mean of 2.1 years, mean LDL cholesterol was 22 mg/dL lower, and at 5 years mean SBP was 4.7 mm Hg lower in the polypill arm. In a median follow-up of 5 years, the primary endpoint occurred in 3% of the intervention arm and 4.9% of the control arm (HR 0.62; 95% CI 0.53-0.73; p<0.001). The number needed to treat (NNT) to prevent one event was 52 over 5 years. The effects of greater magnitude were reduction of AMI, stroke and need of revascularization, in all cases with HR between 0.52 and 0.59; for cardiovascular death, the HR was 0.65, 95% CI 0.52-0.81. There were no differences in death from all causes. In the aspirin stratum, the incidence of the primary endpoint was 2.6% in the intervention arm and 4.8% in the control arm (HR 0.53, 95% CI 0.41-0.67) with an NNT at 5 years of 37. The main differences were in AMI, stroke, and cardiovascular death, with no difference in death from all causes. In the non-aspirin stratum, the incidence of the primary end point was 3.3% in the intervention arm and 4.9% in the control arm (HR 0.68, 95% CI 0.57-0.81), and the NNT at 5 years it was 66. The main differences were in AMI, stroke, and revascularization, with no difference in all-cause death.

The SECURE study clearly presents differences with those mentioned: it is a secondary prevention study, with patients 13 years older, with a higher prevalence of risk factors. It is logical, for these reasons, that the incidence of major events has been higher in SECURE; it is paradoxical that the baseline figures for BP and LDL cholesterol have been lower than in the primary prevention studies, but surely more frequent prior treatment can explain the difference. As in the studies cited, the polypill is triumphant over its comparator; but some doubts arise regarding the responsible mechanisms. In SECURE, as we saw, adherence was 10% higher with the polypill than with drugs administered individually; we would have expected, therefore, lower levels of LDL cholesterol and BP in this arm. However, this did not happen. At 2 years, the same BP was verified in both arms (135.2/74.8 mm Hg with polypill, 135.5/74.9 mm Hg with usual treatment) and the same happened with LDL cholesterol (67.7 vs. 67.2 mg/dL). Therefore, the greater adherence does not seem to have resulted in better control of the most important risk factors (when this is one of the arguments most frequently put forward to justify the use of the preparation); and, in turn, despite similar figures for BP and LDL cholesterol, the evolution of the patients was better with the polypill. Two facts that still await an answer. The authors mention the possibility that the beneficial effect is actually due to the pleiotropic effects of statins and ACEI (argument that has been repeated for many years, without convincing evidence that this is the real responsible for the better evolution, although a possible role should not be dismissed either); and because greater adherence also implies greater use of aspirin, included in the polypill, and which has a precise indication in secondary prevention. Some voices have been heard that, given the lack of a solid response to the doubts raised, the results are meaningless. We believe that the evidence accumulated with thousands of patients in primary and secondary prevention is a very good reason to justify the use of the polypill, if access to treatment is facilitated.

Back to the beginning: the administration of antihypertensive medication in the evening is not better than in the morning. TIME study

Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomized, open-label, blinded-endpoint clinical trial. **Lancet 2022;400:1417-25. https://doi.org/10.1016/S0140-6736(22)01786-X.**

Blood pressure (BP) normally follows a circadian rhythm, with values falling at night and rising on awakening in the morning. This pattern is called a dipper pattern. When this drop in blood pressure is reduced or absent, or, on the contrary, nighttime blood pressure is higher than daytime blood pressure, the risk of adverse cardiovascular events is greater. This has led to different clinical trials testing changing the usual schedule for administering antihypertensive medication, going from the traditional morning administration to an evening administration, to ensure a better night-time drop in blood pressure. In some

trials, this change has resulted in better blood pressure control over 24 hours, and a Spanish group has shown in the Hygia Chronotherapy study a significant reduction in adverse cardiovascular events by taking the treatment administration schedule from morning to night. Some however have questioned the results of the Hygia study, and have argued that the observed effect is exaggerated. Added to this is the fear of a higher incidence of complications when administering drugs at night (falls, stroke), and it is also pointed out that adherence to treatment is lower when administration is left for dinner time or when to go to bed. All of these reasons led to a new clinical trial, the TIME study.

TIME was a randomized, controlled, open-label, parallel-group study with blinded adjudication of events. It was carried out in Great Britain, and included hypertensive patients, treated with at least one drug administered once a day. Patients who received the medication more than once a day, or who worked at night, were excluded. They were randomly assigned in a 1:1 ratio to receive the treatment between 6:00 and 10:00 h, or between 20:00 and 00:00 h. The study did not require face-to-face visits. All the administrative procedures, including the allocation of the schedule for taking the medication, were carried out through an electronic platform. Those taking diuretics were suggested to take them at 18:00 to prevent nocturia. Questionnaires were sent to patients on a regular basis, in the first month after random assignment, and every 3 months thereafter. Each patient was questioned about adherence to treatment, and the incidence of adverse events (digestive intolerance, dizziness, falls, fractures, nocturia, insomnia, etc.). Those who had a home blood pressure measurement device were invited to submit regular blood pressure records. The primary endpoint was the incidence of vascular death and nonfatal acute myocardial infarction (AMI) or stroke. Initially, it was estimated that, in 10 269 participants followed up for 5 years, 631 events would be verified, necessary to demonstrate, with 80% power and $p < 0.05$, a 20% reduction in the primary end point in the evening administration arm compared to the morning. But the low incidence of events led to an increase in the necessary population to almost 20,000 patients. The analysis was done by intention to treat.

Between 2011 and 2018, 21 104 patients were included in the study (10 503 in the evening arm). The mean age was 65.1 years, 42.5% were women, and 12.9% had a cardiovascular history. Mean systolic blood pressure was 135 mm Hg and diastolic 79 mm Hg. The median follow-up was 5.2 years, and the maximum follow-up was 9.3 years. Just over 4% of patients in both arms died before the end of follow-up. Of the 53.6% of patients who reported the usual time for taking their medication before their random assignment, more than 85% did so in the morning. During the study, 11.6% of the patients abandoned the active follow-up of questionnaire responses; almost 63% of them belonged to the evening arm.

The primary endpoint occurred in 3.4% of the evening arm (0.69 events/100 patient years) and 3.7% of the morning arm (0.72 events/100 patient years), without significant difference. There was no difference according to the different prespecified subgroups, nor in the incidence of the different components of the primary end point. At some point of follow-up 30.7% of the participants reported non-adherence to treatment, at a mean of 1.7 years from randomization; lack of adherence was greater in the evening arm (39% vs. 22.5%, $p<0.0001$); at the last visit, 19.8% were non-adherent vs. 7.1%. The evening arm had a slightly lower incidence of falls (21.1% vs. 22.2%, $p=0.048$) and adverse events in general (69.2% vs. 70.5%, $p=0.041$), but there was not a difference in fractures, hospitalization for fractures or glaucoma exacerbation. About 80% of the slightly more than 11 000 patients who reported having a home blood pressure measurement device, submitted at least one blood pressure report: morning blood pressure (usually taken between 8:00 and 9:00 a.m.).) was lower (1.8 mm Hg for systolic and 0.4 mm Hg for diastolic) and the afternoon was higher in the arm that received treatment in the evening; in contrast, in the group with morning treatment, evening blood pressure was lower (1.1 mm Hg lower for systolic and 0.9 mm Hg for diastolic blood pressure).

In Rev Argent Cardiol 2020, vol 88 (6), we presented the results of the Hygia Chronotherapy study, with 19 084 hypertensive patients, with a mean age of 60.5 years; 55.6% men; 24%, diabetics, and 29% with impaired renal function. Follow-up and control were done with ambulatory blood pressure monitoring (ABPM). Mean office BP was 149/86 mmHg, and in the ABPM 131/77 mm Hg; 49.3% had a non-dipper pattern. Patients were randomly assigned to receive treatment in the morning after waking up or in the evening before going to sleep. In a median follow-up of 6.3 years, in ABPM, mean BPs were lower in the night arm (124.3/72.2 mmHg vs. 125.6/73.1 mmHg). This was achieved by reducing the nocturnal mean SBP (114 mmHg vs. 118 mmHg) and DBP (64 mmHg vs. 66 mmHg), with no difference in daytime figures. In the overnight arm, there was a notable decrease in the risk of major cardiovascular events (HR 0.55; 95% CI 0.50-0.61), all-cause mortality (45% reduction), cardiovascular mortality (reduction in 56%) and each of the individual components of the end point (from 34% for the risk of acute myocardial infarction, to 61% for the risk of hemorrhagic stroke).

However, much criticism was leveled at the way the study had been conducted. It was questioned whether the rules of a randomized study had been met; the cleanliness of the procedures was questioned, the way of adjudicating the events was doubted. It was hypothesized that Hygia actually recruited patients from previous studies. The abrupt increase in the number of participants was discussed, from the 5 000 initially proposed to the more than 19 000 finally included. The ABPM was also discussed as a valid way of evaluating

the results, and specifically the control device used in the study, and the very low rate of reported measurement errors, which do not coincide with usual practice.

In the midst of this controversy, the TIME study represents a new blow to the defenders of the nocturnal administration of the medication, since it calls into question its benefit. Unlike Hygia Chronotherapy, the design of the study or the way of carrying it out has not been discussed in academic circles. This is a clearly pragmatic study: a behavior was indicated to the patients and its consequences were verified. Precisely this condition also implies dealing with a certain lack of information: there is data on the behavior of blood pressure in around 40% of the patients (80% of the little more than half that had a home blood pressure measurement device). Sending the data depended on the willingness of the patients to participate, and was greater in older patients, with a greater amount of antihypertensive drugs. In the patients of the evening arm, the abandonment of sending forms was greater, and therefore the rate of associated complications may be underestimated. In any case, it does not appear that any of these differences have substantially influenced the results. A statement from the International Society of Hypertension published just over a month ago supports the need to achieve adequate 24-hour BP control and recommends morning administration of long-acting medications in a single dose as preferential. As always in medicine, we understand that a precise study of the conditions of each patient and the individual behavior of BP is essential to implement the best administration scheme in each case; the routine administration of antihypertensive treatment at evening-night has certainly lost steam, due to the stated reasons for doubting the Hygia results, and the strength of the TIME study data.

Invasive strategy in acute coronary syndromes without elevation of the ST segment. ¿Early or delayed? The last meta-analysis

Kite TA, Kurmani SA, Bountziouka V, Cooper NJ, Lock ST, Gale CP et al. Timing of invasive strategy in non-ST-elevation acute coronary syndrome: a meta-analysis of randomized controlled trials. **Eur Heart J 2022;43: 3148-61. https://doi.org/10.1093/eurheartj/ehac213.**

In the context of non-ST-segment elevation acute coronary syndromes (NSTEACS), an invasive strategy is recommended by all clinical practice guidelines for most patients. There is not so much uniformity about the best moment to establish it. An initial plaque stabilization strategy with antithrombotic agents and statins has been proposed, with deferred coronary angiography, but also an early invasive strategy in order to jugulate the present ischemia and reduce the risk of total vessel occlusion. Two meta-analyses (years 2016 and 2017) of 10 and 8 randomized studies (the latter with individual data analysis) did not show an advantage for an early invasive strategy compared to a delayed one. Since then, new studies have been published, and long-term follow-up results of some of the previous studies have become known. For this reason, a new meta-analysis has just been published.

Randomized studies were included that had compared early and delayed invasive strategies in patients with NSTEACS, with a minimum follow-up of 30 days and all-cause mortality data reporting. Studies comparing a routine invasive strategy with a selective invasive or conservative strategy were excluded. Seventeen studies were included, with 10 209 patients (5 215 in the early invasive arm and the rest in the delayed arm). The median time to angiography in the early invasive arm was 3.43 hours, and in the delayed arm 41.3 hours. There was heterogeneity in baseline characteristics and definition of endpoints. In most of the studies, after angiography, percutaneous coronary intervention (PCI), surgery or medical treatment was decided, except in 4, in which all patients underwent PCI. The median follow-up was 12 months.

For the analysis of all-cause mortality, 16 studies were considered, with 10 155 patients. There was no difference in its incidence, with RR 0.90, 95% CI 0.78-1.04. There was no heterogeneity in the results. In 6 of the studies, the median time to angiography in the deferred branch was <24 hours. Even after excluding these studies, there was no difference between the two strategies. Fifteen studies analyzed the incidence of acute myocardial infarction (AMI) and 13 of recurrent ischemia. No difference was found in the incidence of AMI, but there was a difference in recurrent ischemia in favor of the early invasive strategy (RR 0.57, 95% CI 0.40-0.81), although with high heterogeneity in the results. No difference was seen in the incidence of heart failure, stroke, or major bleeding; the length of hospital stay was shorter in the early invasive branch (median 22 hours less).

Clinical practice guidelines agree in recommending an immediate invasive strategy (within 2 hours of presentation) in patients with NSTEACS at very high risk. Who are these patients? Those with hemodynamic instability, heart failure or cardiogenic shock, malignant ventricular arrhythmia, recurrent or refractory pain, mechanical complications, or extensive ST-segment changes (depression > 1 mm/ 6 leads, with elevation in aVR or V1). These patients have been excluded from randomized studies comparing an early versus a delayed invasive strategy. In general terms, the meta-analysis that we are commenting on, despite notably increasing the number of patients considered (more than 10 000 compared to 6 400 in the most numerous of the previous ones), does not substantially change the concepts that we handle. There is no advantage for an early invasive strategy (within 24 hours) compared to the delayed one if we consider all patients, in terms of hard endpoints (death, AMI; major bleeding). The reduction in recurrent ischemia is remarkable, but it should be noted that it is a softer point, with hetero-

geneity in its definition and evaluation in the different studies. The decrease of one day in the duration of hospitalization is obvious, because it is little less than the difference in the moment of implementation of the invasive strategy. An individual patient data meta-analysis published in 2017 by Jobs et al. in Lancet, on 8 studies and 5334 patients (half of the studies and patients than the current one) suggested that the subgroups of NSTEACS patients who especially benefited from an early invasive strategy were those with elevated cardiac biomarkers at baseline (HR 0.76 , 95% CI 0.58-0.99), diabetes (HR 0.67, 95% CI 0.45-0.99), those over 75 years of age (HR 0.65, 95% CI 0.46-0.93), or with a GRACE score > 140 (HR 0.70, 95% CI 0.52-0.95), although the interaction tests were not conclusive. In fact, troponin elevation, a GRACE score > 140, and dynamic ST-segment changes in adjacent leads are currently recommended criteria to define high risk and thus early invasive behavior. It is worth remembering two things: that the evidence to which we refer comes almost entirely from studies in which conventional troponin T was used, not ultrasensitive; and that the cited GRACE score arises from the model to predict hospital mortality in patients with ACS, and not from those used for other endpoints, in which case the result obtained could differ, and lead to different behaviors. More recent studies are being carried out to prospectively define the use of this cut-off value.

As a limitation of this meta-analysis, we can mention that it is not one of individual patient data, which could have contributed to better define risk subgroups in which an early invasive strategy offered advantages, over and above the criteria already mentioned; therefore, its value is essentially confirming what has already been established, rather than a source of change and improvement.

Differences in the prevalence of cardiovascular risk factors, temporal evolution and prognosis between men and women. A sub-analysis of the PURE Registry

Walli-Attaei M, Rosengren A, Rangarajan S, Breet Y, Abdul-Razak S, Sharief WA et al. Metabolic, behavioral, and psychosocial risk factors and cardiovascular disease in women compared with men in 21 high-income, middle-income, and low-income countries: an analysis of the PURE study. **Lancet 2022;400: 811-21. https://doi.org/10.1016/S0140-6736(22)01441-6.**

A series of metabolic, behavioral, and socioeconomic factors are associated with an increased risk of cardiovascular disease. The association does not always have the same strength in men as in women. For example, it has been pointed out that hypertension (HTN), diabetes (DM) and smoking are associated with a higher risk in women than in men. But it is true that these data come from high-income countries (HIC). The burden of risk factors is higher in low (LIC)- and middle-income countries (MIC), and information from them is scarcer. The PURE study (Prospective Urban Rural Epidemiology) is a prospective cohort study, which at different stages included people from countries with different income levels, and from urban and rural locations, with the purpose of reflecting the existing heterogeneity in the distribution of risk factors and their association with the incidence of cardiovascular events in the world population. In the analysis that we present, the relationship of these factors with cardiovascular evolution in men and women is explored.

The countries were classified as HIC, MIC and LIC according to the 2006 World Bank classification.

The metabolic risk factors considered were hypertension, systolic blood pressure (SBP), diabetes, fasting glucose, waist-to-hip ratio, abdominal obesity, and non-HDL cholesterol. Behavioral risk factors include smoking, alcohol consumption, physical activity (self-reported and taken on a MeTS scale per week, with a cut-off value of 600) and diet (assessed with PURE score). Psychosocial risk factors considered were symptoms of depression and a low level of education (primary or less). Grip strength (assessed with a dynamometer) and household pollution (defined by cooking with kerosene or solid fuels) were added as risk factors to be analyzed. The primary endpoint was the incidence of major cardiovascular events, a composite of cardiovascular death, nonfatal acute myocardial infarction (AMI), nonfatal stroke, and heart failure. The secondary endpoint included the top three.

Of all PURE participants, 155 724 were selected for this analysis, aged between 35 and 70 years, with no history of cardiovascular disease, with at least 3 years of follow-up. Of these, 58.4% were women, with a mean age of 49.8 years at admission, compared to 50.8 years for men. At entry, just over 37% of both men and women lived in HIC, or in the top half according to income level of MIC (Argentina, Brazil, Canada, Chile, Malaysia, Poland, Saudi Arabia, South Africa, Sweden, Turkey, and United Arab Emirates), and the rest in lower-income MIC, or LIC (Bangladesh, China, Colombia, India, Iran, Pakistan, Palestine, the Philippines, Tanzania, and Zimbabwe). Just under half of the men and women lived in rural communities.

Median follow-up was 10.1 years. During it, 4.7% of women and 7.6% of men reached the primary endpoint, with an age-standardized annual incidence of 5 ‰ for women and 8.2 ‰ for men. SBP and blood glucose levels increased with age and tended to be lower in women; the waist-hip ratio was significantly lower in women, while non-HDL cholesterol increased with age in women but not in men. In men, the prevalence of smoking, alcohol consumption and poor physical activity was higher; in women, the presence of depression and lower educational level. In both sexes, diet, grip strength and exposure to pollution were similar. Total and LDL cholesterol levels were higher between 35 and 44 years of age in men, similar in both sexes

between 45 and 54 years of age, and higher in women from 55 years of age. Triglyceride values were higher in men up to 54 years of age, and similar to those of women from 55 years of age.

Let us now go to the strength of association of each of the risk factors with cardiovascular evolution. Among metabolic factors, the strength of association with outcome was similar for all of them between men and women, except for non-HDL cholesterol, which was a stronger predictor in men (HR 1.28 in men, 1.11 in women, p =0.0037). The elevation of total cholesterol (≥200 mg/dL), LDL cholesterol (≥130 mg/dL) and triglycerides (≥150 mg/dL) did not imply an increased risk in women (HR 1.01 in all cases) but yes in men (HR 1.19 for triglycerides, 1.26 for LDL cholesterol and 1.30 for total cholesterol). There was a tendency to greater weight for smoking in men (HR 1.30 vs 1.15 in women, p=0.06). Lower-quality diet was a heavier risk factor in women, depression in men. The association of risk factors with evolution was similar in all country income levels. The population attributable fraction, PAF, (how much of cardiovascular disease in the population can be attributed to each risk factor) was similar for hypertension in men and women, as well as in the case of diabetes; but obesity and a poor-quality diet were associated with higher PAF in women, and smoking and elevated LDL cholesterol with higher PAF in men. In the case of AMI, PAF was similar in men and women for the risk factors considered as a whole: 69.1% in women, 68.3% in men; in the case of stroke, PAF was much lower in women; 47.1% vs 63.1% in men; for cardiovascular death, the difference in PAF was negligible: 79.3% vs 82.5%.

This analysis of the PURE registry ratifies some previous concepts about the differences in cardiovascular profile and evolution between men and women and puts others into question. It confirms that the overall cardiovascular prognosis is worse in men, who have a worse profile of risk factors from an earlier stage, with higher figures (significantly or with a trend) of blood pressure, lipids and glycemia. In men, smoking and alcoholism prevalence is higher; symptoms of depression and lower educational level are more frequent in women. The passing of the years tends to attenuate the differences; even the numbers of LDL cholesterol end up being higher in women. The association of metabolic factors with prognosis in PURE is similar in men and women, except for dyslipidemia, which weighs more in men. This is consistent with a meta-analysis showing that a 1 mmol/l (38.6 mg/dL) reduction in LDL cholesterol reduces the risk of cardiovascular events by 15% in women, but by 28% in men. Where we found a discrepancy with respect to previous data is in the relative weight of diabetes in determining risk. Meta-analysis with almost 1 million patients confirms the higher risk of cardiovascular mortality that diabetes entails in women than in men in the entire age range, especially between 35 and 65 years. Similarly, smoking had been identified as a greater risk factor in women than in men, and in PURE an opposite trend was verified. It is interesting that alcohol consumption appears as a protective factor, more in women than in men. It should be noted, however, that this refers specifically to cardiovascular risk, and does not exempt alcohol from the increased risk of cancer, accidents, and all-cause mortality.

This publication by the authors of PURE confirms the value of large observational studies and the importance of thinking about the different exposure of men and women to risk factors and their specific impact. When the association with outcomes matches that seen in other studies, we can view it as confirmatory data. When there are discrepancies, we understand that we can doubt. How to define if the truth lies in this Registry, or in those that show another reality? Just as we have understood that randomized studies are a biased sample of reality, we must recognize that Registries are too: each one has its own inclusion and exclusion criteria, which define a specific population in each case (for example, here we talk of people between 35 and 70 years old), their definitions, their specific mechanisms to access information, their monitoring methods. The undoubted merit of the article is to emphasize that men and women are not the same; that we must learn to recognize biological, socioeconomic, and behavioral differences. There are still no specific indications in the cardiovascular disease guidelines that differentiate behaviors according to sex. Without going so far, it is desirable that at least special considerations be made in the most notable cases, when it comes to finding the best treatment in each case.

Antibiotic prophylaxis of infective endocarditis: when and how. Data from a large population registry.

Thornhill MH, Gibson TB, Yoon F, Dayer MJ, Prendergast BD, Lockhart PB et al. Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures. **J Am Coll Cardiol 2022;80:1029-41. https://doi.org/10.1016/j.jacc.2022.06.030.**

Infective endocarditis (IE) is an entity associated with high mortality and complications. Thirty to 40% of IE episodes caused by oral streptococci are attributed to invasive dental procedures (IDP). Already in 1955, the AHA established the indication of antibiotic prophylaxis (AP) in case of performing a IDP. However, the true efficacy of AP to prevent IE in this context has never been tested in a clinical trial, and it has even been postulated that the risk of IE may be greater in situations not strictly related to IDPs, but simply to tooth brushing, or chewing, in conditions of poor oral hygiene. The risk of promoting antibiotic resistance in the face of uncontrolled antibiotic use led regulatory agencies to promote the use of AP only in the case of IDP in patients at high risk of IE, and even in Great Britain, AP was discouraged. A retrospective analysis of a large Medicare database in the US, linked to one

of dental procedures among its beneficiaries, helps to clarify the issue.

It included individuals aged at least 18 years, with data from both databases, related for at least 16 months. All hospitalizations for IE between 2000 and 2015 were identified. It was defined in each case if the patient had a high risk of IE (previous history of IE, prosthetic heart valve, valve repair with prosthetic material, unrepaired cyanotic congenital heart disease, congenital heart disease with palliative shunts or conduits, congenital heart defect completely repaired with prosthetic material or device, during the first 6 months after the procedure), moderate (rheumatic heart disease, non-rheumatic valve disease, congenital valvular anomalies, hypertrophic cardiomyopathy), or low/unknown. The dental procedures carried out were classified as a) IDPs: those that involve the manipulation of the gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa (extractions, surgical procedures, supragingival or subgingival scaling or deep cleaning), and endodontic procedures; that is, those procedures that the AHA recommends "should" be covered by AP; b) intermediate dental procedures, those restorative dental procedures that may require AP only if there is gingival manipulation, and c) non-invasive procedures, for example routine dental examination, dental X-rays, or placement of removable prostheses or orthodontics, for which AP is not recommended . For each visit, the most invasive procedure was considered as the index; in a treatment that required several visits, each one was considered independently. An episode of IE was considered new if it was separated by at least 6 months from a previous one. In each case of dental procedure, the incidence of IE was considered in the 30 days and 4 months after the procedure. The crude incidence of IE in each risk group was adjusted for age, sex, and the Charlson comorbidity index.

Of 7 951 972 enrolled in coverage, 0.46% had a high risk of IE; 7.09% moderate risk, and the rest low or unknown risk. In total, 3774 people (475 cases per million) were hospitalized for IE; 34.2% with high risk of IE, 22% with moderate risk and 43.8% with low/unknown risk. The adjusted incidence of IE in the 30 days after a dental procedure was 467.6; 24.2 and 3.8 per million people, respectively. In patients at high risk of IE, and taking non-invasive procedures as a reference, overall, intermediate procedures or IDPs did not imply a significant increase in the risk of IE; but specifically, extractions (OR 9.22) and surgical procedures (OR 20.18) marked high-risk situations. In patients with moderate risk of IE, and taking non-invasive procedures as a reference, intermediate procedures and IDPs did not imply a significant increase in the risk of IE; but again extractions (OR 3.25) were associated with excess risk. And among patients with low/unknown risk, the situation was repeated: in general, intermediate procedures or IDPs did not score significantly higher than non-invasive procedures, but extractions (OR 2.41) and surgical procedures (OR 3 .74) marked situations of significant risk.

AP was prescribed in 32.6%, 9.5%, and 2.9% of IDPs in patients at high, moderate, and low risk for IE, respectively. The most used antibiotics were amoxicillin 2 g (75% of cases) and clindamycin 600 mg (in 17%). AP significantly reduced the incidence of IE in the case of IDPs in high-risk patients (OR 0.38, 95% CI 0.22-0.62), especially in extractions (OR 0.13) and other surgical procedures (OR 0.09). There was no effect of AP in lower risk patients, or in intermediate or non-invasive procedures.

In another type of analysis, the 3774 episodes of IE were specifically considered, and the relationship between dental procedures in the previous month and what had occurred in the 12 months prior to that month was evaluated. A significant association was verified between IDPs in the previous 30 days and hospitalization for IE (OR 2, 95% CI 1.59-2.52)

This one that we present is another observational study of enormous value, which helps to suggest behaviors in a condition that will hardly be explored in randomized studies. A first fact to note: the IE risk classification works. In the Medicare population (> 65 years, or younger, with disabilities), less than 0.5% are at high risk, but they generate a third of all hospitalized IE (more than 60 times what is expected under the null hypothesis). Seven percent have moderate risk, and cause just over 20% of cases (3 times expected); and from the rest (more than 92%), of low or unknown risk, comes a little less than half of the cases (half of what would be expected if the risk were the same in the 3 categories). Extractions and oral surgery have been implicated in increased risk of IE among high-risk patients; if, overall, the IDPs did not show a significant association with the incidence of IE, this was because the deep cleaning procedures unexpectedly presented a negative association with this incidence. The authors hypothesize that patients who undergo deep dental cleaning comply more strictly with oral hygiene, and this may reduce the risk, while in general extractions are more urgent procedures, with less time to get the mouth subjected to an intervention without risk. Even with lower overall risk, extractions in low- or intermediate-risk patients and surgery in low-risk patients implied a significant excess risk of IE. AP use was low: it was 3.7% overall, and even in IDPs in high-risk patients (the riskiest combination), it did not reach 33%. Even so, the beneficial effect of AP in this type of patient was confirmed, which supports the recommendation of the AHA and the ESC. Numerous *limitations can be cited, the most important being the lack of microbiological data and the fact that the prescription of AP is based on administrative data: it cannot be stated with certainty whether each time it was indicated it was actually administered, and whether when it was not indicated some patients did not access it by other means (for example, because they had antibiotics at*

home, and received a verbal indication). Finally, a figure that emerges from a survey among dentists in the US: 63% understand that it is the clinician or the cardiologist who should indicate the AP, not the dentist (perhaps understanding they are the ones who can define a patient's IE risk before a dental procedure); only 30% believe that the conditions and procedures that must receive AP are sufficiently clear. In daily practice we frequently receive the dentist's request to decide on the type and dose of AP. Knowing the above data helps us to be less doubtful and make fewer mistakes when doing so.

New demonstration of the effect of gliflozins in patients with kidney failure: the EMPA-KIDNEY study

Empa -Kidney Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ et al. Empagliflozin in Patients with Chronic Kidney Disease. **N Engl J Med 2022. https://doi.org/10.1056/NEJMoa2204233.**

In the last months of 2020, we knew the results of DAPA CKD study, which included patients at least 18 years old, with or without diabetes, with an estimated glomerular filtration rate between 25 and 75 mL/min/1.73 m 2 and a urinary albumin-creatinine ratio (UACR) between 200 mg/g and 5000 mg/g. They had to be medicated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) at the maximum tolerated dose. Patients with type I diabetes, polycystic kidney disease, advanced heart failure, and those with vascular events or revascularization in the last 2 months were excluded. Patients were randomly assigned in a double-blind manner to dapagliflozin 10 mg daily or placebo. The primary endpoint was a composite of: a) drop in estimated glomerular filtration rate ≥50%; b) end-stage renal failure (filtrate rate <15 mL/min/1.73 m^2 sustained for at least 28 days, need for dialysis for at least 20 days or kidney transplant; c) death of cardiovascular or renal origin. Secondary endpoints were a renal endpoint, composed of those already mentioned, except cardiovascular death; a composite of cardiovascular death or hospitalization for heart failure; and death from any cause. In February 2017, the first patient was included, and in March 2020, when 4304 patients had been randomly assigned and 408 end points had occurred (60% of those planned), the study was suspended due to the notorious superiority of the dapagliflozin arm. Patients mean age was 62 years, 67% were men, 67.5% had diabetes, 10.9% heart failure; mean systolic blood pressure was 137 mmHg. Ninety-seven percent were treated with ACEIs or ARBs. Mean estimated glomerular filtration rate was 43 mL/min/1.73 m^2, and the median UACR was 950 mg/g. The incidence of the primary endpoint was 9.2% in the dapagliflozin arm and 14.5% in the placebo arm (HR 0.61, 95% CI 0.51-0.72, p = 0.000000028). There was a highly significant reduction in the drop in estimated glomerular filtration rate ≥50% (HR 0.53; 95% CI 0.42-0.67) and in the incidence of end-stage renal failure (HR 0.64; 95% CI 0 .50-0.82), both due to a drop in the incidence of filtration <15 mL/min/1.73 m^2 and the need for dialysis for at least 20 d (HR 0.66; 95% CI 0.48 -0.90). The mean annual drop in glomerular filtration rate was 2.86 mL/min/1.73 m^2 in the dapagliflozin arm and 3.79 mL/min / 1.73 m^2 in the placebo arm, an annual difference of 0.93 mL/min/1.73 m 2 (95% CI 0.61-1.25 mL/min/1.73 m^2). There was a significant reduction in the renal end point (6.6% vs 11.3%, HR 0.56; 95% CI 0.45-0.68, p = 0.000000018); of the composite of cardiovascular death and heart failure hospitalization (4.6% vs. 6.4%, HR 0.71; 95% CI 0.55-0.92, p = 0.0089) and of death from all causes (4.7% vs. 6.8%, HR 0.69; 95% CI 0.53-0.88, p = 0.0035). In subgroup analysis, there were no differences according to age, sex, diabetes, glomerular filtration rate or albumin-creatinine ratio. The incidence of serious adverse events was lower in the dapagliflozin arm. The incidence of significant hypoglycemia also differed (0.7% vs. 1.3%, p = 0.03).

We have just learned about a similar study, corresponding to the same pathology, with empagliflozin, the EMPA-KIDNEY study. It included patients with a glomerular filtration rate between 20 and <45 mL/min/1.73 m^2 with any UACR value, or between 45 and <90 mL/min/1.73 m^2, with an UACR of at least 200 mg/g. Patients had to be receiving ACE inhibitors or ARBs, but could be included if the investigator judged that they would not be tolerated. There was a run-in phase of up to 15 weeks, in which patients received placebo and baseline treatment was consolidated. After at least 6 weeks of run-in, blood and urine samples were taken, and once patients were judged fit, they were randomly assigned to empagliflozin 10 mg or placebo. The primary endpoint was the occurrence of renal disease progression or death from cardiovascular causes. Kidney disease progression was defined as end- stage kidney disease (beginning of maintenance dialysis or kidney transplant), a sustained decrease in filtration rate to less than 10 mL/min/1.73 m^2, a sustained decrease in glomerular filtration rate of at least 40%, or death from renal causes. Secondary endpoints were a composite of cardiovascular death and hospitalization for heart failure, hospitalization from any cause, death from any cause, and a composite of end-stage renal disease and death from any cause. Investigators defined 1070 primary endpoint events to give the study 90% power with p<0.05 2-tailed to demonstrate an 18% reduction with empagliflozin. It was suggested that if, after 624 events, an HR with empagliflozin of 0.778 was found for the primary endpoint (with p<0.0017) and the same HR for the secondary endpoint of terminal renal failure and death from any cause (with p<0.05), the study could be suspended.

Between February 2019 and April 2021, 8 544 patients were screened; 8 184 entered the pre randomization phase, and 6 609 were effectively randomized.

Their mean age was 63.8 years, 66.8% were men, and 46% had diabetes. The mean estimated glomerular filtration rate was 37.3 ± 15.5 mL/min/1.73 m^2, and the median UACR was 329 mg/g. Eighty-five percent were medicated with ACEI or ARB. In March 2022 the interim analysis showed, with 624 events, that the two conditions cited for discontinuing the study had been met. Follow-up was completed in July, with a median of 2 years. At the end of the first year of follow-up, 90% of the patients in both arms had taken more than 80% of the allocated tablets. At the last visit, 16.9% in the empagliflozin arm and 19.4% in the placebo arm had discontinued treatment.

The primary endpoint occurred in 13.1% of the empagliflozin arm and 16.9% of the placebo arm (HR 0.72, 95% CI 0.64-0.82, p<0.001). The rate of first and subsequent hospitalizations for any cause was lower with empagliflozin (24.8 vs. 29.2 hospitalizations per 100 patient-years; HR, 0.86; 95% CI, 0.78-0.95; p=0.003). There was a significant reduction in kidney disease progression (11.6% vs 15.2%, HR 0.71, 95% CI, 0.62-0.81). In contrast, there was no significant decrease in the composite hospitalization for heart failure or cardiovascular death (4% vs. 4.6%), cardiovascular death (1.8% vs. 2.1%) or death from any cause (4.5% vs. 5.1%).

As in all the studies with empagliflozin in different contexts, an attenuation in the drop in glomerular filtration was verified with the use of the drug. Considering the slope from the beginning of the study, the annual difference was 0.75 mL/min/1.73m^2. If the changes from 2 months after randomization are considered, and the initial drop in glomerular filtration rate due to reduced hyperfiltration is ruled out, the difference was greater: 1.37 mL/min/1.73m^2. Overall, in the empagliflozin arm, a reduction in weight of 900 g, in systolic and diastolic blood pressure of 2.6 and 0.5 mm Hg, and in UACR of 19%, compared to placebo, was verified.

We had already verified the nephroprotective effect of gliflozins in studies in diabetes, and in the context of heart failure. The results of EMPA-KIDNEY confirm those of DAPA-CKD regarding its beneficial effect on the evolution of patients with kidney failure. Some differences between the two studies deserve to be highlighted. The presence of diabetes was lower in EMPA-KIDNEY (46% vs 67% in DAPA-CKD). This coincided with a significantly lower UACR in EMPA-KIDNEY (329 mg/g vs 950 mg/g). In contrast, the average glomerular filtration rate was lower (37 vs 43 mL/min/1.73 m^2 *), and, in fact, in DAPA-CKD only 14.5% had < 30 mL/min/1.73* m^2*, compared to 34.5% in EMPA-KIDNEY. Worse glomerular filtration rate, but less albuminuria and diabetes in EMPA-KIDNEY … what could be expected regarding the prognosis?*

The annual incidence of the composite endpoint of worsening renal function, renal death, and cardiovascular death was, in the placebo arms, 7.5% in DAPA-CKD, and 8.9% per year in EMPA-KIDNEY. In both cases the reduction was significant with the tested drug. The incidence of cardiovascular death or hospitalization for heart failure was 3% per year in DAPA-CKD (with a significant reduction of 29% per year with dapagliflozin) and 2.4% in EMPA-KIDNEY (with no significant effect of empagliflozin); cardiovascular death 1.7% in DAPA-CKD and 1.06% in EMPA-KIDNEY (in both cases without significant reduction with gliflozins) and death from all causes 3.1% in DAPA-CKD (with reduction significant with dapagliflozin) and 2.6% in EMPA-KIDNEY (no significant effect of empagliflozin).

In summary, EMPA-KIDNEY patients appear to have had a higher incidence of clinical renal endpoints (but note that the definition was not similar in both studies; in DAPA-CKD a persistent drop in glomerular filtration rate ≥ 50, vs. 40 % in EMPA-KIDNEY) but slightly better cardiovascular and global prognosis than those of DAPA-CKD. Reduction of the primary end point with empagliflozin occurred mainly in patients with UACR > 300 mg/g; 48% of patients had values below. Albuminuria has been shown to be, in different meta-analyses, an even stronger predictor than glomerular filtration rate in the context of kidney failure. It is possible that the lower rate of cardiovascular events in EMPA-KIDNEY compared to DAPA-CKD is associated with a clearly lower UACR, and therefore with a lower chance of demonstrating a significant effect on hospitalization for heart failure or cardiovascular death, and death of all causes. The authors report that a meta-analysis in plan for publication, considering the large studies with gliflozins in kidney failure, confirms an overall reduction of 23% for the composite of cardiovascular death or heart failure and 14% for cardiovascular death. This seems to close the circle on the remarkable effect of this family of drugs in patients with heart failure, diabetes, and kidney failure.

SAC moves forward to the face-to-face mode

La SAC avanza en la presencialidad

After great expectations, October 19 arrived, the long-awaited day of the reunion to share the wonderful world of Cardiology. The most fascinating and attended event of Argentine cardiology and the Spanish-speaking world. With it, the Society complements its primary objective of medical education. The return to face-to-face allowed us to have a dynamic and enriching exchange with each of the participants. Learning in society undoubtedly benefits us and helps us grow in the path of professional practice.

Because repeating the words of a renowned pedagogue, knowledge is socially constructed and leads to more advanced cognitive development. Even in times of artificial intelligence, one of the skills that will make a difference will be the ability to live learning.

The Argentine Congress of Cardiology fills all these needs.

In this particular year, we have exceeded all the most optimistic expectations. The great work of the Scientific Committee provided us with a balanced and updated program with a focus on daily practice. It was deployed in 131 Round Tables, in addition to Clinical Case Sessions, Conferences, Controversies, Dialogues with experts, Workshops, etc. In addition, 279 free topics and 6 consensuses were presented, which shows the great activity developed by our members. This, added to the presence of prominent national and international personalities, attracted more than 12 000 professionals from the field of cardiology, mainly doctors, nurses and technicians, and, as has happened in other years, with a strong participation of colleague's various countries of America. We have the support of the most prominent cardiology societies such as the American Heart Association, American College of Cardiology, New York ACC Chapter, European Society of Cardiology, Pan American Health Organization, Inter-American Society of Cardiology, South American Society of Cardiology, Word Heart Federation, etc.

The enthusiasm and eagerness to learn that was reflected in all the participants is contagious and prompts a renewed commitment of the SAC to Continuing Medical Education.

Dr. Héctor Deschle[MTSAC]
President of the Argentine Society of Cardiology

Argentine Journal of Cardiology
Revista Argentina de Cardiología

ARGENTINE SOCIETY OF CARDIOLOGY
Azcuénaga 980 - (C1115AAD)
CABA - República Argentina
Tel. (54 -11) 4961-6027/8/9
E-mail: info@sac.org.ar - Web site: www.sac.org.ar