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LETTER FROM THE EDITOR

The Argentine Journal of Cardiology Turns 90 Years Old

La Revista Argentina de Cardiología cumple 90 años

JORGE THIERER[1, MTSAC]

In 2024, the Argentine Journal of Cardiology turns 90 years old. Created in 1934, three years before the Argentine Society of Cardiology was founded, the Journal was the Society's official scientific and dissemination publication from the start. It is noteworthy that, contrary to what might be expected, it was not the Society that decided to launch the Journal, but rather the Board members of the Journal, authors and co-authors, who founded a Society. This just reflects the enormous drive and the vision of those outstanding men of our national cardiology. And, since then, the Argentine Journal of Cardiology has been the permanent place for publishing basic and clinical research, review and opinion articles and for discussing ideas. Over the years we have all felt the desire and pride to publish here.

But it is not easy or free. Keeping the Journal active and maintaining a standard of quality that is constantly being improved involves the work of many people, from the active search for material, the careful checking and correction of texts, statistical analysis, references and figures, to the accurate translation into English to provide a more universal content, and the tireless administrative task to comply with the regulations. When we compare what we initially received with the final result we deliver, which must satisfy authors, ourselves and readers, we feel that the job is done.... only to have to start again the next day, or the same evening, to prepare the next issue.

All our work is meaningless without senders and recipients. We are merely the transmission medium. And that is why we never tire of thinking about how to enhance the appeal of the Journal for each one. We understand the work at the Journal as an act of service and dedication. We want a better Journal because that means a better Society and a stronger national cardiology. And despite being 90 years old, the Argentine Journal of Cardiology remains young, fresh, and embellished. In addition to the advances mentioned by Carlos Tajer in his editorial, I would like to point out that we have recently added HTML to our traditional PDF format for improved visual presentation, introduced color to our publications, redesigned and updated the of editorial policies and developed our own website (rac.sac.org.ar), which is user-friendly and navigable, facilitating wider dissemination of our content. All these requirements have been demanded by the evaluators in order to meet the criteria to be indexed in PubMed. All the members of the Journal team, the Society's directors and the Society as a whole are motivated by the desire to be included in PubMed, which has been a long-awaited goal. For years, all those who have served on the Editorial Board (Oliveri, Doval, Tajer, Borracci, Pomés Iparraguirre, Trainini, Lowenstein, Arias, Lucas, Díaz, and many others) have worked tirelessly towards this goal. And so does the current Committee, from Claudio Higa, the Deputy Director, to each of the Associate Directors and members, with the irreplaceable help of Patricia López Dowling, the editorial coordinator, and the designers and translators always committed to their task. We hope that in the next presentation we will be able to achieve it. Effort and dedication have not been lacking.

Personally, working for so many years at the Journal allowed me to initially enter with awe, and over time, to become part of a circle of cardiologists whom I admired, with whom I could talk and exchange ideas, allowed me to learn about different disciplines, and, above all, made me feel useful. That is why I always saw the Journal as my place in the enormous space of the Society. Happy birthday!

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EDITORIAL

New Precordial Leads and Regional Vectocardiograms

Nuevas derivaciones precordiales y VCGS regionales

PEDRO BRUGADA[1]

A few months ago, I received an invitation from cardiologist Dr. Alejandro Bermejo to preface his book *Lógica Electrocardiográfica... desde casi cero* (Electrocardiographic logic… from almost zero). My initial reaction was very simple: a new book on electrocardiography? What could be written again, more than a hundred years after the development of the technique? My reaction changed immediately upon reading the manuscript. Alexander had broken all known rules and was bringing to the world a work with a totally unprecedented construction that blends the most intimate of cellular electrophysiology with micro- and macroscopic anatomical pathology and surface electrocardiogram to create a didactic product like I had rarely seen. How could my foreword contribute to the success of his creativity? Clearly, I wanted to show my appreciation for his efforts and the results obtained. And the only thing I could think of was to compare his work with that of cooks and musicians. Without repeating myself, I believe that these comparisons also apply to the work carried out by Drs. Mc Loughlin and Di Diego that is published today in this issue of the Argentine Journal of Cardiology. (1)

The kitchen of any restaurant has a wide variety of ingredients, but they are not infinite. When grouped according to their origin, a few key categories remain: vegetables, meat, fish, fruits and dairy products. Curiously, and despite this limitation of ingredients, every year dozens, if not hundreds, of cookbooks appear worldwide. Books with new ideas on how to cook, present, and mix different ingredients to create something new. And the result is, in general, indeed a new cuisine sometimes as different as the "molecular" cuisine of the famous Catalan Ferrán Adriá of "El Bullí", indisputably the Picasso of 20th and 21st century cuisine. Why, then, was I surprised by a new book on electrocardiography?

Things get worse with music. The ingredients are even scarcer than in the kitchen: just seven notes, and that is all. How do musicians manage to make us enjoy new songs every week? Well, in cooking as in music, it's all in the details. A tomato sauce can be spicy, sweet, salty, bitter or a combination of these flavors. A glass of milk with coffee has dozens of varieties: *macchiato, cappuccino, cortado*, Americano with milk, among many more varieties. In addition to the seven basic notes, music also incorporates flats and sharps, note duration and rhythm. This is how genius chefs and musicians surprise us with new recipes and songs every day.

This occurs consistently in any area of science. Creative researchers are always searching for and finding new details in normal or abnormal phenomena, details that contribute to scientific progress to improve the welfare of mankind. The combination of knowledge, curiosity and entrepreneurial spirit is what distinguishes the scientist who discovers from the scientist who spends his or her life repeating the experiments of others. Mc Loughlin and Di Diego are discoverers, as evidenced by the numerous publications on the field of electrocardiography. Again, they show us their expertise today with their study of the precordial bipolar leads. As they explain, while their use is not new, their interpretation is, especially when combined with regional vectocardiography. And as they also suggest, the current possibilities of computation and use of artificial intelligence allow for the integration of these leads into a standard ECG. As with cooking and music, the details that the authors present to us today will drive progress in electrocardiography. In modern cardiology, automatic interpretation of tracings is a universal fact. Although algorithmic interpretation of the electrocardiogram has very clear advantages, its introduction has resulted in a decline in the interest

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among new physicians in interpreting the tracings by themselves. Serge Barold (unpublished data) has clearly stated his great concern about the growing lack of interest in electrocardiography among resident physicians. Perhaps the article by Mc Loughlin and Di Diego will not raise the curiosity of all physicians, but it will be an important contribution when their leads are routinely incorporated into the automatic interpretation of the electrocardiogram. I encourage all cardiologists in an educational role to present this article to their residents to stimulate interest in electrocardiography. I will certainly do so with my residents.

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EDITORIAL

Those Happy Years

Aquellos años felices

CARLOS TAJER[1, MTSAC]

At the end of the 1990s, the Argentine Society of Cardiology decided to revamp the journal and invited Raúl Oliveri to lead this transformation. After a year under his leadership, I was invited to join the Editorial Board. Under his management, great changes were made in many aspects. At that time, authors were asked to submit their work on paper or diskettes, ¡¡but the publisher in charge rewrote the entire magazine and threw out the electronic support!! The secretarial work was carried out by Carmen Sarría, who taught us the various political aspects of the editorial management, and was complemented by Patricia López Dowling, with a level of excellence. Then, under the leadership of Hernán Doval, a new aesthetic and a commitment to opinion editorials took shape. Over the years, an Editorial Board was formed with Jorge Trainini, Jorge Lowenstein, Raúl Borracci, Jorge Thierer, and Horacio Pomés Iparraguirre, a remarkable group, and each meeting included an exchange on current intellectual issues, from chaos theory to art aesthetics. Let me tell you a little anecdote. Together with Hernán, we had published an article which had a p-value of 0.048, which was significant. We received a letter from Raul Borracci, a cardiovascular surgeon with a postgraduate training in biostatistics, with an elegant critique and a new calculation that brought the p-value to 0.051, which was not significant. We responded to him with an article that we still use for our research course, *The illusion of significant p*, commenting that the difference in probability between our statement and his was 3 in 1000, i.e., it either met the religious rule of significance or did not, but in terms of truth-error it was irrelevant. It was clear to us that Raul had a fine mind and critical vocation, so we invited him to join the journal, of which he became the Editor and contributed to on several occasions. Under Hernán's leadership, we started the so far epic and unsuccessful journey for being included in the PubMed. We studied the subject in detail and took successive steps: inclusion of the journal in other international indexes (Scielo, Embase, Scopus), full publication in Spanish and English, electronic format, addition of foreign colleagues to the Editorial Board, and consultation with companies. I started to participate in the SAC in 1983 in the Council of Cardiovascular Urgencies, and I developed several tasks in different areas, such as the creation of the Research Committee, but my great dream was to become the Director of the Journal, which I effectively exercised between 2009 and 2012. It was an enjoyable time, with a lot of editorial and creative work, and we developed different strategies to improve the flow of original research, such as thematic issues by invitation and others. We even created a blog to share stories and experiences of SAC members. The spirit of the group has always been one of cooperation with all authors to improve their work when necessary. Sometimes I almost completely rewrote some papers that had interesting data but were not publishable, with long explanations to the authors who accepted them. I undertook to write the bimonthly editorials according to tradition, which allowed me to delve into very different subjects. For example, I wrote an article on metaphors for thinking about medicine, which I had reviewed by Professor Guiomar Capuscio, a Head Professor with a PhD in Medicine, and another on evolutionary medicine, a journey into evolutionary biological thought, always enriched by the debates in the committee. Several of these articles were compiled in two books that were later published by El Zorzal and were very well received. In 2012, I was offered a political career, vicepresident and president of the SAC, which was neither a personal ambition nor a dream, and which turned out to be a very complex experience for which I was not properly prepared. I remember those years at the Journal with great affection and nostalgia, and I remain committed to collaborate in the challenges of today's new world of networks and liquid thinking.

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ORIGINAL ARTICLE

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

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

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ABSTRACT

Background: The current crisis in the national healthcare system is impacting on the development of cardiology practice.
Objectives: To know the current situation of cardiologists in their professional practice in terms of working conditions, satisfaction with their salaries and their representation by the Argentine Society of Cardiology, and their opinion on forms of continuing medical education.
Methods: A closed anonymous survey was sent via the Society corporate email, social networks, and direct WhatsApp contacts. The RedCap platform was used. The Likert scale was implemented in multiple choice answers.
Results: A total of 393 cardiologists were surveyed; 27% were female. The mean age was 56±9 years. Fifty percent of cardiologists worked in public or private healthcare institutions without medical residency, an average of 40±10 hours per week. A high percentage believed it would be useful to create care networks for main diseases. More than 90% felt that they are not adequately paid and that they are not properly represented by the trade union. A total of 89.9% considered that the medical residency is the best system of training. Between 76.1% and 80.2% were in favor of completing the residency with a doctorate or master's degree, respectively. Finally, 53% agreed with the need for recertification.
Conclusions: Medical professional practice is evenly distributed between public and private institutions, with and without medical residency. Most cardiologists do not work in care networks, but a high percentage express the need and willingness to do so.
Most cardiologists are dissatisfied with their salaries, and also feel they lack an adequate trade union representation.
Regarding postgraduate education and training, as in previous surveys, it is confirmed that the medical residency is the best system of training and it should be complemented by a doctorate and/or master's degree in the specialty in view of the constant updating and advances in cardiology.

Keywords: Health policy - Cardiology education - Medical training - Cardiology - Residency - Goals of care

RESUMEN

Introducción: La crisis actual del sistema de salud nacional afecta el desarrollo de la práctica cardiológica.
Objetivos: Conocer la situación actual de los cardiólogos en su actividad profesional respecto a las condiciones de trabajo, conformidad con su remuneración y representación ante la Sociedad Argentina de Cardiología, y su opinión en cuanto a las formas de educación médica continua.
Material y métodos: Encuesta cerrada, anónima, enviada a través del mail corporativo de la Sociedad, redes sociales y contactos directos de WhatsApp. Se utilizó la plataforma RedCap. Se implementó la escala de Likert en las respuestas que tenían múltiples opciones.
Resultados: Se encuestó a 393 cardiólogos, el 27 % mujeres. La edad media fue 56 ± 9 años. El 50 % trabaja en el ámbito público o privado sin residencia, una media de 40± 10 horas semanales. Un alto porcentaje cree conveniente generar redes de atención en

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las principales patologías. Más del 90 % piensa que no está correctamente remunerado y que no tiene una representación gremial adecuada. El 89,9 % considera que la residencia es el mejor sistema formativo y entre el 76,1 % y el 80,2 % aprueba completarlo con doctorado o máster de posgrado, respectivamente. Finalmente, 53 % está de acuerdo con la necesidad de la recertificación.
Conclusiones: El accionar médico está distribuido de manera similar entre entidades públicas y privadas, con y sin residencias médicas. La mayoría no trabaja en redes de atención, pero en un alto porcentaje expresa la necesidad y adherencia a realizarlo. La mayor parte de los cardiólogos está disconforme con su remuneración, y siente que carece de una representación gremial adecuada. Con respecto a la educación y formación de posgrado, se ratifica, como en encuestas previas, que la residencia es el mejor sistema formativo y debería complementarse con doctorados y/o maestrías de la especialidad atento a la permanente actualización y progreso de la cardiología.

Palabras claves: Política sanitaria - Educación cardiológica - Formación médica - Cardiología -Residencia - Metas de atención

INTRODUCTION

In 2023, a year of changes in Argentina –a presidential election, rising inflation and shortly after the end of the COVID-19 pandemic– in which physicians were able to express their concerns, there were also debates about how cardiologists are suffering from this crisis (which is reflected in their fees, the daily treatment of patients and the difficulty of ensuring that this is optimal, based on the best available evidence), and how this is reflected in the efforts and desires of colleagues to continue updating, research and improvement studies. Therefore, the Health Policy Area of the Argentine Society of Cardiology (APS SAC) conducted a first survey on three points on which more information is needed: the current situation of cardiologists in their professional practice, their perceptions of work conditions and remuneration and their representation in the Society, and their opinion regarding training in their specialty and continuing medical education activities.

METHODS

An observational, cross-sectional study was performed to evaluate different settings of cardiologists' lives in Argentina. A questionnaire validated by the Ethics and Research Committee of the SAC was used, according to different metric characteristics. The survey was conducted between June and September 2023 and was anonymous.

The questionnaire was self-administered, and sent via the Society corporate email, social networks, and WhatsApp contacts. The RedCap platform was used in accordance with the Society recommendations.

The questionnaire consisted of 16 questions separated into three domains or dimensions that measured the following: 1) the cardiologist's relationship with the Society (5 questions), 2) the quality and professional recognition of the cardiology activity (7 questions), and 3) continuing medical education (4 questions). Most of the questions were asked with a five-option Likert-type ordinal response scale. (1) In addition to the questionnaire, demographic (age, sex) and occupational (income level, workload) characteristics were collected to relate them with the other domains.

Descriptive statistics were used; qualitative variables were expressed as frequencies and percentages, and quantitative variables as mean and standard deviation.

A link to the survey is attached to Annex 1.

RESULTS

Sample demographic characteristics

A total of 393 cardiologists were surveyed; 109 (27%) were female and the mean age was 56±9 years. Of the respondents, 320 (81%) were members of the SAC, and 34 (9.67%) did not belong to any scientific entity. Ninety-five (95) respondents (24.9%) were members of the SAC and another scientific entity. Of all the respondents, 276 (70.73%) lived in the Metropolitan Area of Buenos Aires (AMBA), that is, the Autonomous City of Buenos Aires and some adjacent districts of the province of Buenos Aires.

Most of them had more than 20 years of professional practice (Figure 1). An average of 40 hours of work per week was reported. Fifty percent (50%) of cardiologists worked in public or private healthcare institutions with medical residency (Figure 2).

Regarding the scope of care, most of cardiologists referred that they should focus on primary (prevention and promotion of cardiovascular health) and secondary care (diagnosis and treatment of cardiovascular diseases), and only 33 (8.4%) cardiologists referred that they should only work in critical care areas.

When cardiologists were asked whether they should work in cardiovascular disease networks, the vast majority answered in the affirmative (373, 95%), however, only a half was part of a network (207, 52.7%).

Regarding remuneration and economic satisfaction, more than 90% of a total of 371 respondents disagreed with their incomes and salary (Figure 3).

The lower their salaries, the greater their personal dissatisfaction and the worse their vision of the future, which was clearly reflected in the question on how professionals see themselves in the next five years: 289 (73.5%) saw themselves in the same or worse conditions than today.

Finally, 365 respondents (92.8%) considered that economic, social and trade union representation of cardiologists is inadequate.

When asked about the APS SAC, 300 (76%) answered that they did not know it or did not think they know enough about it; 17% of them answered in the affirmative, 4% knew it, but they considered it irrelevant, and the rest did not answer. However, 329 (83%) agreed that the SAC should evaluate and actively participate in the hierarchization and remuneration of the medical profession. (2)

Finally, in terms of continuing medical education, when asked about the best system of medical specialty training, 353 (89.9%) agreed that it was the residency. In the context of the current debate on the best sys-

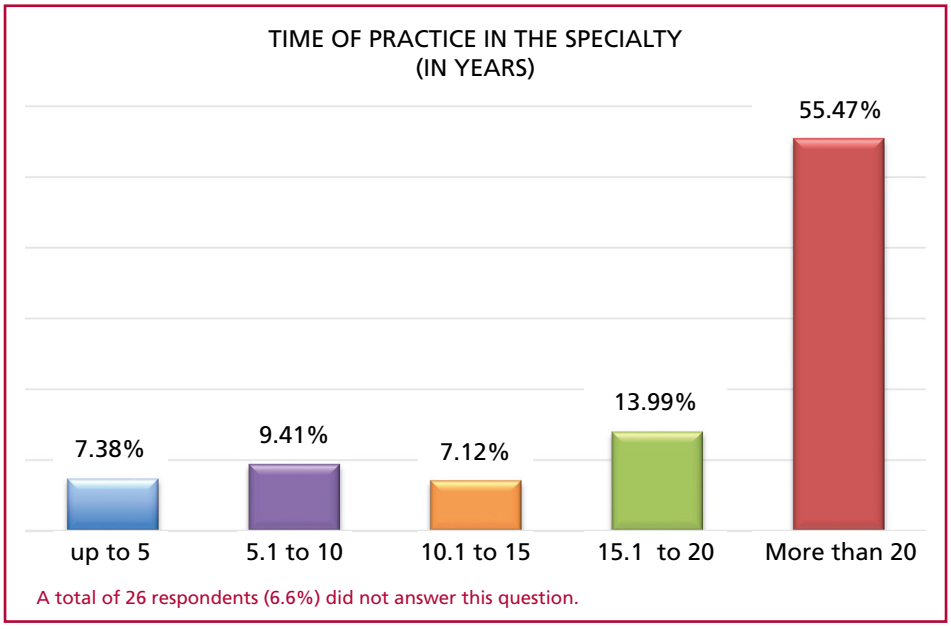

Fig. 1. Time of professional practice, in years.

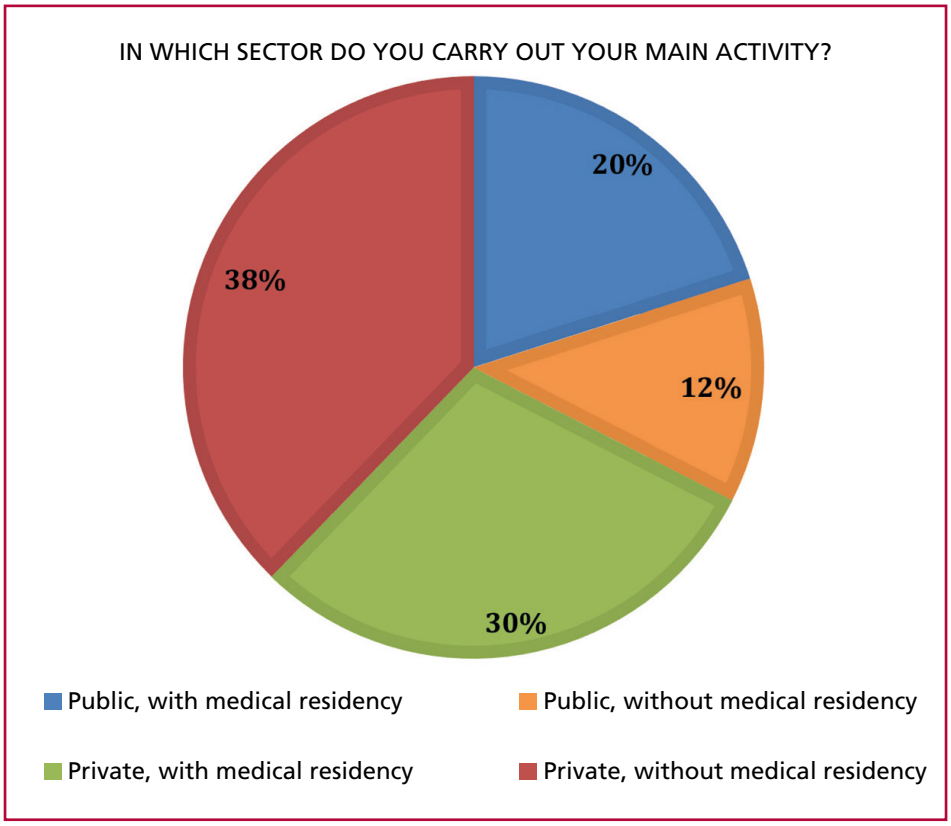

Fig. 2. Cardiology practice scope.

tem of specialty training and the type of residency that should be developed, the responses were as follows: 59 (15%) answered that it should be a Cardiology course following the residency in Internal Medicine; 37 (9.2%) were in favor of the residency in Cardiology following the residency in Internal Medicine; 37 (9.4%) agreed with direct entry into the residency in Cardiology; and 253 (64.4%) agreed with a 1-year residency in Internal Medicine followed by a 3-year residency in Cardiology. Seven respondents did not answer this question.

Regarding the new current scenarios for postgraduate training and, in particular, continuing education,

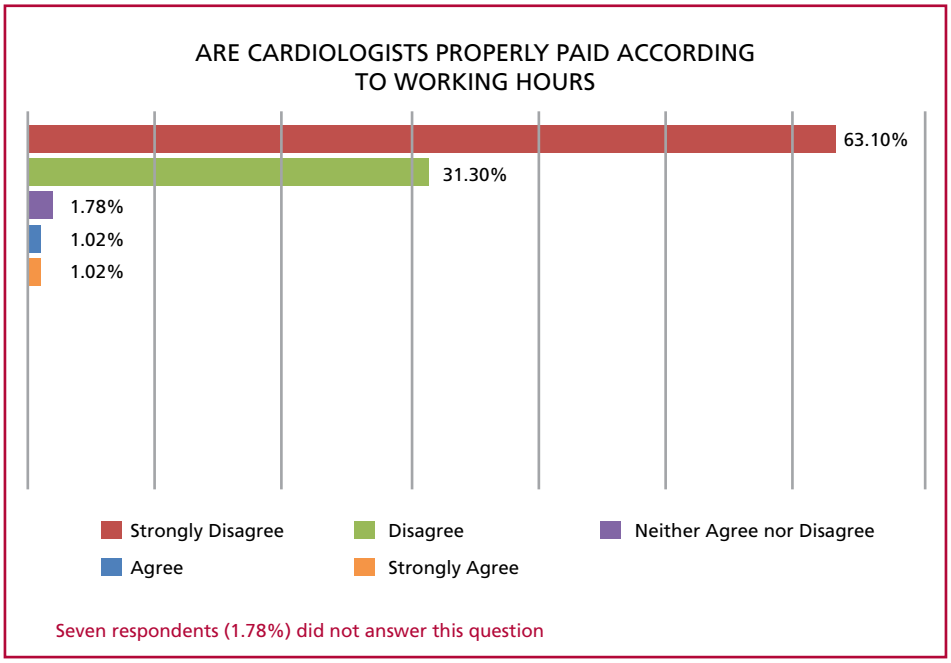

Fig. 3. Cardiologists' views on remuneration in relation to working hours

299 (76.1%) and 315 (80.2%) were in favor of a doctorate and master's degree training, respectively. (3)

To conclude, we asked about the professional peer recertification: 212 (53%) agreed/strongly agreed, and only 1 out of 5 disagreed or strongly disagreed with the professional recertification process.

DISCUSSION

According to the survey, cardiologists believe that care should be focused on primary and secondary care, an aspect that confirms the position of the SAC for the last quarter of the century, which has defined the cardiologist as a physician focused on cardiovascular prevention in primary and secondary care (4,5). Another striking aspect is the strong conviction to work in care networks. In this sense, there are initiatives in Argentina (6-8) similar to those in the European countries, (9) such as Spain, Germany, Italy and also in our own country, where the "Stent for Life" network is laying the foundations for the construction of a care system for acute myocardial infarction. (10) The networks should help to increase knowledge and promote the development of new strategies for a better management of the different cardiac diseases.

The lack of satisfaction with remuneration is clear and has been identified in several reports over 20 years. Today, it is exacerbated by the increased burden of training, work scenarios and demands. Physicians must respond satisfactorily to the diverse demands of patients, who are increasingly interested in and knowledgeable about various aspects of their health. All this must be done without any remuneration commensurate with a consultation time that satisfies both doctors and patients, at any level of care. (11,12)

As cardiologists, we are not unaware of the current situation in our country, so we have decided to evaluate our situation in particular. From our survey and comparing some points with a similar survey conducted in 2014 by Borracci et al., we may conclude that the relationship between salary and satisfaction is maintained in a direct way: the higher the salary, the higher the satisfaction. (13)

In terms of personal development, cardiologist satisfaction, and quality and time of consultations, the concept of the Triple Aim concept (improving the patient´s experience, improving the clinical outcomes of the population, reducing per capita costs of health care), (14,15) has given way to the concept of the Quadruple Aim, which necessarily includes physician satisfaction, with equal emphasis on quality of care, system resources, patient satisfaction and professional satisfaction. (16)

Regarding the postgraduate training system, the vast majority recognize the residency as the best training system. (17,18) Nevertheless, and according to the CONAREC survey presented at the last Congress on Cardiology, 83% of future cardiologists are considering the possibility of emigrating to practice the profession in other countries. (19)

The survey revealed dissatisfaction in many areas of cardiology. In this sense, at the time of writing this document, an ad hoc group called "Cardiología Unida" (United Cardiology) is working. This group is led by several scientific entities, including the Argentine Society of Cardiology (SAC), the Argentine Federation of Cardiology (FAC), the Argentine Cardiology Foundation (FCA), the Argentine College of Cardiology (CAC), the Argentine College of Interventional

Cardioangiologists (CACI), the Argentine College of Cardiovascular Surgeons (CACCV) and the Argentine Civil Association of Vascular Surgery and Angiology (ACCVAA). (20)

It is clear that the concept of the Quadruple Aim appears to be a complex objective that involves many different actors and constantly challenges us as a society in terms of updating, training and new aspects of quality and patient-centered management. (21)

We believe it is important to highlight that the Argentine Society of Cardiology has a relevant role to play as an advisory body to official organizations in terms of optimizing the quality of care and training, remuneration and recertification of professionals in their specialty. In this sense, the Health Policy Area (APS) is a valuable tool for the relationship between our Society and those organizations. However, it is necessary to recognize that more than half of the respondents are not aware of the activities of the APS or do not consider them relevant. Nevertheless, the vast majority answered that the SAC should evaluate and actively participate in the hierarchization and remuneration of the medical profession. (2)

This should lead us to reflect on the need for greater implementation and promotion of activities and proposals related to the quality of care, continuing medical education and the hierarchization of the cardiologist medical profession, through the joint work of the APS and the Recertification Area and the joint task with the Argentine College of Cardiology (CAC) regarding appropriate remuneration.

Limitations

Given the volatility of the Argentine currency and the many discussions in the public and private sectors about salaries and a potential increase for cardiologists, in the survey, we did not ask for the amount earned by each colleague.

The survey provides insights into the cardiologists' thinking, but it may not be definitive in a changing scenario.

Most of the cardiologists who answered the survey were from the AMBA.

Young and female cardiologists were under-represented.

The survey did not include other stakeholders in cardiovascular health.

CONCLUSIONS

Medical professional practice is evenly distributed between public and private institutions, with and without medical residency. Most cardiologists do not work in care networks, but a high percentage express the need and willingness to do so. Most of them are dissatisfied with their salary and feel that they are not properly represented by the trade union.

The medical residency is still considered the best system of training, and it is accepted that it should be complemented by postgraduate medical education through a doctorate and/or master's degree in the specialty.

Finally, it should be noted that most cardiologists consider that the SAC should evaluate and actively participate in the hierarchization and remuneration of the medical profession.

Conflicts of interest

None declared.

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

Acknowledgments

Research Area of the Argentine Society of Cardiology.

Annex I. Health policy area survey

http://redcap.sac.org.ar/redcap/surveys/?s=HEWTKTPEKR978KJF

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ORIGINAL ARTICLE

Presence of Dysautonomia as a Predictor of Structural Heart Disease in Patients with Chagas Disease

Presencia de disautonomía como predictor del desarrollo de cardiopatía estructural en pacientes con enfermedad de Chagas

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ABSTRACT

Background: Several studies have demonstrated the presence of autonomic dysfunction in early stages of Chagas disease (ChD). The Valsalva maneuver (VM) has been widely used to assess autonomic function in many conditions. The Valsalva ratio (VR), which the ratio of maximal to minimal heart during the VM, is one of the most widely used tests for assessing autonomic function. The role of dysautonomia assessed by the VR as a predictor of early development of structural heart disease in Chagas disease patients without overt heart disease has not been well studied.
Objective: The aim of this study was to evaluate whether the VR can predict early development of structural cardiac abnormalities during the follow-up of patients with ChD.
Methods: Patients with positive serology test for Chagas disease were screened. Patients with abnormal electrocardiogram (ECG), abnormal 24-hour Holter monitoring or abnormal echocardiogram were excluded. The VM was performed with continuous recording of the R-R interval on the ECG. The VR was calculated by dividing the longest RR interval after VM by the shortest RR interval during VM. A VR <1.1 was considered abnormal result.
The primary end point was the development of structural heart disease, defined as any of the following: left ventricular (LV) dilatation (LV diastolic diameter > 60 mm in men or > 55 mm in women), LV dysfunction [LV ejection fraction (EF) drop > 10 points or LVEF < 50%], complex ventricular arrhythmia or second-degree atrioventricular block type Mobitz II or greater.
Results: A total of 200 patients were included; mean age was 45 ± 8 years and 44% were female. Abnormal VR occurred in 24% (n = 48). Median follow-up was 38 months (interquartile range, IQR, 19 - 43). The primary end point occurred in 4.5% (n = 9).
On multivariate analysis, abnormal VR was an independent predictor of the primary end point (HR 3.81, 95 % CI 2.81- 5.92; p=0.011). The area under the ROC curve was 0.77 (95% CI 0.63-0.92).
Conclusions: An abnormal VR at baseline is a predictor of early development of structural heart disease in patients with ChD considered to be stage 0, with moderate discrimination capacity.

Keywords: Chagas disease - Dysautonomía - Valsalva ratio - Prognosis

RESUMEN

Introducción: Varios estudios han demostrado la presencia de disfunción autonómica en etapas tempranas de la enfermedad de Chagas (ECH). La maniobra de Valsalva (MV) ha sido ampliamente utilizada para evaluar la función autonómica en diversas patologías. El Índice de Valsalva (IV), la relación entre la máxima taquicardia y bradicardia inducidas por la MV estándar, es una de las pruebas más utilizadas para evaluar la función autonómica. El papel de la disautonomía evaluada mediante el IV como predictor temprano del desarrollo de cardiopatía estructural en pacientes con Chagas sin cardiopatía demostrable ha sido poco estudiado.
Objetivo: Evaluar si el IV es un predictor del desarrollo temprano de alteraciones estructurales cardíacas en el seguimiento de pacientes con ECH
Material y métodos: Se incluyeron prospectivamente pacientes con serología positiva de Chagas. Se excluyeron los pacientes con anormalidades en el electrocardiograma (ECG), el ECG Holter de 24 horas o el ecocardiograma. Se realizó una MV con registro continuo del intervalo R-R en el ECG. El IV se calculó dividiendo el intervalo RR más largo después de la MV por el intervalo RR más corto durante la MV. Se consideró IV anormal un valor <1,1. Fue punto final primario del estudio el desarrollo de cardiopatía estructural, definido como uno de los siguientes: dilatación del ventrículo izquierdo (VI) (diámetro diastólico > 60 mm en hombres o >55 mm en mujeres), deterioro de la función ventricular (caída > 10 puntos de la fracción de eyección -FEVI-, o FEVI <5 0%), arritmia ventricular compleja o bloqueo auriculoventricular de segundo grado Mobitz II, o mayor.

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Resultados: Se incluyeron 200 pacientes, edad 45 ± 8 años, 44 % mujeres. Se encontró IV anormal en el 24% (n=48). La mediana de seguimiento fue de 38 meses (rango intercuartílico, RIC, 19-43). El punto final primario se presentó en el 4,5 % (n=9). En el análisis multivariado, el IV anormal fue un predictor independiente del punto final primario (HR 3,81, IC 95 % 2,81- 5,92; p=0,011). El área bajo la curva ROC fue de 0,77 (IC95% 0,63-0,92)
Conclusiones: La presencia de IV anormal basal es un predictor de desarrollo de cardiopatía estructural en pacientes con ECH estadio 0, con una capacidad de discriminación moderada..

Palabras claves: Enfermedad de Chagas - Disautonomía - Índice de Valsalva - Pronóstico

INTRODUCTION

Chagas disease (ChD) remains an important health issue in Latin America and in recent decades it has also spread to other regions including the United States and Europe due to migratory processes. In Argentina, it is estimated to affect between 1.5 and 2 million people, with between 350 000 and 500 000 suffering from some degree of heart disease. (1,2)

The chronic stage of ChD has a variable period in which there is no evidence of structural heart disease or involvement of other organ. This period is known as indeterminate or chronic ChD without overt structural heart disease. (3,4) However, about 30% of patients with positive serology will develop some type of structural heart disease along the course of the disease. In these patients, risk assessment represents an important challenge.

Several studies have demonstrated the presence of autonomic dysfunction in early stages of ChD. (5-8) These abnormalities could be involved in the progression of the disease.

The Valsalva maneuver (VM) has been widely used to assess autonomic function in many conditions. (9) The Valsalva ratio (VR), which is the ratio of maximal to minimal heart during the VM, is one of the most widely used tests for assessing autonomic function, because it is simple, reproducible and inexpensive. (9,10)

The role of dysautonomia assessed by the VR as a predictor of early development of structural heart disease in ChD patients without overt heart disease has not been well studied.

The aim of this study was to evaluate whether the VR, as an expression of dysautonomia, can predict early development of structural cardiac abnormalities during the follow-up of patients with ChD.

METHODS

We conducted a prospective study in a single center with a follow-up program for patients with ChD. Between July 2016 and July 2018, patients with at least two positive serology tests for Trypanosoma cruzi (indirect hemagglutination, ELISA, or indirect immunofluorescence) were included in the study. A medical record was taken to all the patients, including physical examination and electrocardiogram (ECG), Doppler echocardiography and 24-hour Holter monitoring.

To be included, patients should not have overt heart disease, defined as absence of cardiovascular symptoms or signs, normal cardiovascular physical examination, normal ECG, echocardiogram without significant abnormalities and 24-hour Holter monitoring within normal parameters. Patients with a history of hypertension, diabetes mellitus, thyroid disease, ischemic heart disease, neurologic disease or kidney failure were excluded.

Patients who met the inclusion criteria were asked to perform the standard VM. The standard procedure is as follows: the patient lies in the supine position and is asked to blow through a mouthpiece connected to a manometer until reaching an expiratory pressure of 40 mm Hg. Once this pressure is reached, the patient maintains it for 15 seconds under constant supervision. Then, the mouthpiece is released and the patient continues breathing normally. An ECG is continuously recorded throughout the procedure, starting 15 seconds before expiration and continuing for 15 seconds thereafter.

The VR was calculated by measuring (in milliseconds) the shortest RR interval during the maneuver (denominator) and the longest RR interval shortly after the maneuver (numerator). Thus, the formula is: longest RR interval shortly after the maneuver/shortest RR interval during the maneuver = VR (Valsalva ratio). A VR < 1.1 was considered an abnormal result.

Patients were monitored periodically with scheduled medical interviews according to the institutional ChD follow-up program based on medical criteria.

The primary end point was the development of structural heart disease, defined as any of the following: left ventricular (LV) dilatation (LV diastolic diameter > 60 mm in men or > 55 mm in women), LV dysfunction [LV ejection fraction (EF) drop > 10 points or LVEF < 50%), complex ventricular arrhythmia or second-degree atrioventricular block type Mobitz II or greater.

The study was approved by the institutional review board and all the patients signed an informed consent form before being included.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as percentage. Continuous variables with normal distribution were compared using the Student's t test and the Wilcoxon test was used for variables with skewed distributions. Categorical variables were compared using the chi-square test and Fisher's exact test if any of the variables had an expected frequency < 5.

The Cox proportional hazards model was used for univariate analysis of the end point of development of structural heart disease. The VR was included as a continuous variable and as dichotomous variable (normal or abnormal). Those variables that resulted in significant differences between the groups with and without dysautonomia were also included. Predictor variables with a p value < 0.10 on the univariate analysis were included in a multivariate model. A survival analysis was performed using the Kaplan-Meier method for the VR dichotomized into normal/abnormal.

A ROC curve was constructed to establish the area under

the curve (AUC) and evaluate the discriminative capacity of the VR. A p value < 0.05 was considered statistically significant. All calculations were performed using Epi-Info 7 and Statistix 8 software packages. Epidat 3.1 was used to construct the ROC curve.

RESULTS

Of 280 patients evaluated, 80 were excluded for presenting any of the exclusion criteria. A total of 200 patients were included; mean age was 45 ± 8 years and 44% were women. Table 1 shows the baseline characteristics of the population. The VR was 1.22 ± 0.12 and was abnormal in 24% of the patients (n = 48).

The abnormal VR group had higher E/e' ratio on the Doppler echocardiogram (9.48 ± 2.5 vs. 7.1 ± 1.8, p <0.001) and lower S-wave in tissue Doppler imaging (0.08 ± 0.02 vs. 0.10 ± 0.02 cm/s, p = 0.023). In addition, there was trend at the limit of significance in baseline diastolic blood pressure (DBP) and maximum heart rate (HR) reached in the baseline 24-h Holter monitoring. The rest of the variables had no differences between the groups.

Median follow-up was 38 months (interquartile range 19 - 43) and the end point of development of structural heart disease occurred in 4.5% (n=9). Of these, 3 patients had increased diastolic diameter without ventricular dysfunction, LVEF decreased in 1, 4 had ventricular arrhythmia and 1 patient had second-degree AV block. There were no deaths during follow-up and only 1 patient was hospitalized for a scheduled pacemaker implantation.

Table 2 shows the univariate and multivariate analysis for the primary end point.

On multivariate analysis, both VR as a continuous variable (HR 1.02, 95 % CI 1.01-1.06, p = 0.042) and abnormal VR (HR 3.81, 95 % CI 2.81- 5.92; p=0.011) were independent predictors of development of heart disease. Figure 1 shows the Kaplan-Meier curve and the ROC curve. The area under the ROC curve was 0.77 (95% CI 0.62- 0.93) (Figure 2).

DISCUSSION

In our study, we found that in a population of patients with ChD without overt heart disease, an abnormal VR was associated with early development of structural heart disease at a relatively short follow-up period of 3 years. Patients with an abnormal VR had a more than 3.5-fold increased likelihood of developing early heart disease, with moderate discrimination ability (AUC 0.77).

Over 20 years ago, Olivera et al. (11) found a reduction in VR among patients with ChD without overt cardiovascular disease compared to healthy controls. In addition, during follow-up, abnormal VR was associated with the development of second-degree AV block in ChD patients. Later, Ribeiro et al. (12) published a meta-analysis of 7 studies with more than 350

Table 1. Baseline characteristics

	Total (n=200)	Normal VR (n=152)	Abnormal VR (n = 48)	p
Age (years)	47 (6)	48 (5)	46 (5)	0.176
Women, n (%)	89 (44.5)	67 (44)	22 (45)	0.655
SBP (mm Hg)	117 (14)	117 (14)	116 (15)	0.712
DBP (mm Hg)	68 (11)	69 (10)	66 (13)	0.053
Valsalva ratio	1.22 (0.12)	1.32 (0.10)	1.01 (0.02)	<0.001
24-h Holter monitoring				
Mean HR	73 (8)	73 (8)	72 (7)	0.423
Minimum HR (bpm)	52 (6)	52 (6)	53 (4)	0.825
Maximum HR (bpm)	120 (15)	121 (22)	115 (15)	0.052
Echocardiogram				
LVDD (mm)	47 (4.2)	47 (4.4)	46 (3.7)	0.721
IVS (mm)	9.2 (1.1)	9.2 (1.1)	9.5 (2.2)	0.232
LAA (cm2)	17.5 (3.9)	18.1 (3.6)	17.4 (4)	0.303
LVEF	63 (5)	63 (5)	63 (5)	0.675
E/A ratio	1.26 (0.43)	1.21 (0.4)	1.28 (0.35)	0.324
E/e' ratio	7.9 (3.1)	7.1 (1.8)	9.48 (2.5)	<0.001
S-wave TDI (m/s)	0.09 (0.02)	0.10 (0.02)	0.08 (0.02)	0.023

DBP: diastolic blood pressure; HR: heart rate; IVS: interventricular septum in diastole; LAA: left atrial area; LVEDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; TDI: Tissue Doppler imaging; VR: Valsalva ratio
Quantitative variables are presented as mean (SD).

patients (including the study by Olivera previously mentioned) and found that the VR was decreased in patients with ChD without overt structural heart disease compared to patients without ChD.

The VR assesses the integrity of cardiac autonomic function based on heart rate responses associated with the baroreflex mechanism which is responsible for stabilizing blood pressure. (9) It is a simple, reproducible, inexpensive method that does not require major equipment. However, it is important to note that the VM involves a complex mechanism of autonomic regulation which encompasses the sympathetic and parasympathetic nervous systems. During the maneuver, blood pressure and bradycardia occur simultaneously, while at the end of the test blood pressure decreases and heart rate increases. Thus, a normal VR reflects an adequate baroreceptor response to the rise and fall of blood pressure, while a reduced VR reflects vasovagal dysfunction. (13,14)

Traditionally, a VR > 1.5 has been considered normal. (10) However, some studies have considered an abnormal VR when it is ≤ 1.1. (15-17) We decided to use this latter cut-off point because it is more specific of autonomic dysfunction. (17)

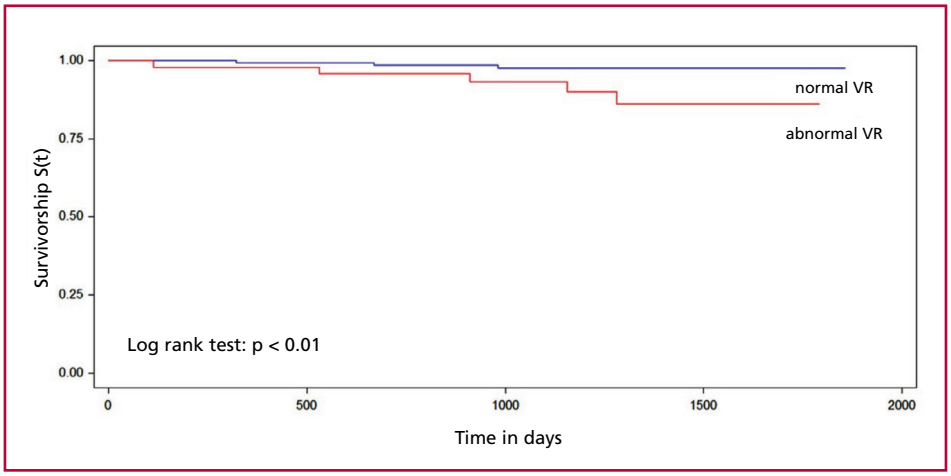
Impaired autonomic function has also been demonstrated in early stages of ChD compared to controls using other methods, such as heart rate variability, respiratory sinus arrhythmia magnitude (18,19) or chronotropic incompetence during exercise stress test. (19) These abnormalities occur early in the course of the disease and before the development of left ventricular dysfunction. (20) However, these tests have not evaluated whether the presence of dysautonomia predicts progression to ChD. Recently, a small study found a higher rate of exercise-induced ventricular arrhythmias and autonomic dysfunction in ChD patients without overt heart disease compared to controls without ChD. (21) Moraes et al. analyzed a cohort of 550 elderly patients with positive serology for ChD in Brazil, followed-up for 14years and found that the presence of dysautonomia was not independently associated with sudden death after adjusting for age and cardiovascular risk factors. (22)

The pathogenesis of vagal dysfunction remains unclear. Some authors have described denervation related to parasympathetic neuroganglionar lesions probably due to inflammation. (23) The role of circulating autoantibodies against muscarinic receptors that could cause desensitization and/or downregulation of these receptors has also been studied. (8) Several studies have shown increased activity of anti-M2 and anti-β1 antibodies in ChD patients with evidence

Table 2. Univariate and multivariate analysis for the primary end point

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
VR (continuous)	1.03	1.01 – 1.04	0.042	1.02	1.01-1.06	0.042
Abnormal VR	4.31	2.76 – 6.22	0.012	3.81	2.81 – 5.92	0.011
E/e' ratio	1.03	0.99-1.04	0.074	1.01	0.93-1.06	0.212
S-wave TDI	1.01	0.93-1.02	0.224	--	--	--

95% CI: 95% confidence interval: HR: hazard ratio: TDI: VR: Valsalva ratio: TDI: Tissue Doppler imaging



VR: Valsalva ratio

Fig. 1. Kaplan-Meier curve: normal/abnormal VR for the primary end point of development of structural heart disease.

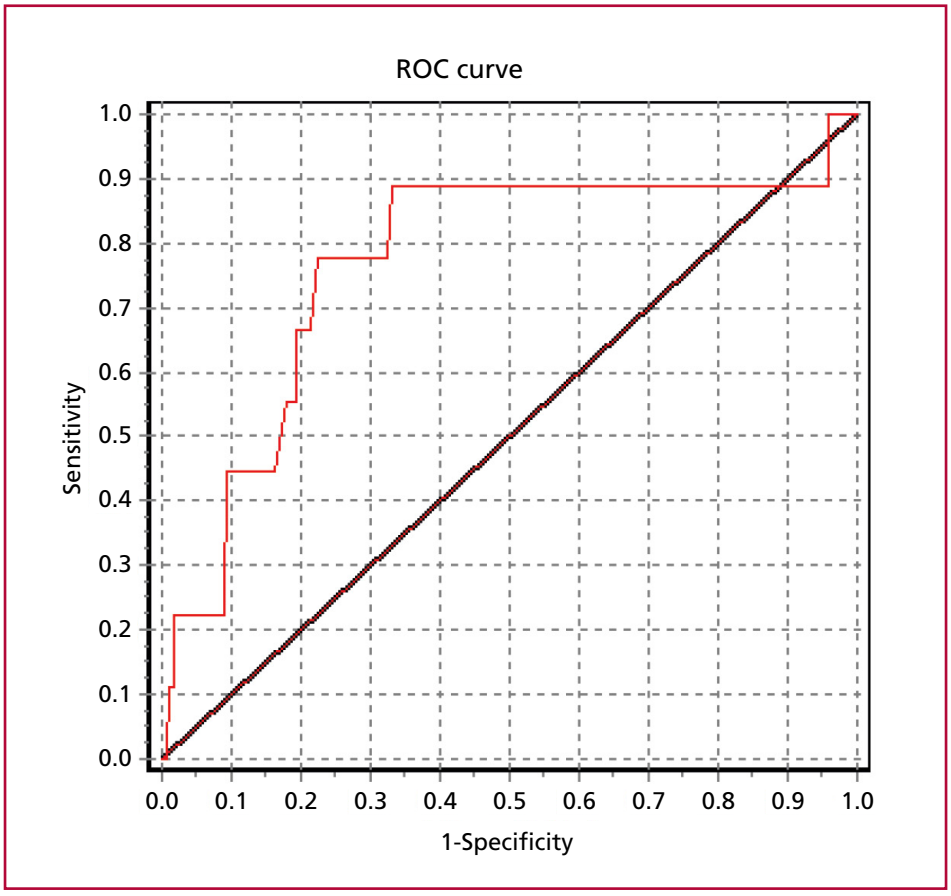


Fig. 2. ROC curve. VR as a continuous variable for the primary end point of development of structural heart disease.

AUC: 0.77 (95% CI: 0.62-0.93)
VR: Valsalva ratio

of dysautonomia but with preserved ventricular function. (5)

In the present study, we found that progression to structural heart disease was 4.5% in slightly more than 3 years, which is about 1.4% per year. A recently published meta-analysis that included 23 studies found an average progression rate of 1.9% per year in patients with indeterminate ChD. This review included studies conducted in Argentina and Brazil more than 10 years ago. (24) More recently, a cohort of patients with indeterminate ChD showed a progression rate of 1.48% per year. (25) Notably, the events were mild, and no patients died during follow-up. This is similar to the systematic review by Gonzalez et al. , which revealed a remarkably low incidence of sudden cardiac death in patients with ChD without overt disease. (26)

Study limitations

Our study has some limitations. First, it is a single-center study, with a relatively short follow-up period for the type of disease. Although the progression rate was similar to the one reported, the small number of events limits the analysis. Dysautonomia was assessed using a single method, the VR. Most studies used more than one method to assess dysautonomia. We decided to use the VR because it is inexpensive, easy to perform and quite feasible to use in daily practice.

CONCLUSION

An abnormal baseline VR is a predictor of early development of structural heart disease in patients with ChD considered to be stage 0, with moderate discrimination ability.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Endovascular Revascularization in Chronic Limb-Threatening Ischemia

Revascularización endovascular en isquemia crítica de miembros inferiores

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ABSTRACT

Background: Management of chronic limb-threatening ischemia (CLTI) is based on surgical or endovascular arterial revascularization. Over the past two decades, the widespread adoption of endovascular treatments has increased their application in patients with CLTI.
Objective: The aim of this study was to describe the results of infrainguinal endovascular revascularization of patients with CLTI due to chronic obstructive arteriopathy.
Methods: We conducted a retrospective analysis of a prospectively followed cohort of 211 patients with CLTI undergoing endovascular treatment between January 2015 and December 2020.
Results: Of the total angioplasty procedures performed, 100 were below the knee (47.4%), 63 were above the knee (29.9%) and 48 were combined (22.7%) procedures. A total of 167 patients (79.2%) underwent primary balloon angioplasty procedures, and stents were placed in 44 (20.8%) cases. Mortality at 30 days was 0.95%. Survival rate at 1.3 and 5 years was 87%, 65% and 51%, respectively. Lower limb salvage was 78% at 1 year, 72% at 3 years and 68% at 5 years. At least one surgical or endovascular reintervention was required in 65.8% of the patients and 63.7% required at least one readmission. Wound healing was achieved in 121 patients, 118 were able to ambulate and 59 had independent ambulatory ability. Only 57 patients (29%) presented ideal results, which means that they achieved limb salvage, wound healing, elimination of ischemic pain and the attainment of independent ambulatory ability during follow-up.
Conclusions: Infrainguinal endovascular revascularization in CLTI proved to be safe and achieved favorable salvage rates. However, the results include a low rate of full functional recovery due to poor independent ambulatory ability and wound healing and high need for reinterventions during follow-up.

Keywords: Chronic limb-threatening ischemia - Peripheral artery disease - Endovascular - Hospital readmissions

RESUMEN

Introducción: El tratamiento de la isquemia crítica de miembros inferiores (ICM) se basa en la revascularización arterial quirúrgica o endovascular. En las últimas décadas, la generalización y perfeccionamiento de las técnicas endovasculares ha incrementado su indicación en pacientes con ICM.
Objetivo: Describir los resultados de la revascularización endovascular infrainguinal de pacientes con ICM por arteriopatía obstructiva crónica.
Material y métodos: Análisis retrospectivo de una cohorte seguida prospectivamente de 211 pacientes con ICM y tratamiento endovascular, entre enero de 2015 y diciembre de 2020.
Resultados: Se realizaron 100 angioplastias infrapatelares (47,4%), 63 suprapatelares (29,9%) y 48 combinadas (22,7 %). En 167 casos (79,2 %) se trató de angioplastias primarias con balón, y en 44 (20,8 %) de angioplastias con colocación de stent. La mortalidad a los 30 días fue de 0,95 %. La supervivencia fue del 87% al año, 65 % a los 3 años y 51% a los 5 años. El sal¬vataje de miembro inferior fue del 78% al año, 72 % a los 3 y 68 % a los 5 años. El 65,8 % de los pacientes requirió al menos una reintervención quirúrgica o endovascular y el 63,7 % una reinternación. Curaron las lesiones tróficas 121 pacientes, 118 deambularon, y 59 en forma independiente. Solo 57 pacientes (29%) presentaron resultados ideales, es decir salvaron el miembro inferior, curaron las lesiones o lograron la desaparición del dolor isquémico y deambularon en forma independiente.
Conclusiones: La revascularización endovascular infrainguinal en ICM fue segura y presentó buenas tasas de salvataje; sin embargo, entre los resultados resaltan una baja tasa de recuperación funcional completa por la escasa deambulación inde¬pendiente; baja tasa de curación de lesiones, y elevada necesidad de reintervenciones en el seguimiento.

Palabras clave: Isquemia critica de miembro inferior - Enfermedad arterial periférica - Endovascular - Readmisión hospitalaria

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INTRODUCTION

Chronic peripheral artery disease (PAD) is primarily due to atherosclerotic obstruction of the arteries of the lower limbs. Chronic limb-threatening ischemia (CLTI) is the most advanced stage, affecting 11% of patients with PAD and is defined as ischemic rest pain and/or wounds with tissue loss (ulceration or gangrene) in the lower extremities. (1-3) It is associated not only with high risk of lower limb loss, impaired functional status and adverse effects on quality of life, but also with high probability of cardiovascular events such as ischemic heart disease or stroke and death. (4,5)

In the absence of arterial revascularization, the annual incidence of major lower extremity amputation is 25% with mortality rates of 20-30% at 2 years in patients with CLTI. (6,7) The objective of arterial revascularization (either by open bypass surgery or endovascular revascularization with balloon angioplasty with or without stent implant) in CLTI is to improve distal perfusion of the stenotic area or arterial occlusion to eliminate rest pain and achieve wound heling and lower limb salvage and reduce mortality. (8-10)

Over the past two decades, the widespread adoption of endovascular treatments has increased their application in patients with CLTI. This is due to advancements in the technique and the introduction of new technologies which have resulted in reduction in the morbidity rate. (11-13)

The objective of our study is to report the traditional aspects of treatment, including lower limb salvage, morbidity and mortality, wound healing, ambulatory status and functional recovery, as well as the need for hospitalization and reinterventions. Furthermore, the study aims to contribute to the understanding of the outcome of patients who underwent endovascular treatment for CLTI.

METHODS

We conducted a retrospective analysis of a prospectively followed cohort of 211 patients with CLTI due to chronic obstructive peripheral artery disease who underwent endovascular treatment by percutaneous balloon angioplasty, with or without stenting, between January 1, 2015, and December 31, 2020. Patients with a diagnosis of arterial injuries, aneurysmal disease, and acute lower limb ischemia were excluded.

The information was obtained from the database of the Operating Room Department of our hospital and from the medical records. Follow-up information was retrieved from the most recent assessment of patients who were still alive and who had visited the outpatient clinic or by contacting the patients and/or their families by telephone. Seven patients (3.3%) were lost to follow-up.

Demographic variables, cardiovascular risk factors, length of hospital stay, site of endovascular treatment, stent placement, lower limb salvage, complications, reinterventions, hospital readmission, intraoperative mortality, in-hospital and 30-day mortality, and overall survival were analyzed. The postoperative functional recovery was also evaluated based on the ability to walk independently or with assistance, as well as wound healing or elimination of ischemic pain.

All the patients underwent angiography and the revascularization procedures were classified as above and below-the-knee angioplasties, depending on whether the intervention was performed above or below the joint line of the knee. Combined angioplasty was considered when revascularization was performed above and below the knee.

All the statistical calculations were performed using STATA and RStudio software packages. Qualitative variables are presented as frequency and percentage and quantitative variables are expressed as mean and standard deviation or median and interquartile range (IQR). Survival was analyzed with Kaplan-Meier actuarial curves. Univariate and multivariate analyses were performed to define independent predictors of events. The significance level accepted was an alpha error of 0.05. Population projections were also calculated with their 95% confidence intervals (95% CI).

RESULTS

Of the 211 patients analyzed, 143 (67.8%) were men. Mean age was 67.9 ± 11 years. The most common risk factors were diabetes mellitus and hypertension (Table 1).

Within the diagnosis of CLTI, 198 patients (93.8%) had in limb wounds (ulcer or gangrene) and 13 (6.1%) had pain at rest. Of the total angioplasty procedures performed, 100 were below-the-knee procedures (47.4%), 63 were above-the-knee-procedures (29.9%) and 48 were combined (22.7%) procedures. One hundred and sixty-seven (79.2%) were primary balloon angioplasties, and a stent was implanted in 44 (20.8%) with stent placement (in cases of occlusions, residual stenosis or arterial dissection with no flow restoration after angioplasty). Angioplasty was performed on a single vessel in 56.4% of the cases, and on 2 or more vessels in the remaining cases. The femoral artery was treated in 85 cases (40.2%), the popliteal artery in 50 (23.7%), the anterior tibial artery in 80 (37.9%), the posterior tibial artery in 59 (27.9%), the fibular artery in 38 (18%) and the tibiofibular trunk in only 24 patients (11.3%). Double antiplatelet therapy with acetylsalicylic acid and clopidogrel was indicated in the postoperative period. Median length of hospital stay following surgery was 7 days (IQR 2-19). After hospital discharge, median follow-up was 42 months (IQR 20 - 58 months) in 196 patients (excluding the 8 deaths during hospitalization and the 7 patients lost to follow-up).

Table 1. Demographic data and comorbidities (n = 211)

Age	67.9 ± 11 years
Male sex	147 (67.8%)
Diabetes mellitus	174 (82.5%)
Hypertension	171 (81%)
Current smoking	122 (57.8%)
Dyslipidemia	101 (47.9%)
Coronary artery disease	49 (23.2%)
Stroke	24 (11.4%)

Lower limb salvage

Overall salvage rate was 73%; the probability of lower limb salvage at 1, 3 and 5 years was 0.78 (95% CI 0.72-0.83), 0.72 (95% CI 0.65-0.78) and 0.68 (95% CI 0.60-0.75), respectively (Fig. 1A). The probability of salvage was analyzed according to the anatomic location of the angioplasty procedure. In above-the-knee angioplasty procedures, the probability of salvage at 12 months was 0.82 (95% CI 0.69-0.89) and 0.73 (95% CI 0.58-0.83) at 3 and 5 years. In below-the-knee angioplasty procedures, the probability of salvage at 12 months was 0.76 (95% CI 0.69-0.83), 0.72 (95% CI 0.63-0.79) at 3 years and 0.66 (95% CI 0.56-0.74), with no significant differences at 5 years (p=0.361) (Fig. 1B).

Complications

The most common complications were thrombosis of the treated vessel in 21 patients (9.9%), cardiovascular events in 11 (5.2%), and sepsis related to the revascularized limb in 9 (4.2%). Two patients (0.9%) presented retroperitoneal hematoma, and one of them required surgery due to active bleeding. Of the 11 patients with cardiovascular events, 10 presented an

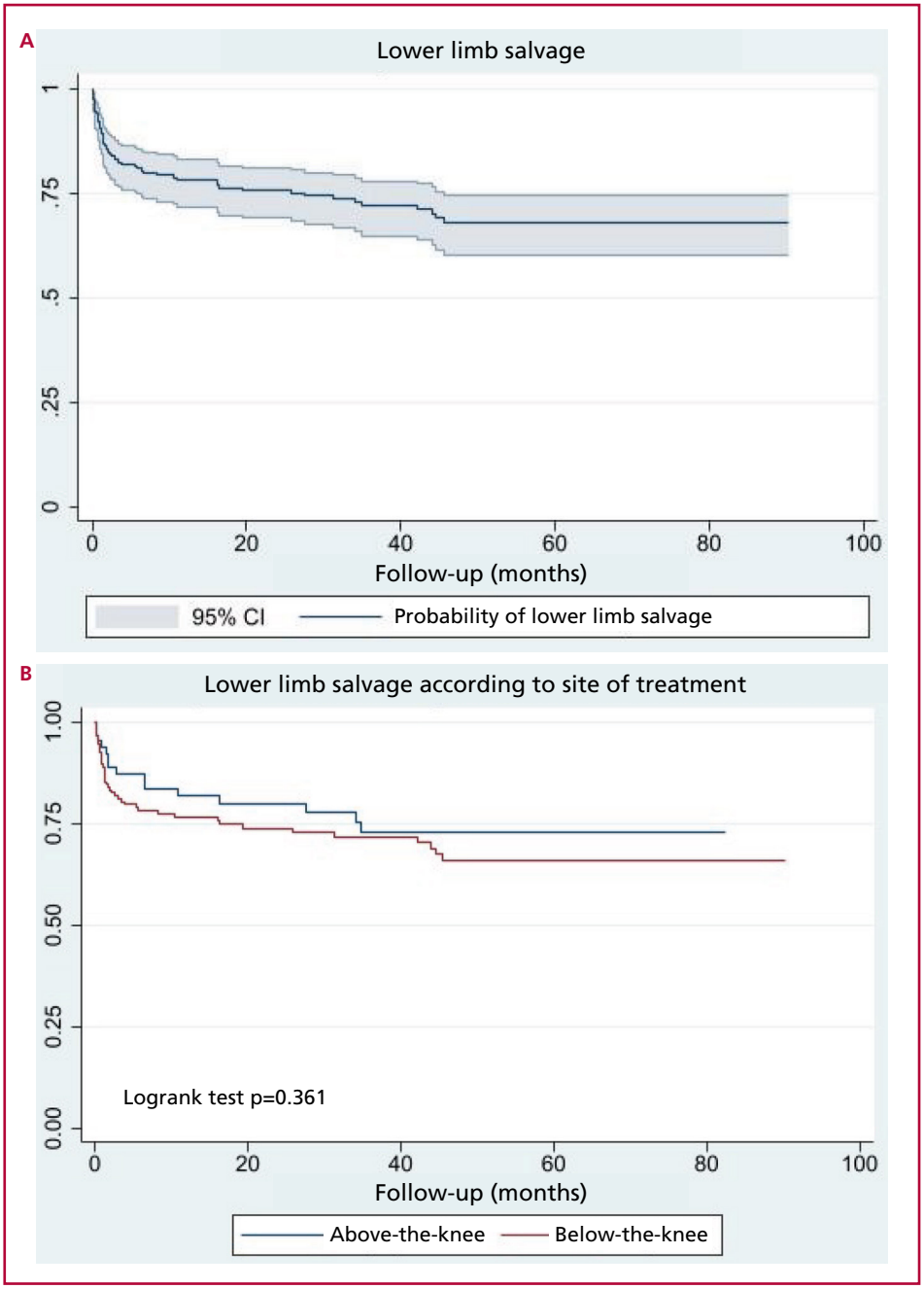

Fig. 1A. Kaplan-Meier curve for lower limb salvage. **1B.** Kaplan -Meier curve for lower limb salvage according to above-the-knee or below-the-knee treatment.

acute coronary syndrome and 1 had decompensated heart failure. Among these patients, 90.9% died within 4 years of follow-up.

Reinterventions

A total of 350 reinterventions were required following endovascular treatment of the lower limb in 211 patients with CLTI. These included reoperations of the treated lower limb, revascularization of the contralateral limb, coronary artery revascularization, valve replacement, and carotid artery or aortic surgery.

The mean number of reinterventions was 2.5 ±1.7 (median 2). Between one to seven reinterventions (surgical and/or endovascular) were documented during follow-up in 139 of the 211 patients (65.8%) (Table 2).

A total of 37.9% of patients (80 cases) required at least one cardiovascular surgical reintervention (endovascular or conventional) within 30 days after treatment. Of these, 88.7% (7 cases) were related to the revascularized lower limb. During the first year after treatment, there were 122 cases (57.8%) with cardiovascular surgical reinterventions (endovascular or conventional), related to the treated lower limb in more than 90% of cases (111 patients).

Table 2. Surgical and/or endovascular reinterventions for CLTI (n = 139).

Reinterventions	Frequency	Percentage
1	58	41.7%
2	25	17.9%
3	20	14.4%
4	14	10%
5	13	9.3%
6	2	1.4%
7	7	5%

CLTI: Chronic limb-threatening ischemia

Survival

There was no operative mortality. Mortality at 30 days was 0.95% (2 patients, 1 due to pre-existing cancer). In-hospital mortality was 3.8% (8 patients, in 7 cases due to sepsis related to soft tissue or bone infection in the operated lower limb).

In the overall survival analysis after endovascular revascularization of the 211 cases, the probability of survival at 1, 3 and 5 years was 0.87 (95% CI 0.82-0.91), 0.65 (95% CI 0.58-0.72), and 0.51 (95% CI 0.43-0.58), respectively (Fig. 2). The most common causes of death during follow-up were sepsis related to the revascularized lower limb (34.4%), cardiovascular events (25.2%) and COVID-19 (10.4%).

On univariate analysis, the factors significantly associated with long-term mortality were stroke (HR 2.02; 95% CI 1.19-3.42; p=0.009), age > 65 years (HR 1.61; 95% CI 1.05-2.46; p=0.028) and coronary artery disease (HR 1.79; 95%CI 1.16-2.76; p=0.008). Multivariate analysis showed a significant association of the same factors with mortality: stroke (HR 1.78; 95% CI 1.04-3.05; p=0.034), age > 65 years (HR 1.56; 95% CI 1.01-2.39; p=0.041) and coronary artery disease (HR 1.63; 95% CI 1.04-3.05; p=0.031) (Table 3).

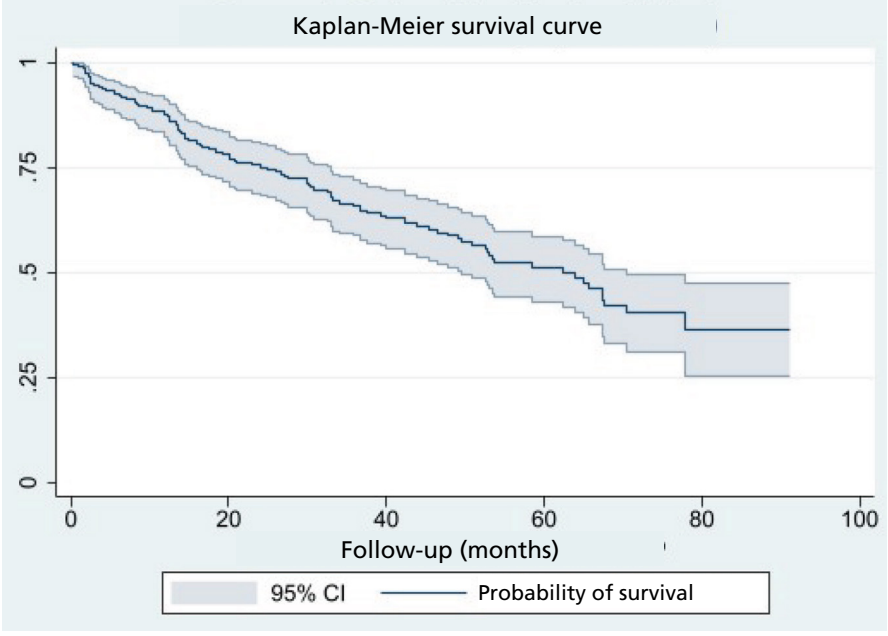

Fig. 2. Kaplan-Meier survival curve.

A total of 196 patients followed-up after discharge were considered for the analysis of readmissions, wound healing and ambulatory status after revascularization. The 8 in-hospital deaths and the 7 patients lost to follow-up (3.3%) were excluded.

Readmissions

Between 1 and 6 readmissions occurred during follow-up in 125 of the 196 patients (63.7%) analyzed (Table 4). A total of 23 patients (11.7%) were readmitted at least once within 30 days of discharge due to an adverse event in the revascularized limb. Sixty patients (30.5%) required readmissions related to the revascularized limb within the first year.

Wound healing

Wound healing or resolution of ischemic rest pain occurred in 121 patients (61.7%) during follow-up; 95 (48.4%) were also able to ambulate and 57 (29%) were independently ambulatory. In the logistic regression analysis, wound healing had a clearly positive impact with an OR of 8.26 (95% CI 4.29–15.98), indicating a more than eightfold increased likelihood of ambulation.

Ambulation

Ambulatory status was evaluated during the last follow-up control after hospital discharge. For the analysis, we considered whether the patients required assistance for ambulation (cane, crutches, walker, prosthesis or help from other persons) or achieved independent ambulatory ability.

A total of 118 patients (60.2%) ambulated, 59 (30.1%) were fully independent and 59 required some type of assistance. We defined ideal results in patients with a diagnosis of CLTI who underwent endovascular treatment and achieved full functional recovery during outpatient follow-up visits. These results include limb salvage associated with wound healing or resolution of rest pain and independent ambulatory ability and were observed in 57 patients (29%).

DISCUSSION

Chronic limb-threatening ischemia is the most severe manifestation of PAD due to atherosclerotic disease of the lower extremities. Treatment of CLTI includes medical therapy to reduce cardiovascular risk factors, revascularization to improve arterial perfusion of the lower extremity, and management of infections and wound healing with local care.

The optimal modality of revascularization in CLTI remains controversial and is the focus of the most recent randomized controlled trials. The BEST-CLI trial reported that in patients with CLTI who were suitable candidates for surgical or endovascular interventions, revascularization with a single segment of great saphenous vein was superior to endovascular therapy to reduce major adverse limb events or death. The results were similar when a great saphenous vein conduit was not available. (14) The BASIL-2 trial showed

Table 3. Univariate and multivariate analysis of factors associated with long-term mortality (n=211).

		Univariate analysis	
Risk Factors	**HR**	**95% CI**	**p**
Age > 65 years	1.61	1.05 - 2.46	0.028
Male sex	0.96	0.62 - 1.47	0.860
Diabetes Mellitus	1.22	0.70 - 2.12	0.477
Current smoking	0.77	0.52 - 1.16	0.223
Coronary artery disease	1.79	1.16 - 2.76	0.008
Stroke	2.02	1.19 - 3.42	0.009
		Multivariate analysis	
Risk Factors	**HR**	**95% CI**	**p**
Age > 65 years	1.56	1.01 - 2.39	0.041
Coronary artery disease	1.63	1.04 - 2.54	0.031
Stroke	1.78	1.04 - 3.05	0.034

Table 4. Readmissions after endovascular treatment for CLTI (n = 125)

Readmissions	Frequency	Percentage
1	75	60%
2	27	21.6%
3	8	6.4%
4	5	4%
5	6	4.8%
6	4	3.2%

CLTI: Chronic limb-threatening ischemia

that vein bypass first revascularization strategy was associated with a 35% increased risk of major amputation or death in patients with CLTI. (15) In a meta-analysis of randomized controlled trials comparing both techniques, Mufarrih et al. concluded that there is no difference in clinical outcomes between endovascular surgery and conventional surgery as the first revascularization strategy in CLTI. (16)

Kodama et al. assessed the impact of revascularization on ambulation in patients with CLTI and infrainguinal revascularization (surgical and endovascular) and found that the proportion who ambulated at baseline decreased to 40% at 3 years. Advanced age, reduced mobility at the time of revascularization, and being on dialysis were associated with ambulation loss during follow-up. (17) Taylor et al. analyzed more than 800 patients with CLTI and surgical or endovascular revascularization and described that 70.6% of patients were able to maintain ambulation at 5 years. The independent predictors of poor functional outcome were impaired ambulatory status at presentation, dementia, and diabetes mellitus. (18)

Historically, studies on revascularized CLTI patients considered the absence of major amputation as a successful clinical outcome. However, limb salvage rate does not always indicate a successful outcome because patients may survive for an extended period without undergoing a major amputation but with ischemic wounds, rest pain or die before symptoms are relieved. Therefore, we consider that wound healing is an important goal after revascularization for CLTI.

Okazaki et. al. reported that endovascular revascularization was associated with longer wound healing time and lower wound healing rate (60% at 1 year) compared to surgical revascularization. Among other risk factors, a history of coronary artery disease, congestive heart failure, and dialysis requirement were associated with a significantly shorter wound-free period. (19) Browder et. al. found that, except in patients with CLI and an ankle-brachial index <0.4, revascularization was not associated with better wound healing time and wound-free period. (20) Sano et. al. showed that a non-ambulatory status was an independent risk factor for impaired wound healing after revascularization, and delayed healing time. (21)

In our series, wound healing after revascularization had a favorable impact on patients' ability to ambulate during follow-up.

The need for hospital readmission and reinterventions in the outcome of patients revascularized for CLTI is well known. (14,15) Hospital readmissions are mainly due to cardiovascular causes. (22) In the case of endovascular and/or surgical reinterventions, they are generally necessary to achieve complete wound healing in the treated lower limb. In a review of 59 714 patients revascularized for CLTI, Martínez et al. reported readmission rates at 30 days and 1 year of 19.2% and 40.3%, respectively. (23) Ochoa Chaar et al. analyzed 1410 cases with endovascular revascularization for CLTI. They found that 49% had at least one hospital readmission per year and the most common reasons were related to tissue wounds or infection of the revascularized limb. (24) In the BASIL-2 trial, the reintervention rate was 19% in patients with below-the-knee revascularization in the endovascular group, while in the BEST-CLI the rate of major and minor reinterventions was 23.5% and 33%, respectively, in the endovascular group, cohort 1 (compared with single greater saphenous vein bypass). (14,15) In Argentina, Jozami et al. evaluated patients with CLTI who underwent endovascular treatment and reported reintervention and amputation rates of 21.4% and 14.3%, respectively, at one year. (11)

In our series, we recorded a high rate of reinterventions and hospital readmissions mainly due to the revascularized lower limb. However, the population analysis revealed that patients had significant distal artery involvement, (tibial and fibular arteries), reflected in the high proportion of below-the-knee or combined treatments, and that most patients had diabetes. In patients revascularized for PAD, diabetes is an independent risk factor for hospital readmission and high rates of major adverse events in the lower limb, such as major amputation of the revascularized limb and/or reintervention in the revascularized segment. (25)

In our experience, endovascular treatment was safe with low 30-day mortality (<1%). The 5-year mortality rate is consistent with that reported for patients revascularized for CLTI. (14,15,22) In terms of functional recovery, more than half of our population ambulated (with or without assistance) and achieved wound healing. On the other hand, only one third of patients presented ideal results, which means that they achieved full functional recovery, limb salvage associated with wound healing and independent ambulatory ability during follow-up.

Patients with CLTI constitute a heterogeneous group so it is difficult to standardize treatments in advanced stages of the disease considering the systemic cardiovascular risk (comorbidities), the anatomical complexity of the atherosclerotic arterial obstruction (severity and number of vessels affected), and the extent of tissue injured in the limb. In our opinion, an initial technical success in endovascular revascularization does not necessarily guarantee an optimal clinical response. The outcome of patients with CLTI requires close monitoring and consideration of reinterventions (open and/or endovascular) and hospital readmission if necessary.

Our study has some limitations. We made a retrospective analysis of a prospectively followed cohort from a single center. The choice of endovascular revascularization treatment was not randomized. Ischemic wounds were not stratified by their location and extent. Finally, the ambulatory status was not evaluated before revascularization.

CONCLUSION

Infrainguinal endovascular revascularization in CLTI proved to be safe with good limb salvage rates. However, the results indicate that the rate of full functional recovery was low because independent ambulatory ability and wound healing rates were low and there was high need for reinterventions during follow-up.

Ethical considerations

Clinical research protocol, Approved on 3/27/23 by the Ethics Committee of the Hospital de Clínicas "José de San Martin" U.B.A.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

3D Analysis of Geometry and Fluid Dynamics During Presurgical Planning of Patients with Single Ventricle and Heterotaxy Syndrome in Pre-Fontan-Kreutzer Stage

Análisis 3D de la geometría y fluidodinámica durante el planeamiento prequirúrgico de los pacientes con ventrículo único y síndrome de heterotaxia en el estadio pre Fontan-Kreutzer

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ABSTRACT

Background: The aim of the Fontan-Kreutzer procedure is to obtain a balanced distribution of hepatic venous flow to both lungs in order to achieve a favorable long-term clinical condition. These patients, due to the continuous passive hepatic venous flow to the lungs develop long-term liver disease, (cirrhosis), plastic bronchitis or protein-losing disease. If there is an unbalanced distribution of hepatic venous flow to the lungs, arteriovenous fistulas in the pulmonary parenchyma begin to develop, leading to decreased arterial oxygen saturation.
Objective: The aim of this study was to predict and avoid an unbalanced distribution of hepatic venous flow to the lungs after total cavopulmonary connection surgery at the Fontan-Kreutzer stage through the use of fluid dynamics analysis.
Methods: Two patients with a single ventricle and complex anatomy were studied and underwent pre-surgical planning by modeling in three dimensions (3D) the digital shape of the anatomic segmentation through the DICOM format of the contrast-enhanced axial computed tomography. Then, the model of the virtual surgery was performed to apply computational fluid dynamics to the chosen surgical technique, in order to evaluate the balanced distribution of hepatic venous flow to the lungs.
Results: Computational fluid dynamics applied in the different proposed surgical techniques to complete the total cavopulmonary connection in the Fontan-Kreutzer stage predicted a distribution of 60% to 65% hepatic venous flow to the right pulmonary artery and 35% to 40% to the left pulmonary artery.
Conclusions: The 3D reconstruction methodology of each patient's anatomy combined with computational fluid dynamics modeling obtained by the present interdisciplinary group, allowed developing different surgical scenarios specific to the patients under study. The physics approach of a medical problem has allowed favorable results and constitutes a systematic method towards the application of precision medicine. This personalization has the advantages of studying in advance the anatomy of the patients in virtual form, essential for proposing different surgical scenarios and optimizing surgical times. The evaluation of physiological quantities for different scenarios by means of simulation, enabled the approximation of hepatic venous flow distribution to both lungs, determining which strategy minimizes or avoids fistula formation in the patient. This has a direct impact on the improvement of long-term outcomes after completing the total cavopulmonary connection at the Fontan-Kreutzer stage.

Keywords: Fluid dynamics - Fontan Kreutzer

RESUMEN

Introducción: En la cirugía de Fontan-Kreutzer se busca obtener una distribución equilibrada del flujo venoso hepático hacia ambos pulmones para lograr una condición clínica favorable a largo plazo. Estos pacientes, debido al flujo continuo pasivo venoso hepático

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hacia los pulmones desarrollan a largo plazo enfermedad hepática (cirrosis), bronquitis plástica o enfermedad perdedora de proteínas. Si se produce una distribución desbalanceada del flujo venoso hepático hacia los pulmones comienzan a desarrollarse fistulas arteriovenosas en el parénquima pulmonar, que llevan a la disminución de la saturación arterial de oxígeno.
Objetivo: Predecir y evitar una desbalanceada distribución del flujo venoso hepático hacia los pulmones después de la cirugía de conexión cavo-pulmonar total en el estadio de Fontan-Kreutzer a través de utilizar el análisis de la fluidodinámica.
Material y métodos: Dos pacientes con ventrículo único con anatomía compleja fueron estudiados y se realizó en ellos el planeamiento prequirúrgico modelando en 3 dimensiones (3D) la forma digital de la segmentación anatómica a través del formato DICOM de la tomografía axial computada con contraste. Luego se realizó el modelo de la cirugía virtual para poder aplicar a la técnica quirúrgica elegida la fluidodinámica computacional que permite evaluar la distribución balanceada del flujo venoso hepático hacia los pulmones.
Resultados: La fluidodinámica computacional predijo en las distintas técnicas quirúrgicas propuestas para completar la con¬exión cavo-pulmonar total en el estadio Fontan-Kreutzer una distribución del flujo venoso hepático hacia la arteria pulmonar derecha de 60 % a 65 % y a la rama izquierda de 35 % a 40 %.
Conclusión: La metodología de reconstrucción 3d de la anatomía de cada paciente combinada con el modelado por fluido dinámica computacional obtenida por el presente grupo interdisciplinario, permitió modelar diferentes escenarios quirúrgicos específicos para los pacientes en estudio. La aproximación desde la física de un problema médico permitió obtener resultados favorables y constituir un método sistemático hacia la aplicación de la medicina de precisión. Esta personalización presenta las ventajas de estudiar con antelación la anatomía de los pacientes en forma virtual, esencial para proponer diferentes escenarios quirúrgicos y optimizar los tiempos en cirugía. La evaluación de cantidades fisiológicas para diferentes escenarios, mediante simulación, permitió aproximar la distribución del flujo venoso hepático hacia ambos pulmones permitiendo determinar qué estrategia minimiza o evita la formación de fistulas en el paciente. Esto tiene un impacto directo en la mejora de los resultados a largo plazo luego de completar la conexión cavo-pulmonar total en el estadio de Fontan-Kreutzer.

Palabras clave: Fluidodinámica - Fontan-Kreutzer

INTRODUCTION

Newborns have 50% distribution of blood flow towards the cephalic part of the body due to the proportion of the head in relation to the body. When they begin to walk, the metabolic demand of the muscles causes the cardiac output to increase by up to 70% to the lower limbs. For this reason, the therapeutic strategy of the single ventricle leading to univentricular correction consists of a stepwise approach. At 3 to 6 months old, the superior vena cava is connected to the pulmonary artery (Glenn surgery), to increase the effective pulmonary flow and thus blood oxygenation. Then, when the patient starts to walk and the relative cardiac output towards the cephalic region decreases with respect to that of the lower limbs, it is considered necessary to connect the inferior vena cava to the pulmonary artery. This technique, known as the Fontan-Kreutzer procedure, separates the pulmonary from the systemic circulation, improving the effective pulmonary flow and allowing the survival of patients with univentricular hearts. For this circulation to be effective it requires an adequate anatomy with low pressures both in the pulmonary tree as in the single ventricle, since blood circulates by gravity in the inspiratory and expiratory phase depending on the difference between atmospheric and intrathoracic pressures.

In the Fontan-Kreutzer procedure, the aim is to obtain a balanced distribution of hepatic venous flow to both lungs to achieve a favorable long-term clinical condition. These patients, due to the continuous passive hepatic venous flow to the lungs develop long-term liver disease (cirrhosis), plastic bronchitis or protein-losing disease, generating failure of the Fontan system. (1) Balanced distribution reduces the formation of pulmonary arteriovenous malformations and prevents the decrease of arterial oxygen saturation. It also minimizes the loss of blood flow energy to the lungs and avoids the associated thrombosis due to certain localized high and low shear stress sites on the walls of the total cavopulmonary connection system in the Fontan-Kreutzer stage. The hepatic factor is a molecule or an undetermined metabolite essential in this process. If there is an unbalanced distribution of hepatic venous flow to the lungs, absence of the passage of this hepatic factor through the lung tissue takes place and arteriovenous fistulas begin to develop in the lung parenchyma, leading to decreased oxygenation of arterial blood. (2)

Although long-term complications are multifactorial, they may be related to the geometric design of the total cavopulmonary connection affecting the hemodynamic resistance and the balance of hepatic venous flow distribution to the lungs. (3-6)

In patients in whom the hepatic venous flow is to one lung, arteriovenous malformations develop in the contralateral lung. Patients who are prone to the development of arteriovenous fistulas have a 32% to 85% chance of developing them, due to lack of hepatic factor flow through the lungs before performing the total cavopulmonary connection in the Fontan-Kreutzer stage. (7)

In patients with complex anatomy for the total cavopulmonary connection it is difficult to estimate blood flow distribution, taking into account 2 or 3 flow inlets, then the passage of blood through a total cavopulmonary connection with an angled geometry, and that finally flow is distributed in a balanced and equitable way through two pathways to both lungs.

This has led to improvements in preoperative planning and has given rise to new multidisciplinary work methodologies that combine medical knowledge with

the complementary use of tools such as multimedia design of virtual surgeries, and the use of computational fluid dynamics. (8-12)

The novelty of this work is that we were able to plan the surgical treatment of these patients in a personalized way in a public hospital in Argentina with an interdisciplinary group of cardiovascular surgeons, cardiologists, imaging technicians, nuclear physicists and engineers, electronic engineers and multimedia designers.

OBJECTIVE

The aim of this study was to predict and prevent an unbalanced distribution of hepatic venous flow to the lungs after total cavopulmonary connection surgery at the Fontan-Kreutzer stage, by using fluid dynamics analysis.

METHODS

The three dimensional (3D) anatomy of two patients was reconstructed using the DICOM of the computed tomography (CT) scan, adding the 3D design of the selected surgical technique based on the premise of making the straightest and shortest possible connection between the inferior vena cava and the pulmonary artery branches. Computational simulations of fluid dynamics were subsequently performed to estimate the inflow to the Fontan system and the distribution of hepatic flow to both pulmonary artery branches. (Table 1) Defining the hemodynamic conditions for blood flow simulation is a great challenge. In our hospital, echocardiography and catheterization are usually performed for the presurgical evaluation of a patient candidate for total cavopulmonary connection in the Fontan-Kreutzer stage. DICOM data from a CT or magnetic resonance imaging (MRI) scan are required for 3D modeling of the anatomy and eventual design of the virtual surgery. Certain hemodynamic data are necessary for the computer simulation, such as the inflows to the model to be evaluated (single or bilateral Glenn, inferior vena cava or suprahepatic veins, azygos vein, etc.) and the pressure values in the different points of the system. For the latter, we considered the values measured by invasive catheterization. Flows are shown in Table 2. We initially used echocardiography-calculated flows by measuring the velocity time integral (VTI). Flow values are absolutely variable according to the patient's condition; for example, the systemic venous return flow varies significantly during inspiration or expiration or during apnea. In this study, we used the echocardiographic VTI to estimate blood flow calculated as the product of the average velocity and the cross-sectional area of the vessel. (13) Since flow is pulsatile and its velocity varies along the cross-sectional area of the vessel, there is a velocity distribution (flow velocity profile). An average velocity value is obtained by adding all the velocities within the Doppler spectral envelope (velocity time integral). The cross-sectional area is obtained by echocardiography and compared with the CT measurements of the anatomy.

For venous flows, average velocities are measured during several cardiac cycles established by the electrocardiogram, as well as heart rate, and then flow through that vessel is calculated in liters/minute. To consider total flow, the systemic cardiac output was also measured by aortic VTI. (13)

Reconstruction of the anatomical models

Slicer (Kitware, USA) was used for image processing, segmentation and 3D reconstruction, (14) and algorithms from the ITK library (Insight Software Consortium, USA) were developed. (15)

We worked with Blender (Netherlands) (16) to adapt the Fontan procedure connections to the reconstructed 3D models. These were used for computational fluid dynamics calculations. After the virtual surgery, the anatomical model and the proposed surgical reconstruction were loaded into a self-developed online virtual browser to be analyzed in detail and discussed in a clinical surgical meeting.

Patient number 1 had a sequential and segmental analysis of the cardiac anatomy in which an atrial situs inversus, ventricular L-loop and L position of the aorta were observed. The diagnostic methods used were echocardiogram, contrast-enhanced CT, catheterization, and 3D reconstruction, showing a single ventricle with tricuspid atresia and pulmonary atresia (Figure 1).

In patient number 2, the sequential and segmental analysis of the cardiac anatomy performed using echocardiogram, contrast-enhanced CT, cardiac catheterization, and 3D reconstruction of the geometry led to a diagnosis of atrial situs ambiguous, ventricular L loop, and L position of the aorta (right aortic arch) with an unbalanced right-dominant atrioventricular canal with pulmonary atresia and moderate atrioventricular valve insufficiency in the Glenn stage (Figure 2). Figure 3 A shows the left Glenn system in cardiac catheterization together with the anatomy of the pulmonary arteries, 3 B the right Glenn system together with the branches of the pulmonary arteries and 3 C the ambiguous drainage of the inferior vena cava into the single atrium.

Computational Fluid Dynamics

The domain of the study system, defined by the geometric model, is approximated by tetrahedral elements generated by GMSH (C Geuzaine & J-F Remacle, U Liege, Belgium), a generator of finite element meshes. (17) To model the hemodynamic behavior of blood in this system, the continuity and the Navier-Stokes equations (conservation of momentum

Table 1. Hepatic venous flow distribution to right and left branches of pulmonary artery predicted by computational fluid dynamics

Patient	Sex	Age	Estimated systemic flow (L/min)	Hepatic flow to the right pulmonary artery (%)	Hepatic flow to the left pulmonary artery (%)
1. Lateral Tunnel	M	3 years and 10 months	1.86	60	40
2. Extracardiac Tube	M	3 years	2.05	65	35

and mass) are solved. Profiles developed for the velocities (Dirichlet) obtained from VTI and Neumann type measurements for the pressures at the inlets were established. For the outlets Dirichlet-type floating pressure values and Neumann type for the velocities were used. The conditions on the walls were non-sliding. As a result of the simulation, the velocity and pressure components that satisfy these equations were obtained. The results presented were solved with the open-source software OpenFOAM, (18) initially using the SIMPLE (Semi Implicit Method for Pressure Linked Equation) algorithm in steady state. However, it is common for the steady state solution to be unstable and convergence with acceptable tolerances is not achieved, in which case a transient solution is obtained with a PISO (Pressure Implicit with Splitted Operators) type algorithm. This algorithm is limited by the need to keep the Courant number <1 to produce stable solutions, restricting the time step to be used and increasing the simulation time to excessive values. Finally, using a combination of both algorithms, known as PIMPLE, the time step can be increased to reach Courant numbers of around 20, resigning some precision in the temporal evolution, but maintaining the flow values at the outlets. The Courant number is the flow velocity by the time step divided by the mesh size. If it equals 1, it means that the fluid passes through one cell in one time step.

The hepatic venous flow distribution (HFD) was estimated from computational fluid dynamics simulations. It is defined as the ratio of blood flow in the inferior vena cava and the right and left pulmonary arteries and is calculated by tracking particles in the flow lines. This value is considered favorable for distribution values between 40% and 60% for both pulmonary arteries. We studied these clinical metrics in conjunction with flow structures and pressure drops to elucidate the mechanisms that lead to greater energy dissipation or a certain distribution of hepatic flow. To estimate the value of the hepatic venous flow distribution, a software was developed that calculates and displays the trajectory lines for a given set of particles that travel through the simulated fluid.

This quantity is calculated by the time integral of the velocity field components obtained from the computational fluid dynamics calculation. By visually counting these lines, the percentage of hepatic venous flow distribution towards the pulmonary artery branches is estimated. This can be observed in Figure 4 A, which displays the velocity distribution in the pulmonary artery branches with an extracardiac tube in patient 1. Figure 4 B shows the velocity distribution in the pulmonary arteries with a lateral caval tunnel in patient 2. To perform calculations, we assume that the vessel walls are rigid; (19-21) and that the parameters related to the efficiency of the total cavopulmonary connection, such as the power loss and distribution of the hepatic venous flow in a patient

Table 2. Flow and VTI data by echocardiography

	Structure	Diameter (cm)	VTI (cm)	Radius (cm)	Radius^2 (cm^2)	Area (cm^2)	Volume (cm^3)	Average speed (m/s)	Flow (L/min)
Patient 1	SVC/Glenn	0.8						0.22	0.67
	IVC	1.2						0.15	1.05
	RPA	1.0							
	LPA	0.9						0.14	0.55
	Aorta	16.5						0.18	2.14
Patient 2	Right Glenn	0.7	21	0.35	0.1225	0.35	8.1		0.69
	Left Glenn	0.5	25	0.25	0.0625	0.20	4.9		0.42
	IVC	0.8	22	0.4	0.16	0.50	11.0		0.94
	Aorta	1.7	8.5	0.85	0.7225	2.27	19.3		1.64

Echocardiographic flow and VTI data.
IVC: inferior vena cava; LPA: left pulmonary artery; RPA: right pulmonary artery; SVC: superior vena cava; VTI, velocity time integral.

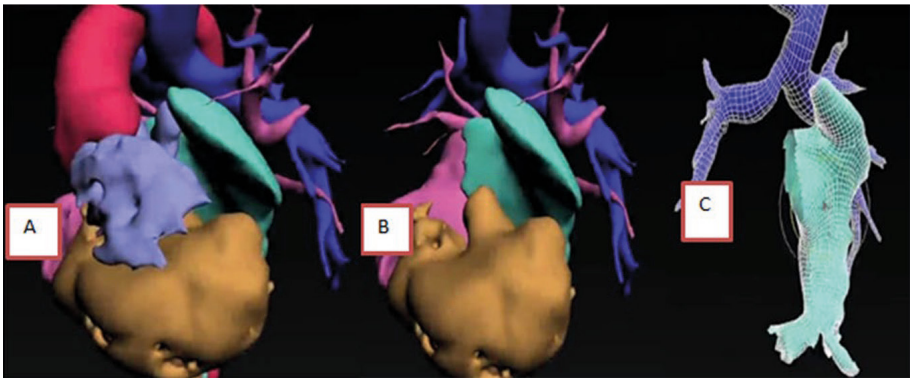

Fig. 1 Patient 1. **A** and **B**: 3D reconstructed images showing in an anterior view the aorta exiting in L-position from the single ventricle of left morphology (pearly colored structure). In Fig. **A**, **B** and **C** the drainage of the suprahepatic veins in a position of atrial situs inversus is shown in turquoise. The pulmonary branches to the Glenn system are seen in blue

with an intraatrial rerouting do not change significantly compared to using a fluid-structure interaction model. We also assume that blood behaves as an incompressible Newtonian fluid, with a constant viscosity of 3.71 mPas and a density of 1060 kg/m. The boundary conditions for the hemodynamics of a single ventricle broadly include the vessel walls and ends. (22) For the vessel ends, boundary conditions given by the clinical measurements described above will be imposed and we will assume flow rate values averaged over one or more cardiac cycles. We assume that the conditions of both the systemic flow rate and the inlet distribution are preserved before and after surgery (the physiological conditions in the rest of the system do not change). (23-31)

RESULTS

Computational fluid dynamics in the different surgical techniques proposed to complete the total cavopulmonary connection in the Fontan-Kreutzer stage predicted a distribution of the hepatic venous flow towards the right pulmonary artery of 60% to 65% and to the left pulmonary artery of 35% to 40%. (Table 1).

Distribution of hepatic venous flow

Figure 5 A shows the simulation of the hepatic flow distribution in patient 1 with an extracardiac tube technique resulting in 65% of the hepatic venous flow

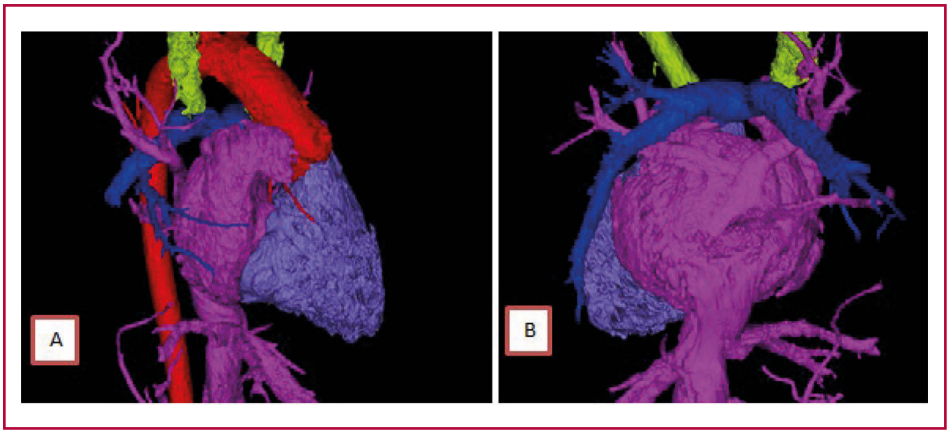

Fig. 2. Patient 2. **A** and **B**: 3D reconstruction image. The single atrium receiving the pulmonary veins and the inferior vena cava can be seen in fuchsia. B shows the ambiguous drainage of the inferior vena cava into the single atrium. In both figures, the geometries of the two Glenn systems draining into the pulmonary artery structure (blue) are visualized in light green. The ventricular L-loop is also seen in the purple structure. The L position of the aorta is seen in red.

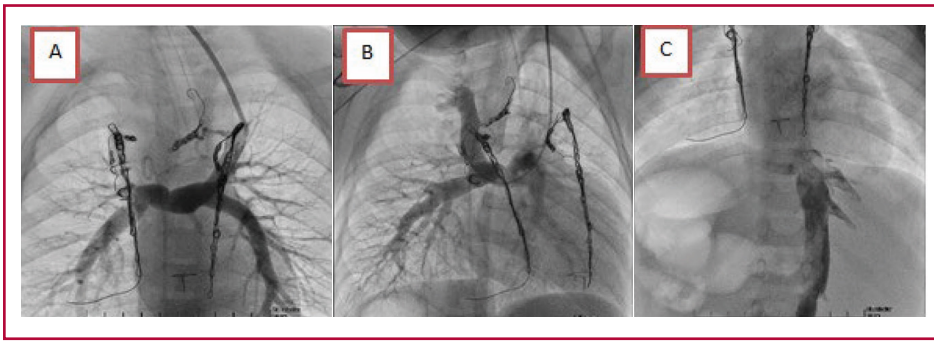

Fig. 3. A: The left Glenn system is observed in cardiac catheterization along with the anatomy of the pulmonary arteries. **B:** the right Glenn system is seen together with the branches of the pulmonary arteries. **C:** the ambiguous drainage of the inferior vena cava is seen in the single atrium.

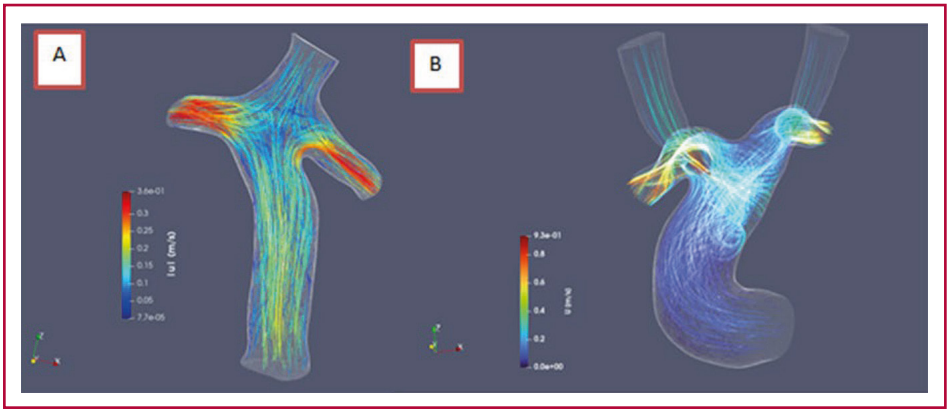

Fig. 4. A: Distribution of velocities in the pulmonary arteries with an extracardiac tube in patient 1. **B:** Distribution of velocities in the pulmonary arteries with a caval lateral tunnel in patient 2.

to the right pulmonary artery and 35% of the hepatic flow to the left pulmonary artery using a systemic flow rate of 1.86 liters/minute. Figure 5B shows that in patient 2 the fluid dynamics simulation indicates that with the Fontan technique of lateral caval tunnel the hepatic flow is distributed 60% to the right pulmonary artery and 40% to the left pulmonary artery using a systemic inflow rate of 2.05 liters/minute.

Both patients had a satisfactory postoperative outcome with 95% oxygen saturation and survival was 100% at discharge. Due to the excellent 4-year evolution we are extending this presurgical planning to patients with a single ventricle and complex anatomy and physiology. Neither of these two patients developed pulmonary arteriovenous fistulas.

DISCUSSION

Patients with a diagnosis of single ventricle present a wide range of anatomical variations that pose a challenge to plan and predict the ideal surgical reconstruction for the Fontan-Kreutzer procedure. Prospective virtual modification of the patient's anatomy to simulate a surgical approach combined with computational modeling provided information on the physiological impact of different surgical decisions.

Simulations performed before the interventions were useful in achieving a successful approach that was demonstrated by the surgical technique used in each patient; however, using magnetic resonance imaging we have been unable to perform a study of the distribution of hepatic venous flow to the lungs after each intervention. Given the variation in the balance of hepatic venous flow and pulmonary vasculature resistance in the patients studied, as well as the experience of several pediatric surgeons and cardiologists who have performed flow simulation for patients diagnosed with a single ventricle, it is clear that it is not possible to predict hepatic flow distribution based on clinical experience alone, even at large centers with substantial experience with these patients. Factors that determine the distribution of hepatic venous flow to the lungs include the position of the systemic veins (single or bilateral superior vena cava side), the inferior vena cava side, the number of suprahepatic veins and the distance from their output orifice to the single atrium, the angulation of the veins as they enter the pulmonary arteries, and the balance of flow between the different venae cavae and other hemodynamic factors.

It should be noted that the assembly of the interdisciplinary group is a hard teamwork of many hours, with professionals from different scientific fields in our country, and entails continuous learning to be able to use these tools in the clinical setting of patients within a public hospital. A very important point is the 3D design of the surgical technique to achieve a model as close as possible to the geometric reality of the anatomy of each patient. (32,33) The close collaboration between the engineers of the modeling team and the surgeons is essential to translate the details of the surgical approach planned by the surgeons into the virtual model.

CONCLUSION

The 3D reconstruction methodology of the anatomy of each patient combined with the computational fluid dynamics modeling obtained by this interdisciplinary group, allowed designing different surgical scenarios specific to the patients under study. The physics approach of a medical problem has provided favorable results and constitutes a systematic method towards the application of pre-operative medicine. This customization offers the advantages of studying the patient's anatomy in advance in a virtual way, which is essential

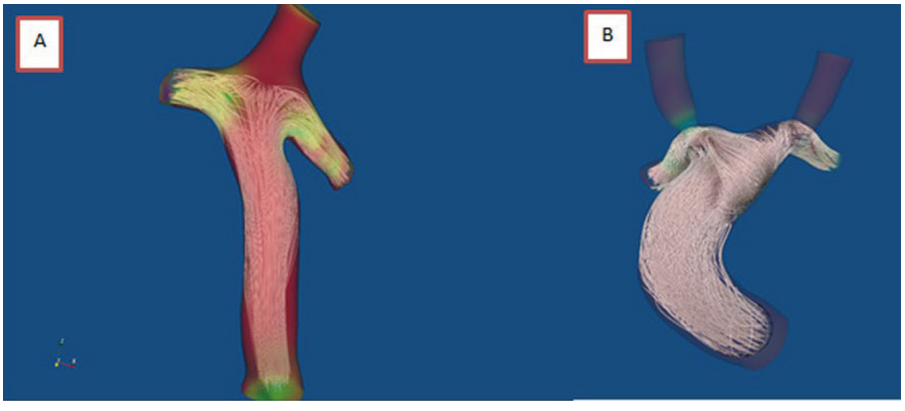

Fig. 5 Distribution of hepatic venous flow to pulmonary arteries. **A:** The simulation of the hepatic flow distribution in patient 1 using an extracardiac tube technique shows a distribution of 65% of hepatic venous flow to the right pulmonary artery and 35% of hepatic venous flow to the left pulmonary artery with a systemic flow rate of 1.86 liters/minute. **B:** The fluid-dynamics simulation in patient 2 shows that with the caval lateral tunnel technique, the hepatic flow is distributed 60% to the right pulmonary artery and 40% to the left pulmonary artery, using a systemic inflow of 2.05 liters/minute.

for proposing different surgical scenarios and optimizing procedural times. The evaluation of physiological quantities for different scenarios through simulation, allowed the approximation of hepatic venous flow distribution to both lungs, determining which strategy minimizes or avoids the formation of fistulas in the patient. This has a direct impact on improving long-term outcomes after completing the total cavopulmonary connection at the Fontan-Kreutzer stage.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Coronary Artery Bypass Grafting in Argentina. Subanalysis of the ARGEN-CCV Registry

Cirugía de revascularización miocárdica en Argentina. Subanálisis del Registro ARGEN-CCV

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ABSTRACT

Background: Coronary artery bypass grafting (CABG) continues to be widely used to treat coronary artery disease, mainly in patients with technical difficulties in performing angioplasty, as well as in patients with diabetes mellitus. CABG data from the ARGEN-CCV registry are presented. This registry shows the current data on cardiovascular surgery (CVS) in Argentina.
Objective: To determine the in-hospital course of patients undergoing CABG.
Methods: ARGEN-CCV is a prospective, multicenter registry of patients undergoing CVS in Argentina, from which peripheral vascular surgery and repair of congenital heart disease were excluded. For this analysis, only patients who underwent CABG were analyzed.
Results: A total of 700 patients were included. Seventy percent (70%) were elective surgeries, and extracorporeal circulation (ECC) was used in 50.6% of the cases. In total, 38.6% of patients were diabetic, 22.4% had a history of left ventricular dysfunction and 38.1% had left main coronary artery disease. The left internal mammary artery to the left anterior descending artery graft was the most commonly used (94.6%). The recorded mortality was 6.9% and in patients with left ventricular dysfunction it was 13.1% vs. 5.1% in the rest ($p<0.001$). In the multivariate analysis 3 post-surgical variables, inotropic use, low cardiac output syndrome and renal failure, were predictors of mortality, strongly influenced by a history of left ventricular dysfunction.
Conclusion: We observed a high percentage of patients with diabetes and patients with left main coronary artery disease as well as high surgical morbidity and mortality, particularly in those patients with left ventricular dysfunction.

Keywords: Registry - Cardiovascular surgery - Coronary artery bypass grafting

RESUMEN

Introducción: La cirugía de revascularización miocárdica (CRM) continúa siendo ampliamente utilizada para tratar la enfer¬medad coronaria, fundamentalmente en pacientes que plantean dificultades técnicas para realizar angioplastia, así como en pacientes con diabetes mellitus. Se presentan los datos de CRM del registro ARGEN-CCV, que muestra los datos actuales de la cirugía cardiovascular (CCV) en Argentina.
Objetivo: Conocer la evolución intrahospitalaria en pacientes sometidos a CRM.
Material y métodos: ARGEN-CCV es un registro prospectivo, multicéntrico de pacientes sometidos a CCV en Argentina, del que se excluyeron las cirugías vasculares periféricas y la reparación de cardiopatías congénitas. Para este análisis se analizaron solo los pacientes sometidos a CRM.
Resultados: Se incluyeron 700 casos. El 70 % fueron cirugías programadas y en el 50,6 % se usó circulación extracorpórea (CEC). Tenía diabetes el 38,6 % de los pacientes, 22,4 % tenía antecedente de disfunción ventricular izquierda y 38,1 % lesión de tronco de coronaria izquierda. El puente mamario izquierdo a la arteria descendente anterior (DA) fue el más utilizado (94,6 %). La mortalidad registrada fue de 6,9 % y en los casos con disfunción ventricular izquierda fue de 13,1 % vs 5,1 % en el resto ($p<0,001$). En el análisis multivariado 3 variables postquirúrgicas, uso de inotrópicos, síndrome de bajo gasto cardíaco e insuficiencia renal, fueron predictores de mortalidad, fuertemente influidos por el antecedente de disfunción ventricular izquierda.
Conclusión: Se observó un porcentaje elevado de pacientes diabéticos, con enfermedad del tronco de la coronaria izquierda y alta morbimortalidad quirúrgica, especialmente en aquellos con disfunción ventricular izquierda.

Palabras clave: Registro - Cirugía cardiovascular - Revascularización miocárdica

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INTRODUCTION

Coronary artery disease is a well-known cause of morbidity and mortality worldwide, which has led to the search for medical and surgical advances in its management, showing good outcomes and implications on life expectancy. (1,2)

In recent years, percutaneous coronary intervention has gained ground, but coronary artery bypass grafting (CABG) is still widely used, even more so in patients with technical difficulties in performing coronary angioplasty and in those with diabetes mellitus, given its good long-term prognosis. The efficacy and safety of the procedure are related to the experience of the surgical teams and centers. Together with the control of cardiovascular risk factors and medical treatment of coronary artery disease, it is undoubtedly a procedure with a positive impact on survival and quality of life. (3-5)

Currently, there are some clinical tools to assess the indication and potential risks and benefits of a procedure such as a CABG and to make a rational decision. The European System for Cardiac Operative Risk Evaluation (EuroSCORE II) and the score of the Society of Thoracic Surgeons (STS) are tools developed based on clinical variables to assess the risk of in-hospital and 30-day mortality. We also have the ArgenSCORE, a predictive method developed in Argentina. (6-9)

In addition, it is necessary to know the mortality rate of this procedure at a local level, which, together with the above-mentioned tools, will allow an adequate decision-making threshold to be established. It is also important to gather all the factors that may cause poor and undesirable postoperative outcomes, so it is necessary to identify the variables that have a negative impact on prognosis and thus adjust the provision of health services. (10,11)

OBJECTIVES

This analysis aimed to determine the in-hospital course of patients who underwent CABG in a registry of cardiovascular surgery in Argentina (ARGEN-CCV) and the preoperative, operative, and immediate postoperative factors associated with in-hospital mortality.

METHODS

A multicenter, cross-sectional study was carried out, including patients over 18 years of age admitted to hospital for an elective or emergency cardiovascular surgery (CVS). Preoperative, operative and postoperative data were obtained during hospitalization. Surgeries for repair of congenital heart disease and peripheral procedures were excluded. This project was conducted by the Argentine Society of Cardiology and the Argentine College of Cardiovascular Surgeons, and was promoted as the National Registry of Cardiovascular Surgery in Argentina (ARGEN-CCV). A total of 1515 patients were included in 48 public and private centers in Argentina for a 13-month period, between July 2021 and August 2022. The project was registered in ClinicalTrials.gov NCT0519916. For this analysis, 700 cases with CABG were exclusively considered, and the other categories as well as combined surgeries were excluded.

Statistical analysis

Continuous variables were expressed as mean and standard deviation for those with normal distribution and as median and interquartile range (IQR) 25%-75% for those with non-Gaussian distribution. Qualitative variables were expressed as percentages. Comparisons between groups were performed using Student's t-test or Wilcoxon test according to the distribution for continuous data, and 2x2 tables were used, as well as the chi-square test with Yates' continuity correction for categorical variables. A p level <0.05 was considered significant. Uni- and multivariate logistic regression analyses were performed to identify independent variables of mortality, mortality, with their odds ratio (OR) and 95% confidence interval (95% CI). The Hosmer-Lemeshow test and the ROC curve were calculated for the corresponding model. Data were collected in REDCap and the analysis was performed with R software. (12,13)

Ethical considerations

The study was approved by the Ethics Committee of the Argentine Society of Cardiology.

RESULTS

A total of 700 patients who underwent exclusively CABG were included. In total, 70% of the surgeries were elective, 28% were emergencies and 2% were urgencies. The mean age was 64 ± 9.5 years; 16.3% were female, 81.4% had arterial hypertension, 38.6% diabetes mellitus, 42.3% acute myocardial infarction, 18.9% previous angioplasty and 22.4% some degree of left ventricular dysfunction. The most frequently affected vessels were the left anterior descending artery (95.3%), the circumflex artery (77%), the right coronary artery (71.6%) and the left main coronary artery (38.1%). Table 1 shows the main preoperative variables. In 93% of the cases, at least two bypasses were performed, and extracorporeal circulation (ECC) pump was used in 50.6% of them, with a median of 90 minutes (IQR 70-110); the median aortic clamping time was 50 minutes (IQR 25-74), the rest of the preoperative variables are shown in Table 2.

Regarding the main postoperative complications, the use of inotropic drugs was observed in 69.3% of the cases, being noradrenaline (85%) the most commonly used drug; atrial fibrillation was observed in 21.3%, low cardiac output syndrome in 12.6%, and bleeding in 8.3%. Overall in-hospital mortality was of 6.9% and the median number of inpatient days was 8 (IQR 6-13) (Table 3). In patients with a history of left ventricular dysfunction, in-hospital mortality was 13.1% compared to 5.1 % in those without it ($p<0.001$).

The mortality predictors in the univariate analysis are shown in Table 4. In the multivariate logistic regression model, the following postoperative variables were identified: use of inotropic drugs (OR 6.11; $p=0.015$), low cardiac output syndrome (OR= 3.09; $p=0.003$) and renal failure (OR= 5.76; $p=< 0.001$) (Table 5). Several variables known to have an impact on mortality, such as age, ECC time and aortic clamping

Table 1. Main preoperative variables

	n=700
Age, years, mean (SD)	64 (9.5)
Female, %	16.3
Cardiovascular risk factors	
Arterial hypertension, %	81.4
Diabetes mellitus, %	38.6
Dyslipidemia, %	64.7
Active smoking, %	22.4
Hereditary family history of coronary artery disease, %	14.9
Cardiovascular history	
Stable chronic angina, %	18.4
Heart failure, %	10.1
Acute myocardial infarction, %	42.3
CABG, %	6.7
Coronary angioplasty, %	18.9
Atrial fibrillation, %	4.6
Left ventricular dysfunction, %	22.4
Peripheral vascular disease, %	12.7
Stroke, %	5.1
Obstructive sleep apnea, %	3
COPD (moderate and severe), %	16.3
Reason for consultation	
Dyspnea, %	33.1
Precordial pain, %	81.4
Syncope, %	2.4
Acute pulmonary edema, %	2.3
Tachyarrhythmia, %	2
Involved coronary vessels	
Left main coronary artery, %	38.1
Left anterior descending artery , %	95.3
Left diagonal artery, %	23.4
Left circumflex artery, %	77
Lateral ventricular artery, %	10.6
Right coronary artery, %	71.6
Preoperative complexity	
Use of intra-aortic balloon counterpulsation, %	2.9
Use of Swan-Ganz catheter, %	1.7
Use of inotropic drugs, %	2.1
Mortality risk scores	
EuroSCORE II, median (IQR)	1.3 (0.8-2.4)
ArgenSCORE, median (IQR)	2.8 (1.8-5.8)

CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease;
IQR: interquartile range 25-75%; SD: standard deviation

Table 2. Intraoperative variables

	n=700
Distal beds	
Good, %	42.6
Regular, %	49.3
Bad, %	7.9
Operative times	
ECC time in minutes, median (IQR)	90 (70-110)
Aortic clamping time in minutes, median (IQR)	50 (25-74)
Use of ECC, %	50.6
Coronary artery bypass grafts	
Left internal mammary artery to left anterior descending artery, %	94.6
Right internal mammary artery to right coronary, %	24.4
Radial artery graft, %	4.4
Venous graft, %	80.1
Endarterectomy, %	2.3
Intraoperative complications	
Hemorrhage, %	4.3
Intraoperative cardiac arrest, %	1.6
Re-entry into ECC, %	0.9

ECC: extracorporeal circulation; IQR: interquartile range 25-75%.

Table 3. Postoperative data

	n=700
Intubated patients admitted to the recovery room, %	53
Low cardiac output syndrome, %	12.6
Need for inotropic drugs, %	69.3
Need for Swan-Sanz catheter, %	9.1
Postoperative infarction, %	3.3
Atrial fibrillation, %	21.3
Atrioventricular block, %	2.3
Complex ventricular arrhythmia, %	1.7
Temporary pacemaker, %	16
Permanent pacemaker, %	1.4
Renal failure, %	12.1
Bleeding, %	8.3
In-hospital mortality, %	6.9
Inpatient days, median (IQR)	8 (6-13)

IQR: interquartile range 25-75%.

time, bleeding and others were explored but they were not found to be statistically significant in this cohort. The history of left ventricular dysfunction, which was significant in the univariate analysis, was not significant in the multivariate analysis: its OR significantly modified the rest of the variables when included in the model. This suggests that it is a confounder, and that in the patients who developed these complications, this is probably explained by the fact that most of them were those who had a history of ventricular dysfunction. The area under the curve of this model was 0.79 (95% CI 0.72-0.85) (Figure 1). The Hosmer-Lemeshow test yielded a value of p= 0.738.

DISCUSSION

The ARGEN-CCV registry shows the results of cardiovascular surgery in Argentina after a decade since the last CONAREC XVI registry in 2010. Compared

Tabla 4. Univariate logistic regression model, mortality predictors.

Mortality predictors	OR	95% CI	p
Age	1.05	102-1.09	<0.001
History of left ventricular dysfunction	2.82	1.52-5.16	<0.001
Surgery without ECC	1.97	1.07-3.75	0.033
Clamping time	0.98	0.97-0.99	0.009
Postoperative use of inotropic drugs	10.73	3.27-66.13	<0.001
Postoperative low cardiac output syndrome	7.63	4.05-14.30	<0.001
Postoperative renal failure	9.23	4.91-17.44	<0.001

Tabla 5. Multivariate logistic regression model, mortality predictors

Mortality predictors	OR	95% CI	p
History of left ventricular dysfunction	1.12	0.53-2.32	0.751
Postoperative use of inotropic drugs	6.11	1.76-38.56	0.015
Postoperative low cardiac output syndrome	3.09	1.45-6.51	0.003
Postoperative renal failure	5.76	2.85-11.54	<0.001

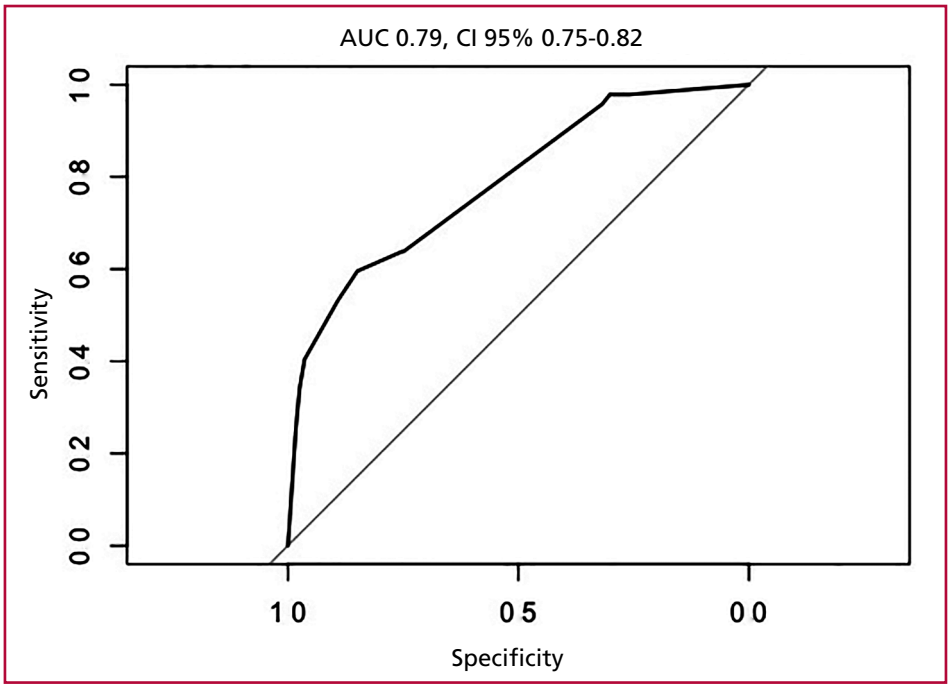

Fig. 1. Mortality prediction model. ROC curve.

AUC: area under the curve

to the previous registries, CONAREC III in 1993 and ESMUSICA in 1997, we can observe the advances in cardiovascular surgery in the last almost 30 years, with improvements in the materials used, new surgical techniques and an increasing number of patients undergoing CABG after being excluded from percutaneous procedures. (14-16)

This registry shows a high prevalence of diabetic patients (38.6%) compared to previous registries where the highest percentage reported was 30.4% (CONAREC XVI), showing the worrying progression of this well-known cardiovascular risk factor. (17) In terms of anatomy, 38.1% had severe involvement of the left main coronary artery, which is also the highest locally reported to date.

The most widely used grafts were the left mammary artery graft, followed by the vein graft, the right mammary artery graft and, to a lesser extent, the radial artery graft with almost half of the patients undergoing surgery without ECC.

During hospitalization, with a median of 8 days, a high use of inotropic drugs was observed, being noradrenaline the most commonly used. This drug is used to elevate blood pressure, mainly in the first hours of the patients' recovery, when greater lability is observed. This does not appear to reflect a genuine situation of low cardiac output syndrome, in which drugs with greater cardiotonic power such as dobutamine are used. Almost half of the patients were admitted to the recovery room extubated. Atrial fibrillation was the most frequent complication, followed by low cardiac output syndrome, renal failure, and bleeding.

Overall in-hospital mortality was 6.9%, higher than that reported in the CONAREC XVI registry, which was 4.3% for the CABG group. However, when comparing patients with a history of ventricular dysfunction, we found two clearly different groups: the mortality of patients with a history of ventricular dysfunction exerts traction on the overall mortality, as it was 13.1% versus 5.1% in the rest of the patients; nevertheless, high mortality is observed in patients with good ventricular function. (18) Consistent with this observation, in the multivariate analysis, the variables that best predict mortality are related to left ventricular dysfunction. This particular group of patients undoubtedly has the worst prognosis. Although this type of outcome is within the expected range of possible complications, according to the surgical teams, the magnitude of data helps to reinforce the necessary precautions to seek tools to improve the prognosis since, as we know, in several cases surgery is the only technically possible option.

Two of the most widely used perioperative scores, EuroSCORE and ArgenSCORE, were also used in the registry population. Although this work does not seek to validate data from these scores, the mortality predicted by these tools was significantly lower than that observed, which is consistent with a similar behavior observed in other Latin American populations. (19)

In addition, it is very important to highlight that this study was carried out during a very specific period in the history of the world health system and, therefore, in Argentina: the COVID-19 pandemic caused by SARS-Cov-2. It is difficult to isolate the context to evaluate the outcomes; specifically, the patients were enrolled in the registry during the period known as DISPO (preventive and mandatory social distancing) established by the National Executive Power, which had direct consequences on social behavior and affected the dynamics of the health system. As is well known from local and international reports, there was a decrease in the number of cardiology consultations by the population, many centers were converted to meet the demand for COVID-19 and health personnel experienced a saturation that complicated routine care. (20,21)

In spite of this, the ARGEN-CCV registry was able to be conducted and provided us with data on the reality in context, more than a decade after the last multicenter registry in Argentina.

One of the weaknesses of this registry was that the data obtained in both public and private centers, despite the considerable number compared to previous registries, may not reflect the reality of all the institutions, and a greater participation of centers and number of cases may be necessary to validate or refute the results.

CONCLUSION

In the ARGEN-CCV registry, in patients undergoing coronary artery bypass grafting we observed a higher percentage of diabetic patients and patients with left main coronary artery disease than in previous local registries. Despite the years that have elapsed since the last coronary artery bypass grafting registry, there is evidence of persistent surgical morbidity and mortality, particularly in patients with left ventricular dysfunction.

Conflicts of interest

None declared.

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

Acknowledgments

Special thanks are given to the centers participating in the registry at a time of difficulties in the health system and to the ARGEN-CCV group.

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New Electrocardiographic Leads and Regional Vectorcardiograms

Nuevas derivaciones electrocardiográficas y vectorcardiogramas regionales

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ABSTRACT

Precordial bipolar leads (PBL) provide new information from the standard 12-lead ECG. These leads are an ideal complement to the traditional unipolar leads (V1 to V6) of the ECG because they are practically perpendicular to the latter and allow evaluation of the right-to-left and anteroposterior precordial axes, as well as the construction of regional vectorcardiograms (RVCG) that enable the selection of the specific myocardial region to be studied without interference from other parts of the heart.
An important advantage is that, using the appropriate software, it is possible to simultaneously generate the standard ECG and VCG as well as the new leads and RVCG. All this information can be derived from data stored in a hospital database, provided they have been digitally recorded by a simultaneous 12-channel ECG. This means that no additional electrodes or cables and no extra technical work are required.
Using typical ECG data, various bipolar leads, weighted unipolar leads, RVCG and ECG circular charts can be created. These new displays have made it possible to identify previously undetected abnormal electrophysiological patterns.

Keywords: Electrocardiography - Myocardial ischemia – Arrhythmia - Myocardial infarction

RESUMEN

Las derivaciones bipolares precordiales (PBL, Precordial Bipolar Leads, por su denominación en inglés) proporcionan nueva información a partir del ECG estándar de 12 derivaciones. Estas derivaciones son un complemento ideal de las derivaciones unipolares clásicas (V1 a V6) del ECG porque son prácticamente perpendiculares a estas últimas y permiten evaluar los ejes precordiales derecha-izquierda y anteroposterior, así como crear vectorcardiogramas regionales (VCGR). Los VCGR posibilitan la selección de la región miocárdica específica que se desea estudiar sin interferencias de otras partes del corazón.
Una ventaja importante es que, usando el software adecuado, es posible generar simultáneamente tanto el ECG y el VCG estándar como las nuevas derivaciones y VCGR. Toda esta información puede derivarse de los datos almacenados en la base de datos de un hospital, siempre y cuando hayan sido registrados digitalmente por un ECG de 12 canales simultáneos. Esto significa que no se requieren electrodos o cables adicionales, ni trabajo técnico extra.
Con el uso de los datos del ECG clásico, se pueden crear diversas derivaciones bipolares, unipolares ponderadas, vectorcar¬diogramas regionales y gráficos circulares del ECG. Estas nuevas presentaciones han permitido identificar patrones electro¬fisiológicos anormales que antes no habían sido identificados.

Palabras claves: Electrocardiografía - Isquemia miocárdica - Arritmias - Infarto de miocardio

INTRODUCTION

Precordial bipolar leads (PBL) have been described more than a century ago. In addition to the Lewis, Nehb, Cossio and Fontaine leads, (1-4) PBL are commonly used in operating room and intensive care monitoring and also in the Holter study. However, their use is empirical, not systematized and their electrodes are not the same as those of the standard ECG. In contrast, this review analyzes a new systematized electrocardiographic method that does not require additional cables or extra technical work, since it is based on the processing of data obtained from a simultaneous 12-channel digital electrocardiogram, either from a patient or stored in a database. (5,6) Recombination of recordings allows the creation of various bipolar leads, weighted unipolar leads and regional

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vectorcardiograms, as well as ECG circular charts. (7) These new presentations not only help in the detection of electrocardiographic pathologies, but also, as with PBL, show electrical phenomena in the right-left and anteroposterior axes that are not visible in the 12 standard ECG tracings.

RATIONALE FOR PRECORDIAL BIPOLAR LEADS (PBL)

A PBL measures the potential difference between two classic precordial electrodes, one designated as positive and the other as negative. It is important to remember that standard ECG precordial leads are unipolar leads (PUL), using the central Wilson terminal as neutral and an electrode applied to the skin as positive. By different combinations of PUL V1 to V6, up to 15 PBL can be generated, almost perpendicular to the midline joining the originating PUL, and study the cardiac sector between the two PUL electrodes. (8) For example, Fontaine lead II is similar to PBL V4-V1 or V5-V2. (4)

Therefore, PBL created from V1 to V4 explore the right-left axis, while V6-V3 does so in an oblique plane and V6-V4 examines the anteroposterior axis (Figure 1).

DESCRIPTION OF THE NEW METHODOLOGY

This new technology involves the generation of PBL, weighted precordial unipolar leads (WPUL) and the construction of regional vectorcardiograms (VCGR), plotting a PBL versus a PUL or a WPUL. Moreover, since they are digital data, reliable measurements can be made of the time and amplitude of electrical phenomena, which is crucial for detecting time and amplitude alterations secondary to myocardial ischemia.

The digital ECG standards studied to apply our new methodology are from the STAFF III and PhysioBank ATM: PTB DIAGNOSTIC ECG databases, which are publicly available. (9-11)

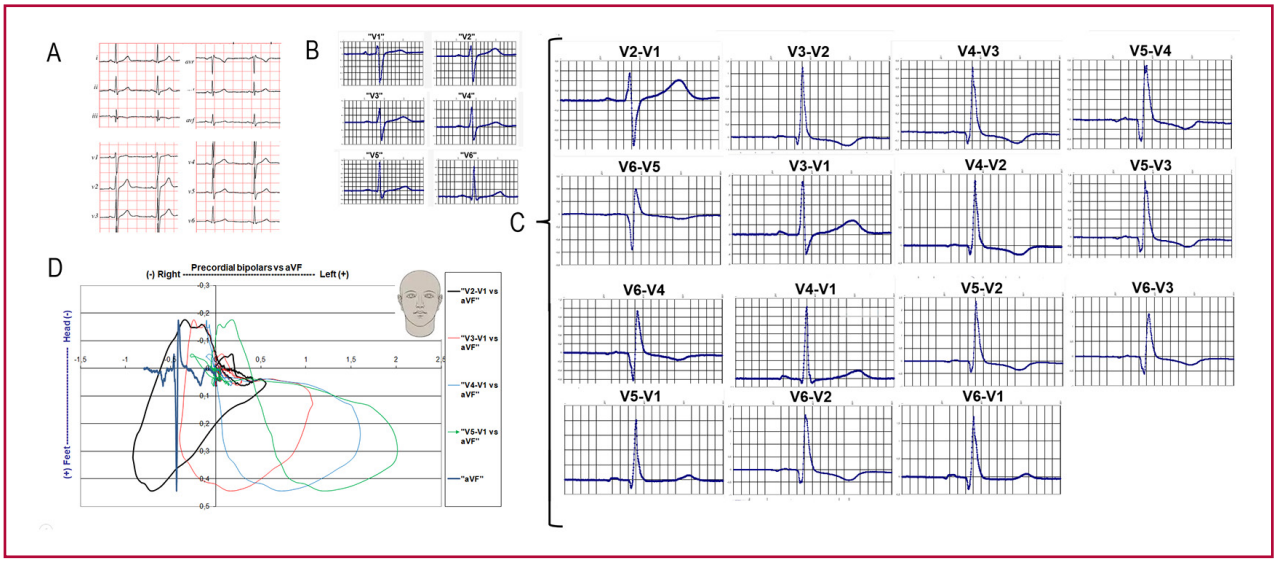
Precordial bipolar leads (PBL)

It is important to remember that leads I, II and III of the standard ECG are bipolar. Therefore, PBL simply consist of selecting one of the precordial electrodes as the right arm (negative) and the other as the left leg or arm (positive). As a working rule, we have established that the leftmost electrode is considered positive [e.g., V2 (+) V1 (-), V6 (+) V1 (-), V6 (+) V4 (-), etc.].

Then, by comparing V2 with V1, we obtain PBL V2-V1, and by doing so between V6 and V4, we obtain PBL V6-V4. PBL V2-V1 is especially important, as it scans the retrosternal area and is highly sensitive to septal and right ventricular (RV) disorders.

Weighted precordial unipolar leads (WPUL)

Weighted precordial unipolar leads are created using complementary ratios of two PUL. The most common ratio is the average of the two (50% of each). Therefore, WPUL V2+V4 is equal to the average of both and should be equivalent to PUL V3 (or PUL V5 in the case of WPUL V4+V6). Similarly, WPUL V1+V2 would be equivalent to having an electrode in the middle of the sternum. This method has been validated in



PBL: precordial bipolar lead; PUL: precordial unipolar lead.

Fig. 1. Control patient. A. Standard simultaneous 12-channel ECG. B. Digital tracings of PUL in "A" differ in that they are plotted to show more detail, sacrificing the relative amplitude comparison. C. The 15 PBL that can be created with the standard ECG PUL, using the leftmost electrode as positive and the rightmost electrode as negative. Note that the lateral PBL (V6-V4 and V6-V5) have their positive electrode to the back, so they start with a significant Q wave, indicating that the initial vector has a postero-anterior direction. D. Comparative graph showing the PBL loop in the frontal plane, built using aVF as a cephalocaudal reference

other publications (5-7) and is routinely used in many electrocardiographic machines to calculate some of the standard leads. (12,13)

Regional electrical activity loops (regional vectorcardiograms: RVCG)

These loops are created by combining classic PUL or WPUL with PBL, which are perpendicular to the former. Regional vectorcardiograms allow the study of the septum and anterior wall, (14) as well as the cardiac apex. (15) In addition, they magnify local electrical phenomena compared with other regions. To facilitate interpretation, especially for users unfamiliar with vectorcardiography, it is possible to add to these loops the tracings that give them origin. Using the coordinate axes to indicate time and voltage, the two measurements can be compared. For example, the "X" axis represents the voltage of the "right-to-left" lead, but also constitutes the time base for the anteroposterior lead (Figure 2). On the other hand, the opposite is true for the "Y" axis. This not only allows observation of the RVCG loop distortions, but also facilitates estimation of time and electrical amplitude of each phenomenon.

Monitoring the progress of cardiac activation (Circular ECG)

Unlike the ECG recording slip, the circular ECG presents all the leads of a plane superimposed in a circle, where the radius represents amplitude and the perimeter represents time. This representation facilitates the appreciation of temporal differences in electrical activity, which makes it especially useful for observing pre-excitation syndromes (Figure 3). (7)

REPRESENTATION OF REGIONAL ELECTRICAL ACTIVITY

Since each PBL scans a particular region of the myocardium, it is not possible to analyze all of them in one review. Therefore, in this review we focused only on that related to the retrosternal area leads.

Weighted unipolar lead V1+V2 (WPUL V1+V2)

As mentioned above, this lead represents the average of the classic V1 and V2 leads. Therefore, it is positioned in the center of the sternum, perpendicular to PBL V2-V1. This spatial arrangement allows the construction of a RVCG that explores the retrosternal area in the transverse plane. In addition, using the cephalocaudal aVF lead associated with PBL V2-V1, a retrosternal frontal plane RVCG can be generated. In the latter case, although the amplitudes are slightly dissimilar, the spatial arrangement is maintained.

Precordial bipolar lead V2-V1 (PBL V2-V1)

This lead is similar to placing the right arm electrode in V1 and the left arm electrode in V2. It is one of the most useful leads because it examines the right-left axis of the retrosternal space, which is not explored in the standard ECG. The center of this lead is in the middle of the sternum and clearly defines the patient's electrical right and left. This distinction is important to contrast the differences between these new leads and those of the standard ECG; while in the latter it is accepted that the first vector is directed to the right, we have observed in 43 of 52 (83%) controls that in PBL V2-V1, the first vector is directed to the left (unpublished data). This discrepancy may be attributed to the fact that PBL V2-V1 only encompasses the retrosternal sector, whereas the traditional ECG considers the whole heart, resulting in different initial vectors.

Regional retrosternal vectorcardiogram (WPUL V1+V2 vs. PBL V2-V1 and aVF vs. V2-V1)

As mentioned above, the creation of these two RVCGs allows a three-dimensional appreciation of retrosternal electrical activity (Figure 2).

In the transverse plane, the efferent branch of the retrosternal RVCG QRS loop points to the left and forward while the afferent branch ends in the right and posterior quadrant, drawing an oval. In the case of anterior wall infarction, septal electrical forces are lost and the leftward deflection of PBL V2-V1 disappears (Figure 4, right panel). (12) In complete left or right bundle branch blocks, the loop formed by PBL V2-V1 vs. WPUL V1-V2 points backward. (7) PBL V2-V1 is especially useful in right coronary artery (RCA) occlusion because it shows a rightward shift of the ST-segment, suggesting right ventricular ischemia. (16)

NEW METHODS AND CARDIAC PATHOLOGY

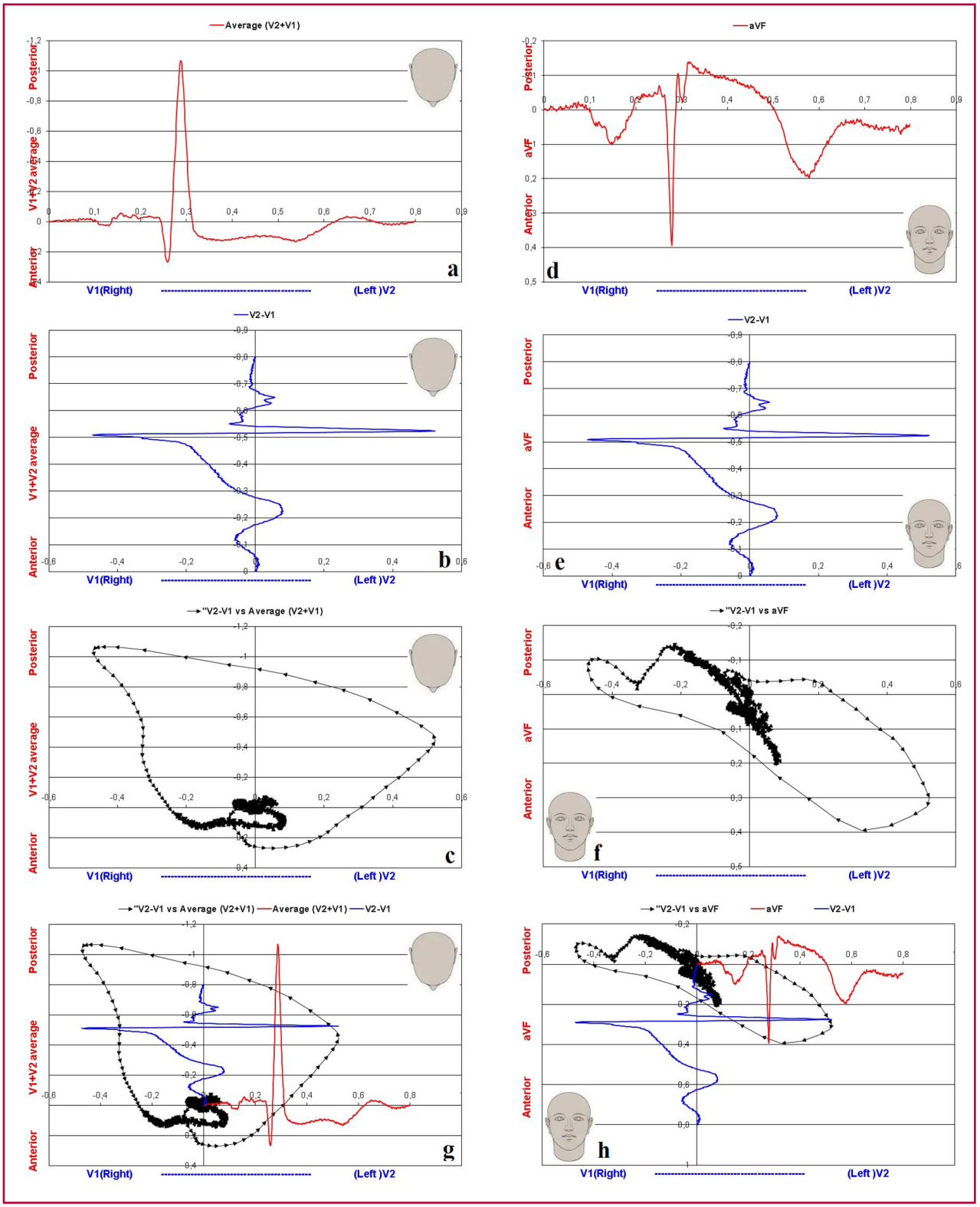
Acute myocardial infarction

Because PBL V2-V1 focuses on the retrosternal region and excludes much of the left ventricle, the initial normal QRS vector, unlike the standard ECG, tends to point to the left. This transverse retrosternal RVCG loop is oval, counterclockwise, and passes through all four quadrants.

In patients with anterior myocardial infarction, necrosis overrides the electrical forces of the interventricular septum. (7) As a result, electrical forces from the right ventricle take on greater representation and deflect the vectors to the right. In this pathology, PBL V2-V1 may present three different patterns: a. QS (indicating absence of leftward forces in PBL V2-V1), b. Initial Q (i.e., the initial vector goes to the right) and c. Negative notch after the onset of the QRS wave, giving a "bitten apple" pattern in the RVCG of the area (Figure 4).

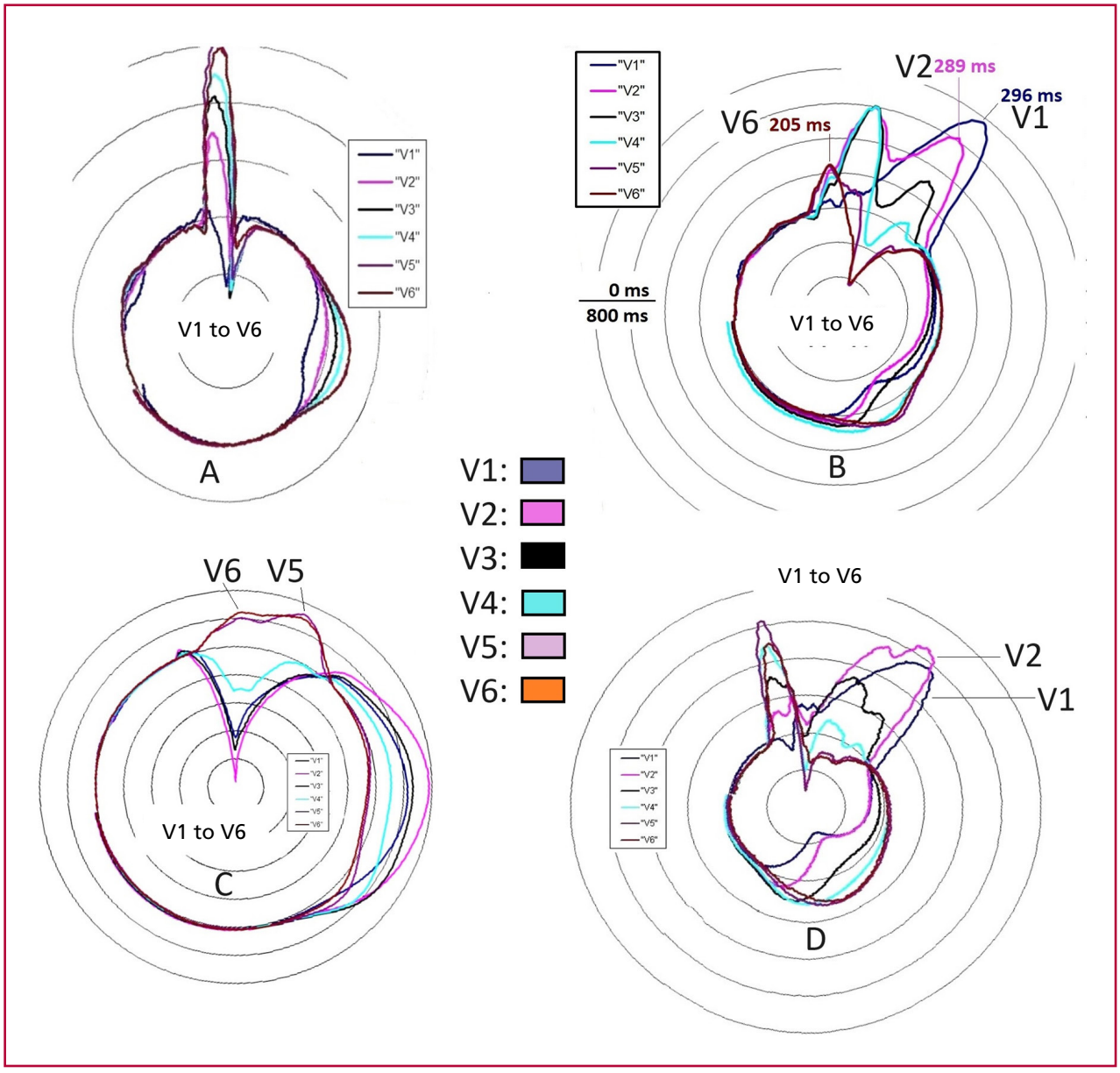
Hyperacute ischemia

Precordial bipolar leads have been shown to be particularly useful in the evaluation of ST-segment elevation in hyperacute ischemia. In a study of sixteen patients presenting with acute proximal left anterior descending artery (LAD) occlusion, the retrosternal transverse loop showed two typical patterns: 1. QRS folding or 2. QRS transport. (17)



RCA: right coronary artery; PBL: precordial bipolar lead; RVCG: regional vectorcardiogram; WPUL: weighted precordial unipolar lead.

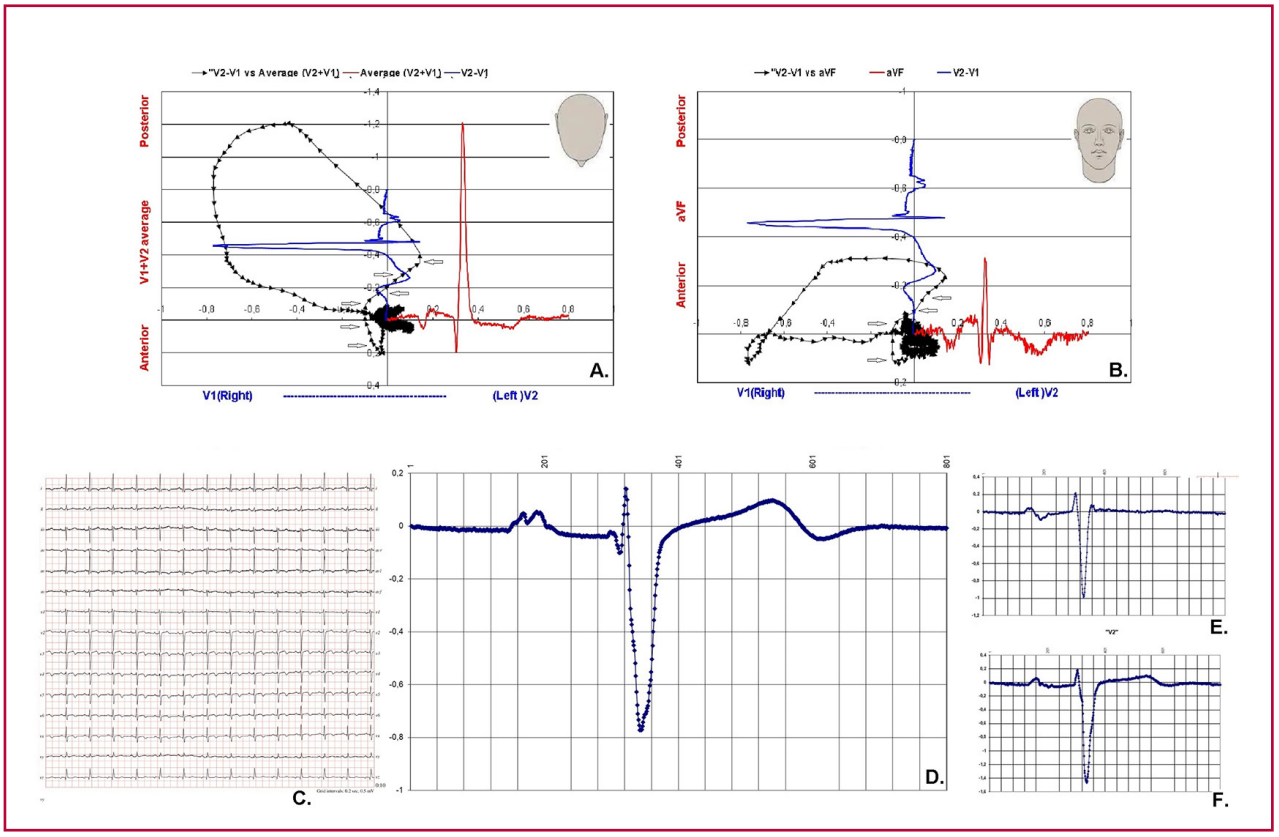
Fig. 2. Patient with RCA middle third occlusion. Panels a, b, c and g: retrosternal transverse plane. Panels d, e, f and h: retrosternal frontal plane. Panels a and d show only the unipolar lead and its influence on the loop (a: WPUL V1+V2 and d: aVF). Panels b and e show PBL V2-V1 and its influence on the loop. Panels c and f show the sum of the two leads and the loop they generate. Panels g and h integrate the traces and the RVCG loop. It is important to note that in the transverse plane there is continuity in the QRS complex loop and the T-wave loop, which generates the "omega" sign of ischemia. In all panels, the "X", "Y" and "Z" axes represent time (milliseconds) for one tracing and amplitude (mV) for the other. In aVF, the positive vector is directed towards the patient's feet. Therefore, in these graphs, the aVF tracing is inverted compared with the standard ECG



RBBB: complete right bundle branch block; LBBB: complete left bundle branch block; WPW: Wolf Parkinson White.

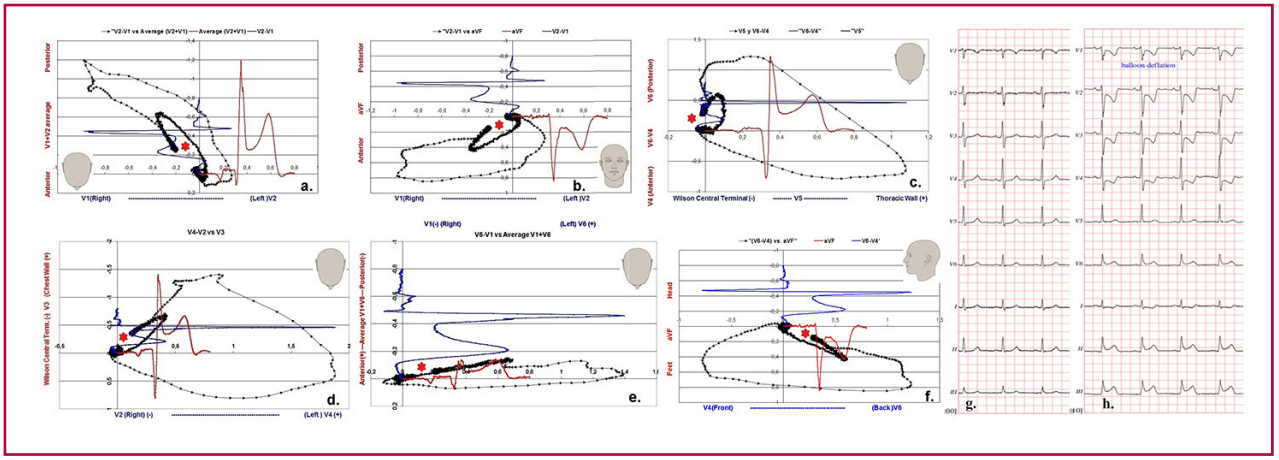
Fig. 3. A. Normal circular ECG of the transverse plane (V1 to V6). **B.** Circular ECG in a patient with WPW syndrome. Depolarization is seen to begin in V6 (205 ms) while V2 and V1 show a delay (289 and 296 ms respectively). V1 peaks 91 ms after V6. The dissociation between left and right precordial leads suggests two different depolarization pathways. **C.** Circular ECG in LBBB. The typical "plateau" of V5 and V6 is observed, as well as the negative depression in V1 to V4. **D.** Circular ECG in a RBBB. A delay is seen in the final portion of V1 and V2. Normally, the delay in V1 is greater than in V2

In turn, in a group of 45 patients, 16 with left anterior descending artery (LAD) occlusion, 17 with right coronary artery (RCA) occlusion and 12 with circumflex artery (Cx) occlusion, 100% showed lesion current in PBL V2-V1. (16-18) The direction of the lesion current varied in these patients: in 16 of the 45 patients (15 with LAD occlusion and 1 with RCA occlusion), the lesion current was to the left, whereas in the remaining 29 (1 with LAD occlusion, 16 with RCA occlusion and 12 with Cx occlusion), the lesion current was to the right. Importantly, these lesion currents, which are always present in the retrosternal loop, can coexist (especially in cases of Cx occlusion) with lesion currents of opposite direction in standard PUL V5 and V6. This may generate electrical cancellation on the 12-channel ECG (Figure 5). (16-18)



PBL: precordial bipolar lead; RVCG: regional vectorcardiogram.

Fig. 4. 75-year-old male patient with a 2-day evolution anterior infarction. Tracings and retrosternal RVCG in transverse and frontal plane (A and B), standard ECG (C), PBL V2-V1 (D), and standard PUL V1 and V2 (E and F) are shown. In both RVCG, the bitten apple sign (arrows) is observed due to a rightward return of the initial portion of the QRS, indicating momentary predominance of the electrical forces from the right. Note that subtraction of the V1 recording (E) from V2 (F) causes the P negative portion of V1 to become positive, forming a bimodal P in the PBL (D). The PBL V2-V1 tracing shows a negative wave after the onset of the QRS which translates into the "bitten apple" sign in RVCG.



PBL: precordial bipolar lead; WPUL: weighted precordial unipolar lead.

Fig. 5. Transverse (a, c, d and e), frontal (b) and sagittal (f) planes. Baseline (panel g) and ischemic (panel h) ECGs. Coordinate axes represent millivolts and milliseconds.
Panel a: PBL V2-V1 vs. average WPUL V1+V2. Panel b: PBL V2-V1 vs. aVF. Panel c: PBL V6-V4 vs. V5. Panel d: PBL V4-V2 vs. V3. Panel e: PBL V6-V1 vs. average WPUL V1+V6. Panel f: PBL V6-V4 vs. aVF. All loops were obtained during maximal ischemia. In panels a and b a lesion current is seen directed to the right while in panel c the same current is directed backwards. In panels d and e the lesion current is directed to the left while in panels b and f the J point and ST-segment are deflected downwards. A positive omega sign is observed in all the loops (asterisk).

Additionally, the presentation of the loops in two axes or in three dimensions allows to clearly identify the J-point, the ST-segment deflections and the omega sign even when no displacement of this is observed in the standard ECG (Figure 5). (19)

Complete left bundle branch block (LBBB)

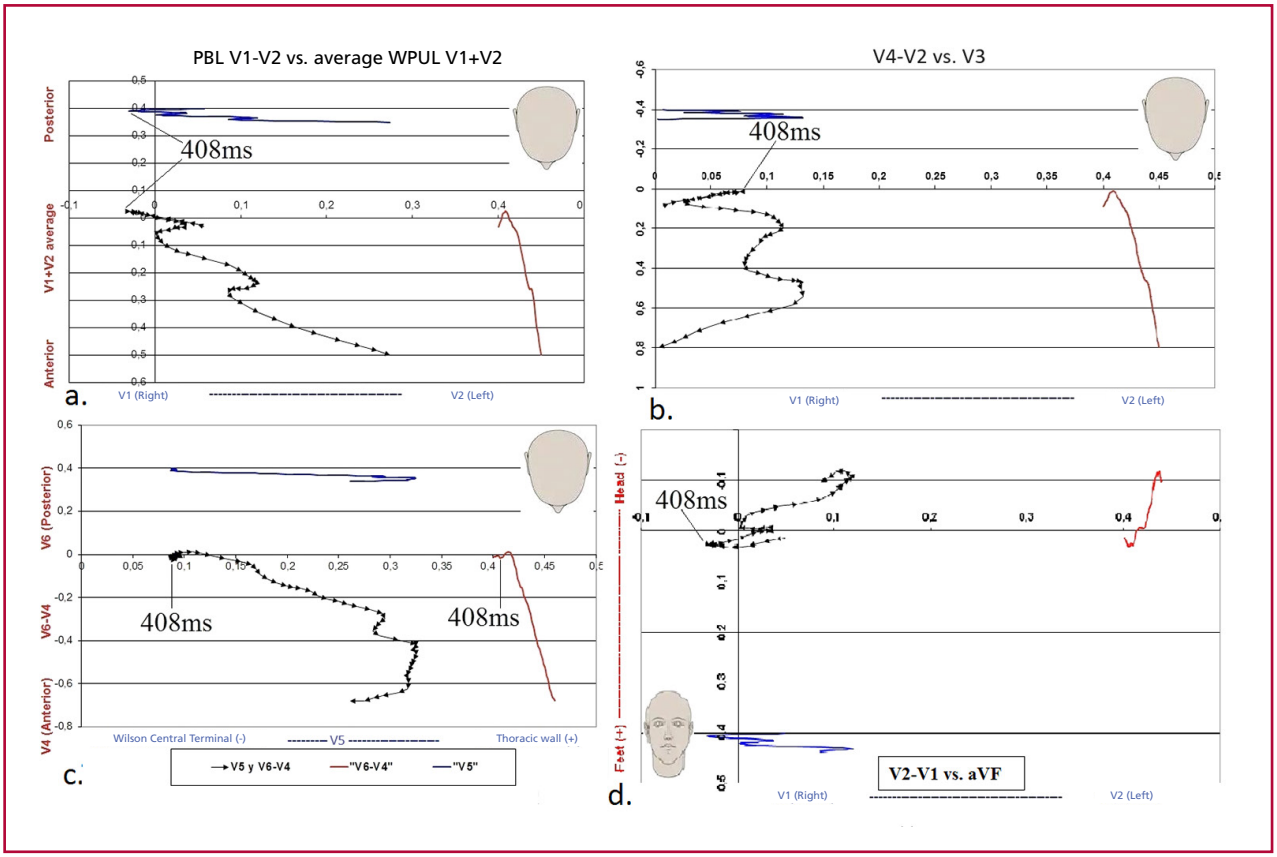
As mentioned above, PUL V5 constitutes the midpoint between PUL V6 and V4. When conduction disorders suppress the forward-pointing vectors, PBL V6-V4 tracing shows only an R wave, without the initial Q seen in healthy patients. In cases of LBBB, where the initial septal depolarization is abnormal, the entire QRS loop observed from PBL V6-V4 is posterior to the PUL V5 axis. In addition, because in LBBB, PUL V1 and V2 have the same negative amplitude and are almost simultaneous (both electrodes are stimulated at almost the same time), PBL V2-V1 will be of very small amplitude and will only show the slightest differences between the two in time. (5-7) The circular ECG will very clearly show the delayed activation with a typical wide-mouth "pac-man" figure in the right precordial leads and a "plateau" figure in the left leads (Figure 3, panel C).

Complete right bundle branch block (RBBB)

In patients with RBBB, the final QRS forces in PUL V1 show a significant delay, with an increase in voltage, so that it always appears posterior to the PUL V2 peak R wave. Also, the normal time difference between the intrinsic deflection of PUL V6 and PUL V1 is reduced. (5-7) In the circular ECG, the delay of the PUL V1 peak R wave is clearly observed (Figure 3, panel D).

Arrhythmias

Because these new methods analyze only one beat at



PBL: precordial bipolar lead; PUL: precordial unipolar lead; RVCG: regional vectorcardiogram; WPUL: weighted precordial unipolar lead.

Fig. 6. Onset of an arrhythmia as seen from different RVCG. The first 393 ms and the last 350 ms of the QRS loops have been removed to show the onset of the arrhythmia.
Panel (a): PBL V2-V1 vs. WPUL V1+V2. Panel (b): PBL V4-V2 vs. WPUL V3. Panel (c): PBL V6-V4 vs. PUL V5. Panel (d): PBL V2-V1 vs. aVF. The initial tracing shows the last 15 milliseconds of the normal beat before the arrhythmia, which begins at 408 ms. In the 3 panels of the transverse plane, the vectors at the end of the normal beat and at the beginning of the ectopic beat are almost identical, but of opposite direction, whereas in the frontal plane (d), there is a U-turn with the normal part slightly more caudal than the abnormal one. It should be noted that when the observation point varies from (a) to (b), there is a specular inversion of the tracing. In (c), the phenomenon is observed from the lateral side (PBL V6-V4 vs. PUL V5) and the tracing of the arrhythmia onset is reduced to one point.

a time, the investigative or diagnostic value of this methodology is limited. Figure 6 shows the onset of an arrhythmia after balloon inflation in the proximal LAD. Only an interval of approximately fifty milliseconds from the onset of the arrhythmia is shown, which was examined using different RVCG. (19)

In the case of pre-excitation syndromes, the circular ECG shows with high accuracy the activation sequence of the various ECG leads, and allows clear identification of the area that depolarizes first (Figure 3, panel B).

CONCLUSION

Although electrocardiography is almost 150 years old, this new information supports the implementation of new electrocardiographic diagnostic methods, resulting in a valuable addition to current clinical practices. Weighted PUL that match PUL V3 and V5 allow verification of correct electrode positioning. Moreover, PBL, due to their proximity to the myocardium, provide signals of higher amplitude and quality, with a better signal-to-noise ratio (PBL V6-V1 is similar to the standard ECG lead I, but with much higher amplitude and signal-to-noise ratio). Given that PBL V2-V1 has a high sensitivity for detecting ischemic ST-segment changes, it would be highly desirable to use it in patients with suspected acute myocardial infarction. This would involve repeating the ECG but placing the electrode of the right arm in V1 and that of the left arm in V2.

Although experienced cardiologists can make accurate diagnoses with the traditional ECG, it is important to consider that electrocardiograms are often interpreted by less experienced physicians, for whom any assistance would be beneficial. Therefore, it would be desirable to incorporate an algorithm into electrocardiography machines to show the additional diagnostic information provided by this new methodology.

In addition, it is important to keep in mind that many hospitals store their electrocardiograms in databases. The ability to access these records and reprocess data from prior studies could reveal new signs of previously undocumented pathologies. (20)

Ethical considerations

The authors report that approval by the corresponding ethics committee does not apply.

An informed consent request does not apply.

Artificial intelligence was not used in this article.

There was no sex or gender bias in the present work.

Financing

None

Conflicts of interest

None declared.

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

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SCIENTIFIC LETTER

Hypertrophic cardiomyopathy associated with genetic variant MYBPC3:c.1119 C>G (p.Tyr373Ter)

Cardiomiopatía hipertrófica asociada a variante genética en MYBPC3:c.1119 C>G (p.Tyr373Ter)

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Hypertrophic cardiomyopathy (HCM) is a genetic disease with a pathophysiological basis characterized by left ventricular hypertrophy not explained by another cardiac, systemic or metabolic condition. Although in the past it was considered a rare entity, in the United States the prevalence of asymptomatic cases is 1:500 inhabitants and 1:3000 inhabitants for symptomatic cases. (1) These data suggest that HCM is a common disease that may be under-diagnosed and of increasing importance for cardiologists in their clinical practice.

We report the case of a 65-year-old male patient who sought medical care due to palpitations which appeared two months before consultation, without chest pain, dyspnea or syncope. Among the most important antecedents, he had a 30-year-old son with a positive genetic test for hypertrophic cardiomyopathy associated with MYBPC3 mutation. The patient denied episodes of sudden cardiac death in his family. The physical examination was normal.

The initial workup included an electrocardiogram and a 24-hour Holter monitoring which showed sinus rhythm with isolated premature atrial contractions. The ambulatory blood pressure monitoring was normal and the transthoracic echocardiogram revealed a left ventricular ejection fraction of 63%, preserved wall motion, basal anteroseptal hypertrophy of 20 mm without dynamic left ventricular outflow tract obstruction (Figure 1), mild aortic regurgitation, mild mitral regurgitation with no systolic anterior motion, and absence of diastolic dysfunction. The patient underwent cardiac magnetic resonance imaging which demonstrated diastolic basal anteroseptal segment thickness of 22 mm with intramyocardial late enhancement, and diastolic inferoseptal segment thickness of 16 mm. There were no other hypertrophic segments or left ventricular outflow tract obstruction (Figure 2).

Based on these findings, we decided to perform a gene panel for HCM, which identified a nonsense variant in heterozygous state in MYBPC3 gene c.1119C>G (p.Tyr373Ter), classified as a pathogenic variant by PVS1, PM2 and PM6 criteria. (2) Medical therapy with bisoprolol 5 mg daily was initiated, reducing the symptoms. The estimated risk of sudden cardiac death using the HCM Risk-SCD score was low (2.2%), indicating that the patient was not yet a suitable candidate for devices for sudden cardiac death prevention or septal myectomy. (3)

Hypertrophic cardiomyopathy is a disease with a predominantly autosomal dominant inheritance pattern, with incomplete penetrance. It primarily affects sarcomere proteins. Left ventricular hypertrophy can have any distribution pattern; however, it is most common in the basal anterior septum, followed by the left ventricular anterior free wall. (1) It should be suspected when end-diastolic left ventricular wall thickness is ≥ 15 mm on echocardiogram or cardiac magnetic resonance imaging. In patients with a positive genetic test or family history of HCM, the diagnosis should be considered with values ≥ 13 mm. (3)

The clinical presentation varies from asymptomatic cases to patients with palpitations, chest pain, syncope and sudden cardiac death in young people and athletes. (1). Besides left ventricular outflow tract obstruction, it is important to identify other risk markers for sudden cardiac death, such as non-sustained ventricular tachycardia, ventricular wall thickness ≥ 30 mm, syncope, and left atrial diameter (also important in atrial fibrillation, the most common arrhythmia in HCM). (2) A detailed medical record, physical

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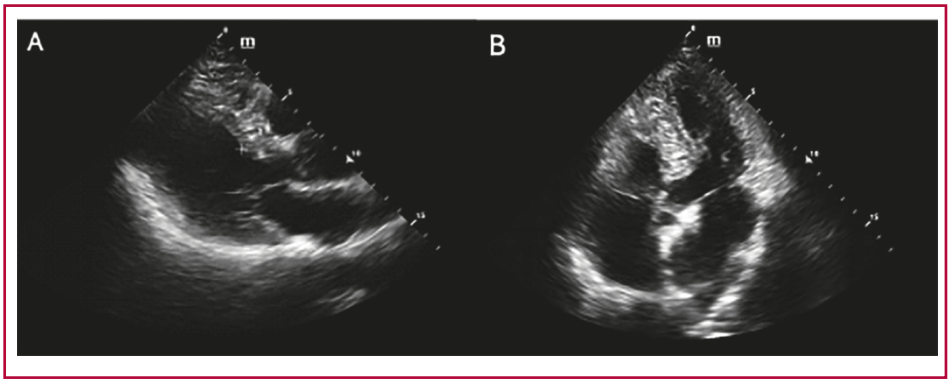

Fig. 1. Transthoracic echocardiogram. **A**) long axis view and **B**) 4-chamber-view, showing increased interventricular septum thickness.

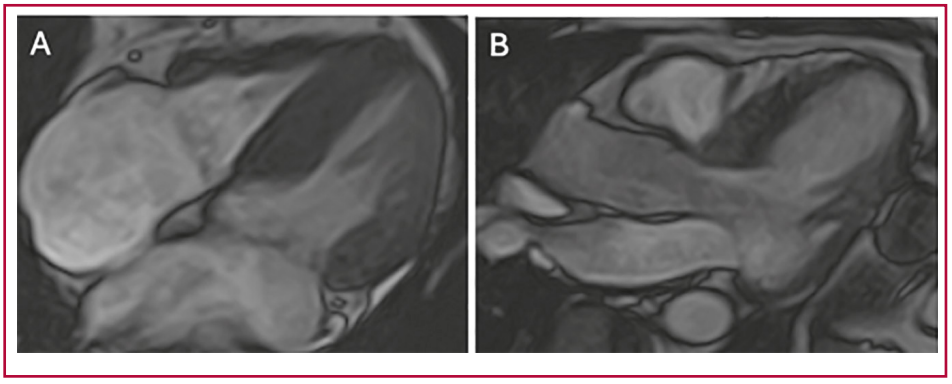

Fig. 2. Cardiac magnetic resonance imaging. **A**) Four chamber view with significant thickening of the interventricular septum. **B**) Left ventricular outflow tract, with absence of obstruction.

examination and complementary tests are essential to rule out diseases that may mimic HCM, such as RASopathies, lysosomal or glycogen storage diseases, Fabry disease and amyloidosis.

While echocardiography and cardiac magnetic resonance imaging are essential for diagnosing this condition, other diagnostic tests, such as electrocardiogram, 24-hour Holter monitoring, ambulatory blood pressure monitoring and genetic testing are also crucial for a comprehensive evaluation, prognosis and tailored management plan. The toolkit for this entity includes cardioselective beta-blockers, non-dihydropyridine calcium channel blockers, disopyramide, septal reduction therapy and, more recently, mavacamten.

The most common variants occur in the MYH7 (β-myosin heavy chain) and MYBPC3 (myosin-binding protein C) genes with penetrance of 65% and 55%, respectively, according to the meta-analysis by Topriceanu et al. which evaluated the penetrance of sarcomeric gene variants in HCM. (4) Most cases of MYBPC3 mutations are characterized by a late onset and a favorable clinical course; (5) however, Herrera et al. have described MYBPC3 variants linked to sudden cardiac death. (6) Even so, the European Society of Cardiology states that the role of sarcomeric variants as a predictor of sudden cardiac death independent of existing risk-prediction models remains to be demonstrated. (3) The mechanisms underlying the development of HCM in the context of sarcomeric variants include haploinsufficiency (when one copy of a gene is inactivated or deleted and the remaining functional copy of the gene is not adequate to produce the needed gene product to preserve normal function), increased calcium sensitivity, and direct toxicity of the defective protein. (5) In particular, the MYBPC3:c.1119 C>G (p.Tyr373Ter) variant causes a premature termination codon, forming a truncated protein that is explained by the haploinsufficiency phenomenon. Although this variant has a record in ClinVar, it is not present in population databases, and its allele frequency in gnomAD (Genome Aggregation Database) is not documented. In our case, this variant was associated with a favorable clinical course and low risk of sudden death. Nevertheless, further case studies and prospective research are required to validate this information.

In conclusion, the phenotype of the clinical presentation is variable in patients with MYBPC3 variants. Therefore, it is important to characterize genetic variants and their clinical outcomes in order to individualize the optimal medical therapy and to establish a reliable clinical prognosis. To the best of our knowledge, this would be the first case report of the MYBPC3:c.1119 C>G (p.Tyr373Ter) variant and its potential favorable phenotypic correlation.

Ethical considerations

The patient signed an informed consent form for the development of this study. Approval from the institutional review

board was not required, since, according to the 2016 International Ethical Guidelines for Health-related Research Involving Humans (CIOMS), this research is safe. We declare that this article does not contain any personal information that could be used to identify the patient.

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Conflicts of interest
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(See conflicts of interest forms on the website).

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SCIENTIFIC LETTER

Recurrent Infective Endocarditis Due to *Klebsiella Pneumoniae*

Endocarditis infecciosa recurrente por Klebsiella pneumoniae

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Infective endocarditis (IE) is the inflammation of the heart's lining and valves of infectious origin. (1) It is classified as acute, subacute, and chronic. (2) It is also necessary to differentiate whether a native or prosthetic valve is involved, the number of valves affected, and the form of acquisition (in the community or associated with health care). (3)

In developed countries, IE has an annual incidence of approximately 2.7 to 10 cases per 100 000 persons per year. In Colombia, the incidence is around 0.25 to 0.31 per 100 000 inhabitants, translating into approximately 500 cases annually. Mortality varies among different populations but may range from 15% to 45% of cases, depending mainly on the age and the patient, whether it affects a native or prosthetic valve, and the causal microorganism. (1,2)

In 80 to 90% of cases, gram-positive bacteria such as streptococci, staphylococci, and enterococci are IE most frequent causative agents. In a smaller proportion, HACEK gram-negative bacilli (*Haemophilus spp., Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella spp.*), non-HACEK gram-negative bacilli, and fungi are isolated in this pathology. (2)

Several factors favor this infection, including bicuspid aortic valve, mitral valve prolapse, congenital cardiac malformations, rheumatic fever, valve prostheses (especially those recently implanted), implantation of intracardiac devices, age over 60 years, male sex, immunosuppression, and long-term venous access devices. (3)

We present the case of a 56-year-old male, farmer, without medical history of cardiovascular risk factors or illness. He consulted a first-level hospital for lower abdominal pain, fever, chills, dysuria, pollakiuria, urinary urgency, and urinary retention. The patient presented with a heart rate of 80 bpm, respiratory rate of 20 breaths per minute, blood pressure of 110/80 mm Hg, oxygen saturation of 92% on room air and a temperature of 38.2°C. Physical examination revealed diaphoresis, hypogastric pain, and a ballon-like bladder. Laboratory tests showed leukocytosis (24 700 cells/μL, 95% neutrophils), hemoglobin 11.8 g/dL, platelet count 28 000, sodium 123 mmol/L, potassium 4 mmol/L, and blood urea nitrogen (BUN) 158 mg/dL. Prostate specific antigen (PSA) was elevated at 10.4 ng/mL.

The urinary tract tomography revealed bilateral perirenal inflammatory changes. Blood cultures identified *Klebsiella pneumoniae ESBL ssp* (producing extended-spectrum beta-lactamase), resistant to several antibiotics including ceftazidime, ceftriaxone, and ciprofloxacin, but sensitive to imipenem, meropenem, tigecycline, and amikacin. Meropenem was started. The patient progressed to septic shock and multiorgan dysfunction and was admitted to the Intensive Care Unit (ICU) requiring vasopressor support, transfusion of hemocomponents due to severe thrombocytopenia (8000/μL), and renal replacement therapy. A transthoracic echocardiogram was performed with findings suggestive of vegetations. A transesophageal echocardiogram (TEE) showed multiple vegetations in the aortic valve with valvular stenosis and severe regurgitation . A diagnosis of possible native valve endocarditis was made (according to Duke criteria), (4) and he was referred to a higher complexity institution for aortic valve replacement with a mechanical prosthesis without complications. He completed 42 days of antibiotic coverage and was discharged.

One week later, he was readmitted to our institution due to dyspnea on exertion and lower limb edema that progressed to anasarca. The patient presented

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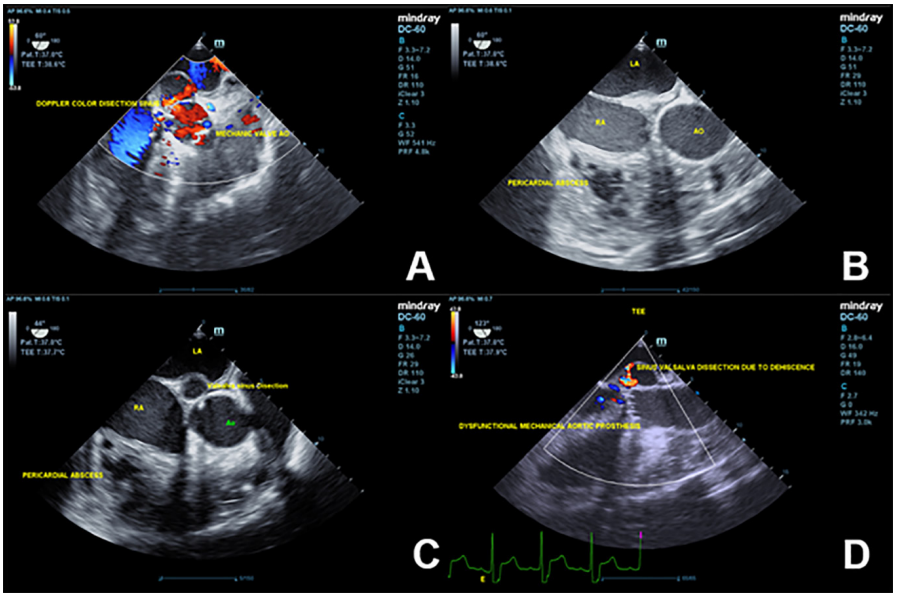

Fig. 1. A. Transesophageal echocardiogram showing a mechanical aortic prosthesis with dissection of the sinus of Valsalva. Note the color Doppler flow of the dissection jet. **B.** Transesophageal echocardiogram with septated pericardial space image compatible with abscess. LA: Left Atrium, RA: Right Atrium, AO: Aorta. **C.** Transesophageal echocardiogram in short axis view for large vessels where the dissected sinus of Valsalva is observed; inferior to the right atrium, a fibrinoid image is observed in the pericardial space. LA: Left Atrium, RA: Right Atrium, AO: Aorta. **D.** Transesophageal echocardiogram showing mechanical aortic prosthesis with dehiscence and aneurysm of the sinus of Valsalva; below the aortic valve, there is rupture of the interventricular septum, with color Doppler flow from the left ventricle to the right ventricle

with a heart rate of 72 bpm, respiratory rate of 20 breaths per minute, blood pressure of 87/52 mmHg, and oxygen saturation of 92% on FiO2 of 28%. The temperature was 36°C. Physical examination revealed a surgical wound without discharge, aortic diastolic murmur, and grade III lower limb edema. Laboratory findings included leukocytes 12 470/μL (88% neutrophils), hemoglobin 11.8 g/dL, platelet count 328 000 / μL , sodium 131 mmol/L, potassium 4 mmol/L, creatinine 3.5 mg/dL, and BUN 50 mg/dL. Blood cultures again identified *Klebsiella pneumoniae ssp* producing ESBL, with similar resistance patterns to previous admission but now also sensitive to ertapenem and cefepime. A new set of blood cultures was positive for *Klebsiella pneumoniae ESBL* growth. Given the recent surgical history, a transesophageal echocardiogram was performed, showing a dysfunctioning mechanical aortic prosthesis, sinus of Valsalva aneurysm, and an image suggestive of vegetation in the anterior mitral chord, and pericardial abscess. (Figure 1) A diagnosis of possible prosthetic valve endocarditis (according to Duke criteria) (4) due to *Klebsiella pneumoniae* was made, and the patient was treated with meropenem for 42 days under the direction of the infectious disease department. Finally, he was again referred to a cardiovascular referral center for further surgery which was successfully performed. The patient recovered and continued with his treatment.

Gram-positive bacteria mainly cause IE; gram-negative organisms (GN) are relatively rare causative agents associated with significant morbidity and mortality. Among the GN organisms causing IE, the HACEK group stands out; other GN organisms are less frequent and have attracted attention because of their propensity to develop and spread resistance, their high attributable mortality, and their association with increased healthcare costs. (5) Among the latter, *Klebsiella pneumoniae* accounts for an incidence of approximately 1.5% of cases of IE but with a mortality rate of up to 20%. (3-5)

A systematic review of the literature on Klebsiella endocarditis was published in 2021 by Petros Ioannou et al. Up to February 2021, 67 cases were reported, 45 due to *Klebsiella pneumoniae*; the aortic valve was the most frequently involved and in 16% of patients it affected the prosthetic valve. The main clinical features were fever in 98% of cases, sepsis in 78%, shock in 31%, paravalvular abscess in 15%, and heart failure in 21% of cases. (5) These findings are consistent with those found in our patient who initially presented with native aortic valve involvement and later with prosthetic aortic valve involvement, in addition to the fact that he presented with clinical characteristics similar to those reported in that study, plus the finding of paravalvular abscess. A case report of *Klebsiella pneumoniae* IE associated with emphysematous cystitis described a patient with urinary tract infection that progressed to septic shock. (5,6) Transesophageal echocardiography showed vegetation and perforation of the mitral valve, and also renal dysfunction (creati-

nine 2.7 mg/dl), leukocytosis (27 000 /μL), thrombocytopenia (17 000/μL), and hypoalbuminemia (2.3 mg/dL). Compared with our case and except for valvular involvement, both patients share similar characteristics, highlighting the presence of thrombocytopenia, renal injury, and hypoalbuminemia. (5)

This case of IE relapse, initially of the native valve and later of the prosthetic valve due to Klebsiella pneumoniae, highlights several essential aspects in the clinical management of this entity. While infective endocarditis is an uncommon complication of valvular prostheses, *Klebsiella pneumoniae* as the etiologic agent is even more unusual and deserves special attention due to its potential virulence and antimicrobial resistance.

Worldwide, most prosthetic valve-associated IE cases are caused by organisms such as *Staphylococcus aureus, Streptococcus viridans*, and *Enterococcus spp*. However, a greater diversity of pathogens is observed in Latin America and other developing regions, including gram-negative bacteria such as *Klebsiella pneumoniae*. (5,6) This may pose additional challenges in diagnosis and treatment, especially in settings with limited microbiology and laboratory resources. In addition, the lack of epidemiological data reporting the causative agents and their distribution by population, coupled to the clinical features with which patients debut, that differ from one patient to another, means that clinical suspicion and treatment may only sometimes be timely. (5)

Diagnosing infective prosthetic valve endocarditis is challenging due to variability in clinical presentation and laboratory findings. Early identification of *Klebsiella pneumoniae* as the causative agent was crucial to guide appropriate antimicrobial treatment in the present case. (5) However, in areas with limited microbiology resources, diagnosis may be delayed or missed, with severe consequences for the patient. This can lead to heart failure of valvular origin, sepsis, embolic stroke, and even death. (6)

Treatment of infective prosthetic valve endocarditis also presents unique challenges, especially in cases caused by gram-negative bacteria such as *Klebsiella pneumoniae*. Selection of appropriate antibiotics is crucial, but increasingly common antimicrobial resistance can complicate this process. In addition, surgical management may sometimes be necessary to remove infected tissue and restore valve function. (1,6)

This case report presents an uncommon manifestation of infective aortic prosthetic endocarditis caused by *Klebsiella pneumoniae*, which adds value to medical knowledge by providing a detailed description of the clinical presentation and an accurate diagnosis of the etiologic agent. In addition, follow-up during treatment offers valuable information on the therapeutic response and the need for surgical intervention. However, the limited availability of advanced microbiological tests may have affected the speed of diagnosis. Also, the generalization of findings from a single case may be limited, highlighting the need for additional studies for better understanding. Furthermore, more than the duration and completeness of follow-up may be required to assess full long-term prognosis. At the same time, the lack of comparative data with other similar cases makes it difficult to interpret and contextualize the results.

In conclusion, Non-HACEK GN organisms are rarely responsible for IE, and are mainly related to IE associated with intravenous drug use or IE associated with health care in patients with complex comorbidities (end-stage renal disease, neoplasia). It is essential to follow up on this disease since knowing this type of case allows to determine the multidisciplinary team's diagnostic and therapeutic strategies.

Ethical considerations

This report was written following Helsinki's declaration. The institutional bioethics committee endorsed this work and recognized this research as safe. Informed written consent was obtained from the patient when he moved to the general ward.

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Conflicts of interest

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Total Knowledge of the Circulatory System

El conocimiento total del sistema circulatorio

JORGE C. TRAININI[MTSAC]

William Harvey's work produced a boom in the study of the circulatory system, not only at the level of its anatomical integrity, but also in an attempt to understand it as a mechanical system. It also stimulated the analysis of the respiratory process, with the harvest of achievements that allowed the total understanding of blood physiology.

The description of these findings includes the capillaries; the chyliferous vessels; the lymphatics; new anatomical studies on the heart and blood vessels; the beginning of mechanical circulatory reasoning and the biochemical study of respiration. Although his account sectorizes the knowledge, we should know that all the fragments involved in the structured understanding of the subject were given in a concomitant way until reaching the full understanding of the circulatory system.

MARCELO MALPIGHI AND CAPILLARY VESSELS

After Harvey had completed his brilliant description of the circulation of the blood, there still remained to be discovered a link in its physiology: the passage from the arteries to the veins. For such an event to occur, something more than reflexive supposition or direct vision was needed. In this sense, the origin of the optical microscope, although Galileo Galilei (Pisa, 1564-1642) was one of the first to use it around 1610, seems to correspond to the Dutchman Zacharias Jansen and Cornelius Drebbel (1573-1674) around 1590, independently. This construction had been carried out by assembling a biconvex lens (objective) with a biconcave one (eyepiece).

The advent of the microscope has enormous relevance for the understanding of capillary circulation. The term microscope was introduced by John Faber (1570-1640), of the *Accademia dei Lincei* (Rome). Although there are studies of blood vessels by the Englishman Thomas Willis (1621-1675), the first observations appear with a paper by Pierre Borel (circa 1620-1689) in 1653, *Observartionum microscopicarum centuria*.

But the great microscopists were essentially the Italians Marcello Malpighi (1628-1694) and Lorenzo Bellini (1643-1704); the Dutch Anton van Leeuwenhoek (1637-1680) and Jan Swadermmerdam (1632-1723); and the English Nehemiah Grew (1641-1712) and Robert Hooke (1635-1703). The latter wrote the first treatise devoted exclusively to the description of the microscope and also to the objects observed. Hooke's book *Micrographia* (1665) details the observation of the cell (*celullae*) on a cork slide.

Marcello Malpighi or Malpigio was born on March 10, 1628, paradoxically the same year of the publication of *De Motu Cordis*, in Crevalcore, near Bologna. He began his studies in philosophy and then embraced the medical discipline. Graduated as a physician in 1653, he was Professor of Medicine in Bologna, Pisa and Messina. In Pisa, he met Giovanni Alfonso Borelli (1608-1679), professor of mathematics, who strove to apply experimentation with an atomistic-mechanical integration. It was in Borelli's laboratory that the spiral fibers of the heart were described around 1657. Malpighi returned to Bologna where he continued his studies and was later appointed archiatrist to Pope Innocent XII; he died in Rome on November 29, 1694. His autopsy was performed by a famous physician, Giorgio Baglivi (1668-1707).

His work, based on the vision through the microscope, was remarkable. In one of his early writings, together with the microscopist Carlo Fracastori (died 1672), he described the missing link for the circulation to be complete: the capillary circulation. Although in Harvey's text *De Motu Cordis* some reference is made to *carnis porositates*, it was far from giving it the physiological meaning actually offered by Malpighi. His writing *De pulmonibus observationes anatomicae*, which appeared in Bologna in 1661, four years after Harvey's death, consists of excellent plates, taking the frog's lungs as an object of study. This circumstance was ideal for the description of the capillaries, since the lungs are provided on their surface with capillaries, being an organ endowed with transparency. He also found them in the mesentery. For his part,

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Franz de le Boë "*Sylvius*" (Dutch, 1614-1672), suggested that the capillaries consist of a single tunic, since transudation through them would otherwise be impossible.

Borelli, who was an iatromechanical physiologist, had introduced Malpighi to the concept of experimentation and the physical-mathematical model in biology. In his research Malpighi performed the injection of water into the pulmonary artery and collected it in the pulmonary veins, as a demonstration of the existence of the capillary system. He himself says of Borelli: "*He was pleased to lead me to the study of free and democratic philosophy, and to this I owe the progress I have made in philosophizing*". His work was diverse and wide-ranging. He studied embryonic development, dental structure, liver, kidney, spleen, plants and insects. In the hedgehog, he made the description of red blood cells in the text *Exercitatio omento, pinguedine et adiposis ductibus* (Bologna, 1665), although he did not deepen his knowledge, facts that would be reserved to Swammerdam (works in frogs) and fundamentally to Leeuwenhoek. Let us remember that in 1658 the German Athanasius Kircher (1602-1680), in studies carried out on plague, had found red blood cells, but he thought that they were the cause of this disease, without glimpsing its significance.

Anton van Leeuwenhoek was active in the development of microscopic study. He built his own lenses, achieving up to 300 magnifications in his microscopes. Not being a physician, his work was based on his interest in optics. In 1688 he made a complete study of red blood cells, and also studied the capillary circulation in the membranes of palmipeds and in the mesentery of the frog. He also succeeded in observing the reticular structure of the cardiac muscle. His work was published by the Royal Society of London.

The visual verification of blood circulation would have to correspond to Lazaro Spallanzini. A priest by profession, he was born in Scandiano, near Modena, in 1729, and was a professor in the latter city and in Pavia. He wrote several works, including *Del azione del mori ne' vasi sanguigni* (Modena, 1768) and *De fenomeni della circolazione* (Modena 1777).

In 1771 he observed in a chicken embryo the red blood cells circulating from the arteries to the veins. His account in 1773 describes the event in these words: "*The room in which I found myself was not sufficiently lighted, and wishing in any case to satisfy my need, I decided to examine the egg in direct sunlight. Having placed the egg in Lyonnet's little machine, I soon directed the lens at it and, notwithstanding the great brightness that surrounded it, I was able, by sharpening my eyes, to see the blood flowing through the complete circuit of the umbilical, arterial and venous vessels. Then, seized with unexpected joy, I exclaimed eureka! eureka!*".

In addition to the circulatory process, Spallanzini investigated the generation of living beings, digestion and respiratory function. His phrase: "*The voice of nature must prevail over that of philosophy*" demonstrates his scientific stature. He died in Pavia in 1799.

REVIEW ARTICLE

Brief History of Argentine Cardiology, Argentine Society of Cardiology and Training in the Specialty *

Breve historia de la Cardiología argentina, de la Sociedad Argentina de Cardiología y de la formación en la especialidad

AMANDA GALLI [1]

ABSTRACT

In Argentina, the development of cardiology started in the first decade of the 20th century with the publication of books by Professor Abel Ayerza and Professor Francisco Arrillaga. The first electrocardiograph arrived in 1912, at the initiative of Bernardo Houssay. In 1934, the Argentine Journal of Cardiology appeared. The Argentine Society of Cardiology (SAC) was founded in 1937. The scientific activities consisted in presenting papers and clinical cases. The first World Congress of Cardiology was held in Paris in 1950. The VII World Congress of Cardiology was held in Buenos Aires in 1974, jointly organized by the SAC and the Argentine Federation of Cardiology.

In 1946 the first residency in cardiology was created. In 1978, the SAC started the Cycles of Update Courses and Conferences on Advances in Cardiology, while the Biannual Course on Cardiology started in 1980. From 1992 to 2005, this course was part of the Cardiology Specialist Course of the University of Buenos Aires, UBA (subjects Cardiology I and II). In 2005 the UBA decided that all specialization courses be held in a hospital facility with a department of cardiology. Currently, the Biannual Course is a contribution to the theoretical training of residents. Seventy-nine residency programs nationwide participate in the course, which means, on average, about 300 residents as students per year. Since the enaction of the Higher Education Law (1995), only the universities are allowed to grant specialist degrees. The current trend is the integration between residency programs and university courses.

Keywords: Development of Argentine cardiology - Training of cardiologists

RESUMEN

La Cardiología argentina comienza a desarrollarse en la primera década del siglo XX con la publicación de los libros de los profesores Abel Ayerza y Francisco Arrillaga. El primer electrocardiógrafo llega en 1912, por iniciativa de Bernardo Houssay. En 1934 aparece la Revista Argentina de Cardiología. En 1937 se funda la Sociedad Argentina de Cardiología (SAC). Las actividades científicas consistían en la presentación de trabajos y discusión de pacientes. EI primer Congreso Mundial de Car¬diología se celebra en París en 1950 y en 1974 el VII Congreso Mundial de Cardiología se realiza en Buenos Aires organizado en forma conjunta por la SAC y la Federación Argentina de Cardiología.

En 1946 se crea la primera residencia de Cardiología. En 1978 se inician en la SAC los Ciclos de Actualización y Jornadas de Avances en Cardiología; en 1980 se comienza a dictar el Curso Bianual de Cardiología. A partir de 1992 y hasta 2005 este curso forma parte de la Carrera de especialista en Cardiología de la Universidad de Buenos Aires, UBA (Cardiología I y II). En 2005 la UBA decide que todas las carreras de especialización deben tener sede en un servicio hospitalario. Actualmente el Curso Bianual es una contribu¬ción a la formación teórica de los residentes. Participan 79 residencias de todo el país lo que significa, en promedio, unos 300 residentes como alumnos por año. A partir de la Ley de Educación Superior (1995) sólo las Universidades pueden entregar títulos de médico especialista. La tendencia actual es la articulación entre Residencia y Carrera Universitaria.

Palabras claves: Desarrollo de la cardiología argentina - Formación de cardiólogos

Cardiology is a clinical specialty, branch of Internal Medicine, focused on the promotion of cardiovascular health and prevention, diagnosis, treatment and rehabilitation of disorders of the circulatory system at all stages of life. Although the literature on Cardiology dates back more than 370 years (Harvey, 1628), Cardiology as a clinical specialty separate from internal medicine began to emerge in 1950. (1)

Various authors agree in establishing the birth of Argentine Cardiology with the description of "cardíacos negros" or black cardiac disease, a clinical presentation with cyanosis, bronchopulmonary signs and

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* Amanda Galli, based on: Demartini A. Historia de la Sociedad Argentina de Cardiología. Desde su fundación hasta 1969.SAC. Buenos Aires.1987

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symptoms, and heart failure, made in 1909 by Professor Abel Ayerza. His disciple, Francisco Arrillaga, published in 1912 what could be considered the first Argentine book on cardiology: *Secondary sclerosis of the pulmonary artery (black cardiac disease)* [*Esclerosis secundaria de la arteria pulmonar (cardíacos negros*]).

The introduction of the first electrocardiographs in the country represented a significant impulse for the development of national Cardiology. The first electrocardiograph was imported in 1912 at the initiative of Professor Bernardo Houssay to be used in the Medical Physics Department of the School of Medicine of the University of Buenos Aires. In 1915, Dr. Francisco Arrillaga published his book *The clinical relevance of the electrocardiogram* (*La importancia clínica del electrocardiograma*), which led to the regular use of the method. In 1924, Dr. Tiburcio Padilla published his book on electrocardiography and in 1933 Dr. Antonio Battro presented his book *Arrythmias* (*Arritmias*).

Experimental cardiology had a privileged place at the Institute of Physiology of the School of Medicine of the University of Buenos Aires, under the head of Professor Bernardo Houssay, while clinical Cardiology was developed in the Internal Medicine wards of public and university hospitals nationwide. At *Hospital de Clínicas de Buenos Aires*, education on Cardiology took place in the chairs of Professors Castex, Merlo and Padilla. This department quickly stood out for its contributions in the field of semiology and cardiovascular pathophysiology. In 1932, Dr. Pedro Cossio and Dr. Isaac Berconsky performed the first catheterization in America and the third in the world.

In the City of Buenos Aires, the XII ward at *Hospital José Ramos Mejía* directed by Dr. Rafael Bullrich had an outstanding performance. In 1934, Dr. Bullrich created the so-called Dispensaries for the Care of Cardiac Diseases which depended on the Public Health Care of the city of Buenos Aires. These dispensaries gave rise to the current departments of cardiology of the public hospitals in the city. Two physicians who worked with Dr. Rafael Bullrich played a pivotal role in the development of the specialty: Dr. Eduardo Braun Menéndez and Dr. Blas Moia. When Dr. Braun Menéndez finally dedicated himself to research with Professor Bernardo Houssay, Dr. Blas Moia became the head of the Cardiology area and in 1932 he became the director of *Archivos Médicos del Hospital Ramos Mejía*, the seed of what would become the Argentine Journal of Cardiology founded in 1934 on the initiative of Moia and Braun Menéndez. The journal was the seventh cardiology journal in the world and the first to publish abstracts in English, French and German.

The Argentine Society of Cardiology (SAC) was founded on April 9, 1937, at an assembly held at the Institute of Physiology of the School of Medicine of the University of Buenos Aires, the SAC. (2)

The first Board of Directors was made up of:

- Antonio Battro and Pedro Cossio, secretaries
- Eduardo Braun Menéndez, treasurer
- Blas Moia and Alberto Taquini, members of the board of directors
- Oscar Orías, delegate to the Argentine Journal of Cardiology

The Argentine Journal of Cardiology became the official organ of the SAC.

The scientific activities consisted of presenting papers and clinical cases.

The first World Congress of Cardiology was held in Paris in 1950, under the chairmanship of Professor Charles Laubry. During this congress the statutes of the International Society of Cardiology were approved, and only two years later, in 1952, the II International Congress of Cardiology was held in Buenos Aires, with Dr. Pedro Cossio as president.

Dr. Alberto Demartini provided a particularly interesting description of the organization of the First Argentine Congress of Cardiology. (3) In 1954 the Board of Directors of the SAC accepted Dr. Rodolfo Romero's proposal to organize a national congress. However, "*such a name was not allowed by the National Government at that time because, by a resolution of the National Executive Power, such a name could only be used by events promoted by the Government or by the official political party. Therefore, they had to be called* "*Conferences*". The First Argentine Congress of Cardiology (called *Conferences*) was held in Mar del Plata in March 1955, under the chairmanship of Dr. Fernando Battle. It was attended by about 300 cardiologists, many of them from inland cities. In October 1957, the II Argentine Congress of Cardiology was held in the city of Mendoza.

In 1974, the VII World Congress of Cardiology was held in Buenos Aires, jointly organized by the SAC and the Argentine Federation of Cardiology (FAC), which had been founded in 1965 as a Society of Societies.

The event was attended by 10 000 cardiologists from around the world and 2400 scientific papers were presented. In commemoration of this milestone and as a tribute to this congress which has been held annually to the present day, we will celebrate the 50th anniversary of our congress.

Dr. Francisco J. Romano, president of the VII World Congress of Cardiology, stated that:

"*Most of those who register for a congress do so to learn about the most recent developments and to form their own opinions on controversial topics. They also learn about errors and shortcomings in methods, doctrines and therapeutics. The possibilities for the future are outlined. And all this educational task is no longer the exclusive domain of a single lecturer. Keynote lectures and paper sessions give way to symposia and round tables. In these sessions, each individual presents their own thoughts, rather than imposing them. Round tables almost always aim to reach a synthesis of the ideas presented by each member. The Congress offers a unique opportunity to grasp complex concepts in*

a short period, which would otherwise require extensive reading and reflection. Nor should it be forgotten that the educational action is widened and affirmed with the participation of the experiences and statistics of different countries". (4)

Regarding education on cardiology at Hospital de Clínicas, Alfredo Buzzi and Ricardo Gelpi (5) say:

"*It is not by chance that during the period between the end of the 19th century and the beginning of the last century, Argentine medicine witnessed the emergence and brilliance of figures of high scientific level This was made possible by a combination of favorable circumstances, primarily the remarkable advancement of European science and medicine during the latter half of the 19th century and the subsequent institutional order, prosperity and stability that emerged following the national organization in our country.*

Abel Ayerza was one of the first Argentine physicians to take our medical practice beyond national borders".

The history of training cardiologists is parallel to the development of the specialty. The first institution with resident physicians was Ward IV of the former Hospital de Clínicas, headquarters of the *Instituto de Semiología*. In 1944, Dr. Tiburcio Padilla, who was its Associate Professor, created the positions of junior and senior resident physician for former hospital interns once they had graduated, following the suggestion of his disciple Pedro Cossio. What began as a trial period ultimately became a definitive program when the Board of Directors of the School of Medicine (UBA) enacted an ordinance in December 1952 that outlined the duties and responsibilities of the residents. This first residency program in Internal Medicine in Argentina was strongly associated with personalities linked to Cardiology.

Clinical training required the presence of the students in the hospitals, under the close supervision of their professors.

"*...clinical training must be conducted on a rigorously individual basis. It is achieved by providing repeated and persistent care to patients, who must be thoroughly observed, with an accurate and safe technique, using all the resources with a rigorous review. This can only be done in the hospital*." Houssay B, 1927. (6)

Dr. Houssay was very well informed about the international trends in medical education and the development of the profession. He noticed the emergence of a trend towards specialization: new professional profiles and new institutions (such as specialized centers), which had an impact on medical education. Training specialists within a hospital residency program after graduation was the model to follow.

In 1946, the *Pabellón Luis H. Inchauspe* was opened at Hospital Ramos Mejía in the city of Buenos Aires under the head of Dr Blas Moia and the first residency in cardiology was created. The model initially spread throughout the public hospitals of the large cities of the country and in centers associated with university headquarters.

Following the formalization of the medical residency system in 1960, with the approval of Resolution No. 1778 by the Secretary of State for Public Health, there was a significant increase in the number of training centers in public institutions across the different jurisdictions, in prestigious private institutions, community hospitals and Armed Forces.

The medical residency was originally defined as "*a system of professional education for medical school graduates, with in-service training, on a full-time, time-bound basis, to prepare them for the comprehensive, scientific, technical and social practice of a specialty.*" (7)

It was later redefined as "*an educational system for recent graduates whose purpose is to complete their comprehensive formation by making them practice the responsible and effective performance of the corresponding discipline*". (8)

Nowadays, there are approximately 200 residency programs in cardiology in our country.

In accordance with Article 40 of the Higher Education Law (LES) No. 24,521/95, "*it is the exclusive responsibility of university institutions to grant bachelor degrees and equivalent professional degrees, as well as master and doctoral degrees*". Specialist degree - which is not mentioned in the LES -is included in the Standards for the Accreditation of Medical, Biochemical, Pharmaceutical and Dental Specializations (9) and can only be granted by the universities after the specialty has been accredited by the National Commission for University Evaluation and Accreditation (CONEAU). Since the LES was enacted, the trend in training for medical specialists has been the integration of medical residency programs and university medical courses, which are periodically evaluated and accredited by the CONEAU. Only university specialist degrees are valid nationwide and are internationally recognized.

The Teaching Area of the SAC had an active participation in the elaboration of the standards for the accreditation of residency programs in cardiology by preparing a document that was submitted to the National Ministry of Health for the construction of the Frame of Reference. SAC's original position was published in the Argentine Journal of Cardiology. (10,11)

In August 1978, the SAC started the cycles of Update Courses and Conferences on Advances in Cardiology. The theoretical classes were given at the SAC Educational Area at 5 pm and hands-on training took place in cardiology centers in the city of Buenos Aires from 8 am to 4 pm.

In 1980, the Biannual Cardiology Course was launched with classes on Fridays from 5 to 11 p.m. and Saturdays from 8 a.m. to 2 p.m. All the classes were recorded on videotapes that were available for students who had missed a class or wished to review the material. From 1992 to 2005 this course was part

of the Cardiology Specialist Course of the UBA (subjects Cardiology I and II). In 2005, the UBA decided that all specialty courses be held at a hospital facility with a department of cardiology.

The Biannual Cardiology Course has been offered since 1978 as a contribution to the theoretical training of residents. At present, more than 79 residency programs nationwide participate in the course, which means, on average, about 350 residents as students per year.

Briefly, as a timeline, these are some milestones in the development of cardiology in our country.

- 1912. Francisco Arrillaga published *Secondary sclerosis of the pulmonary artery* (*black cardiac disease*) which is considered the first book on cardiology in Argentina.
- 1912. The first electrocardiograph is imported for use in the Medical Physics Department of the School of Medicine of the University of Buenos Aires.
- 1934. The Dispensaries for the Care of Cardiac Diseases -Public Health Care of the City of Buenos Aires -was created.
- 1934. The Argentine Journal of Cardiology was launched.
- 1937. Foundation of the Argentine Society of Cardiology.
- 1946. Creation of the first residency in cardiology at *Hospital Ramos Mejía*.
- 1955. First Argentine Congress of Cardiology (*Conference*).
- 1957. Second Argentine Congress of Cardiology.
- 1965. Creation of the Argentine Federation of Cardiology (FAC).
- 1974. Seventh World Congress of Cardiology in Buenos Aires
- 1978. Beginning of the teaching activities at SAC: courses for residents and continuing education courses, in addition to the traditional scientific activities such as symposia, case conferences and clinical cases.

In 2022, the National Academy of Medicine published a book presenting 14 Argentine physicians who improved world medicine with their biography, scientific contributions and professional and teaching activity. (12) This group includes Bernardo Houssay, Eduardo Braun Menéndez, Mauricio Rosenbaum, René Favaloro, Juan Carlos Parodi and Julio César Palmaz, among others. Each of these doctors made significant contributions to the field of cardiology, resulting in numerous lives being saved.

What will young Argentine cardiologists contribute to the world today? They are probably developing something in a research center or cardiology department. They are working hard under difficult conditions.

"*Innovation is like a candle flame in the wind. Disruptive ideas are often dismissed by our minds, which seek simple explanations for everything. That is why we must learn to question*". (12)

"*Given the number of variables to control and the precarious resources, it is easy to understand the initial failures. Difficulties that sometimes crush the weak, serve to strengthen the prepared spirits*" (12)

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

From Observational Studies and Adjustment to Clinical Decision. Part 2

Del estudio observacional y el ajuste a la decisión clínica. Parte 2

ARTURO CAGIDE[1], MTSAC,

ABSTRACT

In this second part of the review on the analysis of observational studies, we refer to each of the tools we have available, their comparative advantages and disadvantages. And we conclude with the interpretation of the results of the studies that served as examples in the initial part.

Keywords: Observational studies - Multivariate analysis - Adjustment

RESUMEN

En esta segunda parte de la revisión sobre el análisis de estudios observacionales nos referimos a cada uno de las herramientas con que contamos, sus ventajas y desventajas comparativas. Y concluimos con la interpretación de los resultados de los estudios que nos sirvieron de ejemplo en la parte inicial.

Palabras claves: Estudios observacionales - Análisis multivariado - Ajuste

In this second part, we continue to explain the statistical methods, from the most common to the most novel, for the analysis of observational studies.

Propensity Score (PS)

The goal of this methodology is to adjust for confounders so that they are balanced between the intervention and control groups.

Figure 1 illustrates the procedure. The first step is to estimate the statistical association between confounders (or independent variables) and exposure (or dependent variable), again using multivariate analysis (logistic regression).

The propensity score (PS), which represents the likelihood of being exposed to the intervention, adjusted for the presence of confounding factors, is derived from the resulting data.

One benefit of PS over multivariate analysis is that the number of independent variables is not constrained by the prevalence of the treatment. This is because the treatment, intervention, or prognostic factor, in contrast to the outcome, will consistently have a sufficient number of observations. (1)

There is some debate regarding the variables that should be included in the calculation of the PS. In general, all the variables that the investigator deems relevant to a given treatment or intervention should be included. Basically, the variables determining the outcome should also be included. (2,3)

As is the case with any multivariate analysis, the issue is that only known and available independent variables are taken into account. Consequently, the PS may be flawed in predicting exposure to treatment or intervention as a result of that situation.

The ROC curve can be used to evaluate the model in the calculation of the PS. While there is some disagreement about the exact value that should be considered adequate, most authors place it in an area under the curve of 0.80.

There are several procedures to evaluate the association of the intervention with the endpoint (Figure 1). (4)

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a) Matching

In accordance with the aforementioned methodology, each individual will be characterized according to their baseline characteristics or confounding factors, as determined by a specific PS. Some individuals in the intervention group will have a PS similar to those in the control group, so that it is possible to match patients from both groups according to their PS. (Figure 2)

This process generates a (matched) subpopulation whose confounders are balanced between both groups in such a way that they no longer influence on the estimation of the association of the intervention with the outcome.

However, a significant number of individuals from both treated and untreated groups will be excluded because the corresponding pair is not available. This number of excluded individuals is directly related to the level of confounder imbalance between both groups in the original study sample.

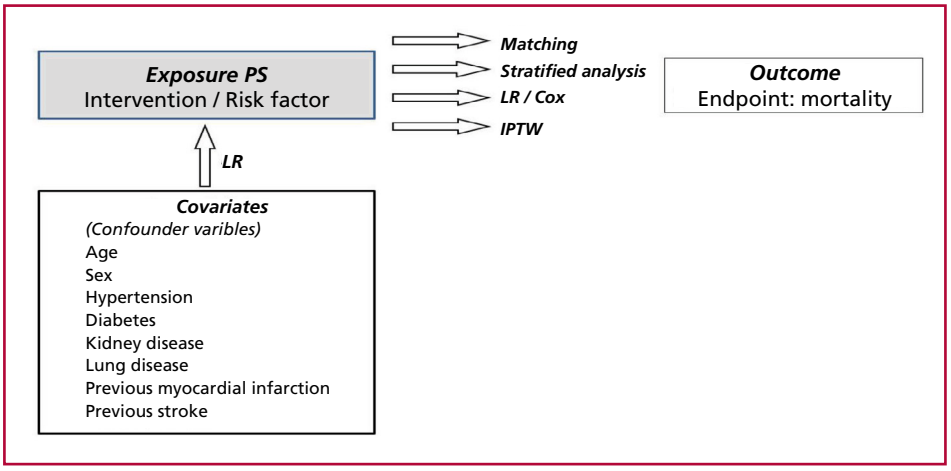
Thus, the conclusion of the study and its translation into practice is limited exclusively to the matched sample and cannot be extrapolated to the entire population.

b) Multivariate analysis and PS

An analysis of this type can be performed by including the intervention (or the prognostic criterion according to the case) and the PS, which represents all the confounders analyzed, as independent variables.

c) Stratified analysis

This method, like multivariate analysis, includes all individuals in the trial. The procedure entails forming strata in accordance with the PS and estimating the association between the exposure variable and



IPTW: inverse probability of treatment weighting; LR: logistic regression

Fig. 1. Propensity score (PS) and derived analysis
The final objective of the study is, as in Fig. 4 (Part 1), to estimate the possible association of the exposure with the outcome. Previously, the association of confounders with exposure is analyzed and the PS is calculated. Then, the PS enables the estimation of the independent association between the exposure and the outcome through the application of diverse statistical methodologies.

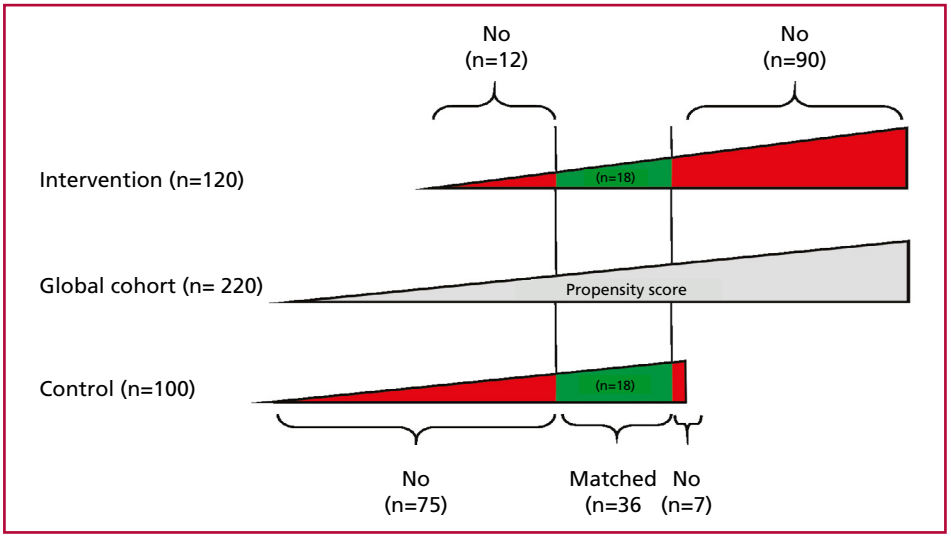


Fig. 2. Matching
Theoretical example of a study of 220 patients, 120 in the intervention group and 100 in the control group. The PS for the entire sample (center), the intervention group (top), and the control group (bottom) is plotted on a scale of increasing values. Each subject in the intervention group is matched with a subject in the control group with an equal or very close PS. This process results in 18 pairs, reducing the original sample size to 16%. (36/220). In the matched sample, confounders from both the intervention group and the control group are "balanced".

the outcome in each stratum. This is followed by the calculation of an overall result, which represents this association (Figure 3).

The standard stratified analysis for confounder balance presents a challenge when attempting to adjust for only some variables. This is because the number of strata increases exponentially when incorporating numerous criteria with few observations in each of them. Applying stratification according to PS incorporates all the baseline characteristics of interest, as confounders.

d) Inverse probability of treatment weighting (IPTW)

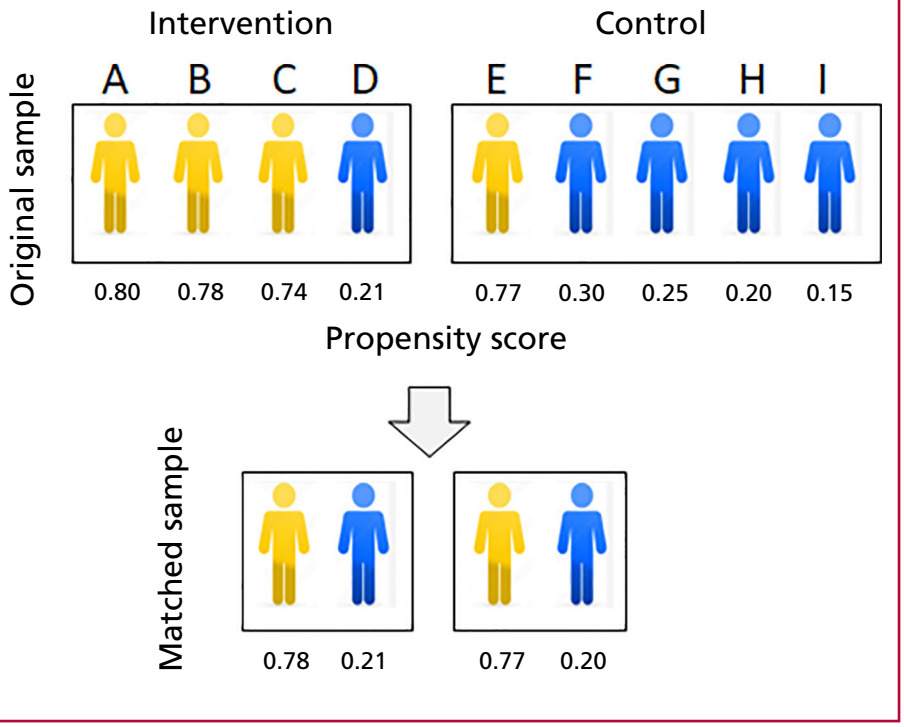
Unlike matching, but similar to stratified analysis, this method includes the entire sample under study. However, while matching achieves adjustment by reducing the population until the confounders are matched in the groups to be compared, with IPTW this objective is achieved by increasing the population with individuals with a similar rate of confounders using a mathematical technique. (5)

Figure 4 is a theoretical example comparing an intervention group with a control group. Age, dichoto-

Fig. 3. Stratified analysis
The individuals were grouped into quintiles according to their PS. The relative risk (RR) for the outcome (e.g., mortality) was estimated for each quintile. The RR of the sample adjusted for the PS and the confounding variables included in it is then calculated.

	Outcome		
PS (quintiles)	Intervention	Control	RR
1°	%	%	1°
2°	%	%	2°
3°	%	%	3°
4°	%	%	4°
5°	%	%	5°

Fig. 4. Matching
Theoretical example of a study comparing an intervention group of 4 individuals with a control group of 5 individuals. The PS was calculated in each group. Age is the confounding variable: <50 years in yellow and ≥50 years in blue. To adjust for age, individuals from each group are matched with those with similar PS values. The original sample of 9 individuals is reduced to 2 pairs (4 individuals).
The age-adjusted sample has been significantly reduced in number.



mized into < 50 and ≥ 50 years, is for this example, the only confounder. In the intervention group there are four subjects, 3 < 50 years and 1 ≥ 50 years; in the control group there are 5 subjects, 1 < 50 years and 4 ≥ 50 years.

The age must be adjusted so that both groups can be compared in terms of a given outcome, for example mortality. For this purpose, the PS, as previously mentioned, is estimated for each group which will undoubtedly be different for each individual.

If the matching strategy were applied, two pairs of 2 patients each, treated and control, could be integrated (Figure 4) sharing similar PS, so that the sample would be limited to only 4 individuals.

Let us now examine the example illustrated in Figure 5.

In contrast to Fig. 4, let us now assume that there is again only one confounder, age.

The probability of receiving the intervention (the PS) in individuals < 50 years is 0.75, while the probability in those ≥ 50 years is 0.20.

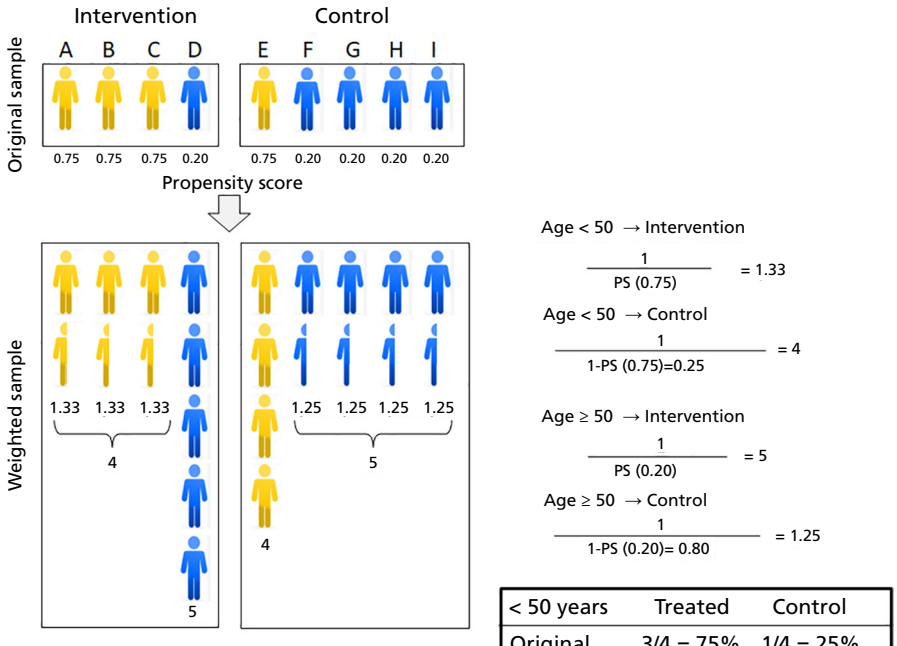
Note that with the same probability of receiving the intervention (PS = 0.75), 3 individuals < 50 years received it and only 1 did not (in the control group). In turn, in those ≥ 50 years with the same probability of receiving the intervention (PS = 0.20) or being in the control group (1-PS = 1-0.20 = 0.80) 4 did not receive the intervention and only 1 received it.

Applying IPTW:

- **< 50 years**: the inverse probability of receiving treatment is 1.33 (1/0.75). Each individual < 50 years who received the intervention will now be represented by 1.33, so that the sum of all of them is 4. The inverse probability of not receiving treatment is 4 [1/1-0.75; the probability of not receiving the intervention is 1 minus the probability of intervention, (1-PS)]: the only subject < 50 years in the control group will be represented by 4 (Figure 5).
- **≥ 50 years**: the inverse probability of receiving the intervention is 5 (1/0.20): in the intervention group the only individual ≥ 50 years will be represented by 5. The inverse probability of being in the control group is 1.25 (1/1-0.20): each individual in the control group ≥ 50 years will be represented by 1.25, so that the sum of all of them is 5.

The formulas illustrate the methodology for calculating the IPTW, which allows for the estimation of how each individual will be represented in the intervention and control groups. The table shows the distribution by age before and after adjustment, which in this particular case is perfect. See explanation in the text.

Please note that in the original sample, the ratio of individuals < 50 years with and without treatment was 3:1. Once IPTW has been applied, the sample is fully balanced in 4. In turn, in ≥ 50 years with and without treatment the original ratio of 1:4 remained equalized at 5.



< 50 years	Treated	Control
Original	3/4 = 75%	1/4 = 25%
Weighted	4/9 = 44%	4/9 = 44%

Fig. 5. Inverse probability of treatment weighting (IPTW) The upper part shows the condition of Fig. 4. The aim is to adjust for age (which in this theoretical example is the only existing confounder), dichotomized into < 50 years (in yellow) and ≥ 50 years (in blue). In individuals < 50 years the probability of receiving the intervention, which is the same in all of them, is 3/4 = 0.75. In those ≥ 50 years the probability of receiving the intervention, which is also the same in all of them, is 1/5 = 0.20. The probabilities calculated in this theoretical case, arising from a simple mathematical calculation, constitute the PS. (The probability of receiving control treatment will be 1 - PS).

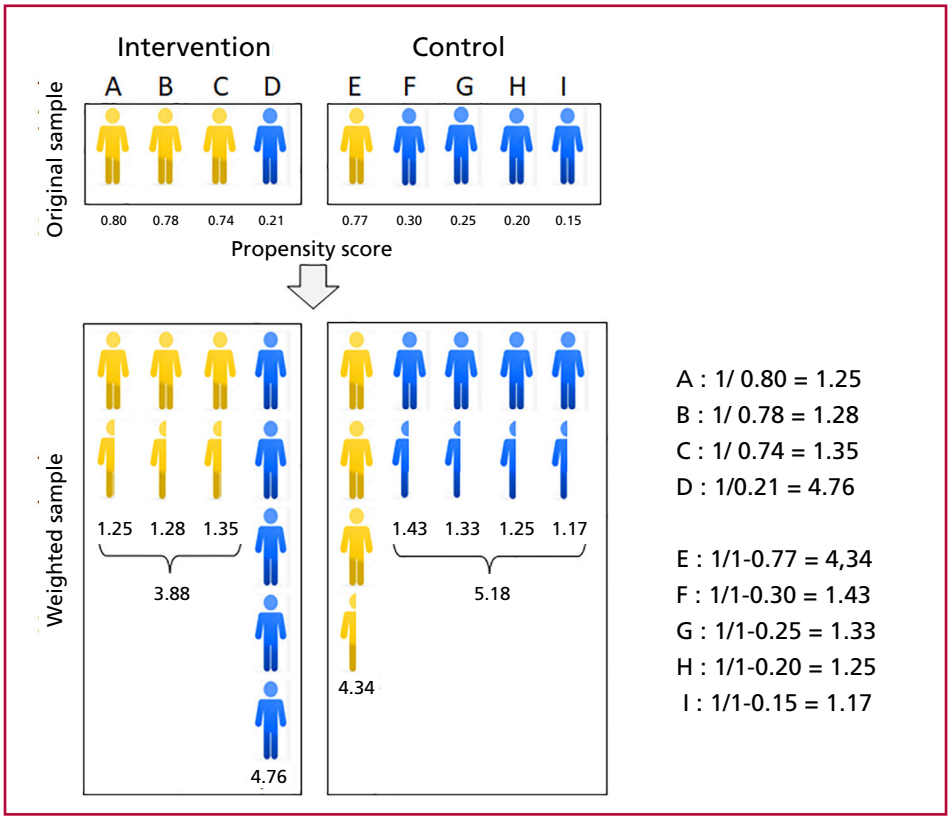


Fig. 6. Inverse probability of treatment weighting (IPTW) Unlike the previous example, the probabilities calculated by the PS vary from one individual to another, as they are influenced not only by age but also by the entire range of confounding variables. Their estimation results from a logistic regression analysis of the covariates with the treatment received (intervention or control). The application of the same methodology illustrated in Figure 5 results in a reduction of the differences, although the adjustment is not mathematically exact. See explanation in the text.

Thus, the IPTW method achieves pseudo-randomization by generating a pseudo-population in which the adjustment for the variable age is mathematically perfect (Figure 5).

The situation described is particularly relevant when considering only one confounding factor. Before adjustment, the PS was the same across all individuals < 50 years (0.75), and those ≥ 50 also exhibited the same PS (0.20).

In a real-world setting, the probability of treatment is influenced by a number of confounding factors. The global effect of these confounders is represented in the PS which will vary from case to case (Figure 6).

The adjustment using IPTW is similar to that explained in Figure 5, applying the individual PS of each patient. The adjustment reduces the imbalance, although certain differences in age distribution between the groups with and without treatment persist due to the fact that other confounders, besides age, influence on the PS. (6)

The strategy described for the variable age should be applied to all the variables or confounders available considered in the calculation of PS.

Estimating the level of adjustment

It is of the utmost importance to ensure the precision of the adjustment when applying the IPTW, as it encompasses the entire population under study, which is likely to exhibit significant differences in the prevalence of multiple confounders. In the case of matching, there may also be imbalance, although to a lesser extent.

To evaluate the level of adjustment achieved, the absolute standardized difference (ASD) is usually used, which is the difference measured in units of the standard deviation for each of the confounding variables after adjustment using IPTW. In general, a difference < 0.10 is deemed an acceptable margin that ensures the adjustment was adequate. However, in some cases, this extends to 0.20, which may detract from the consistency of the conclusions of the study.

Sometimes the ASD is plotted before and after the adjustment to indicate the previous imbalance and the success of the adjustment.

The accuracy of the PS for estimating the probability of being intervened is a conditioning factor of the IPTW methodology. Again, the confounding variables not included, whether unknown or not contemplated, constitute a critical aspect of the statistical procedure.

Back into clinical trials from a methodological perspective

We invite readers to revisit Part 1 of this review to gain a comprehensive understanding of the following considerations.

Trial 1 (7)

- After adjusting for confounders using PS matching, the analysis was conducted on a subset of 1866 patients from the original sample of 9586:

933 in the percutaneous coronary intervention (PCI) group and 933 in the medical treatment (MT) group, that is, 933 pairs. It is evident that there was a significant imbalance regarding certain baseline characteristics. Consequently, PCI was only performed on a selected group of patients with a favorable prognosis. It is therefore essential to address these discrepancies to ensure the validity of the results.

- Such correction was adequate since the standardized difference was < 0.05 for most of the 20 variables considered.
- The adjusted HR of the outcome mortality/nonfatal myocardial infarction (1.49, MT versus PCI) was calculated in the matched sample according to the multivariate Cox model. This was done with the intention of adjusting for any remaining differences by incorporating certain variables.
- The translation of this trial into clinical practice is limited exclusively to the matched group of patients, 85% of the MT group, but only 11% of those in the PCI group.

Trial 2 (8)

- In this case the adjustment was made using IPTW.
- The standardized difference was < 0.05 for all the 13 variables considered (Table 2, Part 1).
- In addition to the standardized difference, Fig. 2 illustrates the effect on the outcome with a relative risk of 0.72. This indicates that patients with prior statin use had a 28% reduction in heart failure as a complication of acute coronary syndrome.

Trial 3 (9)

- The effect of the intervention was estimated using PS according to three statistical criteria (Table 3, Part 1).
  - IPTW (primary analysis): no benefit of anticoagulation in $CHADS_2$ patients ≤ 1, but there was difference in the incidence of major bleeding, which was significantly more common in the treated group.
  - matching and Cox model (secondary and sensitivity analysis). The result showed no benefit of anticoagulation with higher bleeding rate in $CHADS_2$ ≤ 1. This finding aligns with the post-IPTW analysis.
- It is interesting to analyze Figure 1 (Part 1) beyond the result in patients with $CHADS_2$ ≤ 1, which illustrates the standardized difference before and after adjustment. The limit of 0.1 defines the criterion for the level of adjustment. The difference before adjustment was significantly greater in individuals with a $CHADS_2$ score ≤ 1 compared to those with a score of 2. This demonstrates that the variables probably associated with thromboembolism in the former group were markedly different in patients without anticoagulation (low prevalence) compared to those who did not receive such treatment (high prevalence).

Trial 4 (10)

- This is a prognostic study on the risk of type 2 versus type 1 myocardial infarction using IPTW.
- The standardized difference is illustrated in a chart similar to that in Figure 1 (Part 1), but it is clear that the two charts are different. Firstly, the acceptance limit is set at a value < 0.2, which is twice as high as in the previous case. Furthermore, following the adjustment, the differences remained significant, at approximately 0.10. It is possible that the sample size used in relation to the number of covariates was incorrect, resulting in the incorrect calculation of PS.
- The conclusion of the study is limited by imperfect adjustment for confounders (comorbidities).

Trial 5 (11)

- In this case, the aim of this trial was not to evaluate the effect of an intervention or the prognostic value of a new criterion, but to determine the outcome of aortic stenosis. The problem is that in one group of patients, the intervention effectively interrupted the natural history, potentially introducing bias in the non-intervened group (higher risk due to having individuals at lower risk for the intervention) or, conversely, having selected those at high risk for the procedure.
- The IPTW was not designed to compare the treated group with the untreated group. Rather, it was intended to adjust both populations and then compare the adjusted results with the original, untreated population. Table 4 (Part 1) does not detail the standardized difference but compares mortality of the adjusted sample with that of the unadjusted sample in subgroups according to the severity of valvular heart disease.
- For the authors, the non-interventional group represents the actual natural history of aortic stenosis unaffected by the intervention.

CONCLUSION

Randomized studies undoubtedly constitute the highest level of evidence. However, they are also the most complex, time-consuming, and costly studies. Only a few interventions can be evaluated by this methodology.

Observational trials represent a viable option for the evaluation of new prognostic criteria or innovative therapeutic alternatives, particularly when large prospective databases are available. In this context, statistical methodology presents a significant challenge in terms of correcting for variables that may affect the association being studied.

It is crucial for clinicians to become familiar with the terminology, tables, and charts associated with the statistical strategy employed to assess the effect, as this knowledge is vital for decision-making. It is not a matter of understanding the mathematical complexi-

ties involved, but rather the conceptual basis.

Failure to learn these concepts will result in an unquestioning acceptance of expert opinions. It is always preferable to analyze the basic information rather than to resort to that interpreted by others.

Ethical considerations

Not applicable

Conflicts of interest

None declared.

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

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CONTROVERSY

In Severe Aortic Stenosis Without Left Ventricular Dysfunction, do not Wait for Symptoms to Develop

En la estenosis aórtica grave sin disfunción ventricular no hay que esperar la aparición de síntomas

AGONIST

PABLO LAMELAS[1, 2]

INTRODUCTION

Severe aortic stenosis is the valvular heart disease most frequently undergoing valve replacement in middle- and high-income countries. (1) The risk factors for developing aortic stenosis are similar to traditional cardiovascular risk factors. (2) However, randomized trials have not demonstrated that medical treatment with drugs such as statins reduces disease progression. (3) Nowadays we count with two mechanical treatments for severe aortic stenosis: surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). In our environment, the indication of SAVR or TAVI is based on high-certainty guidelines developed for Latin America, where TAVI via transfemoral access is indicated mainly in the elderly. (4)

There is international consensus that severe symptomatic aortic stenosis (either with dyspnea, angina, heart failure, or syncope), or the presence of left ventricular dysfunction (left ventricular ejection fraction < 50%), or the requirement for other heart surgery, are strong indications for aortic valve replacement. (5,6) We will now examine the logical arguments behind the suggestion that limiting the scope of the intervention to those with a more advanced stage or more symptoms may not be the most prudent course of action.

PHILOSOPHICAL ARGUMENT

Severe aortic stenosis is a progressive disease that will progress to sudden cardiac death or heart failure without treatment, which in the best scenario will allow treatment before it is too late. There are many examples in medicine where, in progressive, non-reversible, lethal, and potentially treatable diseases, no symptoms or irreversible damage are expected before indicating an aggressive treatment. Would you wait for a stage I lung cancer to progress to stage II or III before initiating treatment, or would you prefer to treat it as soon as possible? Would you wait for a patient diagnosed with 90% obstruction in the left main coronary artery to have symptoms before treating it? You probably would not wait in either scenario because they are both progressive, non-reversible diseases with high mortality risk, as severe aortic stenosis.

ASYMPTOMATIC IS NOT SYNONYMOUS OF LOW RISK.

There must be no physician who has not wondered why, with the same degree of disease, some patients have symptoms while others are asymptomatic. Two patients may have the same level of aortic stenosis (for example, two men of the same age with aortic stenosis and preserved left ventricular ejection fraction, aortic valve area of 0.7 cm^2 and no other comorbidities). One complains of functional class III dyspnea, while the other has no symptoms and is living a normal life. It is probable that there are biological factors contributing to this phenomenon, but they are not currently relevant as they are not yet understood. We can ascertain that a significant number of patients receive timely treatment due to the early development of symptoms. Conversely, those who have not yet exhibited any symptoms may have to wait for structural damage to be treated. Sudden cardiac death may be the first manifestation in asymptomatic patients. The annual risk of sudden cardiac death in asymptomatic patients is about 1%; during follow-up, half of the deaths occur in asymptomatic patients. (7)

STRUCTURAL DAMAGE MEANS WE ARE TOO LATE

Phillipe Genereaux et al. developed a staging system for severe aortic stenosis. (8) This system is stratified in stages from 0 to 4. Stage 0 is the absence of any type of structural damage, Stage 1 represents the presence of incipient damage, which progresses to increasingly significant damage. Stage 4 is associated with a notable decline in left ventricular systolic function.

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While it is true that the more advanced the structural damage, the lower the probability of regression, there is no guarantee that less advanced stages will revert to stage 0 following the intervention. It has been postulated that the lack of regression of structural damage justifies the worse outcome following the intervention, including cases of sudden cardiac death. (9) On the other hand, the presence of structural damage increases the risk of the procedure. (10) Then, why must we wait for structural damage in asymptomatic patients? The most frequently cited arguments are the risk of the intervention and the durability of the implanted prosthetic heart valve.

PERIPROCEDURAL RISK

Despite following the highest standards, some patients will die or suffer adverse events related to the intervention. They would have probably lived longer if they had not undergone the procedure. However, a proportion of these patients may experience detrimental effects as a result of waiting for symptoms to manifest. This includes, but is not limited to, the mentioned 1% annual risk of sudden cardiac death. (7)

The results have significantly improved in the last decades for SAVR and in the last years for TAVI. The contemporary mortality for both procedures in referral centers is near 1% in low-risk patients. (11,12) We could say that the risk of periprocedural mortality is comparable to the risk of sudden cardiac death within the following year.

Other serious adverse events can occur in the periprocedural period, such as stroke, myocardial infarction and infections, among others. It is very difficult to define the importance of these events compared to the risk of continuing to wait, but the fact that most patients undergo the procedure without significant complications has led many physicians and patients to consider early intervention as a viable option.

DURABILITY OF THE PROCEDURE

A highly experienced mentor once provided me with me the best way to explain to a patient that the prosthetic heart valve has limited durability: “While replacements are available for your problem, the original components are not”.

The evidence shows that the risk of reintervention is relatively low. For SAVR with contemporary prosthetic heart valves, the risk of reintervention is 1.9% at 10 years and 15% at 20 years (5.6% and 46%, respectively, in patients < 60 years). (13) While long-term data for TAVI is not currently available, the evidence from randomized studies (with follow-up periods of 5 to 10 years) indicates that these prosthetic heart valves perform similarly to those used in SAVR. In any case, the indication for TAVI in our environment is restricted to patients with low life expectancy, who are those > 75 years, or younger patients with high surgical risk. (4)

EVIDENCE

If all this makes sense, it should be reflected in the evidence. Multiple meta-analyses of observational studies have shown a marked reduction in mortality with early intervention (from 50% to 70%). (7) However, as these are observational studies, the results are subjected to an inevitable and unwavering risk of selection bias and multiple confounders. Therefore, this evidence does not provide sufficient certainty to change clinical practice if it cannot be reproduced by randomized trials. There are two randomized studies in this regard, the Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial, (14) and the Aortic Valve Replacement vs. Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial. (15)

The RECOVERY study enrolled 145 patients with severe aortic stenosis (aortic valve area ≤ 0.75 cm^2, aortic jet velocity 5.1 m/s) in South Korea and randomly assigned them to SAVR or conservative treatment. At a median follow-up period of 6.2 years, there was a reduction in the primary composite event of operative death and death from cardiovascular causes at follow-up from 15% to 1%, with a hazard ratio (HR) of 0.09, and 95% confidence interval (95% CI) of 0.01-0.67. It should be noted that the study included patients with a significantly elevated transvalvular gradient, that stress testing was not systematically performed, and that the patients’ risk was very low (EuroSCORE II 0.9%) with a perioperative mortality of 0%. The most important limitation was the small number of primary events (12 in total).

The AVATAR study evaluated a composite endpoint of all-cause death, myocardial infarction, stroke, and unplanned hospitalization for heart failure. With a median follow-up of 32 months, a 64% reduction in the primary event was observed (HR 0.46, 95% CI 0.23-0.90). This study included a population with less severe valvular heart disease (mean aortic jet velocity of 4.5 m/s) and all the patients underwent exercise stress testing. One limitation is the shorter follow-up period compared to the RECOVERY trial.

Both randomized studies confirm that in the mid-term the balance would be in favor of intervention in asymptomatic patients, consistent with previous observational evidence. Although it will be 10 to 20 years before we have enough data to get the full picture, we do know that patients who have undergone SAVR with contemporary prosthetic heart valves rarely need reintervention, and the short-term benefit appears to be significant in relative terms. We are also waiting for the results of at least five additional randomized studies evaluating the same research question. (16)

RECOMMENDATIONS IN ASYMPTOMATIC PATIENTS

There are indications for intervention beyond patients presenting with symptoms or those with systolic ventricular dysfunction. These include: 1) a systolic

blood pressure drop ≥10 mm Hg on exercise; 2) a peak aortic jet velocity ≥ 5.0 m/s; 3) an increase in aortic jet velocity of ≥ 0.3 m/s per year in serial testing; and 4) an increase in serum B-type natriuretic peptide level of > 3 times normal in serial testing. (5,6) These recommendations are weak (class IIa for the American or European guideline systems) and are supported by evidence that has demonstrated an adverse prognostic impact despite being asymptomatic patients. Furthermore, patients must be at low risk to be eligible for these indications.

It should be noted that both the American and European guidelines were developed prior to the publication of RECOVERY and AVATAR trials.

CONCLUSIONS

Patients with asymptomatic severe aortic stenosis without systolic dysfunction are at increased risk of morbidity and mortality. Waiting for symptoms to develop puts the patient at increased risk of sudden cardiac death, potentially irreversible structural damage and increased risk in case of intervention. The perioperative mortality rate for both SAVR and TAVI has decreased significantly in recent years as well as the number of patients requiring reintervention during follow-up in more contemporary series. The evidence on this research question, originally derived from observational studies and later from randomized trials with consistent findings, suggests that there is an important benefit in terms of the rate of events, including mid-term mortality. While the guidelines have already established certain indications for intervening asymptomatic patients and there are multiple ongoing trials, it is possible that they will change favoring early intervention when these new trials are integrated into the already published randomized studies.

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ANTAGONIST

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Aortic stenosis is a progressive disease with high morbidity and mortality. The onset of symptoms represents a significant shift in its prognosis, with a one-year mortality rate of around 25% in the absence of valve intervention. (1) Recent evidence has confirmed that even pre-symptomatic severe aortic stenosis and moderate aortic stenosis have a poor prognosis, and that the progressive nature of the disease requires an analysis that must go beyond the divisions imposed by hemodynamic classifications. Nevertheless, it would be an error to assume that, due to the elevated risk of complications associated with severe aortic steno-

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sis, early intervention should be the indication for all patients. How high is the risk of the disease and how high is the risk of its treatment? It is essential to consider this interplay of forces each time we evaluate a patient with severe aortic stenosis who is not yet symptomatic.

In the setting of symptomatic patient, the indication for intervention is clear, although underutilized. On the other hand, in the setting of patients with severe aortic stenosis who do not present symptoms and who are periodically monitored (watchful waiting or conservative treatment), the low rate of major events has supported this approach. We could ask ourselves whether, based on the current evidence, we are exposing patients with asymptomatic severe aortic stenosis to an unacceptably high risk by delaying surgical indication unnecessarily.

First, we need to make sure that the severity of aortic stenosis has been adequately estimated. Secondly, the patient must be undoubtedly asymptomatic, since failure to recognize symptoms is a common scenario that implies a more adverse prognosis than in truly asymptomatic patients. Adaptation and the indolent nature of the disease lead in some cases to a gradual reduction in physical demands which result in lack of awareness of exercise-induced symptoms. Therefore, exercise stress echocardiography is suggested to unmask symptoms in patients with severe aortic stenosis, although its usefulness in elderly patients is less clear. (2,3) In elderly patients, decreased mobility and the presence of comorbidities that can mask symptoms until very advanced stages of the disease, makes the detection of symptoms more complex.

There are methods as cardiac magnetic resonance imaging which can demonstrate interstitial ventricular fibrosis, global longitudinal strain which detects myocardial dysfunction before left ventricular ejection fraction falls, and serum markers (as natriuretic peptides, troponin, etc.) which reflect myocardial damage and overload that occur before the onset of symptoms. Furthermore, in some cases the damage is not reversed even after aortic valve intervention. The presence, extent and reversibility of cardiac damage, particularly fibrosis, inflammation and oxidative stress, play an important role in the prognosis of the disease. In this scenario, the possibility of delaying disease progression and evaluating early treatment of diastolic dysfunction in aortic stenosis with drugs currently available in heart failure treatment, such as sodium-glucose cotransporter 2 inhibitors, is being considered. (4) In the coming years we will learn the effectiveness of new pharmacological strategies designed to mitigate or slow irreversible cardiac remodeling associated with aortic stenosis and its associated ventricular dysfunction. This knowledge will inform the optimal timing for implementing intervention.

Severe aortic stenosis includes risk subgroups, such as those with very severe or critical aortic stenosis (peak velocity > 5m/s), those with concomitant coronary artery disease and/or with rapid hemodynamic progression in whom current guidelines suggest early intervention. We will therefore focus our discussion on those with severe but not critical aortic stenosis, with preserved ventricular function and with an anticipated rate of hemodynamic progression. This is usually a younger and lower risk population within the universe of severe aortic stenosis. In this scenario, how long is it better to wait than to intervene?

Is it time to intervene all severe aortic stenosis regardless of symptoms and ventricular function? One might be inclined to respond in the affirmative. However, in our environment it is sensible to say not yet. The following paragraphs will attempt to identify the rationale behind this cautious warning.

Recent evidence appears to indicate that early SAVR may be a beneficial approach for patients with severe aortic stenosis. The results of the RECOVERY and AVATAR trials support SAVR in patients with asymptomatic severe aortic stenosis. This patient population was notably younger than the typical patient with severe aortic stenosis, and their surgical risk very low (EuroSCORE II of 0.9% in the RECOVERY trial and STS score of 1.7% in the AVATAR trial). (5,6) These findings cannot be applied to elderly patients due to the higher risk of surgical complications, and the competitive risks between the prognosis of aortic stenosis and the impact of comorbidities and frailty. In addition, these findings cannot be applied to TAVI because there is currently no information from randomized studies in asymptomatic patients. Nevertheless, it is important to analyze these studies beyond their conclusions, and to determine their applicable in our real world.

In the RECOVERY study, which included 145 asymptomatic patients < 80 years (mean age 63.4 years) with very severe aortic stenosis, the incidence of the composite end point of death due to SAVR or cardiovascular death was significantly higher in the conservative arm (21%) than in those assigned to early SAVR (7%), HR 0.33; 95% CI 0.12-0.90. It should not be overlooked that the mean peak aortic jet velocity was 5.1m/s (most patients had critical aortic stenosis), that there was a 74% crossover from the conservative arm to SAVR during follow-up, and the most remarkable aspect: the operative mortality of SAVR (in patients undergoing elective surgery and even emergency surgery who crossed over from the conservative arm to the SAVR arm) was 0%. This result surely reflects the excellence of the participating centers, but considerably reduces the external validity of the study. In the conservative group, the cumulative incidence of sudden cardiac death was 4% at 4 years. (5) It should also be noted that given the advanced stage of aortic stenosis, many patients met the criteria for a class IIa indication for elective SAVR. (7)

The AVATAR study included 157 patients (mean age 67 years) and demonstrated that early SAVR reduced the composite primary end point of death, myo-

Table. Published national results of SAVR in patients with symptomatic severe aortic stenosis

	n	Number of centers	Patients´ age (years)	Year	Risk	Isolated AVR	Surgical priority	Postoperative complications	In-hospital mortality	30-day mortality	Mortality by surgical risk
ESMUCICA valvular heart disease patients (9)	241	4 (>300 surgical procedures/ year)	65.8 ± 12	1997			Elective: 90% Urgent: 10%	61.5% (mainly AF and LCO)	(7.9% in text, 8.3% in abstract)	Not reported	Low: 3.8% Moderate: 9.1% High: 27.3%
CONAREC XVI (10)	359	49 (with residency program or similar)	64.8 ± 12.4	2008	EuroSCORE 3.51%-6.51%	100%	Elective: 89% Urgent: 10% Emergency: 0.8%	Elderly: 29.2% LCOS: 17.2% Reoperation: 5.8%	8.9%	Not reported	
David et al. (11)	125	2	71 (36-91)	2015-2017	103 p STS<4 22 p STS 4-7%	70%	Elective: 85.6%	Stroke: 1.6% Reoperation: 2.4%	2.4%	Not reported	
Borracci et al. (12)	422	Universitary centers	69.1 ± 11	2012-2017	EuroSCORE 2 (0.5-32.1) 75% <2.5%	100%	Not reported	Reoperation: 0.9%	3.6%	3.8%	
Stutzbach et al. (14)	934	1 (>300 surgical procedures/ year)	63.5 ± 13	1996-2001	Parsonnet 8.2 ± 3.3	52%	Elective: 83.3% Urgent:14.4% Emergency: 2.2%	AF: 26.5% LCOS: 24.5% Reoperation: 7.9%	5.5%	Elective: 3.1% Overall: 5.5%	Low: 0% Moderate: 2.6% High: 4%
Piccinini et al. (15)	87	1 (>300 surgical procedures/ year)	83 ± 2.5	1997-2008	Logistic EuroSCORE 12.4% ± 15%	100%	Elective: 72%	Stroke: 3% AF: 28% Reoperation: 5%		Elective: 9.5% Urgent: 12.5%	Low: 7.1% Moderate: 15.4% High: 5%
Navia et al. (16)	520	1 (>300 surgical procedures/ year)	76.8 ± 4.7	2010-2017	STS 2.5%±1.2	60.2%	Elective: 100%	AF: 33.7% LCOS: 6.3% Reoperation: 3.5%	3.1%	5.1%	Low: 2.7% Moderate: 5.3%
Fortunato et al. (17)	97	1 (>300 surgical procedures/ year)	79.4 ± 6.18	2007-2017	STS PROM 5.1% (4.4-6)	37%	Elective: 66% Urgent: 32% Emergency: 2.1%	AF: 44.5%	Not reported	5.1%	

AF: atrial fibrillation; AVR: aortic valve replacement; LCOS: low cardiac output syndrome; MV: mechanical ventilation

cardial infarction, stroke or hospitalization for heart failure compared to conservative treatment (HR 0.46; 95% CI, 0.23-0.90; p = 0.02). Operative mortality of SAVR was 1.4%. (6) A recent meta-analysis including these 2 studies and 10 observational studies evaluating SAVR vs. conservative treatment in asymptomatic patients showed a lower overall mortality rate for early SAVR compared to the conservative arm, mainly determined by the results of the 2 aforementioned studies. (8) The risk of stroke and myocardial infarction was similar between both groups. However, there was great heterogeneity in the magnitude of the effect across the included studies (pooled OR 0.40; 95% CI 0.35 - 0.45, $p < 0.01$; $I^2 = 61\%$), without being able to rule out bias. Among the numerous limitations reported, the meta-analysis included open studies which indicated conservative treatment in older and sicker patients, and the impossibility of extrapolating the results to elder patients, to TAVI and to patients with bicuspid aortic valve. The results of several ongoing studies (EARLY-TAVR, EaSY-AS, etc.) are still pending to reinforce the evidence.

In the meantime, we should not simply support an indication for early SAVR by extrapolating the surgical results of the AVATAR and RECOVERY studies to our reality. Although we may feel tempted, it would

not be correct to assume that the external validity of these results is applicable to our complex and heterogeneous local environment. It is essential to have a clear understanding of the surgical mortality rate in our country and the significant constraints on the population's access to surgical or interventional treatment at centers of excellence before extending an indication of this magnitude. Are we aware of the mortality rates of SAVR and TAVI in our country?

The risk of morbidity and mortality associated with SAVR varies widely. There are few contemporary publications in our environment reporting on the mortality of SAVR and even fewer have evaluated mortality in asymptomatic patients. Most publications include patients with symptomatic severe aortic stenosis and very few have updated information (Table). The statistics from the ESMUCICA II study (9) and the CONAREC XVI Registry (10) were gathered over 15 years ago and primarily focus on patients who have undergone coronary artery surgery. In both cases mortality rates of SAVR is high, even in high-volume centers. (9) The multicenter CONAREC XVI registry, which included 359 patients with a mean age of 64.8 years, reported an overall in-hospital mortality of 8.9%. (10) David et al. reported the series with the lowest in-hospital mortality of SAVR (2.4%) in symptomatic severe aortic stenosis with mainly elective procedures in patients with low and intermediate surgical risk (age 71 years). (11) Borracci et al. included 422 consecutive patients operated on with isolated aortic stenosis (age 69 years, left ventricular ejection fraction 58%) with an in-hospital mortality of 3.6%. (12) In the subgroup with low anticipated mortality according to EuroSCORE II, the observed mortality was 1.6%. In a meta-analysis by Borracci et al. which included 1192 low- and moderate-risk patients intervened in university centers, in-hospital mortality after SAVR was 3.1%. (13) In our environment, mortality in elder patients undergoing SAVR is > 3% in the rest of the published studies. (14–17) These publications mostly reflect the results of high-volume centers, with a high rate of publications, which do not necessarily represent the reality of most surgical centers in our country.

In this scenario, TAVI would be a particularly attractive option because it is less invasive than surgery considering that these patients are asymptomatic. However, there is no evidence from randomized studies yet. Moreover, there are few local publications on TAVI in low surgical risk populations. Caponi et al. published a series of 200 patients with symptomatic severe aortic stenosis and moderate to high surgical risk (logistic EuroSCORE =18) undergoing TAVI via the transfemoral access (2009-2016) at a university center. Total in-hospital mortality was 3.5% and 1-year mortality was 11.5%. (18) Progressive training in the technique, combined with the availability of better prostheses, were associated with a lower rate of complications and a lower rate of mortality over time. Boissonnet et al. published a systematic review of 1156 patients (81 years) who underwent TAVI in South America (2008-2015) with an in-hospital mortality of 8.1% and 30-day mortality of 12.5%. (19) More recently, other authors have reported 30-day mortality rates < 5.5% with transfemoral TAVI in low or moderate surgical risk patients. (20) Nau et al. published the results of 770 patients who received TAVI (81 years) in high-volume centers mainly via the transfemoral access (80% with self-expandable valves). In-hospital mortality rate for low, intermediate and high-risk patients categorized by the STS PROM score was 3.9%, 5.9% and 9.6%, respectively. (21) The persistently high rate of pacemaker requirement, coupled with the paravalvular leak, the paucity of data regarding prosthetic durability in younger patients, and the mortality rate associated with the procedure, which has not yet reached 0-1%, make this option inadvisable for the time being.

Therefore, the little that we do know reflects a very different scenario from that of the randomized trials, with a mortality associated with SAVR or TAVI that is at least double or triple that of the AVATAR and RECOVERY trials. In addition, we should keep in mind that, so far, we have only talked about operative mortality and acute periprocedural complications. The studies do not emphasize the incidence of long-term complications of a prosthetic heart valve, or they do not provide much information about them. Even in patients who survive surgery and do not develop perioperative complications, prosthetic heart valves are associated with significant long-term morbidity. The expected complications include paravalvular leak, prosthesis-patient mismatch, pacemaker requirement (mainly in TAVI), prosthetic dysfunction, thrombus formation, thromboembolism, infective endocarditis and problems associated with anticoagulation (bleeding, resistance, etc.). Although the incidence of complications depends on the type of prosthesis, significant complications occur at a rate of approximately 3% per year and procedure-related death rate is 1% per year.

We all know that symptomatic patients who do not receive treatment for aortic stenosis have an ominous prognosis. (22,23) However, real-life studies and registries from the surgical and TAVI eras are still reporting that a high proportion of patients with an indication for surgery or TAVI do not receive adequate treatment. Likewise, frailty, a variable that increases morbidity and mortality, is also not properly assessed in patients with aortic stenosis. Undertreatment is associated with age, comorbidities, reduced left ventricular ejection fraction, perceived surgical risk by the treating physician, and lack of knowledge of the disease. Valvular intervention (either surgical or percutaneous implantation) is appropriate only in patients who are likely to have benefit from the procedure. Treating patients for whom the intervention is futile further overburdens a limited health care sys-

tem and is associated with an incorrect assessment of the patient's benefit and life expectancy prior to the intervention. Despite the efforts to educate the medical system about the benefits of treating patients with symptomatic severe aortic stenosis, there is still an underutilization of surgical and/or TAVI treatment even in scenarios where the prognosis without treatment is unfavorable. (24) Furthermore, the availability of a Heart Team or working group on valvular diseases remains limited in our environment. Additionally, there is a lack of periodic publication of statistics on mortality associated with procedures. Therefore, a reasonable strategy may be to start by improving these aspects in order to make progress in the prognosis and management of patients with severe aortic stenosis in our environment before extending the indication to other less certain scenarios.

In conclusion, when weighing the benefits and risks of a decision for early intervention, the weight of uncertainty and lack of knowledge of local outcomes must be measured in terms of in-hospital mortality for SAVR and TAVI in patients with asymptomatic severe aortic stenosis. In centers of excellence with mortality rates for elective SAVR close to 0%, young patients could choose the early intervention strategy, but this is not the prevailing reality in the local setting. Moreover, valve replacement does not fully eliminate the risk of sudden cardiac death and is also associated with non-negligible complications typical of prosthetic heart valves. Therefore, even if surgical mortality can be minimized, the combined risk of the procedure and late complications of a prosthetic heart valve may outweigh the possibility of preventing sudden cardiac death in some asymptomatic patients with severe aortic stenosis.

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AGONIST REPLY

I agree with many aspects and disagree with very few points. I agree that the subgroup of asymptomatic patients with more critical or rapidly progressive aortic stenosis should benefit from early intervention. For early intervention, I also agree that the center must have morbidity and mortality rates that meet international standards for both TAVI and SAVR. However, the fact that a randomized study (e.g., the RECOVERY trial) has reported 0% of in-hospital mortality in 75 consecutive patients does not mean that the early intervention can only be applied to a center with 0% mortality in its "real-life" reports. It is quite possible that many centers in our environment have an in-hospital mortality for SAVR or TAVI close to 0 or 1% in the last 75 consecutive low-risk patients with a low burden of comorbidities as those "highly selected" for randomized studies such as the RECOVERY study. Furthermore, the references regarding TAVI-related mortality in our environment come from the beginning of the programs (2009) until 5 to 10 years ago and do not represent the results presented in scientific events or contemporary quality audits.

The area where we do not agree is in what to do with asymptomatic and severe, but not critical, aortic stenosis. We know that many patients can wait until symptoms develop; the issue is that we do not know who should not wait. When we prescribe statins in secondary prevention, we know that most patients will not derive any benefit, but as we do not know who will benefit from statin therapy, we prescribe statins to all those who are at risk. Until evidence demonstrating who does not benefit from statin therapy is available, we will continue prescribing statins to all patients in secondary prevention. The same is true in this scenario: just because some patients do not benefit does not mean that we should not offer early intervention to all those who are eligible. To date, randomized studies, consistent with previous observational evidence, suggest benefit from early intervention in these patients. It is important to note that these studies have limitations, primarily due to the low event rates and medium-term follow-up periods. These limitations will be further elucidated with the publication of the multiple ongoing randomized trials in the coming years.

Pablo Lamelas

ANTAGONIST REPLY

Over the past few decades, we have witnessed a revolutionary shift in the field of aortic stenosis, with improvements in its diagnosis, risk stratification and treatment. Early intervention in asymptomatic stages is a topic of current debate. However, we do not know the mortality and morbidity rates of SAVR in most centers in our environment, and we often want to assume that the results of a few international centers of excellence are the overall national results.

As mentioned above, although there is evidence from 2 randomized clinical trials in favor of this strategy, they lack external validity in our setting. One of the aforementioned studies evaluated the intervention in patients with critical aortic stenosis, which is a current indication in the guidelines, and reported a mortality rate of 0%. The other study included patients younger than the usual ones with this disease with results favoring early SAVR and surgical mortality rate < 1.5%. I must keep on emphasizing that these findings cannot be yet applied to elderly patients, to surgical centers with mortality rates > 1.5%, or to TAVI, for which there is still no evidence.

How many of us work in centers that have sustained and published mortality rate <1.5% following SAVR?

We will not be in a position to extend the intervention to asymptomatic severe or moderate aortic stenosis without left ventricular dysfunction until we have access to the information on local surgical results that are similar or close to those of the aforementioned studies. We must always have a clear understanding of the local reality in order to improve it and act accordingly. This will be the first step in enabling us to provide truly beneficial care to our patients.

María Celeste Carrero

Challenges of Anticoagulation in Chagasic Cardiomyopathy and Atrial Fibrillation

Desafíos de la anticoagulación en miocardiopatía chagásica y fibrilación auricular

FACUNDO I. ZUVIRÍA[1]

Chagasic cardiomyopathy (CC) is the progressive form of chronic T. cruzi infection, affecting up to 30-40% of patients in the chronic phase of the disease.

Its manifestations include the development of heart failure, cardiac conduction system disorders and tachyarrhythmias. These phenomena are more frequently observed than in other dilated cardiomyopathies, which confers to CC greater mortality.

Likewise, CC involves a series of specific structural and functional alterations that are associated with a greater thromboembolic potential, such as slow blood flow in the context of heart failure, ventricular aneurysms, intracavitary thrombi, severe atrial dilatation and atrial fibrillation (AF). (1)

The study published by Echeverría et al. evaluates the risk of embolic events in patients with CC and AF who are under anticoagulant therapy. (2)

Although anticoagulants are a standard treatment to prevent ischemic events in patients with AF, this study raises the question of whether conventional anticoagulation, either by direct oral anticoagulants or vitamin K antagonists is sufficient to protect patients with CC. So, the authors analyzed the incidence of systemic embolisms in anticoagulated patients diagnosed with AF, comparing those with CC with those with other forms of cardiomyopathy.

It was striking that, despite being on optimal anticoagulation therapy, patients with CC had a significantly higher cumulative incidence of embolic events compared with those with other cardiomyopathies. This occurred despite the fact that the CC group had a significantly lower CHA_2DS_2-VASc score. (2)

An interesting aspect of this finding is the fact that the embolic risk in CC appears to be distinctive and cannot be fully explained by traditional risk factors, nor by the classic scores suggested by clinical practice guidelines.

Some previous publications have attempted to design specific embolic risk scoring systems in Chagas disease in order to guide the decision of anticoagulation in this population, including variables such as the degree of systolic dysfunction, presence of apical aneurysm, abnormal ventricular repolarization, and age. Unfortunately, due to the lack of external validation, its applicability is restricted. (3)

Another important element highlighted in the study is that the increased risk of embolism in patients with CC persists despite anticoagulation. This suggests the possibility that standard anticoagulation is not sufficient to prevent embolic events in this particular population and that an alternative approach contemplating other associated factors is required.

Although the study has limitations such as the relatively small sample size and the retrospective nature of the analysis, the findings provide valuable information suggesting that patients with CC should be evaluated in a more complex manner and may benefit from personalized anticoagulation treatment approaches, even in the absence of AF.

This underscores the need for further research to develop specific treatment guidelines in these patients, thus optimizing their clinical management.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

We thank Dr. Zuviría for his comments on our article "Risk of embolic events in patients with chagasic cardiomyopathy and atrial fibrillation despite antithrombotic therapy: is anticoagulation sufficient?". Their analysis reinforces the relevance of these findings and underscores the need for further research in this crucial field.

We fully agree with Dr. Zuviría that Chagasic cardiomyopathy (CC) presents a unique challenge in antithrombotic management. The structural and functional alterations characteristic of CC, including ventricular aneurysms, intracavitary thrombi, and severe atrial dilatation, contribute to a distinctive thromboembolic risk profile that transcends conventional risk factors assessed by scales such as the CHA_2DS_2-VASc. (1) Additionally, other pathophysiological mechanisms such as autonomic dysregulation and the presence of intrinsic coagulation disorders also play a role in the elevated risk of embolic events in this population. (2,3)

Dr. Zuviría rightly points out the limitations of specific embolic risk scoring systems for CC, such as the one proposed by Sousa et al. (1) Although these initiatives are valuable, we agree that their clinical applicability is hampered by the lack of external validation. This underscores the urgent need to develop and validate more robust risk stratification tools specific to this population.

A critical aspect emerging from our study is the persistence of elevated embolic risk in patients with CC despite standard anticoagulation. This finding raises fundamental questions about the efficacy of conventional anticoagulation regimens in this population and suggests the need to explore alternative or complementary prevention strategies.

We thank again these valuable comments, and hope that our study will serve as a basis for future research in this field.

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Durability of Biological Prostheses in Aortic Position

Durabilidad de las prótesis biológicas en posición aórtica

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A few years ago, the choice between using a biological or mechanical aortic prosthetic valve seemed a little easier. Currently, the reduced need for anticoagulation associated with the appearance of new valves with better hemodynamic profiles and materials has shifted the balance towards the use of bioprostheses. The problem is that there is still doubt about their durability over time.

Daniel Navia et al, with their article published in the Revista Argentina de Cardiología "Durability of biological aortic valve prostheses: structural deterioration and incidence of events in distant follow-up", help us to understand a little more about the subject. Although it may have the limitations of a 20-year observational study, it allows us to draw important conclusions. As can be seen in the study, late survival in patients with prosthetic biological valves is high, with some differences depending on the age group evaluated. Furthermore, it is evident that structural valve deterioration in this type of valves is infrequent. (1)

These findings are consistent with other studies.

Caus et al analyzed the trends in surgical aortic valve replacement with biological versus mechanical valves in middle-aged patients, and observed that

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there is a greater predilection for the use of biological valves instead of mechanical valves in these patients. In addition, no significant differences were found in early mortality between the two types of valves. (2)

Although some of the clinical guidelines on the management of valvular heart disease consider the indication of biological prosthesis reasonable in patients between 50 and 65 years of age, (3) it is important to individualize the indication, to know the patient's clinical history, comorbidities, life expectancy and factors that may lead to early structural valve deterioration, thus avoiding risks and minimizing reinterventions.

In another article, Daniel Pérez-Carmargo and collaborators analyzed the survival of patients aged 50 to 69 years who received an aortic valve replacement, using biological or mechanical prostheses. The authors found that there is no significant difference in long-term survival between the two types of prostheses. (4)

Further research is needed to better understand the factors that influence the durability of these prostheses, including prosthesis design, sizing and tissue preservation techniques, with the goal of improving their long-term performance. As specialists, it is important to continually review new studies and advances, allowing us to make the best decisions with and for our patients.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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The Independent Variable for Success... our People

La variable independiente del éxito…nuestra gente

It was December 14, 2023. The new Board of Directors took over the leadership of the SAC in a completely new and unpredictable context in Argentina. An elected government with a completely different ideology. In those first months, a shock economic policy determined an enormous unpredictability in all areas of the country. The ignorance of the new rules of the game, the updating of relative prices, the impossibility of planning a budget, the project of dollarization, cutbacks in very sensitive areas such as science and education, a social crisis that was difficult to overcome, the reduction of income and fees for the entire population, created an uncertain future. We, the SAC, were not exempt from all these adversities. I remember the enormous number of hours and meetings that the Board of Directors, the staff of the Society and the sponsors had to spend in those first six months to structure and implement a budget based on strategies that were partly studied and partly intuitive.

There was probably a factor that was overlooked. Not because of ignorance. But because sometimes you do not know how some variables play out in the game "Institution" versus "Circumstances". And we won by a landslide...because of the enormous creative capacity of our members, their love for their Society, their ability to work and their eagerness to learn, unique qualities to overcome any difficulty. And in this combination, and although it may not seem so idyllic, delays in payment were minimal.

And that is how it was. There has been a record number of participants in courses and congresses on Cardiovascular Imaging, Cardiovascular Prevention, Cardiometabolism and Hypertension, in webinars and in attendance to conferences nationwide. Likewise, a tremendous amount of work was done by the Areas and Councils in the generation of consensus and position documents on various topics that place us as regional leaders. The SAC Cardiology Manual, the first in our history. Podcasts, permanent dissemination of all our activities from the ARI and Press and Communication Area, our new SAC streaming channel and the joy and enthusiasm of our people have enriched our institutional life. We are very grateful to our sponsors who have accompanied us because they see in the SAC a mystique of work that is essential for a successful investment.

In a few days we will celebrate the 50th anniversary of a historical milestone for our SAC, which was the organization of the VII World Congress of Cardiology in 1974, which allowed us to open our doors and integrate ourselves definitively with the world. The venue of the Sociedad Rural de Palermo will be the scene of the largest Spanish-speaking congress worldwide. There will be 18 meeting rooms with simultaneous activities, 1300 speakers, 2500 scientific participations, 160 round tables and meetings, 380 papers presented, 57 foreign guests and the presence of the presidents of Latin American Societies, ACC, AHA and European Societies.

A party organized by our members, residents, nurses, technicians, our Foundation and our patients. Our people...!

Víctor Mauro MTSAC,
President of the Argentine Society of Cardiology

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