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Scientific and administrative address

Azcúenaga 980 - (1115) Buenos Aires - Argentina / Tel.: +54-11-4961-6027/8/9 / Fax: +54-11-4961-6020 / e-mail: revista@sac.org.ar

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Writing a New Page

Escribiendo una nueva página

We begin a new year of the Argentine Journal of Cardiology in which we will celebrate its ninetieth anniversary. We have excellent news: we now have our own website at rac.sac.org.ar. The website has been updated with a bilingual version in Spanish and English, and our intention is to make it easy and intuitive to read.

Our goal for the Journal is to create a space for productive exchange, where the scientific work of Argentine cardiologists can be shared and promoted. We welcome authors from around the world to consider publishing their work with us. We want the Journal to be a place for discussion, to keep updated, meet, and grow. It is not only a place for reading, but also for writing original and short articles, opinion articles, editorials, reviews, scientific letters, comments on published work, or images in cardiology. Every paper

is welcome and will be considered for publication. We urge you to read the instructions to authors carefully. This will facilitate the writing process and reduce the time needed to make a final decision.

As usual, this first issue is dedicated to cardiovascular imaging. Artificial intelligence applied to imaging plays a predominant role in the published material, but other aspects of this vital part of everyday cardiology (can we imagine cardiology without imaging tests?) are also well represented. The content originates from various sources, as desired, including original articles and letters from abroad.

Dr. Gastón Rodríguez Granillo and Dr. Mariano Falconi collaborated on editing this issue. We hope that reading it will be useful for everyone.

Jorge Thierer^{MTSAC, }



Relieving Pressure: How Artificial Intelligence is Redefining Echocardiography Practice

Aliviando la presión: cómo la inteligencia artificial está redefiniendo la práctica de la ecocardiografía

MATÍAS CALANDRELLI ^{MTSAC}, 

Echocardiography, an essential tool in modern cardiology, has experienced exponential growth in terms of use and application. This boom is due to several factors, such as increased age of the population, low costs, and extensive availability, as well as technological advances leading to improved image quality.

However, the increased demand and complexity of echocardiography have brought about new difficulties. An international study revealed that 58% of cardiac imaging specialists suffer from burnout, mainly as a result of work overload and administrative tasks. (1) In Argentina, the burnout rate among cardiologists is even higher. (2)

The growing complexity of echo tests has increased both its length and rates of errors and inconsistencies. One paper found that 83% of tests had at least one error or inconsistency, with a linear relationship between the higher number of tests evaluated per hour and an increased rate of error. (3)

In addition to these difficulties, there is the large inter-observer variability that has always characterized echocardiography (more than 10% for some specific measurements). (4)

In response to these challenges, artificial intelligence (AI) has emerged as a promising solution for echocardiography interpretation. Advancements in machine learning enable us to identify images, measure parameters, and even create reports, optimizing workflows and reproducibility of results. (5,6)

This issue of the Argentine Journal of Cardiology (Revista Argentina de Cardiología, RAC) contains a study by Cotella et al. (7) to evaluate the feasibility and efficacy of a new work paradigm using AI for the interpretation of echocardiograms. The algorithm was developed and validated based on the data from the WASE study, a multinational and prospective registry created in order to establish normal echo-

cardiographic values according to the size and function of heart chambers in 2,000 healthy individuals from around the world. (8) The latter is important to minimize some usual biases in AI studies of cardiac images, such as acquisition, exclusion, population, and representation biases. (9) Convolutional neural networks (CNNs) were used to develop an AI model capable of interpreting echocardiograms. The model was able to identify views with 90% accuracy for 2D images and 94% accuracy for echo Doppler images, to rate images according to stacks based on anatomical structures or physiological events, and to automatically measure standard echocardiographic parameters with an excellent correlation with manual measurements by experts. Using AI reduced the echo time of interpretation by 40% and inter-observer variability in 15 of 16 parameters.

These results confirm the AI capacity to revolutionize how cardiologists interpret these tests.

The model being proposed stands out as it is compatible with any equipment brand when using the DICOM format as input and because it encompasses a large amount of workflow, from image rating to parameter measurement. A recent study has even added report creation to the AI functions, reducing the total amount of study time by 70%. (6)

While the AI model is promising, whether it will be applicable to all patients remains unknown. As the authors are aware, a limitation of this study is that only healthy individuals were enrolled. How would this model work in real-world consecutive patients with different conditions? The efficacy of the model might be reduced in these cases, a phenomenon known as data set shift. (10) Previous studies have found errors in left ventricular ejection fraction estimation by AI models in cases of severe ventricular dysfunction; and left ventricular mass automat-

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Cardiac Specialist MD UBA

Master's Degree in Artificial Intelligence and Big Data Applied to Healthcare, Universidad Autónoma de Barcelona

Cardiac Imaging Department Associate Investigator, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

ed measurements also show differences in patients with hypertrophic cardiomyopathy and cardiac amyloidosis versus controls. (5).

Other challenges still affect application of AI models: How will the algorithm manage repeated views, extrasystoles or atrial fibrillation? Will it work best with new algorithms, such as using Transformers for the last CNN layer for rating purposes, which has shown superiority in terms of time series, as in echo videos? (11) Will performance be preserved in cases of poor windows?

In summary, AI is becoming an ally for the echocardiographer, with potential workload reduction and improved accuracy of results. However, there is still a lot to be done: these models need to undergo the complex external validation process in different populations of real-world consecutive patients with various conditions, as well as to adhere to all regulatory and ethical aspects prior to permanent inclusion into clinical practice.

Echographers will be looking forward to that.

Therefore, we can conclude that machines shall not replace physicians, but echocardiographers using AI will be relieved in their work.

Conflicts of interest

None declared.

(See author's conflict of interest form on the website).

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Extended Septal Myectomy in Hypertrophic Obstructive Cardiomyopathy

Miectomia septal ampliada en la miocardiopatía hipertrófica obstructiva

NICHOLAS SMEDIRA 

This paper by Seia and the multidisciplinary team from the Instituto Cardiovascular de Buenos Aires, Argentina, (1) is an important examination of the hemodynamic impact and echocardiographic changes after an extended septal myectomy in patients with hypertrophic obstructive cardiomyopathy. It is especially important in the current era, when multiple new modalities for the treatment of left ventricular outflow tract obstruction are becoming available. The team is to be recognized for their outstanding surgical results and for the detailed short and medium-term echocardiographic evaluations.

They have shown that a patient undergoing an extended septal myectomy at a center of excellence, can expect resolution of symptoms, with a low risk of mortality and a low risk for heart block requiring a permanent pacemaker. The echocardiographic findings show a durable elimination of the left ventricular outflow tract obstruction with continued improvement in myocardial diastolic function, ventricular hemodynamics, mitral regurgitation along with reverse remodeling of the left atrium.

A frequent critique of a paper like this is that a large percentage of the patients had additional cardiac surgical procedures including 46% of the patients who also underwent a mitral valve intervention, 20% had coronary artery bypass grafting and 18% of the patients had a maze procedure. As a result, it is challenging to attribute all the improvement in echocardiographic parameters just to the extended septal myectomy.

The authors have focused on the echocardiographic changes; however, not mentioned but implicit in their results and for all centers treating patients with HCM, is that a multidisciplinary team of surgeons and cardiologist have performed a com-

prehensive assessment of the clinical, imaging and echocardiographic findings and have treated all important cardiovascular issues.

Atrial fibrillation is one example. Patients with hypertrophic cardiomyopathy are estimated to have a 25% lifetime incidence of atrial fibrillation. Surgical reviews have shown that only a small percentage of patients with atrial fibrillation undergo concomitant surgical ablation at the time of cardiac surgery. The fact that 18% of the study's patients underwent a Maze procedure suggests that the team is aggressively treating atrial fibrillation, which when left untreated can be a significant burden for patients with hypertrophic cardiomyopathy.

As new drug therapies, like myosin inhibitors and less invasive percutaneous approaches to septal reduction become available, it is increasingly important to take an in depth assessment of all cardiovascular issues impacting the patient's clinical state and cardiac function. With that information a multidisciplinary team including surgeons, imaging specialists, interventionalists and electrophysiologists can develop a comprehensive course of treatment and then strive to achieve the excellent results of the team at the Instituto Cardiovascular de Buenos Aires.

Conflicts of interest

None declared.

(See author's conflict of interest form on the website).

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Staff Surgeon, Cleveland Clinic
Surgical Director of the Hypertrophic Cardiomyopathy Center
Professor of Surgery, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University

Optimizing Echocardiograms Interpretation with the Application of Machine Learning in the WASE Study

Optimización de la interpretación de ecocardiogramas con la utilización de Machine Learning en el estudio WASE

JUAN I COTELLA¹, KARIMA ADDETIA¹, TATSUYA MIYOSHI², KALIE KEBED¹, ALEXANDRA BLITZ³, MARCUS SCHRECKENBERG³, NIKLAS HITSCHRICH³, ALDO D. PRADO⁴, EDUARDO FILIPINI⁵, MTSAC, RICARDO RONDEROS⁵, VICTOR MOR-AVI¹, ROBERTO M. LANG¹, FEDERICO M. ASCH²

ABSTRACT

Background: The growing number of echocardiographic tests and the need for strict adherence to international quantification guidelines have forced cardiologists to perform highly extended and repetitive tasks when interpreting and analyzing increasingly overwhelming amounts of data. Novel machine learning (ML) techniques, designed to identify images and perform measurements at relevant visits, are becoming more common to meet this obvious need for process automation.

Objective: Our objective was to evaluate an alternative model for the interpretation and analysis of echocardiographic tests mostly based on the use of ML software in order to identify and classify views and perform standardized measurements automatically.

Methods: Images came from 2000 healthy subjects, 1800 of whom were used to develop ML algorithms and 200 for subsequent validation. First, a convolutional neural network was developed in order to identify 18 standard echocardiographic views and classify them based on 8 thematic groups (stacks). The results of automatic identification were compared to classification by experts. Later, ML algorithms were developed to automatically measure 16 Doppler scan parameters for regular clinical evaluation, which were compared to measurements by an expert reader. Finally, we compared the time required to complete the analysis of an echocardiographic test using conventional manual methods with the time needed when using the ML model to classify images and perform initial echocardiographic measurements. Inter- and intra-observer variability was also analyzed.

Results: Automatic view classification was possible in less than 1 second per test, with a 90% accuracy for 2D images and a 94% accuracy for Doppler scan images. Stacking images had a 91% accuracy, and it was possible to complete the groups with any necessary images in 99% of cases. Expert agreement was outstanding, with discrepancies similar to those found between two human readers. Applying ML to echocardiographic imaging classification and measurement reduced time of analysis by 41% and showed lower variability than conventional reading methods.

Conclusion: Application of ML techniques may significantly improve reproducibility and efficiency of echocardiographic interpretations and measurements. Using this type of technologies in clinical practice may lead to reduced costs and increased medical staff satisfaction.

Key words: Artificial intelligence - Machine learning - Echocardiography

RESUMEN

Introducción: El número creciente de estudios ecocardiográficos y la necesidad de cumplir rigurosamente con las recomendaciones de guías internacionales de cuantificación, ha llevado a que los cardiólogos deban realizar tareas sumamente extensas y repetitivas, como parte de la interpretación y análisis de cantidades de información cada vez más abrumadoras. Novedosas técnicas de machine learning (ML), diseñadas para reconocer imágenes y realizar mediciones en las vistas adecuadas, están siendo cada vez más utilizadas para responder a esta necesidad evidente de automatización de procesos.

Objetivo: Nuestro objetivo fue evaluar un modelo alternativo de interpretación y análisis de estudios ecocardiográficos, basado fundamentalmente en la utilización de software de ML, capaz de identificar y clasificar vistas y realizar mediciones estandarizadas de forma automática.

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Address for reprints: Federico M Asch, MD. MedStar Health Research Institute and University of Georgetown. 100 Irving St, NW. Washington DC 20010. USA. Federico.asch@medstar.net. @FedericoAsch

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² MedStar Health Research Institute, Washington, DC

³ TOMTEC Imaging Systems, Unterschleissheim, Germany

⁴ Centro Privado de Cardiología, Tucumán, Argentina

⁵ Instituto Cardiovascular de Buenos Aires, CABA, Argentina

Material y métodos: Se utilizaron imágenes obtenidas en 2000 sujetos normales, libres de enfermedad, de los cuales 1800 fueron utilizados para desarrollar los algoritmos de ML y 200 para su validación posterior. Primero, una red neuronal convolucional fue desarrollada para reconocer 18 vistas ecocardiográficas estándar y clasificarlas de acuerdo con 8 grupos (*stacks*) temáticos. Los resultados de la identificación automática fueron comparados con la clasificación realizada por expertos. Luego, algoritmos de ML fueron desarrollados para medir automáticamente 16 parámetros de eco Doppler de evaluación clínica habitual, los cuales fueron comparados con las mediciones realizadas por un lector experto. Finalmente, comparamos el tiempo necesario para completar el análisis de un estudio ecocardiográfico con la utilización de métodos manuales convencionales, con el tiempo necesario con el empleo del modelo que incorpora ML en la clasificación de imágenes y mediciones ecocardiográficas iniciales. La variabilidad inter e intraobservador también fue analizada.

Resultados: La clasificación automática de vistas fue posible en menos de 1 segundo por estudio, con una precisión de 90 % en imágenes 2D y de 94 % en imágenes Doppler. La agrupación de imágenes en *stacks* tuvo una precisión de 91 %, y fue posible completar dichos grupos con las imágenes necesarias en 99% de los casos. La concordancia con expertos fue excelente, con diferencias similares a las observadas entre dos lectores humanos. La incorporación de ML en la clasificación y medición de imágenes ecocardiográficas redujo un 41 % el tiempo de análisis y demostró menor variabilidad que la metodología de interpretación convencional.

Conclusión: La incorporación de técnicas de ML puede mejorar significativamente la reproducibilidad y eficiencia de las interpretaciones y mediciones ecocardiográficas. La implementación de este tipo de tecnologías en la práctica clínica podría resultar en reducción de costos y aumento en la satisfacción del personal médico.

Palabras claves: Inteligencia artificial - Machine learning - Ecocardiografía

INTRODUCTION

The usual interpretation of a complete echocardiographic test involves review of multiple groups and types of images, whatever their order of acquisition. The echo technician needs to classify and incorporate the information contained in all images and to interpret them in order to report any anatomical and/or cardiovascular function features. Therefore, it is not uncommon to perform several reviews of a large number of images, which might become a long and tiresome process for the professional. In addition, once any relevant images have been identified, a significant number of echocardiographic measurements need to be performed following the recommendations by major international associations guidelines. It is important to consider that measurements may vary significantly across readers. (1-8) Even though it is difficult to determine the exact amount of time required by this selection, categorization, and quantification process during an echocardiographic test, the possibility of making these stages shorter is highly attractive to optimize the entire process and workflow involved.

Recent studies have shown that both imaging classification and echocardiographic measurements can be automated using machine learning (ML) techniques. (9-11) Our hypothesis is that these new tools might optimize the entire clinical interpretation process for echocardiographic tests and complete it in a faster and more reproducible manner than conventional manual techniques, eventually contributing to a more efficient and improved workflow for the staff involved. This new approach might include: (a) automated identification of the type and view of the echocardiographic image, (b) classifying and sorting images into categories or groups (*stacks*) defined by predetermined anatomical structures, (c) fully automated measurements with standard parameters for every structure, and (d) manual correction of these automated measurements (if necessary) in order to improve accuracy.

Our objective was to analyze the feasibility of this new work paradigm by evaluating its impact on the efficiency and reproducibility of human interpretation.

METHODS

Images and population

We have used several echocardiographic tests in an attempt to represent a wide range of zoom, depth, zone of interest width, focus, gain, and image quality. These tests were performed in 2000 healthy subjects, previously included in the WASE study (World Alliance Societies of Echocardiography normal values study). The objective of the study was to determine normal values for multiple quantifiable echocardiographic parameters. (12) Subjects came from 19 sites in 15 countries and included a large group of adults of both sexes, and various races, ethnic and age groups. These tests used different marketed echocardiographic systems available and followed the latest recommendations from the American Society of Echocardiography (ASE). (13) Images were rated by an expert according to the type of image (2D, pulsed wave Doppler, etc.) and echocardiographic view (4 chambers apical, long axis parasternal, etc.). Regular measurements were performed by a central echocardiography expert (core laboratory) with strict adherence to the latest recommendations. (14) For our study, we used images from 1800 subjects to develop and train ML algorithms (training group), while the remaining 200 were used to evaluate these algorithms (testing group).

Study design

The study was divided into 3 protocols. *Protocol 1* was designed to develop ML algorithms and evaluate accuracy for automated identification of the type of image and echocardiographic view, similarly to the approach used in recent studies (9-11), as well as to classify these images in *stacks* according to certain anatomical structures or reference “physiological events” (for example, mitral valve, diastolic function), which would eventually guide image review and interpretation. *Protocol 2* was designed to develop and evaluate ML accuracy for automatic measurement of conventional echocardiographic parameters, similar to those used by Zhang et al. (10). Finally, *Protocol 3* was designed to determine the feasibility and effectiveness resulting from the

combination and integration of these protocols into echo reading, assessing efficiency (time saving) and reproducibility (measurement variability) parameters, and comparing these results to current interpretation and measurement methods.

The evaluation of Protocol 1 included developing and training a convolutional neural network (CNN) using measurements provided by an independent reader (TM) unfamiliar with development of the ML algorithm. Protocol 2 was evaluated by comparing measurements provided by the ML algorithm to those supplied by a second reader (KA), coming from a site different from that of the first reader. Finally, Protocol 3 compared the performance of 2 readers (KA and KK) who did not take part in the ML algorithm development and training phase.

Development of ML software, as well as the study design, were the result of the collaboration between the investigators involved (MedStar and University of Chicago) and TOMTEC Imaging Systems (Unterschleissheim, Germany). Principal investigators (RML, FMA) had unrestricted data access and analyzed data independently from TOMTEC, assuming full responsibility for the findings presented here.

Convolutional Neural Network algorithm

Training to detect every parameter of interest was conducted through a cascade strategy including 3 subdetection stages. This initial setup was supplemented by an image pre-processing mechanism in order to standardize any resulting information. This included detection of the ultrasound bundle area, deletion of any additional information inserted in echocardiographic images, and intensity and color adjustment for DICOM files.

Initially, for an approximate estimation of the position, size, and orientation in space of the relevant structure, every CNN subdetector was regressively fed with a subsample of images having a fixed resolution of less than 20% the number of pixels in the original image. In a second stage, every detector received the area and structure of interest from each image in order to reduce any changes in terms of scale and position. Image resolution for this second stage was standardized to average resolution (mm/pixel) for all images to make up for any potential change in resolution of individual images. In this case, relevant structures were identified using regressive CNN, as in the first stage of the process. Finally, for the third stage, we used a more refined set of images with improved localization of relevant structures (as compared to the previous stage). As before, regressive CNN made this possible.

Training in every subdetection stage was performed using a subset of measurements such as the ground truth. During training, every detector could analyze information input based on these measurements assumed as the ground truth, together with 32 augmented versions of such input. The increase was possible thanks to mild rotations and scale variations in the area of interest, leading to effective identification of a large number of variants and structures.

Protocol 1: automated image identification and stacking

The CNN was trained to identify 18 standard echocardiographic views: 6 corresponding to two-dimensional echocardiography (2D), and 12 corresponding to tissue Doppler imaging (TDI), pulsed wave Doppler (PW), and continuous wave Doppler (CW). 2D images included apical views in 2, 3 and 4 chambers (A2C, A3C and A4C, respectively), as well

as long and short axis parasternal views (PLAX and PSAX, respectively), and subcostal view (SC). TDI included septal and lateral sampling from the mitral annulus and lateral portion of the tricuspid annulus. PW images were collected across the left ventricular outflow tract (LVOT) on apical view, the mitral inflow tract on four-chamber view, and the right ventricular outflow tract (RVOT) on PSAX view. CW showed aortic flow evaluation on apical view, as well as mitral regurgitation flow on four-chamber apical view, tricuspid regurgitation flow on four-chamber apical view and PSAX, and pulmonary flow on PSAX view. All these images were used as CNN input to create our library with different types of images and echocardiographic views.

Then, the CNN was trained to identify views and types of images in an independent set of test images for subsequent allocation or classification of each of these images in 8 stacks based on the following parameters or structures: left ventricular (LV) systolic function and size, LV diastolic function, right ventricular (RV) and right atrial (RA) function and size, valves (mitral, aortic, tricuspid and pulmonary), and pericardium. Table 1 shows a list of the images required to complete each stack. Finally, the results of automatic image identification and classification were compared to the “ground truth” predetermined by the expert reader.

Protocol 2: automatic analysis accuracy and reproducibility

After every image was automatically classified according to type and view, and after selecting the cardiac cycle phase for measurements, a ML monitored algorithm was trained to measure 16 standard parameters regularly quantified in clinical practice. These parameters included interventricular septum diastolic thickness, diastolic and systolic LV internal diameter, LV posterior wall diastolic thickness, LVOT midsystolic diameter, LVOT velocity time integral (VTI), left atrial (LA) maximum volume on A2C and A4C, LV end-diastolic and end-systolic volumes, mitral valve inflow E wave and A wave, and mitral lateral and septal annulus tissue velocity. All chamber volumes were measured using the biplane Simpson method.

The accuracy of these automatic measurements was compared to that of manual measurements collected by an expert reader from the test group of 200 subjects. Also, in a subset of 30 randomly selected tests, differences between automatic ML measurements and those provided by a reference expert reader were compared to inter- and intra-observer human variability by repeated blinded measurements. To assess interobserver variability, measurements were independently performed by two echocardiography expert cardiologists using conventional interpretation and measurement methods. Finally, to determine intraobserver variability, one of these experts, again fully blinded to previous measurements, re-read the same echocardiographic tests at least two weeks after the first analysis.

Protocol 3: efficiency and reproducibility of the ML assisted approach

In this protocol, both experts independently repeated interpretation of the 30 tests at least 2 weeks later, this time, using ML assistance. In this case, experts could use any stacks and measurements that were automatically established by algorithms, making any necessary adjustments to improve accurate identification and measurement of relevant structures or events. For both sessions, the time required to complete analysis of the echocardiographic test depended on the workstation being used, and intra and interobserver variability was evaluated for all previously

Type of Image and Echocardiographic View Allocation by Experts (Ground Truth)	A2C	A3C	A4C	PLAX	PSAX	SC	MVann(l) DTI	MVann(m) DTI	TVann(l) DTI	Api LVOT PW	A4C MVinfl PW	A4C PVinfl PW	A4C TVinfl PW	PSAX RVOT PW	Api. AV CW	A4C MVinfl PW	A4C/PSAX TVinfl CW	PSAX PV CW	Other
A2C	98.0	0.4	1.2	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
A3C	2.7	94.9	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7
A4C	2.0	2.6	91.2	0.4	0.3	3.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
PLAX	0.0	0.1	0.1	90.2	0.1	9.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PSAX	0.2	1.0	0.5	2.3	86.3	9.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
SC	0.0	0.0	0.0	0.0	0.8	99.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MVann(l) DTI	0.0	0.0	0.0	0.0	0.0	0.0	96.2	1.9	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MVann(m) DTI	0.0	0.0	0.0	0.0	0.0	0.0	8.7	87.0	4.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TVann(l) DTI	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Api LVOT PW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	94.0	0.0	0.7	0.0	5.3	0.0	0.0	0.0	0.0	0.0
A4C MVinfl PW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.1	95.7	0.0	3.3	0.0	0.0	0.0	0.0	0.0	0.0
A4C PV infl PW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	98.9	1.1	0.0	0.0	0.0	0.0	0.0	0.0
A4C TVinfl PW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.7	94.3	0.0	0.0	0.0	0.0	0.0	0.0
PSAX RVOT PW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.9	0.0	0.0	1.3	94.8	0.0	0.0	0.0	0.0	0.0
Api. AV CW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	95.4	0.0	0.0	4.6	0.0
A4C MVinfl PW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.1	74.2	17.7	0.0	0.0
A4C/PSAX TVinfl CW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	0.0	98.0	0.7	0.0
PSAX PV CW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	3.1	95.4	0.0
Other	0.8	26.7	96.2	0.0	0.8	8.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	54.2

Abbreviations: A2C, A3C and A4C = 2, 3 and 4 chamber apical, respectively; PLAX, PSAX, SC = long axis parasternal, short axis parasternal, and subcostal, respectively; MVann (l), MVann (s), TVann (l) = lateral mitral annulus, septal mitral annulus, and lateral tricuspid annulus, respectively; Api LVOT = apical view of the left ventricular outflow tract; Api AV = apical view of the aortic valve; MVinfl, TV infl, PVinfl = mitral, tricuspid and pulmonary valves inflow tracts, respectively; CW = continuous wave Doppler; PW = pulsed wave Doppler

Fig. 1. Identifying the type and view of echocardiographic images: agreement between automated ML measurements and manual expert measurements. Each cell represents the percentage of agreement for every type of image and view being evaluated. The cells have different colors depending on the percentage of agreement: red (0%), orange (0.1%-50%), yellow (50.1%-90%) and green (90.1%-100%).

described parameters. Finally, times of analysis with and without ML assistance were compared.

Statistical analysis

The accuracy of the automated method for type of image identification and echocardiographic view, as well as comparison versus experts, was quantified as the percentage of correct classifications based on the total number of analyzed image sequences. For every parameter, consistency between ML measurements and reference values collected by experts was evaluated using linear regression methods, and bias and limits of agreement tests using the Bland-Altman method. In order to compare different parameters, biases were expressed as the percentage of the average value of each parameter (% bias). Intra and interobserver variability for every parameter was quantified using variation coefficients, defined as the absolute difference among repeated measurements expressed as mean percentages. The statistical significance of variations in the time of analysis with and without ML assistance was determined by the Student's t test using two-tailed paired measurements. P-values <0.05 were considered significant.

Ethical considerations

The study was approved by the ethics committees of each institution and patient consent was obtained according to local regulations.

RESULTS

Protocol 1

The CNN performed automatic classification of echocardiographic views with an average of 0.87 seconds per test. The CNN was able to identify types of images and echocardiographic views with a 90% accuracy for 2D images and a 94% accuracy for Doppler images. Figure 1 shows data corresponding to agreement between ML and the expert's reader "ground truth" classification for each echocardiographic view. While agreement was excellent in most cases, the largest number of errors occurred when classifying non-standard sub-optimal views, wrongly identified as A3C (and noted as "Other"). The CNN was able to separate and group images in stacks with a 91% accuracy. When counting the number of views required to complete every stack, ignoring those that were considered unnecessary, the final composition of each image stack showed a 99% agreement between ML and expert readers (Table 1).

Protocol 2

Automatic ML measurements showed excellent agreement versus reference values collected by experts, as shown by high correlation rates, small bias-

Table 1. Composition of echocardiographic imaging groups (stacks) according to the relevant topic or structure, and percentage of complete automatic machine learning classifications.

Relevant Stack or Group	Echocardiographic Image Type and View		% Complete Stacks
	2D Views	Doppler	
Left Ventricular Systolic Function and Dimensions	*Long axis parasternal *Short axis parasternal - baseline *Short axis parasternal - mid *Four chambers apical *Two chambers apical *Three chambers apical		99.5%
Left Ventricular Diastolic Function	*Four chambers apical *Two chambers apical *Subcostal	*Mitral valve four chambers apical *Mitral valve four chambers apical - mid *Mitral valve four chambers apical - lateral *Tricuspid valve four chambers apical	100%
Right Ventricular and Atrial Function and Dimensions	*Long axis parasternal *Right ventricular inflow tract *Short axis parasternal *Four chambers apical *Four chambers apical - focus on right ventricle *Subcostal		99%
Mitral Valve	*Long axis parasternal *Short axis parasternal - baseline *Four chambers apical *Two chambers apical *Three chambers apical *Subcostal	*Long axis parasternal mitral valve *Four chambers apical mitral valve *Two chambers apical mitral valve *Three chambers apical mitral valve *Four chambers apical pulmonary valve *Four chambers apical tricuspid valve	99.8%
Aortic Valve	*Long axis parasternal *Short axis parasternal - aortic valve *Five chambers apical *Three chambers apical	*Five chambers apical aortic valve *Five chambers apical left ventricular outflow tract *Three chambers apical aortic valve *Three chambers apical left ventricular outflow tract	96%
Tricuspid Valve	*Right ventricular inflow tract *Short axis aortic valve *Four chambers apical *Four chambers apical - focus on right ventricle *Subcostal	*Right ventricular inflow tract tricuspid valve *Short axis parasternal tricuspid valve *Four chambers apical tricuspid valve	99.4%
Pulmonary Valve	*Right ventricular outflow tract *Short axis aortic valve	*Short axis parasternal aortic valve *Short axis parasternal pulmonary valve	98.4%
Pericardium	*Long axis parasternal *Four chambers apical *Subcostal		100%

Table 2. Evaluation of Machine Learning (ML) Algorithm

	Linear Regression	Bias ± SD	Bland Altman Test		
	Pearson Coefficient r		% Bias	Lower Limit of Agreement	Upper Limit of Agreement
IVSd Thickness (mm)	0.65	-0.11 ± 1.3	-1.5	-2.7	2.4
PWd Thickness (mm)	0.64	-0.04 ± 1.1	-0.5	-2.2	2.1
LVIDs (mm)	0.78	0.85 ± 2.5	3	-4.2	5.9
LVIDd (mm)	0.82	0.65 ± 3.1	1.5	-5.6	6.9
LVOT diam (mm)	0.82	0.85 ± 1.5	4.1	-2.1	3.8
LVd Vol A2C (ml)	0.91	6.6 ± 12.5	6.5	-18.4	31.6
LVd Vol (A4C) (ml)	0.94	7.4 ± 9.5	7.8	-11.5	26.3
LVs Vol (A2C) (ml)	0.87	-0.5 ± 6.2	-1.3	-12.9	11.9
LVs Vol (A4C) (ml)	0.89	0.6 ± 5.6	1.6	-10.7	11.8
LA Vol (A2C) (ml)	0.87	11.8 ± 10.3	25	-8.9	32.5
LA Vol (A4C) (ml)	0.89	8.6 ± 8.5	18	-8.4	25.6
LVOT VTI (cm)	0.91	0.46 ± 1.7	2.2	-2.8	3.8
E Vel (cm/s)	0.96	-0.01 ± 0.05	-1.1	-0.11	0.09
A Vel (cm/s)	0.95	-0.01 ± 0.05	-1.1	-0.11	0.1
E' vel (l) (cm/s)	0.96	-0.03 ± 1.3	-0.2	-2.62	2.56
E' vel (s) (cm/s)	0.96	-0.03 ± 1.21	-0.3	-2.45	2.39

Agreement between measurements and reference values obtained automatically using ML and manually collected by experts in 200 tests. Pearson linear regression coefficient (r) and Bland-Altman bias and limits of agreement test have been included. Positive bias represents ML overestimation, while negative bias represents underestimation.

Abbreviations: SD = standard deviation; IVSd = interventricular septum diastolic; PWd = posterior wall diastolic; LVIDs = left ventricular internal diameter systolic; LVID = left ventricular internal diameter diastolic; LVOT diam = midsystolic left ventricular outflow tract diameter; LVd Vol A2C and A4C = left ventricular diastolic volumes on 2 and 4 chambers apical view, respectively; LVs Vol A2C and A4C = left ventricular systolic volumes on 2 and 4 chambers apical view, respectively; LA Vol A2C and A4C = left atrium maximum volume on 2 and 4 chambers apical view, respectively; LVOT VTI = left ventricular outflow tract velocity time integral; E Vel and A Vel = mitral inflow early (E) wave velocity and late (A) wave velocity; E' vel (l) and E' vel (s) = mitral lateral and septal annulus tissue velocity, respectively.

es, and narrow limits of agreement for most parameters under analysis (Table 2). The largest relative biases occurred for left atrial volumes both in A4C and A2C (18% and 25% of reference values), followed by left ventricular volumes (6.5% and 7.8% of reference values). For the remaining parameters being assessed, relative biases were very small, with values lower than 3%. The analysis of the subset of 30 tests showed that differences between ML and expert measurements were similar to differences between manual measurements by two human technicians (Table 3).

Protocol 3

Conventional interpretation of a complete echocardiographic study required an average of 11 minutes and 33 seconds (9:29 for reader #1 and 13:36 for reader #2). On the other hand, when using ML assistance through stacking and automated measurements, the average time needed to complete evaluation of a test was 6 minutes and 48 seconds (4:50 for reader #1 and 8:45 for reader #2). This means that using ML may reduce an average 40% the time required

to interpret an echocardiographic test using current conventional methods (49% for reader #1 and 36% for reader #2). Please note that, as compared to the manual method, ML reduced inter-observer variability in 15 of 16 measurements (Table 3), except for LVOT diameter, which had a highly reproducible measurement using both methods.

DISCUSSION

In the last decade, the use of artificial intelligence for medical imaging has increased remarkably thanks to the possibility of assistance throughout various stages of the interpretative and diagnostic process. (15,16) While the purpose of artificial intelligence has been primarily evaluated using static radiology images, application of techniques such as ML to echocardiography has relatively fallen behind. This could be at least partly explained by the technical challenges posed by echocardiography, such as lower spatial resolution or quality of image versus other techniques like computed tomography or nuclear magnetic resonance, and also by the dynamic aspect of echocardiographic images (use of videos),

Table 3. Comparison between automatic ML reference values and measurements by an expert reader using conventional measurement methods, including intra and interobserver variability for each of these methods

	Conventional Manual Interpretation		Automatic ML- Only Interpretation Vs Manual Interpretation	ML Interpretation + Corrections Vs Manual Interpretation
	Intraobserver Variability	Interobserver Variability		
IVSd thickness (mm)	7 ± 5	11 ± 8	14 ± 10	0 ± 1 *
PWd thickness (mm)	8 ± 7	15 ± 13	17 ± 15	1 ± 3 *
LVIDs (mm)	3 ± 2	8 ± 6	10 ± 10	3 ± 5 *
LVIDd (mm)	2 ± 2	4 ± 4	6 ± 5	0 ± 1 *
LVOT diam (mm)	2 ± 3	4 ± 3	5 ± 4	6 ± 14
LVd Vol (A2C) (ml)	10 ± 9	20 ± 13	14 ± 10	6 ± 8 *
LVd Vol (A4C) (ml)	7 ± 5	22 ± 7	16 ± 8	4 ± 5 *
LVs Vol (A2C) (ml)	11 ± 9	23 ± 14	27 ± 19	3 ± 4 *
LVs Vol (A4C) (ml)	9 ± 7	32 ± 13	35 ± 16	4 ± 5 *
LA Vol (A2C) (ml)	14 ± 9	17 ± 22	14 ± 10	9 ± 9
LA Vol (A4C) (ml)	13 ± 13	18 ± 13	16 ± 8	9 ± 8 *
LVOT VTI (cm)	5 ± 4	7 ± 5	8 ± 7	1 ± 4 *
E Vel (cm/s)	4 ± 4	8 ± 7	6 ± 5	3 ± 16
A Vel (cm/s)	3 ± 3	14 ± 11	14 ± 11	3 ± 16 *
E' vel (l) (cm/s)	7 ± 9	10 ± 20	11 ± 17	2 ± 8
E' vel (s) (cm/s)	4 ± 4	6 ± 8	8 ± 7	0 ± 0 *

Values represent variation coefficients (see text for more details). For abbreviations, see Table 2.

*p<0.05 for automated ML interpretation.

which requires large amounts of data and information in an extremely short time. However, recent studies have overcome many of these obstacles using new ML techniques especially designed to identify echocardiographic types and views, (9-11) or for automated measurement of regular echocardiographic parameters in clinical practice. (10, 17, 18) For example, using artificial intelligence as a guide to collect echocardiographic images has allowed users with little ultrasound training to collect images of a quality similar to those obtained by an expert technician. (19) We believe that our study is the first to combine these new ML techniques for imaging identification and classification based on common predetermined features. It is also the first study to show the potential impact of this new tool in terms of reducing the time required to complete an echo analysis, with subsequent improved efficiency for the echo lab workflow.

It is true that cardiologists in general and echocardiography specialists in particular are used to identifying, classifying, and analyzing large numbers of images, with no need for a previous grouping or stacking process. Nevertheless, the growing number of tests and the need to strictly adhere to the recommendations in echocardiographic quantification guidelines have evidenced a new scenario, where inclusion of automated mechanisms for these repetitive tasks is becoming increasingly necessary. ML-based

technology is especially suitable to solve this kind of problems thanks to its exclusive ability to identify and classify images, (9-11) and even to identify specific components or structures within these images requiring segmentation and/or measurement. (10) In this study, we proposed that combining all these ML capabilities may contribute to facilitate diagnostic interpretation throughout several stages of the process, ranging from classification to measurements.

The initial hypothesis behind this study was that applying a variety of ML techniques might involve a disruptive change in the way echocardiographic tests are currently read and interpreted. Ultimately, our purpose is to optimize the complex and extensive interpretation process of echocardiographic tests through the increased efficiency, accuracy, and reproducibility of readings that ML may provide.

As in previous publications, (9-11) using CNN in our study allowed a computer to identify rapidly and accurately most potential types and views of an echocardiographic image. According to this classification, images were sorted and presented to expert readers in thematic stacks, a useful and practical approach when answering a certain clinical question. Therefore, this tool practically removed the need to identify, classify, and visually group various anatomical structures, while (at least virtually) doing without human measurements of regular echocardiographic parameters. In fact, our results have shown that differences be-

tween measurements obtained automatically with no manual adjustments and those collected by an expert were no larger than differences observed between two readers with the same experience and training. Therefore, ML assistance to interpret echocardiographic images helped reduce to less than 10% the variability in measurements for most parameters being evaluated, which is ideal for a qualitative assessment of the cardiovascular function. In addition, ML algorithms combination of identification, stacking, and automatic measurement abilities (with manual correction if necessary) allowed readers, on the one hand, to significantly reduce their usual time of analysis, and on the other hand, to reduce interobserver variability when quantifying most evaluated parameters.

A major advantage of the software being developed and evaluated in this study is its theoretical independence from the manufacturer (vendor) of echocardiographic systems, as it was designed to interpret images in DICOM format coming from any of these systems, allowing them to be used by any laboratory or department, regardless of the echocardiographic method being used.

One limitation of our study is that it only included healthy subjects who were previously tested in the WASE study. However, other ML software has been validated by several authors and in patients with a wide range of cardiovascular conditions. (9-11, 20, 21) Thus, revalidating said software was not among the objectives of our study, which was exclusively focused on evaluating an alternative path for the interpretation of echocardiographic images. It is therefore unlikely that including patients with a condition might affect our findings.

To conclude, ML techniques may significantly improve the efficiency and reproducibility of echocardiographic imaging interpretation by using thematic stacks based on common structures and through automated measurements that can be corrected. Applying this type of technology will save time and money, mostly by improved process efficiency, higher medical staff satisfaction, and increased diagnostic performance.

Conflicts of interest

AB, MS, and NH are employees of TOMTEC. KK has received funding from the T32 Cardiovascular Sciences Training Grant (5T32HL7381). The remaining authors have no conflicts to declare. (See authors' conflict of interests forms on the web).

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PRINCIPAL INVESTIGATORS IN THE WASE STUDY

Ricardo Ronderos, MD, FASE, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; Gregory Scalia, MD, FASE, GenesisCare, Brisbane, Australia; Ana Clara Tude Rodrigues, MD, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; Wendy Tsang, MD, Toronto General Hospital, University of Toronto, Toronto, ON, Canada; Mei Zhang, PhD, Qilu Hospital of Shandong University, Jinan, China; V. Amuthan, MD, DM, Jeyalakshmi Heart Center, Madurai, India; Ravi Kasliwal, MD, FASE, Medanta Heart Institute, Medanta, India; Anita Sadeghpour, MD, FASE, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran; Eduardo Bossone MD, FASE, University of Salerno, Salerno, Italy; Denisa Muraru, MD, University of Padua, Padua, Italy; Masao Daimon, MD, PhD, The University of Tokyo, Tokyo, Japan; Masaaki Takeuchi, MD, PhD, FASE, University of Occupational and Environmental Health, Kitakyushu, Japan; Pedro Gutierrez-Fajardo, MD, FASE, Hospital Bernardette, Guadalajara, Mexico; Kofo O. Ogunyankin, MD, FASE, First Cardiology Consultants Hospital Ikoyi, Lagos, Nigeria; Edwin S. Tucay, MD, FASE, Philippine Heart Center, Quezon City, Philippines; Seung Woo Park, MD, Samsung Medical Center, Seoul, Korea; Mark J. Monaghan, PhD, King's College Hospital, United Kingdom; Karima Addetia, MD, University of Chicago, Chicago, IL; James Kirkpatrick, MD, FASE, University of Washington, Seattle, WA.

ADDITIONAL INVESTIGATORS IN THE WASE STUDY (in country alphabetical order)

Argentina: Aldo D. Prado, Centro Privado de Cardiología, Tucumán; Eduardo Filipini, Instituto Cardiovascular de Buenos Aires, Buenos Aires.

Australia: Agatha Kwon and Samantha Hoschke-Edwards, GenesisCare, Brisbane.

Brazil: Tania Regina Afonso, Hospital Israelita Albert Einstein, Sao Paulo.

Canada: Babitha Thampinathan and Maala Sooriyakanthan, Toronto General Hospital, University of Toronto, Toronto, Ontario.

China: Tiangang Zhu and Zhilong Wang, Peking University People's Hospital, Beijing; Yingbin Wang, Mei Zhang, and Yu Zhang, Qilu Hospital of Shandong University, Jinan; Lixue Yin and Shuang Li, Sichuan Provincial People's Hospital, Sichuan.

India: R. Alagesan, Madras Medical College, Chennai; S. Balasubramanian, Madurai Medical College, Madurai; R.V.A. Ananth, Jeyalakshmi Heart Center, Madurai; Manish Bansal, Medanta Heart Institute, Medanta, Haryana.

Italy: Luigi P. Badano (currently at the University of Milano-Bicocca and Istituto Auxologico Italiano, IRC-CS, Milano) and Chiara Palermo, University of Padua, Padua; Eduardo Bossone (currently at Antonio Cardarelli Hospital, Naples), Davide DiVece, and Michele Bellino, University of Salerno, Salerno.

Japan: Tomoko Nakao, Takayuki Kawata, Megumi Hirokawa, and Naoko Sawada, University of Tokyo, Tokyo; Yousuke Nabeshima, University of Occupational and Environmental Health, Kitakyushu.

Korea: Hye Rim Yun and Ji-won Hwang, Samsung Medical Center, Seoul.

Nigeria: Dolapo Fasawe, First Cardiology Consultants Hospital Ikoyi, Lagos.

Left Ventricular Remodeling After Myocardial Infarction: A Perspective from Gated-SPECT Myocardial Perfusion Imaging

Remodelado del ventrículo izquierdo postinfarto: una mirada desde la perfusión miocárdica gated-SPECT

LUCAS SAN MIGUEL¹, MTSAC, , LAURA BRODSKY¹, , OSVALDO H. MASOLI¹, MTSAC, 

ABSTRACT

Background: Gated single-photon emission computed tomography (gated-SPECT) myocardial perfusion imaging is a suitable technique for measuring the infarct scar size and defining its territory. Analyzing patients with small and medium myocardial infarctions that develop reduced left ventricular ejection fraction (LVEF) could provide additional information of the factors that contribute to adverse remodeling and its outcome.

Objectives: a) To evaluate the prevalence of reduced LVEF and associated factors in a population of patients referred for gated-SPECT imaging, and b) to define the prevalence of adverse remodeling and associated factors in the subgroup of patients with intermediate to low necrotic burden.

Methods: We conducted a retrospective analysis of consecutive patients undergoing gated-SPECT imaging during 2017. Patients with significant valvular heart disease or arrhythmias that could difficult adequate ECG gating were excluded from the study. Adverse remodeling was considered as the combination of reduced LVEF (LVEF < 50%) with percent myocardium scar < 20%.

Results: A total of 1902 patients were included. The prevalence of reduced LVEF was 8% (n = 148). On multivariate analysis, the variables with independent association with ventricular dysfunction were male sex (OR 2.50; 95% CI 1.30-4.90, p = 0.005), diabetes (OR 1.83; 95% CI 1.12-3, p = 0.01), and percent myocardium scar > 6.6 % (OR 39; 95% CI 25-61.28, p = 0.00001). In the subgroup of patients with scar burden < 20 % (n = 197), the prevalence of adverse remodeling was 25 % (n = 50). On multivariate analysis, diabetes (OR 2.83; 95% CI 1.31 - 6.1 p = 0.007) and male sex (OR 5; 95% CI 1.1 - 22.9, p = 0.007) showed an independent association with adverse remodeling.

Conclusions: Gated-SPECT could be used to assess adverse remodeling and its associated factors. This assessment is the result of combining variables used in daily practice which do not require any additional software.

Keywords: Gated-SPECT – Ventricular remodeling – Post-infarction ventricular dysfunction

RESUMEN

Introducción: El estudio gatillado de perfusión miocárdica con tomografía computarizada por emisión de fotón único, o gated-SPECT (por su denominación en inglés) es un método apropiado para cuantificar la magnitud de la escara necrótica y establecer su territorio. El análisis de pacientes con infartos de pequeña y mediana extensión que evolucionan con deterioro de la fracción de eyección ventricular izquierda (FEVI), podría arrojar luz acerca de los factores que influyen en la presencia de remodelado adverso y la consiguiente evolución a disfunción ventricular.

Objetivos: a) evaluar la prevalencia de FEVI disminuida y factores asociados en una población de pacientes derivados para estudios de gated-SPECT, y b) definir la prevalencia de remodelado adverso y factores asociados en el subgrupo de pacientes con carga necrótica intermedia a baja.

Material y métodos: Realizamos un análisis retrospectivo de pacientes consecutivos que se realizaron gated-SPECT durante el año 2017. Se excluyeron los pacientes con enfermedad valvular significativa o arritmias que produjeran alteración del gatillado. Se consideró remodelado adverso a la conjunción de FEVI disminuida (FEVI < 50%) y porcentaje de miocardio necrótico menor que 20 %.

Resultados: Se incluyeron 1902 pacientes. La prevalencia de FEVI disminuida fue del 8 % (n = 148). En el análisis multivariado, las variables independientes asociadas a disfunción ventricular fueron el género masculino (OR 2,50; IC 95% 1,30-4,90, p = 0,005), la diabetes (OR 1,83; IC 95% 1,12-3, p = 0,01), y compromiso necrótico mayor que 6,6 % (OR 39 IC 95% 25-61,28, p = 0,00001). En el subgrupo de pacientes con carga necrótica menor que 20% (n = 197), la prevalencia de remodelado adverso fue del 25% (n = 50). El análisis multivariado arrojó que la diabetes (OR 2,83; IC 95% 1,31 - 6,10 p = 0,007) y el género masculino (OR 5; IC 95% 1,10 - 22,9 p = 0,007) presentaron asociación independiente con el remodelado adverso.

Conclusiones: La gated-SPECT podría utilizarse en la valoración del remodelado adverso y factores asociados. Dicha valoración surge de la combinación de variables que no requieren un software adicional y se usan en la práctica diaria.

Palabras clave: Gated-SPECT - Remodelado ventricular - Disfunción ventricular post infarto

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Address for reprints: Lucas San Miguel. Jerónimo Salguero 560. (C1177AEJ). Capital Federal. Buenos Aires, Argentina.

Email: lucasanmiguel@gmail.com



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¹ Cardiovascular Imaging Cross-Cutting Specialty. TCba, Buenos Aires, Argentina

INTRODUCTION

Adverse ventricular remodeling is a crucial factor in the development of heart failure after an acute coronary event. It is a process that involves changes in left ventricular (LV) geometry, volume, and function, and is a determining factor of cardiovascular morbidity and mortality. (1)

Adverse LV remodeling is a maladaptive process of the heart to mechanical and neurohormonal changes in the regulation of ventricular size, shape, and function. Cardiomyocyte growth due to increased blood flow, such as during pregnancy, development, or exercise training, is considered physiological and reversible. On the contrary, adverse ventricular remodeling after an acute myocardial infarction (AMI) is associated with a high risk of heart failure and reduced survival. (2,3)

The goal of drug treatment is to improve the mechanics of contraction, for example by reducing the afterload with vasodilators, and to adjust the molecular mechanisms of remodeling. (4) Identifying predictors of remodeling in clinical, biochemical, and imaging data could reveal new targets for treatment. In this sense, understanding the variables that increase the risk of remodeling in patients with MI could represent an opportunity to adjust treatment and improve follow-up.

The infarct size has been described as a predictor of adverse remodeling in animal models. Gated-SPECT myocardial perfusion imaging is an appropriate method for measuring the infarct scar size and defining its territory. (5,6) Analyzing patients with small and medium MIs that develop LV dysfunction could provide additional information about the outcome of adverse remodeling.

The aims of our study were: a) to evaluate the prevalence of reduced left ventricular ejection fraction (LVEF) and associated factors in a population of patients referred for gated-SPECT imaging, and b) to define the prevalence of adverse remodeling and associated factors in the subgroup of patients with intermediate to low necrotic burden.

METHODS

Experimental model

Study population

We conducted a retrospective analysis of consecutive patients undergoing gated-SPECT imaging during 2017.

The imaging test was indicated by the treating physician due to one of the following reasons in patients with and without known coronary artery disease: 1) symptoms of angina or suspected coronary artery disease, 2) electrocardiogram (ECG) abnormalities suggestive of coronary artery disease, 3) abnormal exercise stress test, 4) intraventricular conduction disorders that required pharmacological stress test, 5) new onset symptoms with known coronary artery disease or recent myocardial infarction, 6) abnormal ventricular wall motion demonstrated by another imaging test. Patients > 18 years were included in the study.

Those patients with significant valvular heart disease or significant arrhythmias that could difficult adequate

ECG gating were excluded from the study. The presence of coronary risk factors and clinical status were recorded.

Gated- SPECT protocol for image acquisition

A detailed medical record was obtained before the stress test. The Bruce protocol limited by symptoms was used in patients who underwent an exercise stress test. Heart rate and blood pressure were measured, and a 12-lead ECG was recorded at baseline, the beginning of each stage and during recovery. In patients undergoing pharmacological stress, dipyridamole was administered at 0.56 mg/kg intravenously over a 4-minute period and the radiotracer was injected 3 minutes after the completion of dipyridamole infusion, according to the recommendations of the American Society of Nuclear Cardiology (ASNC). (7)

We performed a one-day protocol with injection of technetium-99m methoxy isobutyl isonitrile (Tc-99m MIBI) at stress and rest using a dedicated gamma camera with dual-detectors and a 90° angle (Ventri camera system, GE Medical Systems, Milwaukee, Wisconsin, USA). Rest images were acquired 30 to 45 minutes after venous injection at rest, and stress images 15 to 20 minutes after peak exercise. The radiotracer dose used was 8-12 mCi in the first injection (rest or stress imaging) and 24-36 mCi in the second injection (stress or rest imaging) following the recommendations of the ASNC guidelines.

Image analysis and quantification

Data were acquired in a 128 × 128 matrix for 32 projections in a step and shoot format. SPECT analysis was performed according to the left ventricular 17-segment model of the American Heart Association. (8) For that purpose, reconstruction into long and short axis projections perpendicular to the heart axis was initially performed, followed by an automated quantitative analysis of the perfusion images using polar map format (normalized to 100%). Automated quantitative analysis was used as complementary data to semi-quantitative visual interpretation. The segments were scored on a scale of 0 to 4 through visual analysis of radiotracer uptake in each segment. The total sum of the scores in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. A SRS greater than or equal to 2 was considered necrosis. The percent myocardium scar was calculated as $SRS \times 100/68$ according to a previous publication. (9) End-diastolic volume (EDV), end-systolic volume (ESV) and LVEF were determined using QGS 2015.2 software program. Gated images were used to assess regional wall motion to discriminate between perfusion defects and attenuation artifacts. If soft tissue attenuation was suspected during the initial supine position acquisition, additional images were acquired in the prone position.

Definition of adverse remodeling

Reduced LVEF was considered as < 50% in rest images.

Adverse remodeling was considered as the combination of decreased LVEF with percent myocardium scar < 20%.

Statistical analysis

Multivariate logistic regression was used to find associations. The dependent variables were reduced LVEF in the first analysis and adverse remodeling in the second. The following variables were considered in the search for an association: age, male sex, hypertension, dyslipidemia, cur-

rent or former smoking, diabetes mellitus (DM), and percent myocardium scar. A cut-off point for myocardium scar significantly associated with ventricular dysfunction was established by a ROC curve and included in the model as a dichotomous variable. Continuous variables with normal distribution were expressed as mean standard deviation (SD) and were compared using the Student's t test, while those with non-gaussian distribution were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney test. Categorical variables were expressed as proportions and were compared using the Fisher's exact test. A p value < 0.05 was considered statistically significant. All calculations were performed using Epi-Info 7.2.2.2 software package.

Ethical considerations

As this was an observational study, we only performed the tests requested by the treating physicians and analyzed the data obtained without any additional intervention. At our institution, patients sign an informed consent form in which they accept that data linked to their test results may be used anonymously for scientific purposes. The patients' identities were blinded during data analysis and preparation of the article.

RESULTS

A total of 1902 patients were included. Mean age was 63 ± 11 years; 12% of the patients had a history of AMI and 29% of myocardial revascularization (Table 1). The prevalence of reduced LVEF was 8% (n = 148). The ROC curve determined that a cut-off value of 6.6% of necrotic myocardium had the best accuracy to diagnose reduced LVEF, with an area under the curve (AUC) of 0.872, 95% CI 0.832-0.912 (Figure 1). On multivariate analysis, the variables with independent association with ventricular dysfunction were male sex (OR 2.50, 95% CI 1.30-4.90, p = 0.005), DM (OR 1.83; 95% CI 1.12-3, p = 0.01), and percent myocardium scar > 6.6 % (OR 39; 95% CI 25-61.28, p = 0.00001) (Table 2).

In the subgroup of patients with necrotic burden < 20 % (n = 197), the prevalence of adverse remodeling was 25 % (n = 50). On multivariate analysis, DM (OR 2.83; 95% CI 1.31 - 6.1 p = 0.007) and male sex (OR 5; 95% CI 1.1 - 22.9, p = 0.007) showed an independent association with adverse remodeling (Table 3).

DISCUSSION

The most significant findings of our study were that DM and male sex were independently associated with decreased LVEF. This association was also verified in the subgroup of patients with low scar burden. Patients with extensive myocardial necrosis are expected to have ventricular dysfunction. Therefore, we tried to elucidate any factors leading to ventricular dysfunction in patients with non-extensive necrosis (< 20%). The prevalence of this phenomenon, which we defined as adverse remodeling, was 25% (n = 50) in this group. In our cohort, some patients with infarctions of similar size developed adverse remodeling, while others maintained preserved LV

volume and LVEF with little or no impairment. DM was found to be independently associated with this phenomenon (Figure 2).

Our results are consistent with those reported by other publications. In patients with DM, the incidence of heart failure after a MI is 60-70% higher than in non-diabetics. (10)

In the 1980s, Jaffe et al. reported a higher incidence of congestive heart failure in diabetic patients, despite smaller infarct size. (11) Two decades later, Aguilar et al. described that patients with DM had a higher rate of cardiovascular events, including heart failure, than those without DM, despite having similar baseline characteristics such as infarct size and systolic function. (12) Prasad et al. reported that patients with diabetes were more likely to have abnormal myocardial perfusion than non-diabetics, despite similar TIMI 3 flow rates after primary percutaneous coronary intervention for an acute coronary syndrome. (13) Finally, in 2020, Van der Bijl et al. described a higher prevalence of diabetes in patients with adverse remodeling and an independent association between DM and heart failure hospitalizations in patients with acute coronary syndrome. (14)

This suggests that there are other factors that contribute to myocardial dysfunction, which could explain the higher frequency of remodeling in this population. These factors include the activation of the inflammatory cascade, oxidative stress, microvascular obstruction, and diastolic dysfunction. (15)

Cardiac magnetic resonance (CMR) imaging is currently the most commonly used non-invasive diagnostic modality for detecting remodeling, assessing its severity, and identifying associated factors. Compared with echocardiography, CMR presents better contrast resolution, higher reproducibility, and

Table 1. Baseline characteristics of the population.

Variable	n = 1902
Age, years, mean $\pm$ SD	63 $\pm$ 11
Male sex, % (n)	66 (1263)
HTN, n (%)	57 (1082)
DLP, n (%)	49 (933)
DM, % (n)	18 (350)
Smoking habits, % (n)	9 (167)
MI, % (n)	12 (235)
Myocardial revascularization, % (n)	29 (544)
LVEF (%), mean $\pm$ SD	65 $\pm$ 14
Reduced LVEF, % (n)	8 (148)
Necrosis on SPECT, % (n)	16 (285)
Low necrotic burden, % (n)	10 (197)

DLP: dyslipidemia; DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention; SD: standard deviation; SPECT: single-photon emission computed tomography.

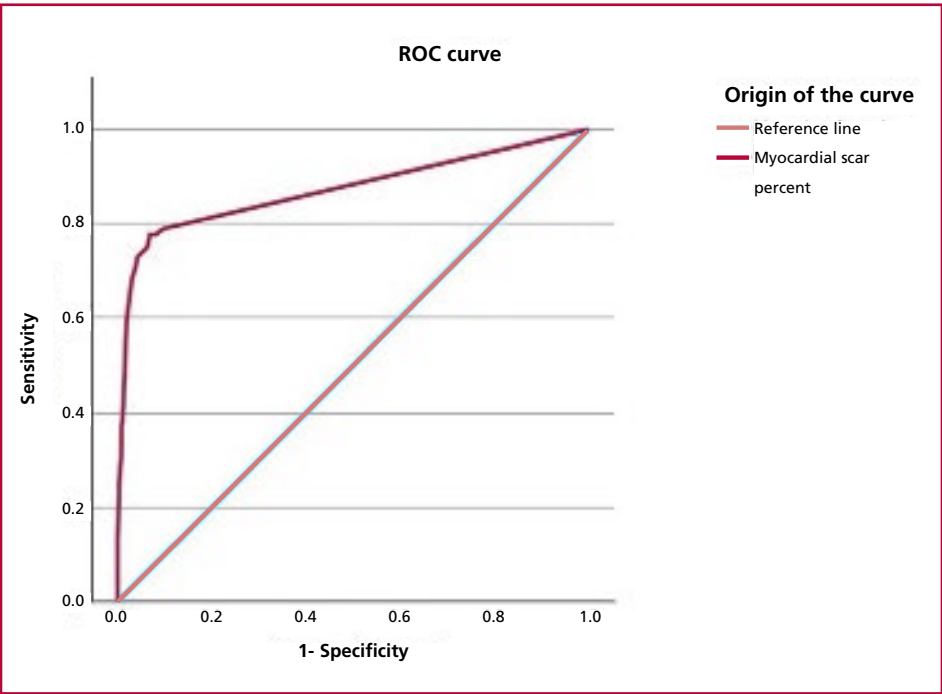


Fig. 1. ROC curve for estimating the myocardial scar percent threshold to induce ventricular dysfunction. The 6.6% cut-off point obtained the highest accuracy for LVEF reduction (sensitivity: 78%, specificity: 93%, AUC 0.872, 95% CI 0.832-0.912).

	OR	95% CI	p
Age	0.99	0.97 – 1.01	0.501
Male sex	2.50	1.30 – 4.90	0.005
HTN	0.87	0.50 – 1.30	0.501
DLP	1.30	0.84 – 20.00	0.204
DM	1.83	1.12 – 3	0.010
Smoking habits	0.53	0.22 – 1.26	0.204
Myocardial scar percent > 6.6%	39	25-61.28	<0.001

CI: confidence interval; DLP: dyslipidemia; DM: diabetes mellitus; HTN: hypertension; OR: odds ratio

Table 2. Factors associated with reduced left ventricular ejection fraction.

	OR	95% CI	p
Age	1.01	0.98 – 1.05	0.202
Male sex	5.00	1.10 – 22.90	0.007
HTN	0.70	0.33 – 1.47	0.501
DLP	1.60	0.75-3.44	0.199
DM	2.83	1.31 – 6.10	0.007
Smoking habits	0.84	0.25 – 2.74	0.199

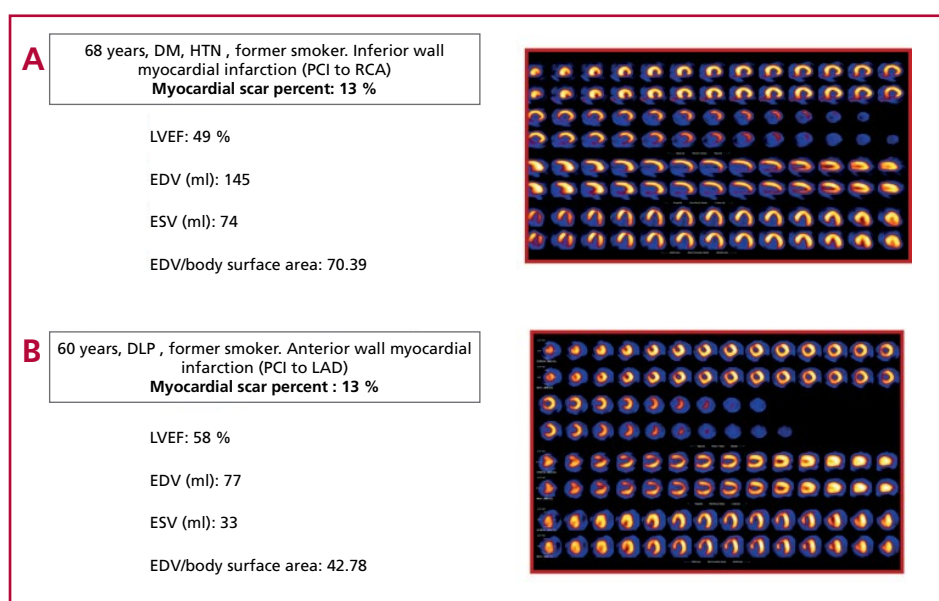
CI: confidence interval; DLP: dyslipidemia; DM: diabetes mellitus; HTN: hypertension; OR: odds ratio

Table 3. Factors associated with adverse remodeling

independence from acoustic windows, and may also provide valuable information regarding the presence and extent of myocardial fibrosis in the form of late gadolinium enhancement (LGE). The extent of LGE is directly related to reverse remodeling. (16) In this context, Monmeneu et al. reported that a lower prevalence of diabetes was related to a higher percentage of salvaged myocardium in patients with ST-segment elevation MI revascularized by angioplasty. (17) In a

review that included 10 randomized studies, Stone et al. observed a strong graded relationship between infarct size, considered as every 5% increase, and mortality and heart failure hospitalization. In this study, the infarct size was measured by gated-SPECT in less than 30% of patients, while CMR was the most commonly used method to measure the necrotic burden. (18) While gated-SPECT is not commonly used in routine practice to assess remodeling, our study

Fig. 2. a) Patient with diabetes and inferior wall myocardial infarction (myocardial scar percent: 13%), increased LV dimensions and ventricular dysfunction). **b)** Patient without diabetes and anterior wall myocardial infarction of similar size (myocardial scar percent : 13%), with normal LV dimensions and LVEF.



DLP: dyslipidemia; DM: diabetes; EDV: end-diastolic volume; ESV: end-systolic volume; HTN: hypertension; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: Right Coronary artery

supports the hypothesis that it can be used for this purpose. There is limited literature analyzing ventricular remodeling after myocardial infarction using this imaging modality. Our group recently published that gated-SPECT could be used to noninvasively assess the main determinants of stroke volume, supporting the possibility of expanding the usefulness of this practice in evaluating patients with ventricular dysfunction. (19)

Gated-SPECT is the most commonly used non-invasive test to rule out ischemia and evaluate risk in patients with a history of coronary artery disease. Strengthening its use in evaluating patients with ventricular dysfunction could simplify the assessment of individuals with ischemic cardiomyopathy. Additionally, the semi-quantitative visual score allows for easy quantification of necrosis without the need for additional software. This method is routinely used in clinical practice and has shown prognostic value. (20)

Study limitations

The limitations of this study include its retrospective, single-center based and observational design, and the potential influence of unmeasured factors on ventricular remodeling. As we did not evaluate a gold standard for determining adverse remodeling, we cannot determine the accuracy of SPECT for assessing remodeling with our design. Additionally, we did not perform clinical follow-up to determine its impact on prognosis.

CONCLUSIONS

Gated-SPECT, the most commonly used noninva-

sive stress test for evaluating ischemic heart disease, could also be used to assess adverse remodeling and its associated factors. This assessment is the result of combining variables used in daily practice which do not require any additional software. This offers a window of opportunity to identify patients who may benefit from treatments currently recommended for more advanced stages. These hypotheses should be confirmed by future prospective studies with a larger number of patients and in randomized studies evaluating relevant clinical outcomes.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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Eccentric Vascular Remodeling: Its Relationship with Metabolic Disorders and Increased Body Mass

Remodelado vascular excéntrico: su relación con trastornos metabólicos y el incremento de la masa corporal

SERGIO GONZÁLEZ¹, MARÍA BREZONI¹, RENZO MELCHIORI¹, PEDRO FORCADA², PAMELA ALARCÓN¹, JORGE CHIABAUT SVANE¹, GUIDO GARCÍA¹, FABIÁN FERRONI¹, CARLOS CASTELLARO¹

ABSTRACT

Background: Recent evidence would establish muscle hypoperfusion as the primary cause of metabolic disorders in response to overfeeding. This centripetal concept on the development of metabolic disorders could involve not only alterations in the microvasculature, but also affect the conductance arteries.

Objectives: The aim of this study was 1- to determine the association between baseline brachial artery diameter (BAD) and flow-mediated vasodilation (FMVD), 2- To analyze the association of both parameters throughout the increase in body mass, 3- To evaluate associations between BAD/FMVD with components of the metabolic syndrome (MS) and 4- To evaluate the independent association of both variables with MS

Methods: A total of 3493 patients were evaluated. Patients <18 and >80 years old, those with previous cardiovascular disease, chronic kidney disease (CKD), collagenopathies, or treated with statins were excluded from the study. Blood pressure (BP), anthropometric parameters and metabolic profile were determined, and the subjects were classified according to the presence of MS conforming ATP-III criteria. BAD was measured in mm and FMVD as percentage. The linear association between BAD and FMVD was assessed, and both variables were analyzed according to deciles of body mass index (BMI). Associations between BAD/FMVD with BP, glucose (Glu), triglycerides (TG) and high-density cholesterol (HDL-C) levels were evaluated. Two logistic regression analyses were performed with MS as dependent variable and BAD or FMVD plus age, gender, BMI, and coronary risk factors (CRF) as independent variables.

Results: A total of 1995 patients (48.2±11 years, 56% men) were admitted in the study. An inverse correlation was found between BAD and FMVD ($r = -0.42$; $p < 0.0001$). BAD increased according to deciles of BMI ($p < 0.000001$), while FMVD showed an inverse relationship with increasing deciles of BMI ($p < 0.000001$). BAD exhibited a direct correlation with BP, Glu and TG; and an inverse relationship with HDL-C ($p < 0.05$ in all cases). FMVD presented an inverse correlation with BP, Glu and TG; and a direct correlation with HDL-C ($p < 0.05$ in all cases). BAD was independently associated with MS adjusted for age, gender, BMI and CRF (OR 1.42, $p = 0.0019$), while FMVD was not (OR 0.98, $p = 0.217$).

Conclusion: Eccentric vascular remodeling was associated with vascular adaptation to increased blood flow demand and with metabolic alterations throughout the increase in body mass. Thus, the dynamic compromise of vasculature could play a decisive role in the development of metabolic alterations occurring synchronously with weight gain.

Keywords: Vascular remodeling -Metabolic syndrome -Obesity -Flow-mediated vasodilation

RESUMEN

Introducción: Existe evidencia reciente que establecería a la hipoperfusión muscular como causa primaria de trastornos metabólicos en respuesta a la sobrealimentación. Esta concepción centripeta del desarrollo de trastornos metabólicos podría implicar no sólo alteraciones en la microvasculatura, sino también afectación en las arterias de conductancia.

Objetivos: 1- Determinar asociación entre diámetro basal de la arteria humeral (D-Hum) y la vasodilatación mediada por flujo (VDMF) 2- Analizar la asociación de ambos parámetros conforme aumenta la masa corporal 3- Evaluar asociaciones entre el D-Hum/VDMF con componentes del síndrome metabólico (SM) 4- Evaluar la asociación independiente de ambas variables con el SM

Material y métodos: Se evaluaron 3493 pacientes. Se excluyeron pacientes <18 y > 80 años, con patología cardiovascular previa, insuficiencia renal crónica (IRC), collagenopatías, y tratados con estatinas. Se determinó presión arterial (PA), parámetros antropométricos y perfil metabólico, y se clasificó a los sujetos de acuerdo con la presencia de SM según el ATP-III. Se midieron D-Hum en mm y VDMF en %. Se analizó la asociación lineal entre D-Hum y VDMF y se analizaron ambas variables según deciles de índice de masa corporal (IMC). Se evaluaron asociaciones entre D-Hum/VDMF con la PA, glucemia (Glu), triglicéridos (TG) y colesterol de alta densidad (HDL-C). Se realizaron dos regresiones logísticas con SM como variable dependiente y D-Hum o VDMF más edad, sexo, IMC y factores de riesgo coronario (FRC) como independientes.

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¹ Hospital Universitario Austral. Officia Cardiometaabolic Center, Cardiology Service, Buenos Aires, Argentina.

² CardioArenales Center, Buenos Aires, Argentina.

Resultados: Ingresaron 1995 pacientes ($48,2 \pm 11$ años, 56 % hombres). El D-Hum y la VDMF presentaron una asociación inversa ($r = -0,42$; $p < 0,0001$). El D-Hum aumentó según deciles del IMC ($p < 0,000001$); la VDMF mostró relación inversa con los deciles crecientes de IMC ($p < 0,000001$). El D-Hum presentó correlación directa con PA, Glu y TG; e inversa con HDL-C ($p < 0,05$ en todos los casos). La VDMF mostró correlación inversa con PA, Glu y TG; y directa con HDL-C ($p < 0,05$ en todos los casos). El D-Hum se asoció en forma independiente con el SM ajustado por edad, sexo, IMC y FRC (OR 1,42, $p = 0,0019$), mientras que la VDMF no (OR 0,98, $p = 0,217$). **Conclusión:** El remodelado vascular excéntrico se asoció con un compromiso en la adaptación vascular ante aumentos en la demanda de flujo sanguíneo y con alteraciones metabólicas a lo largo del incremento de la masa corporal. Así, el compromiso dinámico de la vasculatura podría tener un rol determinante en el desarrollo de alteraciones metabólicas en forma sincrónica con la ganancia de peso.

Palabras clave: Remodelado vascular -Síndrome metabólico - Obesidad -Vasodilatación mediada por flujo

INTRODUCTION

The increase in body mass observed in overweight and obese subjects is associated with hemodynamic alterations, the most important being the increase in plasma volume and vascular dysfunction. From a pathophysiological point of view, different endocrine alterations act concurrently and synergistically in the development of these circulatory alterations.

With the increase in body mass - particularly in obese people - the increase in water and sodium reabsorption prompted by insulin through the activation of the sodium-hydrogen exchanger in the proximal convoluted tubule, (1) hyperreninemia derived from increased sympathetic outflow, (2) decreased tubular flow rate and stimulation of tubuloglomerular feedback, (3) in addition to increased autonomous secretion of aldosterone in dysfunctional adipocytes (4) promotes a circulatory state characterized by increased cardiac output and eccentric remodeling of the cardiac chambers and conductance arteries, which coexists with enhanced tone of the precapillary sphincters and development of peripheral hypoperfusion. Since the delivery of macronutrients to metabolically active organs, such as skeletal muscle and adipose tissue, is largely dependent on adequate perfusion, the inability to increase blood flow during the postprandial period can be associated with metabolic alterations in overweight and obese subjects. As an example, blocking insulin-mediated muscle blood flow reduces glucose consumption in the muscle by 40% according to the euglycemic-hyperinsulinemic clamp technique. (5) In this scenario, the alterations in the structure and function of the conductance arteries that participate in muscle perfusion (which consume 75 to 80% of the total body glucose) (6) added to the increase in peripheral resistance disorders could jointly induce metabolic disorders as a peripheral starting point with the progressive increase in body mass.

METHODS

A total of 3493 patients from the metabolic database of the CARFARE registry (CARDIOMETABOLIC RISK FACTORS REGISTRY), carried out for a cardiovascular prevention program of the Official Cardiometa-bolic Unit, from the Cardiology service of Hospital Universitario Austral from July 2016 to January 2020, were evaluated. These patients un-

derwent a structured, sequential evaluation, on the same date, consisting of laboratory analyses that included urine metabolites and peripheral blood assessments after 12-hour fasting. Subsequently, medical interrogation with data collection on cardiovascular risk factors (CRF) and clinical-cardiological history, weight and height measurements with body mass index (BMI) calculation, baseline blood pressure (BP) (at rest, 3 determinations), and performance of different imaging studies were performed.

For practical purposes, data on the pathological history, CRF, metabolic profile measurements - glucose (Glu), HDL cholesterol (HDL-C) and triglyceride (TG) levels in peripheral blood and flow-mediated vasodilation (FMVD) were used. Obesity was defined according to the World Health Organization (WHO) as $BMI \geq 30 \text{ kg/m}^2$, and metabolic syndrome (MS) according to the IDF Joint Interim Statement and 2019 AHA/NHLBI (7) as the presence of 3 of the following criteria: $TG > 150 \text{ mg/dL}$, $HDL < 40 \text{ mg/dL}$ in men and $< 50 \text{ mg/dL}$ in women, $BP > 130/85 \text{ mm Hg}$, glucose $> 100 \text{ mg/dL}$, and treatment for diabetes mellitus (DM), hypertension (HTN) or dyslipidemia.

A high-resolution vascular ultrasound machine (Philips HD7 XE, Koninklijke Philips N.V) equipped with a 10 MHz linear array probe was used for FMVD. This procedure was performed on the brachial artery, in a quiet environment, at 22°C , with 12-hour fasting, without medication intake, during the morning, and in the absence of antihypertensive drugs for a period of 12 hours. The calculation was performed using the following formula: $FMVD = [(baseline BAD \text{ in mm} - \text{post-ischemia BAD in mm}) / \text{baseline BAD in mm}] \times 100$. Ischemia was induced through 30 mm Hg supra-systolic compression with a cuff placed on the brachial artery of the left arm, 3 to 5 cm above the elbow crease for 3 minutes. The data on baseline BAD and FMVD were collected in mm and percentage, respectively.

For the present analysis, patients aged < 18 and > 80 years, those with a history of ischemic heart disease (chronic stable angina, unstable angina, acute myocardial infarction), heart failure, chronic arrhythmia or significant arrhythmic events, transient ischemic stroke, stroke or peripheral vascular disease, stage III or higher chronic kidney disease, known rheumatological diseases and decompensated chronic diseases, as well as incomplete data, were excluded. Patients treated with statins or β_2 adrenergic agonists, due to their effect on endothelial function, were also excluded from the analysis.

A linear relationship between BAD and FMVD was analyzed, and each of these variables (BAD and FMVD) was subsequently evaluated according to BMI levels. Linear associations between BAD and FMVD with constituent variables of MS (BP, Glu, TG and HDL-C) were evaluated. Two logistic regression analyses were performed to explore the independent association of both variables with MS.

Statistical analysis

Baseline characteristics are expressed as mean and standard deviation for continuous variables, and as number of cases and percentage for categorical variables. Linear correlation is expressed with the Pearson r coefficient in the case of normally distributed variables and Spearman's ρ in those with a non-normal distribution. BMI levels were obtained through stratification into deciles. The analysis of variables according to deciles was carried out using ANOVA in those with a normal distribution, and the Kruskal Wallis test in those with a non-normal distribution. Given the probable collinearity of BAD and FMVD, two logistic regressions were carried out: 1- with MS as the dependent variable and BAD, age, gender, BMI and CRF (dyslipidemia, HTN, DM, smoking, sedentary lifestyle) as independent variables, and 2- with MS as the dependent variable and FMVD, age, gender, BMI and CRF (dyslipidemia, HBP, DM, smoking, sedentary lifestyle) as independent variables. A value of $p < 0.05$ was considered statistically significant. The analysis was performed with MedCalc 20.2.17 statistical software package.

Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki and was approved as part of the Carfare Registry by the Ethics Committee of our institution (19-044).

RESULTS

A total of 1995 patients were included in the study (48.2 ± 11 years, 56% male, BMI 27.9 ± 5.89 kg/m², MS 20.3%). The population presented patients with low prevalence of smoking, dyslipidemia and DM (Table 1).

In the univariate analysis, BAD and FMVD showed a significant inverse relationship (r : -0.42, $p < 0.0001$). BAD increased across BMI deciles ($p < 0.000001$) (Figure 1) and, conversely, FMVD presented a progressive reduction across BMI deciles ($p < 0.000001$) (Figure 2). A direct correlation was found between BAD and BP ($r = 0.26$, $p < 0.001$), Glu ($r = 0.25$, $p < 0.001$) and TG ($r = 0.26$, $p < 0.001$) and an inverse correlation with HDL-C ($r = -0.35$, $p < 0.001$). On the other hand, FMVD presented weaker inverse associations with BP ($r = -0.15$, $p < 0.001$), Glu ($r = -0.11$, $p < 0.001$) and TG ($r = -0.12$, $p < 0.001$) and a direct correlation with HDL-C ($r = 0.14$, $p < 0.001$).

In the first logistic regression analysis, BAD was independently associated with MS, with OR 1.42 (95% CI 1.14-1.77, $p = 0.002$), adjusted for age, gender, BMI, dyslipidemia, smoking, DM, HTN and sedentary lifestyle [Hosmer-Lemeshow test $p = 0.12$, area under the ROC curve 0.77 (95% CI 0.75-0.79)] (Table 2).

In the second logistic regression analysis, FMVD did not show a significant association with MS, with OR 0.98 (95% CI 0.97-1.007, $p = 0.217$) when adjusted for the same variables [Hosmer-Lemeshow test $p = 0.15$, area under the ROC curve = 0.77 (95% CI 0.75-0.79)] (Table 3).

DISCUSSION

Eccentric vascular remodeling, characterized in this study as an increase in baseline BAD, was associated with the development of MS components with the progressive increase in body mass. Thus, the inverse

Table 1. Baseline characteristics (n=1995)

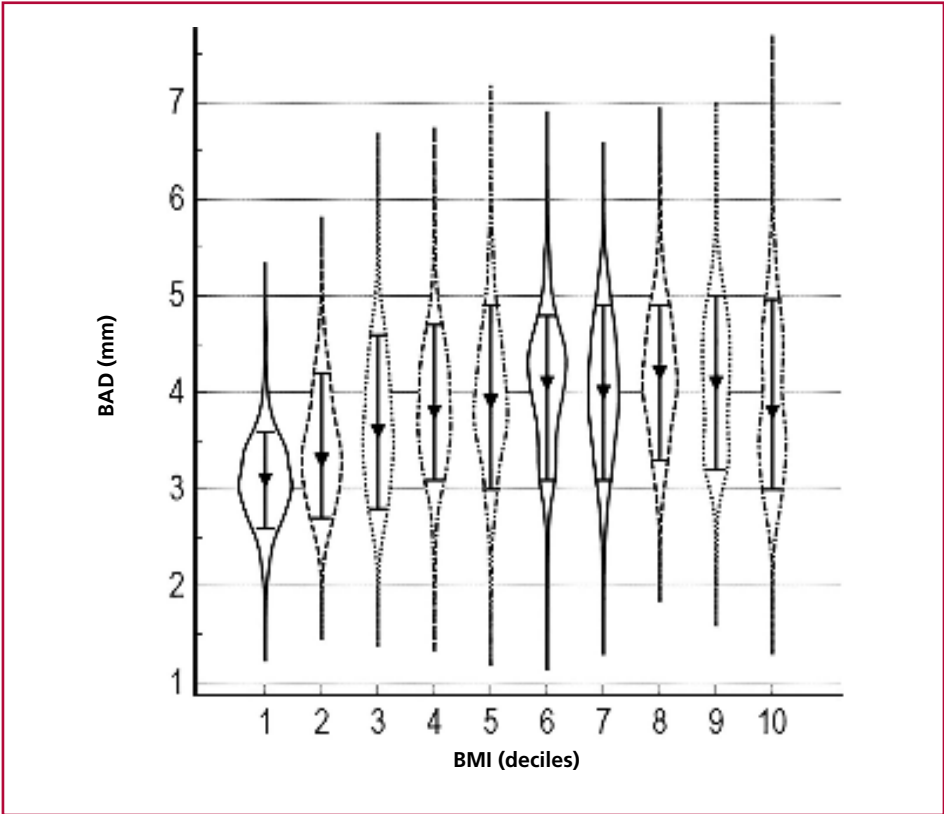
Variable	
Age, years (mean $\pm$ SD)	48.2 $\pm$ 11.2
Male gender (%)	56
BMI, kg/m ² (mean $\pm$ SD)	27.9 $\pm$ 5.9
HTN (%)	26
Smoking (%)	14
DM (%)	4
Dyslipidemia (%)	25.9
Sedentary lifestyle (%)	33

BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; SD: Standard deviation

relationship between vascular remodeling (BAD) and FMVD (mechanism that increases vascular flow in situations of high metabolic demand, such as exercise and the postprandial period) could be linking hemodynamic dysfunction with metabolic alterations in the context of weight gain. Although the impact of metabolic alterations on vascular structure and function is unobjectionable, it is highly probable that at some point in the evolutionary continuum, the alterations in vascular dynamics contribute, in a vicious circle, to the development/enhancement of those metabolic imbalances.

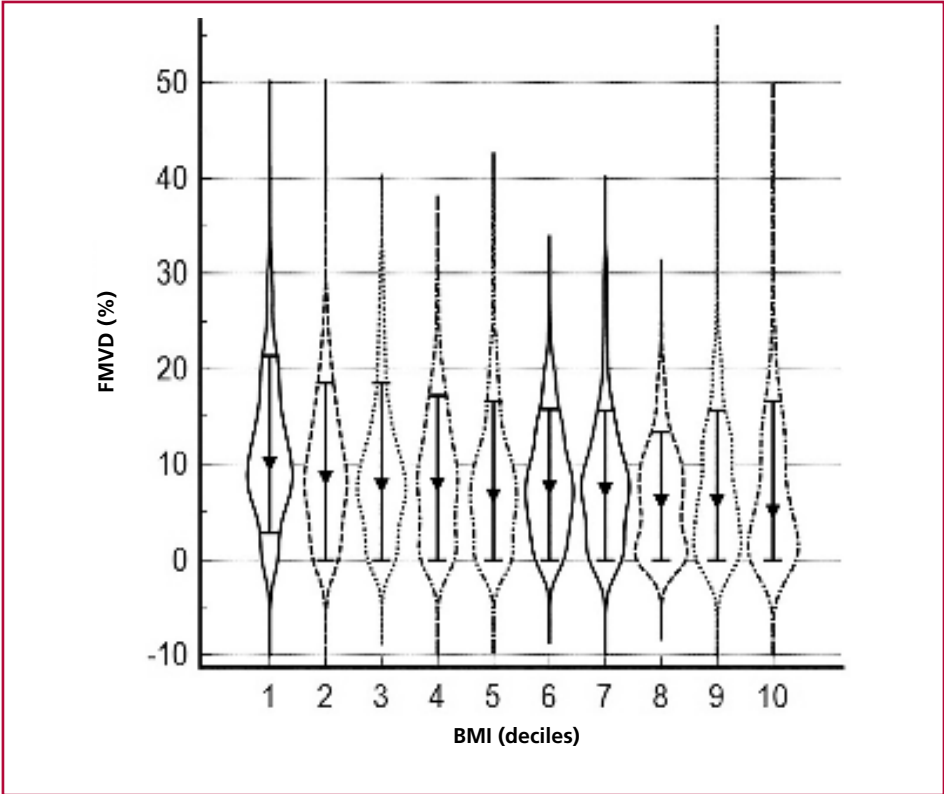
Thus, eccentric remodeling would represent an attempt to ensure adequate muscle perfusion in response to both the increase in intravascular volume and the oversupply of high-energy substrates. Actually, sugars such as glucose (8) or fructose (9) increase the activity of the sympathetic system, with increased cardiac output - a cause of eccentric vascular remodeling - and increased tone of the precapillary sphincters with muscle hypoflow. These adjustments are associated with a drop in the consumption of energy substrates - glucose and triglycerides - and finally with the development of peripheral metabolic alterations. Effectively, different drugs that share sympatholytic/vasodilatory effects such as moxonidine (10), rilmenidine (11) and azelnidipine (12), or nitric oxide donors such as sodium nitroprusside (13) induce improvements in the glycemic and lipid profile in subjects with obesity, MS, or DM.

The association between the observed increase in BAD and its relationship with metabolic alterations does not seem to be a generalized phenomenon with the increase in body mass. In fact, and as an example, 1 in 3 obese people exhibit a "metabolically healthy" phenotype in which no evident metabolic alterations are manifested. (14) These subjects apparently present as distinctive characteristics an adequate subcutaneous lipid reservoir capacity, normally functioning adipocytes, and low levels of inflammation, all in the context of adequate muscle perfusion and microvascular function.



Kruskall Wallis test, $p < 0.000001$. Values expressed as median (10-90% CI).
BAD: Baseline brachial artery diameter. BMI: Body mass index

Fig. 1. Brachial artery diameter according to deciles of body mass index.



Kruskall Wallis test, $p < 0.000001$. Values expressed as median (10-90% CI)
FMVD: Flow-mediated vasodilation. BMI: body mass index

Fig. 2. Flow-mediated vasodilation according to deciles of body mass index.

Table 2. Adjusted brachial artery diameter and its relationship with metabolic syndrome (MS).

Variable	Beta coefficient	Standard error	p	OR	95% CI
Age	0.009	0.006	0.125	1.01	0.99-1.02
Male gender	0.325	0.169	0.054	1.38	0.99-1.92
BMI	0.115	0.013	<0.0001	1.12	1.09-1.15
BAD	0.350	0.112	0.002	1.42	1.14-1.77
DLP	0.384	0.134	0.004	1.47	1.12-1.91
SMK	-0.119	0.179	0.503	0.88	0.62-1.26
DM	0.630	0.263	0.016	1.87	1.12-3.14
HTN	0.773	0.132	<0.0001	2.16	1.67-2.80
Sedentary lifestyle	0.134	0.143	0.347	1.14	0.86-1.51

BMI: Body mass index; BAD: Baseline brachial artery diameter; DLP: Dyslipidemia; DM: Diabetes mellitus; HTN: Hypertension; SMK: Smoking

Table 3. Relationship between adjusted flow-mediated vasodilation and metabolic syndrome (MS).

Variable	Beta coefficient	Standard error	p	OR	95% CI
Age	0.012	0.005	0.024	1.01	1.01 – 1.02
Male gender	0.641	0.135	<0.0001	1.89	1.45 – 2.47
BMI	0.122	0.013	<0.0001	1.13	1.10 – 1.15
FMVD	-0.011	0.009	0.217	0.98	0.96 – 1.00
DLP	0.345	0.134	0.010	1.41	1.08 – 1.83
SMK	-0.122	0.180	0.497	0.88	0.62 – 1.26
DBT	0.662	0.261	0.011	1.93	1.16 – 3.24
HTN	0.772	0.132	<0.0001	2.16	1.67 – 2.81
Sedentary lifestyle	0.103	0.143	0.472	1.10	0.83 – 1.46

BMI: Body mass index; DLP: Dyslipidemia; DM: Diabetes mellitus; FMVD: Flow-mediated vasodilation; HTN: Hypertension; SMK: Smoking

This observation would be in line with recent studies suggesting that adipose tissue oxygenation, determined by the balance between oxygen supply and oxygen consumption, could be a key factor in determining the adipose tissue phenotype in obese subjects. (15,16)

It is highly probable that alterations in vascular function could be linked to the development of modifications in the metabolism of both carbohydrates and lipids in metabolically complicated subjects. Recent studies show that vascular insulin resistance secondary to high-fat diets compromises even short-term skeletal vascular flow. These data suggest that the alteration of blood flow in the skeletal muscle microvasculature is a primary event that would precede whole body insulin resistance in the development of type II DM. (17)

In the same sense, in a large prospective population-based study conducted in middle-aged subjects, the elevated baseline levels of 2 markers of endothelial dysfunction (sE-selectin and sICAM-1) were significantly associated with the risk of developing type II DM, especially sE-selectin, which was found to be a strong independent predictor of incident DM after

adjusting for obesity, other clinical parameters and lifestyle in both men and women. (18)

Concomitantly, evidence has emerged that seems to link fatty deposit hypoperfusion with the development of total body insulin resistance. The inverse association between postprandial increase in adipose tissue perfusion with the degree of insulin resistance suggests that adipose tissue hypoperfusion may affect whole-body insulin sensitivity. Thus, the drop in the supply of glucose, lipids and oxygen to the adipose tissue would generate a decrease in the uptake of energy substrates at the level of subcutaneous fatty deposits, with ectopic accumulation of lipids in viscera and muscle, adipocyte hypoxemia and central and peripheral insulin resistance. (19)

From our point of view, we have observed an interesting association between alterations in the vascular structure and function of the conductance vessels and metabolic abnormalities with weight gain. However, these associations should be interpreted with caution due to the inherent limitations of the study. Actually, with a design which does not allow causality to be imputed, the absence of an objective

measurement of fat mass, and the fact that FMVD was not measured during the postprandial period or adjusted for drugs limit the interpretation of the results. However, it is probable that dynamic alterations in vascular flow behave as inducers of metabolic disorders, particularly during the postprandial period. Recent evidence shows that a fundamental difference between metabolically healthy obese subjects and those with MS lies in a preservation of FMVD during the postprandial period in those metabolically uncomplicated, with an endothelial response similar to that of subjects with normal weight and without metabolic alterations. (20) These findings are reinterpreting the function of the vascular endothelium as a fundamental actor in the control of glucose and carbohydrate metabolism. (21) We must also point out that in the present study the adjustment of hemodynamic variables for each of the drugs was not performed, with the intention of not making the analysis more complex. The study was carried out without the morning administration of the patients' usual medication, which would at least limit the immediate effect of high plasma drug levels.

Finally, it is not possible to completely rule out the fact that the increase in arterial conductance is mainly linked to anatomical modifications secondary to the increase in body mass. Effectively, in a study by Dalli et al. (22) a significant relationship was evidenced between BAD and the arm perimeter. However, the persistence of the association between BAD and MS adjusted by BMI, a parameter closely related with body surface area and, therefore, with arm circumference, would suggest an association independent of anthropometry in this relationship.

CONCLUSIONS

In the present study we have evidenced a relationship between vascular structure and function alterations in conductance arteries with metabolic disorders through increased body mass. A prospective study with the purpose of evaluating insulin-vascular resistance and hemodynamic-metabolic causality with weight gain in subjects prior to the development of MS could help clarify these associations.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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Administration of N-acetylcysteine Attenuates Post-Myocardial Infarction Remodeling

La administración de N-acetilcisteína atenúa el remodelado post infarto de miocardio

MANUEL RODRÍGUEZ¹, MTSAC, GABRIELA PIDAL², ORLANDO BUZZANO³, MARCELO DAMONTE⁴, NÉSTOR LAGO⁵, CARLOS LIGHTOWLER⁶, RICARDO J. GELPI¹, MTSAC, 

ABSTRACT

Background: Ischemic heart disease is the main cause of death in Argentina. The prevailing form of presentation is myocardial infarction (MI), characterized by insufficient blood perfusion, cell death and loss of contractile mass. The evolution of ventricular remodeling causes ventricular dilation, hemodynamic impairment, heart failure, and decreased survival. The oxidative stress occurring during this process could be attenuated by the administration of N-acetyl cysteine (NAC) through increased glutathione levels. **Objective:** The aim of this study was to evaluate the effect of NAC administration on post-MI remodeling.

Methods: New Zealand rabbits were divided into three experimental groups: Control, MI and MI+NAC. A left thoracotomy was performed under general anesthesia, and in the MI groups a branch of the left coronary artery was ligated. Echocardiographic, hemodynamic and morphological studies of the left ventricle were performed at the end of the 28-day post infarction follow-up period.

Results: In the MI and MI+NAC groups, the infarcts were located in the left ventricular free wall and had similar sizes. The administration of NAC prevented non-infarcted area thinning and decreased the dilation caused by the infarction. It also preserved left ventricular systolic and diastolic functions, attenuating the impairment that they suffered as a consequence of the infarction.

Conclusion: These results suggest that NAC administration is a promising therapy to mitigate the unfavorable effects of post-MI remodeling.

Keywords: N-acetylcysteine – Myocardial infarction – Remodeling

RESUMEN

Introducción: El la cardiopatía isquémica es la principal causa de muerte en la República Argentina. La forma de presentación que prevalece es el infarto de miocardio (IM), caracterizado por insuficiente perfusión sanguínea, muerte celular y pérdida de masa contráctil. La evolución del remodelado ventricular provoca dilatación ventricular, deterioro hemodinámico, insuficiencia cardíaca y disminución de la sobrevida. Durante este proceso existe un estrés oxidativo miocárdico que podría ser atenuado mediante la administración de N-acetil cisteína (NAC), a través de un aumento de los niveles de glutatión.

Objetivo: Evaluar el efecto de la NAC sobre el remodelado post IM.

Material y métodos: Se estudiaron durante 28 días conejos neozelandeses en tres grupos experimentales: Control, IM e IM+NAC. Bajo anestesia general se realizó una toracotomía izquierda y, en los grupos con IM, ligadura de una rama de la coronaria izquierda. Al finalizar el período de seguimiento posterior al infarto, se realizaron estudios ecocardiográficos, hemodinámicos y morfológicos del ventrículo izquierdo (VI).

Resultados: En los grupos IM e IM+NAC los infartos estaban ubicados en la pared libre del VI y tuvieron tamaños similares. La administración de NAC evitó el adelgazamiento de la zona no infartada y disminuyó la dilatación provocada por el infarto. También pudo observarse que preservó las funciones sistólica y diastólica del VI, con atenuación del deterioro que las mismas sufrieron como consecuencia del infarto.

Conclusión: Estos resultados sugieren que la administración de NAC es una terapéutica promisoría para mitigar los efectos desfavorables del remodelado post IM.

Palabras clave: N-acetilcisteína – Infarto de miocardio - Remodelado

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Address for reprints: Manuel Rodríguez. Instituto de Fisiopatología Cardiovascular, Depto. de Patología, Facultad de Medicina, Universidad de Buenos Aires. (1114) J. E. Uriburu 950, 2do piso, Buenos Aires, Argentina. e-mail: mrodriguez@fmed.uba.ar



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¹ Institute of Cardiovascular Pathophysiology, Department de Pathology, School of Medicine, Buenos Aires University, Argentina.

² Institute of Cardiovascular Pathophysiology (secondary office of the School of Veterinary Sciences), School of Veterinary Sciences, Buenos Aires University, Argentina.

³ Specialty in Veterinary Clinical Cardiology, School of Veterinary Sciences, Buenos Aires University, Argentina.

⁴ Hospital de Clínicas José de San Martín, Cardiac Surgery Division, School of Medicine, Buenos Aires University, Argentina.

⁵ Experimental Pathology Center, Department of Pathology, School of Medicine, Buenos Aires University, Argentina.

⁶ Institute of Cardiovascular Pathophysiology (secondary office of the School of Veterinary Sciences), School of Veterinary Sciences, Buenos Aires University, Argentina.

INTRODUCTION

Ischemic heart disease is the main cause of death in high and mid-income countries, such as Argentina. (1) This entity involves several clinical-pathological conditions, myocardial infarction (MI) being the most important one. (2,3) This condition takes place when blood perfusion is insufficient to maintain the viability of a myocardial area causing its death, with the consequent loss of contractile mass. (4,5) Additionally, when the infarct size exceeds a certain threshold, a series of structural changes are produced in the walls and ventricular chambers, known as post-MI ventricular remodeling. (6-9) The evolution of this process slowly and progressively generates ventricular dilation, hemodynamic impairment, heart failure and decreased survival during months and even years. (9-12) This unfavorable evolution occurs in approximately one third of patients, and it is essential to develop and employ therapeutic measures than can prevent or mitigate it.

Myocardial oxidative stress increases during post-MI cardiac remodeling and in heart failure due to greater generation of oxygen-derived free radicals [reactive oxygen species (ROS)]. (13) Oxidative stress can be defined as the imbalance between oxidant and antioxidant species in favor of the former. In hearts with MI, this redox imbalance damages cardiac myocyte viability and favors hypertrophy which evolves towards a decompensated phenotype. (14) Glutathione (GSH) is a crucial agent in the antioxidant system of the organism and in redox metabolism, and is one of the main antioxidant defenses. (15) It is synthesized in two stages depending on the availability of substrate and regulatory mechanisms. The regulation step in its synthesis takes place at the level of the gamma-glutamyl-cysteinyl synthase enzyme, and cysteine is the limiting amino acid in the process. (16,17) N-acetyl cysteine (NAC) is a precursor of cysteine that can be administered orally or intravenously to increase the levels of cysteine when GSH concentrations need to be enhanced to favor detoxification processes. Initial clinical studies have demonstrated the efficacy of NAC therapy in the treatment of ischemic heart disease, with mild secondary effects. (18,19) NAC administration after MI has been efficient to reduce cardiac sympathetic hyperactivity, arrhythmic episodes and infarct size in dogs and rats. (20,21) Recent studies have started to evaluate NAC efficacy to control post-MI remodeling. In a pilot clinical trial, patients treated with NAC presented less adverse major cardiac events than those treated with placebo. (22) In another study, use of NAC in patients with congestive heart failure has been promising by facilitating the effects of isosorbide dinitrate and reducing nitroglycerine tolerance. (23)

Based on these considerations, the present study was designed to improve the understanding of the mechanisms involved in the process of post-MI left ventricular remodeling and to evaluate the possible

use of an antioxidant therapy with NAC to relieve the unfavorable events.

METHODS

Experimental model

An experimental model of MI in rabbits was used following the "Guide for the Care and Use of Laboratory Animals" developed by the National Academy of Sciences of the United States of America, updated by the American Physiological Society, (24) and in agreement with the Institutional Committee for the Care and Use of Laboratory Animals (CICUAL) of the Buenos Aires University School of Medicine (Resolution CD 2375/18). To this end, male New Zealand rabbits weighing 2.8 to 3.2 kg, free from infectious and parasitic diseases and which did not present pathological dysrhythmias or echocardiographic abnormalities were included in the study. Following anesthesia induced by intramuscular ketamine (45 mg/kg) and xylazine (0.5 mg/kg), the animals were mechanically ventilated through an endotracheal tube with ambient air using a Harvard respirator (tidal volume 25 ml, respiratory frequency 32-36 cycles/min). A flexible catheter was immediately placed in the marginal vein of the ear and 5% dextrose was infused at 3 ml/min. Using this same venous access, anesthesia was maintained through additional doses of sodium thiopental according to surgical requirements. Electrocardiographic monitoring was carried out during surgery. A left lateral thoracotomy was performed through the fourth intercostal space to expose the heart, and following pericardiectomy a 5.0 silk suture was passed under a prominent branch of the left coronary artery which was ligated to induce MI. Ischemia was confirmed by regional pallor of the cardiac surface. Next, the thoracotomy was closed respecting the different anatomical planes. Antibiotic therapy was then administered (ciprofloxacin, prophylactically) and the animals recovered under analgesia (tramadol 4-5 mg/kg) which was prolonged up to 48 h postoperatively. Animals were housed in specially conditioned cages for 28 days, in a quiet and acclimatized environment, and fed *ad libitum* a balanced commercial diet and water.

Experimental groups

The following experimental groups were defined:

Group 1 (n=10). In this group surgery was performed using the technique described, but no infarction was induced, as the coronary artery was not ligated (Control group). The animals were allowed their natural evolution for 28 days.

Group 2 (n=9) In this group, MI was induced using the technique described above. The animals were allowed their natural evolution until completing the same period of time as group 1 (MI group).

Group 3 (n=8) In this group, MI was produced by the technique described above and N-acetylcysteine was orally administered at doses of 300 mg/kg/day (MI+NAC group) for 28 days.

Once the evolution period was concluded echocardiographic, hemodynamic, and morphological studies were performed.

Echocardiographic studies

At the end of each experimental protocol, echocardiographic studies were performed under mild anesthesia with midazolam (2 mg/kg). A Esaote MyLab ultrasound machine was used, equipped with 4 to 9 MHz micro convex probe. The fol-

lowing left ventricular parameters were measured: interventricular septal thickness, diastolic and systolic diameters, percent fractional shortening and ejection fraction.

Hemodynamic studies

To assess remodeling and cardiac function from a hemodynamic viewpoint, the animals were anesthetized and a catheter was introduced in the right carotid artery connected to a Hewlett Packard 54S pressure transducer and hemodynamic monitoring equipment, to measure arterial pressure. Then, the catheter was advanced to enter the left ventricle (LV) to evaluate left ventricular hemodynamic behavior, with special reference to end-diastolic pressure (EDP).

Morphological studies

After hemodynamic data were obtained, the animals were euthanized with an intravenous lethal dose of sodium pentobarbital and diphenylhydantoin sodium (Euthanyle™). The heart was immediately removed, and after macroscopic evaluation, it was dissected, and the infarct scar was weighed as estimation of infarct size.

Statistical analysis

Numerical data are expressed as arithmetic mean and standard error of the mean, and were analyzed using a statistical analysis software package (GraphPad Prism, GraphPad Software, SanDiego, California, USA). Analysis of variance followed by Tukey's test for multiple comparisons was used for tests of statistical significance. A p value <0.05 was considered statistically significant.

RESULTS

Infarct size assessment confirmed its absence in the Control group, while the MI and MI+NAC groups presented similar infarct sizes (20.5 ± 0.98 g and 18.50 ± 1.39 g, respectively, $p = \text{NS}$) in the left ventricular free wall. Echocardiographic analysis revealed that the end-diastolic thickness of the interventricular septum, that is, in a remote zone from the infarction was 2.93 ± 0.12 mm in the Control group, 2.36 ± 0.15 mm in the MI group ($p < 0.05$ vs. the Control group) and 3.00 ± 0.21 mm in the MI+NAC group ($p < 0.05$ vs. the MI group). At end-systole, the values were 4.68 ± 0.13 mm, 3.84 ± 0.21 mm and 4.71 ± 0.39 mm, respectively. Thus, NAC administration preserved the morphology of the non-infarcted zone, and avoided the thinning produced as part of post-MI remodeling (Figure 1). Regarding left ventricular diameters, the diastolic diameter was 12.94 ± 0.64 mm while the systolic diameter was 8.35 ± 0.50 mm in the Control group. Both diameters were increased in the MI group (20.21 ± 1.14 mm and 14.71 ± 0.77 mm respectively, $p < 0.05$ vs. Control), while these increases were attenuated in MI+NAC group (16.76 ± 1.00 mm and 12.06 ± 0.81 mm, respectively, $p < 0.05$ vs. MI) (Figure 2). This indicates that NAC administration decreased the dilation provoked by the infarction.

Taken together, the preservation of septal thickness and the decreased dilation observed with NAC administration indicate a protective effect of NAC against the adverse remodeling caused by MI.

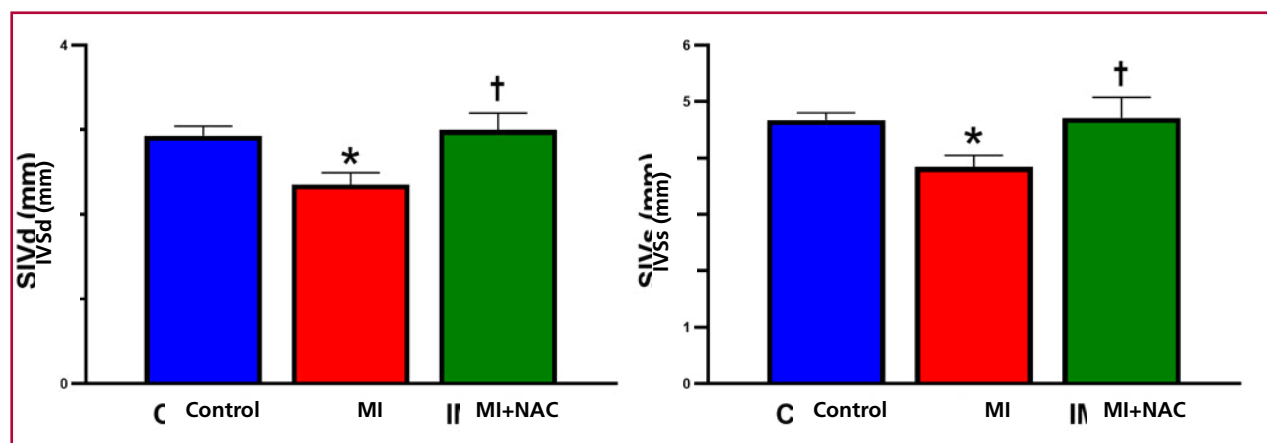
Fractional shortening was $36.54 \pm 1.86\%$ in the Control group; it decreased in the MI group ($22.44 \pm 1.47\%$, $p < 0.05$ vs. Control), while this decrease was attenuated in the MI+NAC group ($30.05 \pm 2.27\%$, $p < 0.05$ vs. MI). Similar results were obtained when left ventricular ejection fraction was considered: $68.10 \pm 2.43\%$ in the Control group, $47.44 \pm 2.81\%$ in the MI group ($p < 0.05$ vs. Control) and $59.20 \pm 2.31\%$ in the MI+NAC group ($p < 0.05$ vs. MI). Therefore, NAC administration in the group with MI, preserved left ventricular function (Figure 3).

Hemodynamic state assessment through arterial pressure showed no differences among the study groups (Figure 4). Conversely, the hemodynamic behavior of the LV showed a clear increase of EDP in the MI group (9.13 ± 1.12 mmHg) compared with the Control group (2.67 ± 0.41 mmHg, $p < 0.05$), which was mitigated by NAC (3.67 ± 1.02 mmHg, $p < 0.05$ vs. MI) (Figure 5). These results suggest that NAC administration after MI preserves left ventricular diastolic function, attenuating the damage caused by the infarction.

DISCUSSION

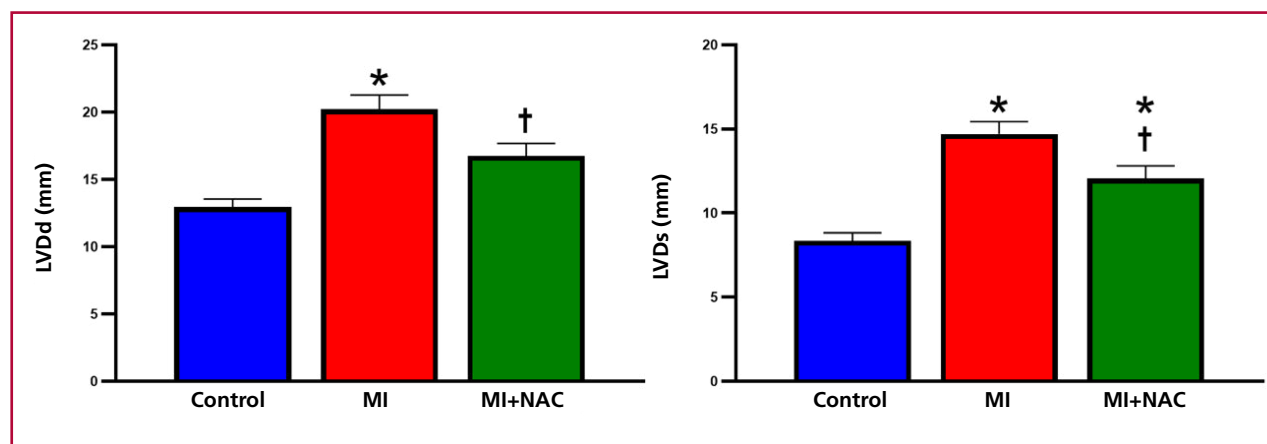
The presence of MI generates a reduction of myocardial contractility as a consequence of loss of functional myocardial mass, but once this acute period is overcome, contractility may continue to decrease due to remodeling and progressive left ventricular dysfunction. The present study used an experimental rabbit model of 28-day evolution myocardial infarction, in which echocardiographic and hemodynamic studies were performed to evaluate the ventricular post-MI remodeling process and the possible use of NAC antioxidant therapy to mitigate its unfavorable effects. These experiments showed a beneficial effect of NAC on the morphology of the non-infarcted area and on ventricular function.

It was possible to observe the preservation of the infarcted area morphology and less post-MI remodeling in the non-infarcted zone, evidencing lower eccentric hypertrophy. Prior studies have shown that MI produces volume overload in the spared sectors, generating cardiomyocyte remodeling with formation of new sarcomeres, among other modifications. (25) The new sarcomeres are positioned in series with the already existing ones, giving rise to greater myocyte longitudinal diameter, which, in turn, generates increased left ventricular chamber volume. It is a peculiar form of eccentric hypertrophy, as it occurs only in the spared territories. (26,27) Although sarcomere addition could be considered as an adaptive response to balance the loss of contractile mass produced by the infarction, it generates a concomitant enlargement of the ventricular chamber, and hence, of ventricular volume, which by increasing wall stress and consequently, myocardial oxygen consumption, can be deleterious.



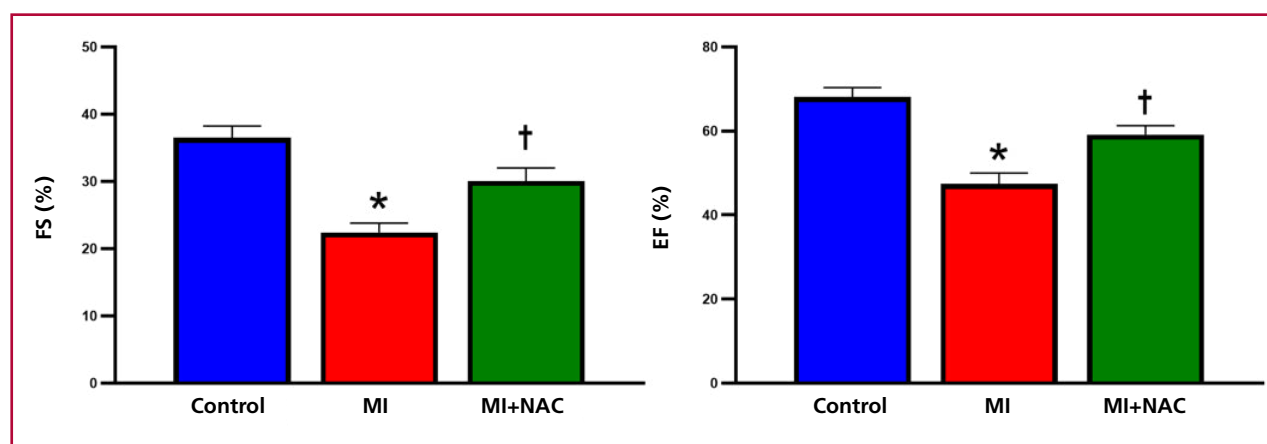
MI: Myocardial infarction; NAC: N-acetylcysteine. *: $p < 0.05$ vs. Control; †: $p < 0.05$ vs. MI

Fig. 1. Interventricular septal thickness in diastole (IVSd) and systole (IVSs).



MI: Myocardial infarction; NAC: N-acetylcysteine. *: $p < 0.05$ vs. Control; †: $p < 0.05$ vs. MI

Fig. 2. Left ventricular diastolic and systolic diameters (LVDd and LVDs, respectively)



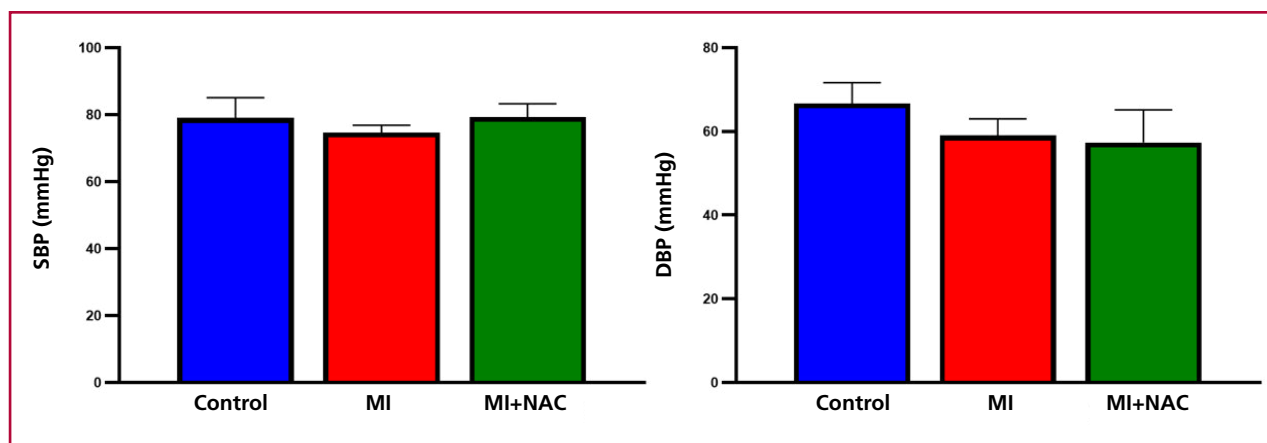
MI: Myocardial infarction; NAC: N-acetylcysteine. *: $p < 0.05$ vs. Control; †: $p < 0.05$ vs. MI

Fig. 3. Percent left ventricular fractional shortening (FS) and ejection fraction (EF).

It is usual to associate an increase in ventricular volume with greater intraventricular pressure, but this is not necessarily so, as disorders that hamper ventricular filling without modifying chamber volume can also provoke an increase in intraventricular pressure. Therefore, for a more rigorous assessment, we performed a left ventricular hemodynamic study, which showed that end-diastolic intraventricular pressure was increased after MI.

Accumulated evidence indicates that the NADPH oxidase family is the main source of ROS in several cardiovascular diseases, and that NAC is able to act as antioxidant, resulting in reduced oxidative stress. (28) The antioxidant effect of NAC implies a direct interaction with ROS, (29,30) or a positive regulation of cysteine and GSH biosynthesis. (31,32) This

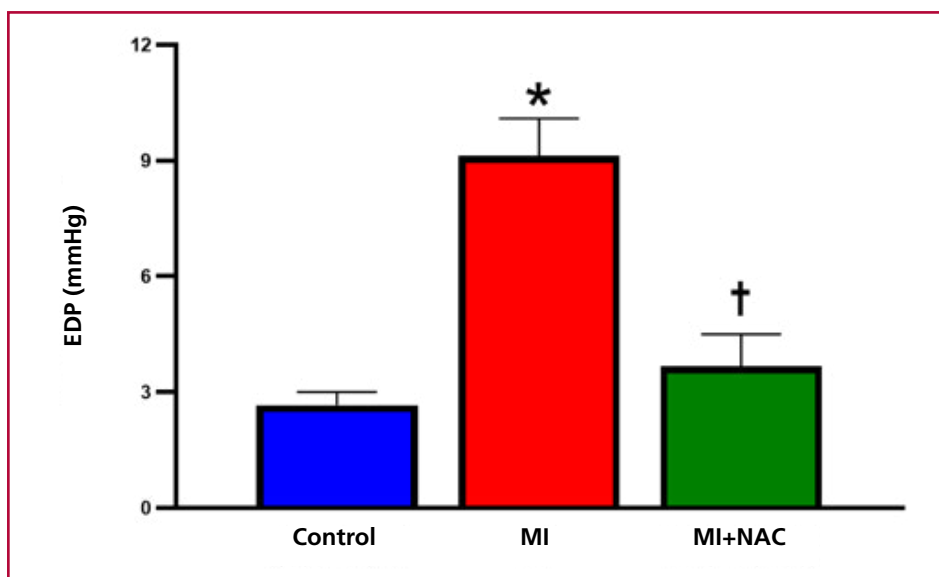
last compound has been reported to be decreased in hearts with MI. (32,33) Recent experimental studies in animals and clinical studies have pointed out that the existence of oxidative stress caused by greater production of free radicals would play a key role in post-MI cardiac remodeling, both in early as late stages. (13) Therefore, use of antioxidant therapies after MI is a developing field of research, in which NAC is especially attractive. In this respect, the combined streptokinase and NAC administration in patients with acute myocardial infarction has been shown to decrease oxidative stress and improve ventricular function. (34) N-acetylcysteine, acting as antioxidant, was also able to reverse inflammation and oxidative stress (35) and of preserving connexin 43 in rat models of MI. (36) Beneficial effects of NAC



MI: Myocardial infarction; NAC: N-acetylcysteine.

Fig. 4. Systolic and diastolic blood pressure (SBP and DBP, respectively)

Fig. 5. Left ventricular end-diastolic pressure (EDP).



MI: Myocardial infarction; NAC: N-acetylcysteine. *: $p < 0.05$ vs. Control; †: $p < 0.05$ vs. MI

on inflammation were also observed in patients using serum values of transforming growth factor beta (TGF- α) and tumor necrosis factor alpha (TNF- α) as indicators. (37) The efficacy of NAC to control post-MI remodeling evaluated in a prospective, double, blind, randomized test clinical trial showed that, compared with a placebo-treated group, patients treated with NAC presented less major adverse cardiac events (including reinfarction) during a one-year follow-up. (22)

Consistently with these results, the assessment of ventricular diameters in our study revealed that NAC administration is able to reduce ventricular dilation produced by MI. The complementary evaluation of left ventricular hemodynamic behavior showed that NAC administration is also able to attenuate the increase of EDP caused by the infarction. Taken together, these results suggest that NAC administration after infarction preserves left ventricular diastolic function, by attenuating the damage elicited by remodeling. Concomitantly, the echocardiographic evaluation showed that NAC administration also attenuates left ventricular ejection fraction impairment.

The results of the present study indicate that NAC administration favorably modifies the initial stages of post-MI remodeling, has a protective effect on the non-infarcted area, decreases dilation and increased EDP and attenuates ejection fraction impairment. Thus, although further studies are necessary to broaden this knowledge, our results suggest that NAC administration is a promising therapy to mitigate the unfavorable effects of post-MI remodeling.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Financing

None.

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Impact of Extended Septal Myectomy on Echocardiographic Changes in Hypertrophic Obstructive Cardiomyopathy

Impacto de la miectomía septal ampliada sobre los cambios ecocardiográficos en la miocardiopatía hipertrófica obstructiva

IVANA SEIA¹, MARCIA GORINA¹, LUCRECIA BURGOS¹, MTSAC, MIRTA DIEZ¹, MTSAC, PAOLA KUSCHNIR¹, JUAN ESPINOZA¹, MTSAC, MARIANO VRANCIC¹, MTSAC, DANIEL NAVIA¹, MTSAC, JUAN PABLO COSTABEL¹, MTSAC

ABSTRACT

Background: Extended septal myectomy (ESM) has proven to be a useful strategy to improve symptoms in patients with hypertrophic obstructive cardiomyopathy (HOCM).

Objective: The aim of this study was to analyze the impact of ESM on short and mid-term structural and functional echocardiographic parameters in patients with HCM and left ventricular (LV) outflow tract dynamic obstruction.

Methods: Preoperative, immediate postoperative (1 month after surgery) and late postoperative (2 to 3 years) echocardiograms of patients undergoing ESM were analyzed.

Results: A total of 94 patients with mean age of 57.6 ± 13.8 years underwent surgery. A significant reduction was observed in maximum septal thickness in the immediate postoperative period, which was sustained in the late postoperative period, and in atrial size in the immediate postoperative period, which deepened in the late postoperative period ($p < 0.001$). Intraventricular gradient at rest dropped from 49.2 to 6.4 mmHg ($p < 0.001$) and then to 4.6 mmHg ($p = 0.224$) in the immediate and late periods and with Valsalva maneuver from 93.9 to 8.7 mmHg ($p < 0.001$), and then to 7.2 mmHg ($p = 0.226$), respectively. Preoperative diastolic function was assessed as grade II in 58.5% of patients, decreasing to 51.7% in the immediate postoperative period and to 29% in the late postoperative period. In agreement with these results, a change was evidenced in the E/e' ratio and pulmonary artery systolic pressure, degree of mitral regurgitation and left atrial dimensions.

Conclusion: In this cohort of patients with HOCM, ESM was associated with a significant improvement in LV diastolic function, reduction in filling and pulmonary pressures and degree of mitral regurgitation, and left atrial reverse remodeling. It is possible that this combination of effects explains the clinical benefits of the intervention.

Key words: Hypertrophic cardiomyopathy, septal myectomy, Echocardiography

RESUMEN

Introducción: La miectomía septal ampliada (MSA) ha demostrado ser una estrategia útil para mejorar los síntomas de los pacientes con miocardiopatía hipertrófica obstructiva (MCHO).

Objetivos: El objetivo de este trabajo fue analizar el impacto de la MSA en parámetros estructurales y funcionales ecocardiográficos a corto y mediano plazo, en pacientes con MCH y obstrucción dinámica del tracto de salida del ventrículo izquierdo (VI).

Material y métodos: Se analizaron los ecocardiogramas en los períodos preoperatorio, postoperatorio inmediato (1 mes post cirugía) y posoperatorio alejado (2 a 3 años) de pacientes sometidos a MSA.

Resultados: Se intervinieron 94 pacientes con una edad media de $57,6 \pm 13,8$ años. Se observó una reducción significativa del máximo espesor septal en el postoperatorio inmediato, que se mantuvo en el posoperatorio alejado, y en el tamaño auricular izquierdo en el postoperatorio inmediato que se profundizó en el alejado ($p < 0,001$). El gradiente intraventricular en reposo pasó de 49,2 mmHg basal a 6,4 mmHg ($p < 0,001$) y de allí a 4,6 mmHg ($p = 0,224$) en los períodos inmediato y alejado, y con la maniobra de Valsalva de 93,9 mmHg a 8,7 mmHg ($p < 0,001$) y de allí a 7,2 mmHg ($p = 0,226$) respectivamente. La función diastólica fue valorada como grado II en el 58,5 % de los pacientes en el preoperatorio, 51,7 % en el postoperatorio inmediato y 29 % en el postoperatorio alejado. En la misma línea se evidenció un cambio en la relación E/e' y la presión sistólica pulmonar, grado de insuficiencia mitral y dimensiones de la aurícula izquierda.

Conclusión: En esta cohorte de pacientes con MCHO, la realización de una MSA se asoció a una mejoría significativa de la función diastólica del VI, reducción de las presiones de llenado y pulmonares y grado de insuficiencia mitral, y remodelado reverso de la aurícula izquierda. Es posible que esta combinación de efectos explique los beneficios clínicos de la intervención.

Palabras claves: Miocardiopatía Hipertrófica - Miectomía septal - Ecocardiograma

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Address for reprints: Juan Pablo Costabel. Instituto Cardiovascular de Buenos Aires, Argentina. Blanco de Encalada 1543. 1428, Buenos Aires, Argentina. E-mail: jpcostabel@icba.com.ar



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¹ Familiar Cardiomyopathy Clinic, Instituto Cardiovascular de Buenos Aires.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a hereditary cardiac disease with complex genetic and phenotypic expression and an estimated prevalence of 1:500 in the general population. (1,2)

Approximately 70% of patients with HCM present some form of dynamic obstruction (HOCM) that contributes to the development of symptoms such as dyspnea and angina. In turn, sufficient evidence shows the impact of dynamic obstruction in the development of functional and structural changes at the cardiac level, as the increase in ventricular filling pressures, pulmonary pressure and left and right atrial dilation. (3,4)

Extended septal myectomy (ESM) has shown to be a useful strategy to improve symptoms and quality of life in patients with HOCM refractory to medical treatment. (3-5)

The purpose of this study was to evaluate the impact of this surgery on the structural changes associated with dynamic obstruction.

The objective was to analyze the short and mid-term impact of ESM in structural and functional echocardiographic parameters in patients with HCM and left ventricular (LV) outflow tract dynamic obstruction.

METHODS

Study design

An observational study was carried out on a prospective cohort of patients undergoing ESM from November 2011 to December 2022. It included patients with possibility of follow-up and a control echocardiogram in the immediate and late postoperative periods.

HCM diagnosis

The HCM diagnosis was performed according to international guideline recommendations, with the presence of increased LV wall thickness in one or more myocardial segments, determined by any imaging technique, in the absence of any other cardiac or systemic cardiac disease that justified it. In adults, a LV wall thickness ≥ 15 mm, or a septal/posterior wall thickness ratio > 1.3 was considered to determine a diagnosis, and for first-degree relatives of a patient with HCM, a LV wall thickness ≥ 13 mm was contemplated for the diagnosis. (2,3)

The HOCM diagnosis was performed according to international guideline recommendations by Doppler echocardiography, when the peak gradient obtained spontaneously and/or using maneuvers (Valsalva, exercise) was ≥ 30 mmHg. (2,3)

Echocardiographic assessment

A two-dimensional ultrasound was used to measure myocardial maximum septal thickness, left atrial (LA) anteroposterior diameter in the long parasternal axis, and atrial area and volume in apical 4-chamber view. Left atrial volume was calculated using the area-length biplane method and the LA volume index using body surface area.

Left ventricular systolic function was quantified by Simpson's rule, in apical 2-chamber and 4-chamber views. (6)

The apical 4-chamber view with pulsed Doppler mitral flow at the mitral valve leaflet tips was used to determine

peak early (E) and late (A) diastolic wave velocities, the E/A ratio and E wave deceleration time, and to classify diastolic dysfunction according to echocardiographic quantification guidelines into normal and grade I, II and III. Early lateral and medial mitral annulus peak diastolic velocities were analyzed with tissue Doppler to assess ventricular filling pressures, considering the ratio between mitral peak E wave velocity and average peak e' wave velocity (E/e'). (7)

According to international recommendations, diastolic function assessment in HCM patients was considered through an integral approach, taking into account all the echocardiographic parameters that include and consider as abnormal values an E/e' ratio > 14 , indexed LA volume > 34 ml/m², difference in the pulmonary vein retrograde A wave duration - transmitral flow antegrade A wave duration > 30 msec, and peak tricuspid regurgitant jet velocity > 2.8 m/s. Normal LA pressure and grade I diastolic dysfunction was considered if < 50 % of these variables reached cut-off values, and elevated LA pressure and grade II diastolic dysfunction when > 50 % of these variables did. In case of 50% discordance, the findings were not conclusive to estimate LA pressure. Grade III diastolic dysfunction was considered in the presence of a restrictive filling pattern and reduced Doppler tissue mitral annulus velocity (septal < 7 cm/s, and lateral < 10 cm/s). (7)

Presence of mitral regurgitation was evaluated with color Doppler ultrasound, and qualitatively graded as mild, moderate and severe, and whether its mechanism was secondary to anterior systolic mitral valve motion, or as a consequence of a valve abnormality, such as prolapse, chordal rupture, mitral valve ring calcification or incorrect positioning of a papillary muscle, or mitral subvalvular apparatus abnormalities. (7)

To assess pulmonary artery systolic pressure (PASP), peak tricuspid regurgitant jet velocity continuous Doppler was used, added to right atrial diastolic pressure, according to the inferior vena cava diameter and its percentage of inspiratory collapse. (7)

The obstructive gradient was identified with color Doppler and quantified with continuous Doppler according to the Bernoulli formula, at rest and with Valsalva maneuver/exercise. (7)

The clinical preoperative, postoperative and follow-up evaluation of patients was performed by cardiologists of the Cardiomyopathy center, and functional class for dyspnea, according to the New York Heart Association (NYHA) classification, presence or absence of angina, syncope, family history of sudden death, cardiovascular risk factors and optimal medical treatment were established (Figure 1).

Follow-up

Transthoracic echocardiograms were performed in the following periods:

- Preoperative period: up to 3 months before surgery
- Immediate postoperative period: 1 month after surgery
- Late postoperative period: between 2 and 3 years after surgery.

Statistical analysis

Quantitative variables are expressed as mean or median with their corresponding standard deviation (SD) or interquartile range (IQR) as appropriate. Categorical variables are presented as frequency and percentage. The Kolmogorov-Smirnov test ($n \geq 30$) and the Shapiro-Wilk test ($n < 30$) were used to evaluate the normality of variables and the application assumptions of each of the tests used.

Chi-square, McNemar, sign, Wilcoxon or ANOVA tests were used as appropriate (2 samples or more, independent or paired)

A two-tailed p value <0.05 was considered significant.

SPSS 19 (Statistical Package for the Social Sciences) was used to perform the analyses.

Ethical considerations

The study was carried out according to national ethical regulations (CABA law 3301), the national law of clinical research in human beings and the declaration of Helsinki, and was approved by the Institutional Teaching and Ethics Committee.

Patients signed an informed consent for the anonymous use of their personal data.

RESULTS

A total of 94 patients, with mean age 57.6 ± 13.8 years, 53% female, underwent surgery during the study pe-

riod, with a median follow-up of 3.3 years (IQR 1.1-5.1) Table 1.

All patients underwent ESM and 43 of them (45.7%) were also subjected to concomitant treatment of the mitral valve or the subvalvular mitral apparatus (9 underwent mitral valve repair, 26 mitral valve plication, 14 second order chord resection, 8 accessory muscle resection, and 3 mitral valve replacement). In addition, aortic valve replacement was performed in 3 patients (3.1%), coronary bypass surgery in 19 (20.2%) and Maze surgery in 17 (18%).

All patients presented complete left bundle branch block after the intervention, and 7.4% required definite pacemaker for complete atrioventricular block, in 5.3% of cases in patients with isolated septal myectomy. Two patients presented atrial fibrillation (AF) in the immediate preoperative and postoperative periods and 5 in the late postoperative period.

Fig. 1. Echocardiographic evaluation of a patient with hypertrophic obstructive cardiomyopathy.



Table 1. Baseline population characteristics.

Variables	n= 94
Age (years), mean $\pm$ SD	57.3 $\pm$ 13.2
Female gender, n (%)	50 (53.1)
HTN, n (%)	59 (62.7)
Dyslipidemia, n (%)	54 (57.4)
Diabetes, n (%)	11 (11.7)
Smoking, n (%)	21 (22.3)
Syncope, n (%)	13 (13.8)
Angina, n (%)	17 (18)
Coronary artery disease, n (%)	19 (20.2)
Pharmacological treatment, n (%)	
Betablockers	65 (69.1)
Verapamil	2 (2.1)
Amiodarone	23 (24.4)
Diuretics	35 (36.1)
ARBs	17 (18)
Family history of sudden death, n (%)	11 (11.7)
Prior alcohol septal ablation, n (%)	6 (6.3)
Prior ICD, n (%)	11 (11.7)

ARBs: Angiotensin receptor blockers; HTN: Hypertension; ICD: Implantable cardioverter defibrillator; SD: Standard deviation

There were 3 (3.1%) interventricular septal defects related with the surgical procedure, and 30-day perioperative mortality was 1 patient (1.06%). Nine patients (9.5%) died during follow-up, 3 related to their underlying disease (3.2%)

Regarding functional class, 89% of patients were asymptomatic during the long-term follow-up.

Structural parameters showed a significant reduction in maximum septal thickness, from 21.3 mm in the preoperative period to 14 mm in the immediate postoperative period, ($p<0.001$) which was maintained in the late postoperative period.

A significant reduction was observed in the left atrial size; its anteroposterior diameter decreased from 49.7 mm to 48.2 mm in the immediate postoperative period ($p<0.001$) to 46.2 mm in the late postoperative period ($p<0.001$). Left atrial volume indexed by body surface area decreased from 57.6 ml/m² to 51.2 ml/m² ($p<0.001$) in the immediate postoperative period, and to 46.1 ml/m² ($p<0.001$) in the late postoperative period. Moreover, left atrial area decreased from 30.1 cm² to 28.2 cm² ($p<0.001$) in the immediate postoperative period, and to 26.3 cm² ($p<0.001$) in the late postoperative period (Table 2 and Figure 2).

Regarding functional parameters, the intraventricular gradient at rest decreased from 49.2 mmHg to 6.4 mmHg ($p<0.001$), and then to 4.6 mmHg ($p=0.224$) in the immediate and late postoperative periods, and

with the Valsalva maneuver from 93.9 mmHg to 8.7 mmHg ($p<0.001$), and 7.2 mmHg ($p=0.226$), respectively. Diastolic function was assessed as grade II in 59.3% of patients in the preoperative period, in 51.6% in the immediate postoperative period, and in 29% in the late postoperative period (Figure 3). Similarly, a change in the E/e' ratio and pulmonary artery systolic pressure was evidenced. Moderate to severe mitral regurgitation decreased from 53.1% in the preoperative period to 8.7% in the late postoperative period and pulmonary pressure from 32 mmHg to 27 mmHg, respectively. Left ventricular ejection fraction (LVEF) decreased from 65% to 60% ($p<0.001$) in the immediate postoperative period and remained at 60% ($p=0.953$) in the late postoperative period.

DISCUSSION

The importance of the results obtained in this work is the significant impact of ESM on the different hemodynamic parameters studied by echocardiography and the clinical improvement of patients. We would like to highlight 4 findings.

First, from a structural point of view, a reduction was evidenced in the LA size measured in all its forms, which appears to be intensified with the passage of time. The probable mechanisms that we understand are involved in this phenomenon are the reduction of mitral regurgitation and of LV filling pressure. In

Table 2. Modification of echocardiographic parameters with the ESM

Variable	Preoperative	Immediate POP	Late POP	p
Maximum thickness (mm), mean $\pm$ SD	21.3 $\pm$ 3.9	14 $\pm$ 3	14 $\pm$ 3	<0.001
Gradient at rest (mmHg), mean $\pm$ SD	49.2 $\pm$ 31.4	6.4 $\pm$ 9.3	4.6 $\pm$ 9.4	<0.001
Valsalva gradient (mmHg), mean $\pm$ SD	93.9 $\pm$ 39.7	8.7 $\pm$ 13	7.2 $\pm$ 14	<0.001
LA volume (ml/m ²), mean $\pm$ SD	57.6 $\pm$ 18.4	51.2 $\pm$ 17.2	46.1 $\pm$ 16.5	<0.001
LA area (cm ²), mean $\pm$ SD	30.1 $\pm$ 5.9	28.2 $\pm$ 5.4	26.3 $\pm$ 5.6	<0.001
LA anteroposterior diameter (mm), (mean $\pm$ SD)	49.7 $\pm$ 6	48.2 $\pm$ 5.8	46.2 $\pm$ 5.4	<0.001
Diastolic function, n (%)				
Normal	0	0	1 (1.2)	<0.001
AF	2 (2.1)	2 (2.1)	5 (5.3)	
Grade I	36 (38.3)	40 (43)	57 (61.3)	
Grade II	55 (58.5)	48 (51.7)	27 (29)	
Grade III	1 (1.1)	0	0	
Mitral valve prosthesis	0	3 (3.2)	3 (3.2)	
E/e' ratio, mean $\pm$ SD	15.7 $\pm$ 4.8	13 $\pm$ 3.3	11.1 $\pm$ 3.2	<0.001
LVEF (%), mean $\pm$ SD	65 $\pm$ 6.2	59.9 $\pm$ 6.1	60 $\pm$ 6.8	<0.001
PASP (mmHg), mean $\pm$ SD	32.9 $\pm$ 9.5	30.1 $\pm$ 7.9	27.5 $\pm$ 8.4	<0.001
Mitral regurgitation, n (%)				
None	0	3 (3.2)	3 (3.2)	<0.001
Mild	44 (46.7)	80 (87.9)	80 (87.9)	
Moderate	38 (40.4)	8 (8.7)	8 (8.7)	
Severe	12 (12.7)	0	0	

AF: Atrial fibrillation; ESM: extended septal myectomy; LA: Left atrial; LVEF: Left ventricular ejection fraction; PASP: Pulmonary artery systolic pressure; POP: Postoperative; SD: Standard deviation

relation to the first, patients undergoing surgery for isolated mitral regurgitation usually show this phenomenon, correlated in the case of mitral valve repair surgery with the degree of residual mitral regurgitation. Regarding filling pressures, the reduction of the dynamic gradient has a verified impact at the level of end-diastole pressure and contributes to this phenomenon. From a prognostic viewpoint, LA size is an independent risk factor for adverse outcomes in patients with HCM, and increased LA volume is associated with an increased risk of atrial fibrillation, thromboembolic stroke, heart failure and cardiovascular mortality, which appears to represent much more than a simple structural change. (8-18) Our findings have been previously reported by Tower-Rader et al., who in a review of 25 patients observed a significant decrease in atrial volume 2 years after myectomy. (19) Similarly, Finocchiaro et al. demonstrated a marked reduction of LA volume in a cohort of 40 patients undergoing septal reduction therapy (myectomy or alco-

hol septal ablation). (20) In a cohort of 44 operated-on patients, Kyung Eun Ha et al. observed a reduction in atrial volume and increased strain of this chamber, consistent not only with the reduction in size but with an improvement in fiber function. (21)

Second, echocardiographic “hemodynamic” assessment showed a reduction in the E/e' ratio and changes in the transmitral filling pattern. These modifications seem to be related with the reduction in LV end diastolic pressure, secondary to the significant reduction that the procedure achieved in the dynamic left ventricular outflow tract gradients both at rest and with Valsalva maneuver. Evidence of this is that the changes are noticeable in the immediate postoperative period. Moreover, both variables tend to improve even more in the late postoperative period, a fact that could be explained by the gradual recovery in diastolic function produced by the relief of the obstruction. This has been also reported by others, such as Nguyen et al, who found in a cohort of 656 patients

Fig. 2. Extended septal myectomy and changes in left atrial volume and E/e' ratio.

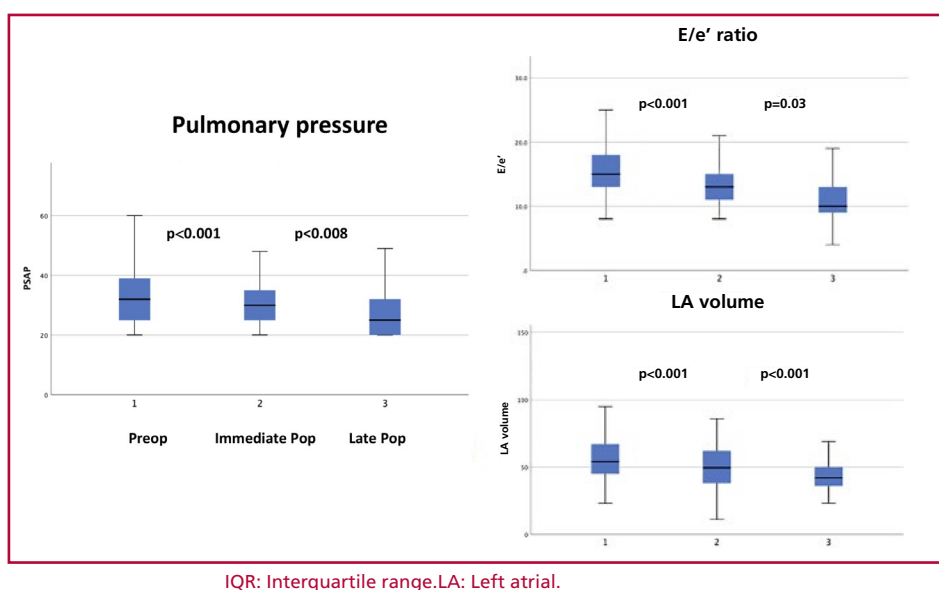
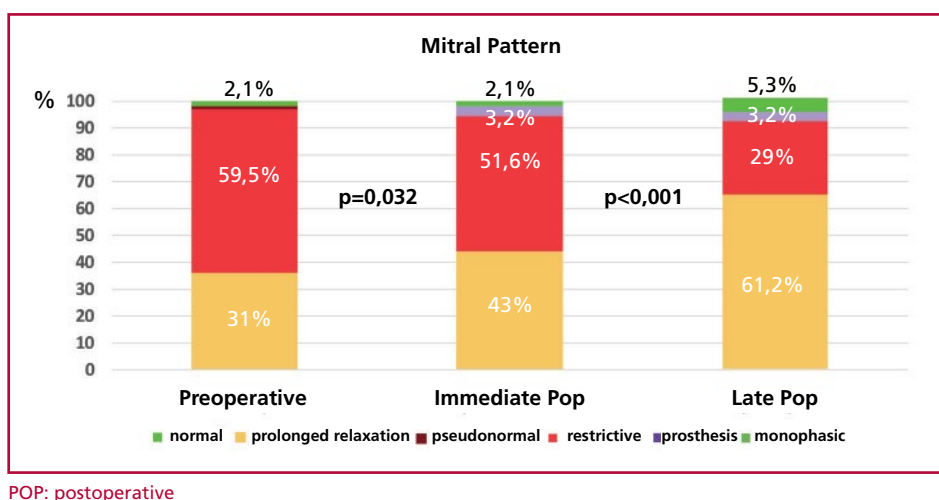


Fig. 3. Modifications in the transmitral filling pattern.



an improvement in the E/e' ratio, which occurred in the early postoperative phase and was maintained in the long-term follow-up. (22) There is evidence that correlates dynamic obstruction with the development of myocardial ischemia and interstitial fibrosis, so we hypothesize that this relief could be generating a retrograde phenomenon. (23,24)

Third, the LVEF drop in the immediate postoperative period could be associated with the impact of the pump used for cardiopulmonary bypass during surgery, but above all to the development of left bundle branch block due to the myectomy. This last phenomenon causes mechanical dyssynchrony and a drop in ejective volume, without ruling out that it has an impact on the reduction of the dynamic gradient. The analysis of the late postoperative period shows a numerical though not significant recovery, requiring greater follow-up for analysis. (23-26) Along the same line, Ha et al. observed a relationship between postmyectomy QRS duration and the drop in LVEF, accompanied by a reduction in non-septal LV longitudinal strain. (21)

Fourth, patients showed a reduction in echocardiographic assessed pulmonary artery systolic pressure that deepened over time. This fact shows that changes in left filling pressures and improvement in diastolic function have an impact on the pulmonary circuit and right chambers, which probably contributes to explaining the clinical improvement of patients. (25,26)

Limitations

The number of patients included may decrease the reliability of several of the data obtained. However, the consistency of the findings suggests a direct relationship between the intervention and the observed changes. We also understand the limitations of the methods to accurately estimate ventricular filling pressures in this scenario, though there is sufficient information to consider that changes in these variables are associated with improvement in diastolic function.

CONCLUSION

In this cohort of patients with HOCM, ESM was associated with a significant improvement in LV diastolic function, reduction in filling and pulmonary pressures and degrees of mitral regurgitation, and reverse remodeling of the left atrium. It is possible that this combination of effects explains the clinical benefits of the intervention.

Conflicts of interest

None declared.

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

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Implications of Artificial Intelligence in Intravascular Imaging Methods

Implicancias de la inteligencia artificial en los métodos de imagen endovascular

CRISTIAN GARMENDIA¹ MTSAC, , NIEVES GONZALO², PABLO J. BLANCO^{3,4}, HÉCTOR M. GARCÍA-GARCÍA⁵

ABSTRACT

Percutaneous coronary intervention (PCI) is one of the primary revascularization strategies in patients with coronary artery disease (CAD). Several studies support the use of intravascular imaging methods to optimize PCI. However, these methods are underutilized in contemporary clinical practice and face challenges in data interpretation. Therefore, the incorporation of artificial intelligence (AI) is seen as an attractive solution to promote and simplify their use.

AI can be defined as a computer program that mimics the human brain in its ability to collect and process data. Machine learning is a sub-discipline of AI that involves the creation of algorithms capable of analyzing large datasets without making prior assumptions, while deep learning focuses on the construction and training of deep and complex artificial neural networks. The incorporation of AI systems to intravascular imaging methods improves the accuracy of PCI, reduces procedure duration, and minimizes interobserver variability in data interpretation. This promotes their wider adoption and facilitates their use. The aim of this review is to highlight how current AI-based systems can play a key role in the interpretation of data generated by intravascular imaging methods and optimize PCI in patients with CAD.

Keywords: Artificial Intelligence - Percutaneous Coronary Intervention - Intravascular imaging

RESUMEN

La angioplastia transluminal coronaria (ATC) es una de las principales estrategias de revascularización en pacientes con enfermedad coronaria aterosclerótica (ECA). Numerosos estudios respaldan la optimización de la ATC mediante métodos de imagen endovascular; sin embargo, estos métodos son subutilizados en la práctica clínica contemporánea y enfrentan desafíos en la interpretación de los datos obtenidos, por lo que la integración de la inteligencia artificial (IA) se vislumbra como una solución atractiva para promover y simplificar su uso.

La IA se define como un programa computarizado que imita la capacidad del cerebro humano para recopilar y procesar datos.

El aprendizaje de máquinas (*machine learning*) es una subdisciplina de la IA que implica la creación de algoritmos capaces de analizar grandes conjuntos de datos sin suposiciones previas, mientras que el aprendizaje profundo (*deep learning*) se centra en la construcción y entrenamiento de redes neuronales artificiales profundas y complejas. Así, se ha demostrado que la incorporación de sistemas de IA a los métodos de imagen endovascular incrementa la precisión de la ATC, disminuye el tiempo del procedimiento y la variabilidad interobservador en la interpretación de los datos obtenidos, promueve así una mayor adopción y facilita su utilización. El propósito de la presente revisión es destacar cómo los sistemas actuales basados en IA pueden desempeñar un papel fundamental en la interpretación de los datos generados por los métodos de imagen endovascular, lo que conduce a una mejora en la optimización de la ATC en pacientes con ECA.

Palabras clave: Inteligencia artificial - Angioplastia coronaria - Imagen endovascular

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Address for reprints: Héctor M. García-García, 110 Irving St NW, Washington DC 20010, United States, Phone: +1 202-877-7000, hect2701@gmail.com; hector.m.garciagarcia@medstar.net



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¹ Department of Interventional Cardiology, Hospital Italiano de Buenos Aires Argentina

² Department of Interventional Cardiology, Hospital Clínico, Madrid, Spain

³ National Laboratory for Scientific Computing, LNCC/MCTI, Petrópolis, RJ, Brazil

⁴ National Institute of Science and Technology in Medicine Assisted by Scientific Computing, INCT-MACC, Petrópolis, RJ, Brazil

⁵ Interventional Cardiology, MedStar Washington Hospital Center, Washington, USA

INTRODUCTION

Despite the remarkable advances achieved in preventive strategies and therapeutic approaches in recent decades, atherosclerotic coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide. (1) Although percutaneous coronary intervention (PCI) is recognized as a fundamental therapeutic strategy for endovascular revascularization in patients with CAD, its benefit is limited by the need for prior and accurate interpretation of data obtained by diagnostic coronary angiography, which has significant limitations in the assessment of vascular involvement due to its characteristics. In this context, and in line with advances in pharmacological treatment strategies, technologies based on imaging and intravascular physiology have been developed and refined to assess the risk of patients with CAD and to improve their treatment.

So far, several studies have supported the optimization of PCI with stent implantation guided by intravascular imaging methods, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT). These methods offer considerable benefits by significantly improving stent implantation and reducing the incidence of adverse clinical events during follow-up. (2-5) However, the use of these optimization techniques is currently limited, possibly due to their cost to healthcare systems, the need for operator experience to accurately interpret the data obtained, and the fact that they can significantly increase the overall procedure time. In this context, the incorporation of artificial intelligence (AI) as a tool to facilitate and simplify the use of intravascular imaging and the interpretation of the information obtained is emerging as an attractive strategy. The aim of this review is to highlight how current AI-based systems can play a key role in the interpretation of data generated by intravascular imaging techniques, and thus improve optimization of PCI in patients with CAD.

RATIONALE FOR ARTIFICIAL INTELLIGENCE

AI can be defined as a computer program that resembles the human brain in its ability to collect and process data. (6) This concept was first coined in 1956 during the Dartmouth Summer Research Project (7) and generated explosive interest in the 1970s to be implemented in biomedical sciences. (8)

Machine learning (ML) is a sub-discipline of AI that involves the creation of algorithms capable of analyzing large datasets without making prior assumptions and learning to identify rules and patterns among variables for prediction and classification. (9) The versatility and great potential of these algorithms are due to their ability to incorporate a wide set of variables from various medical modalities, ranging from clinical parameters to two- and three-dimensional imaging data, taking into account the

multidimensional nonlinear interactions between them. ML approaches can be broadly classified into three categories: supervised learning, unsupervised learning, and semi-supervised learning. (10) Supervised learning is the most common approach in ML, where the system establishes associations from training data obtained from examples that already have an outcome identified by a specialist. The algorithm embeds the specialist's knowledge within the model. In this method, from the given input features, the system outputs a suitable regression or classification analysis of clinical and imaging data. On the other hand, in situations where training data is unavailable or insufficient, unsupervised learning is used to discover hidden structure of data. (10) Finally, semi-supervised learning begins with a small set of labeled data and augments the training data size by gradually labeling unlabeled data. (10) (Table 1).

Deep learning (DL) is a sub-discipline of ML that focuses on the construction and training of deep and complex artificial neural networks. These networks are designed to mimic the learning process of the human brain. Unlike conventional neural networks, which may have only a few hidden layers, deep neural networks have multiple hidden layers, which allow the network to learn hierarchical and abstract features of input data, which make them especially effective for image processing tasks. Convolutional neural networks (CNN) represent a specialized type of artificial neural network specially designed for processing and analyzing the spatial structure of data that has a grid-like topology, such as an image. Several studies have used CNN to automatically characterize atherosclerotic plaques present in the coronary arteries, employing a variety of approaches. (11-13)

Thus, a suitably trained AI system can comprehensively analyze diverse data and provide a diagnosis by interpreting information in a novel way. This makes it an appealing tool for its incorporation into image-based biomedical techniques to improve risk prediction and personalize clinical decisions.

IMPLEMENTATION OF AI IN INTRAVASCULAR IMAGING METHODS

Visualization of the cross-sectional anatomy of the coronary arteries using intravascular imaging methods has high sensitivity in identifying and characterizing atherosclerotic plaques by extracting tissue-specific parameters from the backscattered ultrasound signal. (14,15) In this context, when considering IVUS as a strategy to optimize revascularization by PCI, multiple clinical studies have shown that it reduces adverse clinical events at follow-up compared to standard angiographic guidance. (2-4)

Limitations of IVUS include its limited axial resolution, which makes it difficult to accurately identify thin-cap fibroatheroma (TCFA), and its limited lat-

Table 1. Machine Learning categories.

Category	Description	Subtype	Examples
Supervised learning	Labelled data and results	Classification: Uses an algorithm to assign data into specific categories, reaching conclusions on how to appropriately label those categories within the dataset	Logistic regression, Bayesian networks, Random Forest, Ridge regression, Elastic Net regression, LASSO (Least Absolute Shrinkage and Selection Operator) regression and artificial neural networks.
		Regression: Analyzes the relationship between dependent and independent variables. It is commonly used to make projections	
Unsupervised learning	Detects crucial relationships and similarities in unlabelled datasets	Clustering: Groups unlabeled data based on their similarities or differences	Hierarchical clustering, K-means clustering and Principal component analysis.
		Dimensionality reduction: Reduces the number of data inputs to a manageable size while also preserving the integrity of the dataset; used when the number of features, or dimensions, in a given dataset is too high	
Semi-supervised learning	A combination of supervised learning and unsupervised learning		It includes both labeled and unlabeled results and classes, and is used in image and speech recognition systems.
Reinforcement learning	Based on behavioral psychology, uses a reward function		Utilizes specific reward criteria and is used in medical imaging, analysis and disease detection.

eral resolution which may hinder the proper identification of coronary vascular dissections and atheroma plaques, as well as the correct positioning of stent struts. Considering these limitations, ML-based algorithms offer opportunities to optimize IVUS performance.

OCT has an inherent advantage in the morphological analysis of atherosclerotic plaques due to its high spatial resolution. (16) Compared to IVUS, OCT offers superior resolution, enabling clear visualization of thin fiber layers. However, its ability to penetrate tissues is limited, which lowers its capacity in detecting plaque size, large lipid cores, and external elastic layers. (17) It is important to note that the human eye has limitations, which can lead to the omission of a significant amount of data in the images. Therefore, there is an urgent need to introduce new optimization technologies in intravascular imaging methods to improve diagnostic efficiency and accuracy. AI constitutes a promising option within this framework.

In this scenario, there are DL methods based on adversarial attacks on CNN learning that could be used to transfer knowledge between IVUS and OCT. For example, images acquired with OCT and IVUS could be used to train AI models to increase the resolution of IVUS images. Similarly, IVUS images could be used to train AI models to complement the information of deep atherosclerotic plaque in OCT images. (Figure 1)

INCORPORATION OF AI IN PRE-PROCEDURAL ASSESSMENT

In the assessment before PCI, it is crucial to perform a thorough characterization of the vascular anatomy and atherosclerotic plaque using intravascular imaging methods to adequately select the endovascular technique to be used and the dimensions of the stent to be implanted. In this context, it is essential to identify the following characteristics before PCI, including the morphology and length of the atherosclerotic plaque, the diameter of the coronary vessels, and the predicted outcome of the intervention (Figure 2).

Several studies have explored the feasibility of implementing AI systems to improve accuracy, reproducibility, and speed in the analysis of intravascular imaging methods. In this setting, a multicenter observational study evaluated the accuracy and consistency of an AI system-based approach for automatic plaque characterization using OCT. (18) A post hoc analysis of OCT pullbacks from cohorts of patients with CAD participating in five different clinical trials was performed, dividing these data into two groups: training data set and testing data set. Thus, quantification of plaque burden using a CNN-based DL system for OCT analysis correlated very well with conventional manual pullback measurements (coefficient of determination $R^2 = 0.98$, $p < 0.001$). (18) Furthermore, through an external validation process that included OCT pullbacks different from those previously analyzed, the CNN-based DL system demonstrated an overall diagnostic accuracy of 86.6% (95% CI: 83.7-

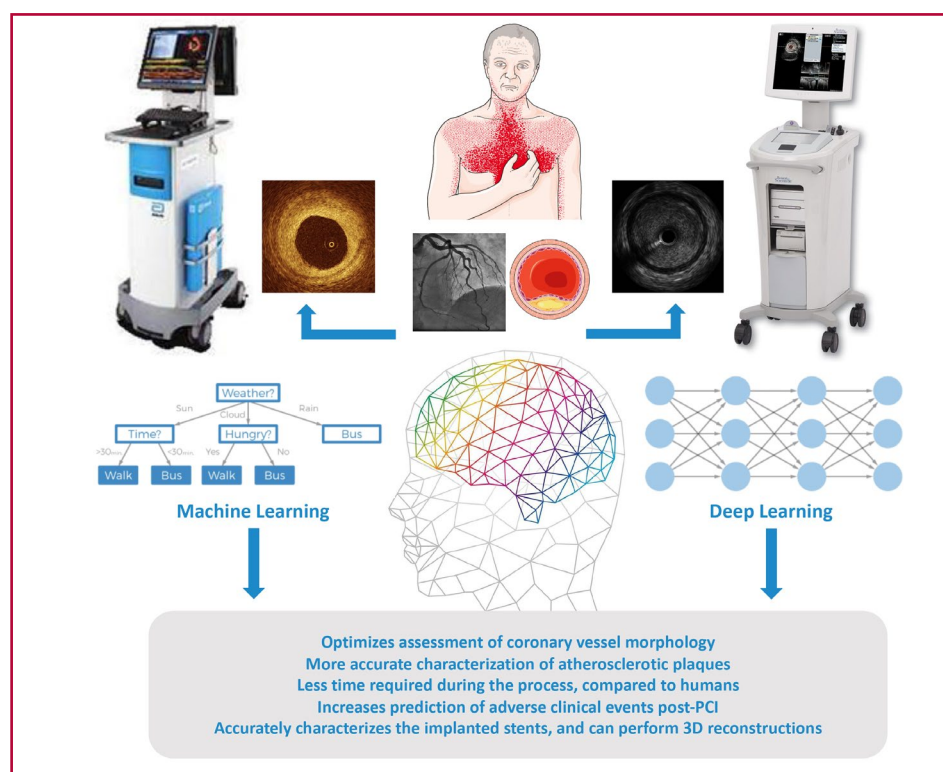


Fig. 1. Benefits provided by artificial intelligence in intra-vascular imaging methods.

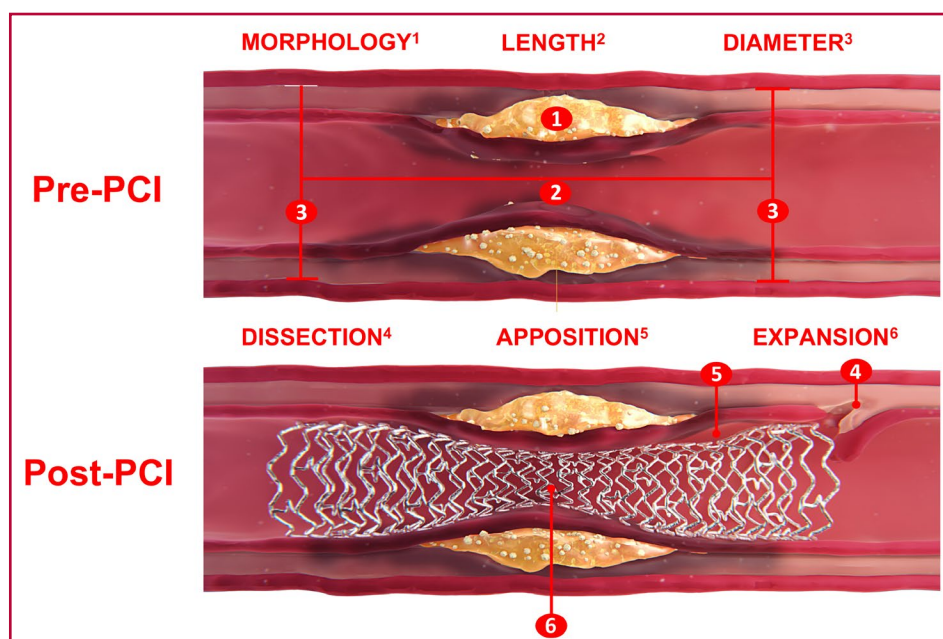


Fig. 2. Artificial intelligence parameters for optimizing percutaneous coronary intervention.

89.1). The software performed the best in fibrous plaques (97.6%; 95% CI: 93.4-99.3%), followed by lipidic plaques (90.5%; 95% CI: 85.2-94.1%) and calcifications (88.5%; 95% CI: 82.4-92.7%). (18) Of note, one of the challenges associated with this type of study is the lack of histological validation, since the initial classification is often based on expert observations.

The incorporation of AI models in the characterization of the coronary arteries by means of OCT has improved the interpretation of atherosclerotic plaques and increased the predictive ability of adverse clinical events during follow-up. In this context, a retrospective observational study analyzed OCT pullbacks in the nonculprit vessel of patients with acute coronary

syndrome. (19) In this analysis, AI was used to determine the optical flow ratio (OFR) as a surrogate parameter of coronary physiology derived from OCT, as well as to identify the lipid-to-cap ratio (LCR), a novel morphologic OCT index that integrates the lipid burden of the atherosclerotic plaque and the cap thickness over the diseased segment. (19) In this regard, determination of OFR and LCR using an AI system demonstrated superior discriminatory ability to predict nonculprit vessel-related major adverse cardiovascular events (NCV-MACE) compared with predictions based on minimum luminal area (MLA) determination and identification of TCFA. The combination of $LCR > 0.33$ and $OFR \leq 0.84$ resulted independent risk factors for NCV-MACE during follow-up. (19) Table 2 presents studies in which AI was used as a strategy to optimize OCT.

IVUS is one of the main intravascular imaging methods for assessing coronary artery calcium, a predictor of adverse cardiovascular events and long-term mortality. (46) One of its limitations is the lack of an automated quantification system for coronary artery calcium. However, this limitation could be overcome by implementing AI systems that provide objective and reproducible automated quantification that correlates with validated coronary artery calcium scores. (47) In this context, a single-center retrospective cohort study evaluated the ability of an AI algorithm trained with IVUS imaging data to quantify coronary artery calcium and its association with adverse clinical events. (48) An IVUS calcium score (ICS) based on an AI model was shown to have a high predictive value for the development of adverse clinical events during follow-up. There was a 51% increased risk of adverse events in patients with an $ICS \geq 85$. This ICS represents the first validated coronary calcium score associated with adverse clinical events since the introduction of computed tomography-derived calcium scoring. (48,49) AI systems have the remarkable ability to distinguish between various coronary artery calcium patterns, such as calcium in the artery wall and calcified nodule. (Table 3)

Prediction of stent under-expansion using AI algorithms

Despite substantial improvements in interventional procedures, stent design, drugs and polymers, and the adoption of therapeutic strategies, acute stent thrombosis and in-stent restenosis remain critical issues. It can be difficult to fully expand a coronary artery stent in a heavily calcified coronary artery lesion. Careful evaluation of these risks of under-expansions before the intervention will aid treatment planning. AI-based systems play a crucial role in obtaining an automated and reproducible prediction since morphological characterization of atherosclerotic plaque and prediction of the risk of stent under-expansion are often challenging procedures.

IVUS is one of the most commonly intravascular procedures used to optimize stent implantation and

has been associated with a decrease in adverse clinical events during follow-up. (2-4) However, IVUS has certain limitations, as determining the minimum stent area (MSA) in a single cross-section does not fully reflect the stent status along the entire vessel length, and there are no guidelines to predict the postprocedural MSA and the degree of stent expansion. In this context, CNN-based AI algorithms can automatically and adaptively calculate the probability of under-expansion after implantation. One study has developed an IVUS-based AI algorithm to predict the post-stenting stent area and the probability of under-expansion. (58) A dataset of pre-procedural and post-stenting IVUS images was obtained and was subsequently divided into a training set and a validation set for the algorithm. A DL CNN-based system was used to create a regression model to predict post-stenting stent area. XGBoost models for binary classification were developed to predict post-stenting stent under-expansion (defined as an $MSA < 5.5 \text{ mm}^2$). MSA predicted by the pre-procedural IVUS-based regression model significantly correlated with those measured on post-stenting IVUS ($r = 0.802$; $p < 0.001$), and an accuracy of 94% was obtained to predict stent under-expansion ($AUC = 0.94$). (58) (Table 3)

Moderate to severe coronary artery calcification is a strong predictor of MACE after PCI. (64) This may be due to stent under-expansion caused by severely calcified plaque and inadequate lesion preparation prior to implantation. In this context, OCT-guided stent implantation provides a thorough assessment of coronary calcification and stent deployment characteristics, including aspects such as expansion, malapposition and stent edge dissection. (65) In addition, DL-based systems have been developed to optimize procedure duration and predict stent under-expansion using OCT. A retrospective single-center study analyzed OCT pullbacks with the goal of developing a DL algorithm to predict stent under-expansion before the procedure. (66) The DL algorithm exhibited remarkable discrimination ability to detect stent under-expansion, with an AUC of 0.853. This finding strongly supports the idea that AI systems may represent an extremely valuable addition to intravascular imaging methods, optimizing PCI. (66) In this context, we currently count with OCT imaging with AI-driven information (Ultreon™ 1.0 Software, Abbott). This software automatically detects the severity of coronary artery calcium, determines external elastic lamina and measures the vessel diameter, which not only increases the accuracy of real-time stenting, but also simplifies the interpretation of the acquired images, reducing inter-observer variability. (67)

Use of AI for segmentation and lumen area dimensions

In the assessment before PCI, it is crucial to accurately measure the vascular dimensions to select

Table 2. Studies using artificial intelligence as a strategy to optimize optical coherence tomography.

Author	Year	Objective	Algorithm used	Results
Athanasiou LS, et al. (20)	2011	To extract a set of features from grayscale OCT images and employ them to classify the atherosclerotic plaque using an ML algorithm.	Random Forest	The ML algorithm associated with OCT accurately characterized the atherosclerotic plaques.
Wang Z, et al. (21)	2012	To propose and validate an OCT-based ML method to analyze fibrous cap volume to identify vulnerable atherosclerotic plaques.	Dynamic Programming	The proposed ML method is fast, accurate and robust, and can be used in future studies to further characterize atherosclerotic plaques.
Ughi GJ, et al. (22)	2013	To develop and validate an ML algorithm to optimize the characterization of atherosclerotic plaques by OCT.	Random Forest	The ML algorithm provided accurate characterization of atherosclerotic plaques.
Xu M, et al. (23)	2014	To propose a ML algorithm for automatic detection of atherosclerotic plaques using OCT.	Support Vector Machine	The proposed ML system is accurate and stable for the detection of atherosclerosis by OCT.
Wang Z, et al. (24)	2014	To examine the quantitative tissue properties that can differentiate plaque erosion from intact fibrous plaques and to develop a computer-aided classification model for in vivo diagnosis of plaque erosion.	Logistic regression	The quantitative logistic regression model can be used to improve the diagnostic accuracy for plaque erosion in vivo using OCT.
Shalev R, et al. (25)	2016	To develop an ML method automatic classification of calcium in OCT images.	Use of filters to select regions for extraction of sub-images (SI's)	The ML algorithm presents high accuracy for characterization of coronary artery calcium in OCT, images which could be used in 'real time'.
Rico-Jimenez JJ, et al. (26)	2016	To present a novel computational method for automated IV-OCT plaque characterization	A-line Modeling	The ML algorithm presents high accuracy for characterization of atherosclerotic plaques.
Xu M, et al. (27)	2017	To propose a DL model for the identification and characterization of fibroatheromas in OCT images.	AlexNet,GoogLeNet, VGG-16, VGG-19	The DL system provides a highly accurate characterization of fibroatheromas.
Shi P, et al. (28)	2018	To develop a DL-based model to identify vulnerable atherosclerotic plaques in OCT images.	Fully CNN, Deep CNN	The DL method presented high accuracy for characterizing vulnerable atherosclerotic plaques.
Guo X, et al. (29)	2018	To create a DL algorithm to characterize atherosclerotic plaque components and quantify fibrous cap thickness.	Least Squares Support Vector Machine (LS-SVM)	The segmentation method base on LS-SVM provided accurate characterization of fibrous cap thickness.
Kolluru C, et al. (30)	2018	To develop neural network-based methods for classifying plaque types in OCT images.	CNN, ANN	The DL model presented high accuracy for classifying atherosclerotic plaque subtypes.
He S, et al. (31)	2018	To analyze the performance of a DL model for characterization of atherosclerotic plaques in OCT images.	CNN	The DL algorithm demonstrated high accuracy to characterize atherosclerotic plaques.
Lee J, et al.(32)	2019	To develop a DL system for automatic segmentation of atherosclerotic plaques based on OCT images.	SegNet	The DL algorithm showed high accuracy for segmentation of atherosclerotic plaques.
Prabhu D, et al. (33)	2019	To develop ML methods to identify fibrolipidic and fibrocalcific A-lines in OCT images.	Support Vector Machine	The proposed classification algorithm is suitable for automated OCT plaque classification and segmentation.
Liu R, et al. (34)	2019	To improve the detection quality of vulnerable plaque using a DL algorithm associated with OCT.	Deep CNN	The proposed DL algorithm has high accuracy to detect vulnerable plaques in OCT images.
Johnson KW, et al. (35)	2019	To use a ML algorithm and transcriptomic data to estimate the predict if fibrous cap thickness will increase in response to statin therapy	Elastic net K top scoring pair	A ML algorithm using transcriptomic models could predict increase in fibrous cap thickness as a result of statin treatment.
Baruah V, et al. (36)	2020	To determine the feasibility of a histology-validated virtual OCT (VH-OCT) algorithm using AI.	CNN	"This note is the first report to classify automatically tissue components with AI based on histological validation and extension into in vivo patient images."

Table 2 (Cont.)

Author E3:I3	Year	Objective	Algorithm used	Results
Lee J, et al. (37)	2020	To develop an ML algorithm for characterization of atherosclerotic plaques using a hybrid learning approach.	Deep CNN	The proposed algorithm could accurately characterize the atherosclerotic plaques.
Lee J, et al. (38)	2020	To develop an automated, two-step DL approach for characterizing coronary calcified plaque	CNN, SegNet	Compared to the standard approach, the two-step DL system is highly accurate for characterization of atherosclerotic plaques in OCT images.
Cha JJ, et al. (39)	2020	To evaluate the usefulness of ML FFR based on OCT and compare it with wire-based FFR.	Random Forest	OCT-based ML-FFR has good correlation with wire-guided FFR.
Chu M, et al. (18)	2021	To develop and validate a DL algorithm for characterization of atherosclerotic plaques in OCT images.	CNN	The DL algorithm for automatic characterization of atherosclerotic plaques in OCT images offers provides excellent diagnostic accuracy in both internal and external validation.
Balaji A, et al. (40)	2021	To develop a DL algorithm for automatic coronary artery segmentation in OCT images.	DeepCap	The AI system linked to OCT demonstrated high accuracy for automatic segmentation of coronary arteries.
Yin Y, et al. (41)	2021	To develop DL algorithm for characterization of atherosclerotic plaques in OCT images.	TwopathCNN	A proposed DL algorithm presented higher accuracy for the characterization of atherosclerotic plaques, compared with conventional DL algorithms.
Li C, et al. (42)	2021	To develop a DL algorithm for automatic quantification of coronary artery calcium in OCT images.	DenseNet, CNN	The proposed DL model presents high accuracy for discriminating coronary artery calcium in OCT images.
Yang G, et al. (43)	2021	To develop a DL model to automatically analyze stents with both thin (≤ 0.3 mm) and very thick (> 0.3 mm) tissue coverage, and an algorithm to accurately analyze stent area for vessels with multiple stents.	CNN	The proposed model can accurately detect stent struts with very thick tissue coverage and analyze stent areas in vessels implanted with multiple stents.
Hong H, et al. (19)	2022	To analyze the role of AI for predicting major adverse cardiovascular events by determining the plaque morphology and coronary artery physiology in OCT images.	Deep CNN	The study identified a novel DL algorithm to characterize the morphology and physiology of atherosclerotic plaques, which can predict the risk of adverse cardiovascular events.
Sun H, et al. (44)	2022	To develop a DL-based AI method for fully automated detection of atherosclerotic plaque erosion.	Mask RCNN with convexity and curvature (RCNN-CK), SVM	The developed DL algorithm presented good ability to discriminate atherosclerotic plaque erosion in OCT images.
Wu P, et al. (45)	2023	To analyze whether OCT and IVUS images can assist each other in stent 3D reconstruction	F1-score	Using AI systems, intravascular images of OCT and IVUS can provide reciprocal assistance to each other in stent 3D reconstruction.

AI: artificial intelligence; ANN: artificial neural network; CNN: convolutional neural network; DL: deep learning; FFR: fractional flow reserve; IVUS: intravascular ultrasound; ML: machine learning; OCT: optical coherence tomography

the adequate stent. Determining the length of the atherosclerotic plaque is crucial to avoid geographic miss during implantation. Additionally, knowing the lumen and vessel diameter is crucial in selecting the appropriate stent for implantation. One of the most arduous tasks when analyzing IVUS datasets is the segmentation of the lumen boundary and external elastic lamina, for which an expert has to manually outline them. This process is performed in the transversal axis and longitudinal view and usually results in large intra and interobserver variability. Additionally, artifacts are often present in IVUS images throughout the longitudinal view, and can lead to errors in lumen segmentation. To

correct these errors, electrocardiogram-gating is necessary. Since this process is crucial for accurate data interpretation, AI algorithms are presented as an accurate and consistent alternative for selecting the correct frames. One study proposed an automated workflow to segment lumen boundaries in IVUS datasets using a DL approach and multi-frame (MF) CNN. The dataset consisted of IVUS pullbacks. After an automated gating, AI identified end-diastolic frames to avoid longitudinal artifacts and performed automated lumen segmentation using the MF-CNN algorithm. The correlation between the actual lumen and that obtained by the DL algorithm was high ($r = 0.99$). (55) (Table 3).

Table 3. Studies using artificial intelligence as a strategy to optimize intravascular ultrasound.

Author	Year	Objective	Algorithm used	Results
Sheet D, et al. (50)	2014	To develop an innovative ML-based technique (SDH) to automatically characterize morphology in IVUS images.	Random Forest	SDH is highly consistent with traditional histology in characterizing calcification, fibrotic tissues and lipids.
Kim GY, et al. (51)	2018	To develop a classification model based on virtual histology to characterize atherosclerotic plaque components in fibrous tissue, fibro-fatty tissue, necrotic core, and dense calcium.	Multi-level classification model consisting of three different nets	The proposed method showed high accuracy for classifying all types of plaques.
Bae Y, et al. (52)	2019	To develop ML models to predict optical coherence tomography (OCT) thin-cap fibroatheroma (TCFA).	ANN, Support Vector Machine, Naïve Bayes	The presence of OCT-TCFA was predicted with high accuracy by ML algorithms.
Jun TJ, et al. (53)	2019	To identify the most accurate method to classify TCFA using various ML classifiers.	Feed-forward neural network (FNN), K-nearest neighbor (KNN), Random Forest, CNN	The CNN classifier performed best, while FNN, KNN and Random Forest classifiers were found to be similar to the physician's TCFA diagnostic criteria.
Wang L, et al. (54)	2020	To identify the most accurate ML classifier to predict atherosclerotic plaque vulnerability change as determined by IVMP.	Generalized linear mixed regression model (GLMM), Support Vector Machine, Random Forest	MPVI was the best single risk factor using both GLMM and Random Forest while plaque area was the best using SVM.
Ziemer PG, et al.(55)	2020	To evaluate the utility of a novel, automated ML system to segment the lumen boundary in IVUS datasets.	Multi-frame convolutional neural network	The proposed ML algorithm is suitable to effectively segment the lumen boundary in IVUS scans, reducing time required and need for manual delineation.
Lee JG, et al. (56)	2020	To determine the usefulness of AI algorithms for identifying functionally significant coronary stenoses (FFR ≤ 0.80).	L2 penalized logistic regression, ANN, Random Forest, AdaBoost, CatBoost, Support Vector Machine	IVUS-based ML algorithms showed good diagnostic performance for identifying ischemia-producing lesions.
Cho H, et al. (57)	2021	To develop IVUS-based ML algorithms for classifying attenuation and calcified plaques.	EfficientNet	The ML algorithm for plaque characterization accurately identifies high-risk coronary artery lesions.
Neleman T, et al. (48)	2021	To develop and validate an ML algorithm to automatically quantify coronary calcifications in IVUS images.	Support Vector Machine	The IVUS calcium score calculated by an ML algorithm was strongly associated with the long-term risk of major adverse cardiac events.
Min HS, et al. (58)	2021	To develop pre-procedural IVUS-based DL models for predicting the occurrence of stent underexpansion.	CNN, EXtreme Gradient Boosting* (XGBoost)	The algorithms accurately predicted (94%) incomplete stent expansion.
Bass RD, et al. (59)	2022	To compare the performance of human readers to the ML algorithm and against the readings from a Core Laboratory for coronary vessel segmentation.	Multi-frame convolutional neural network	Similar assessment of segmentation performed by humans, ML algorithm and core lab, with machines being more time efficient.
Bajaj R, et al. (60)	2022	To train and assess the efficacy of a ML classifier for plaque component classification that relies on IVUS echogenicity and NIRS-signal.	Algorithm J48	The combination of echogenicity with NIRS-signal appears capable of overcoming limitations of echogenicity.
Wissel T, et al.(61)	2022	To propose a fully data-driven strategy to longitudinally detect and subsequently segment stent struts in IVUS frames.	Deep cascade learning	Using the DL algorithm, a reduced risk of ambiguities and false-positive predictions was observed for segmenting stents.
Blanco PJ, et al. (62)	2022	To determine the accuracy of a DL algorithm for automatic segmentation in IVUS images.	Multi-frame convolutional neural network, Gaussian process	The proposed DL approach provides accurate segmentations, which facilitates its implementation in clinical routine by mitigating the costs involved in the manual management of IVUS datasets.
Arora P, et al. (63)	2023	To use a DL algorithm to identify the extent of vascular calcification in IVUS images.	AlexNet, GoogLeNet, SqueezeNet	DL algorithm identify the extension of vascular calcification with high accuracy.

DL: deep learning; FFR: fractional flow reserve; IVUS: intravascular ultrasound; ML: machine learning; MPVI: morphological plaque vulnerability index; NIRS: near infrared spectroscopy; OCT: optical coherence tomography; SDH: stochastic driven histology; TCFA: thin-cap fibroatheroma; VH: virtual histology

This DL algorithm has been extended for lumen and external elastic lamina segmentation with excellent results. (62) In turn, these results were replicated in other studies, such as a post-hoc, cross-sectional analysis of the IBIS-4 study, (68) which evaluated the performance of a DL algorithm based on a MF-CNN for automated lumen and vessel contour segmentation. (59) This study showed that, compared to the determination of vessel structures by human readers, the DL algorithm showed a strong correlation with those of the Core Lab. This offers the advantage of eliminating human inter and intraobserver variability, improving accuracy in lumen contour segmentation, and significantly reducing the time required to complete the analysis (average human time spent per pullback = 47 minutes vs. ML = 1 minute). (59)

Utility of AI to optimize stent implantation

After PCI, it is essential to optimize stent placement to reduce the likelihood of adverse clinical events during follow-up. Intravascular imaging guidance using IVUS or OCT provides clear advantages over conventional angiographic guidance in terms of optimization. However, determining the parameters to be corrected in complex PCI procedures can be a challenging task. In this context, three-dimensional (3D) reconstruction of implanted stents using intravascular imaging methods is useful for addressing implantation issues. Of note, as manual reconstruction is a complicated process, AI algorithms can be a valuable tool. The introduction of DL algorithms has revolutionized automatic stent 3D reconstruction visualized by intravascular imaging methods, enabling reliable and real-time analysis during the intervention. (61) OCT and IVUS have different image styles, share the same anatomic structures, and can be aligned by cross-modal translation. In this context, a study explored the feasibility of using OCT and IVUS to assist each other in DL-based automatic 3D reconstruction of the stents implanted during PCI. The study found that the DL algorithm performs exceptionally well in generating 3D reconstructions of implanted stents, regardless of whether conventional IVUS or high-definition IVUS were used for optimization. This information can be valuable when analyzing potential improvements and optimizations in the implantation procedure. (45) (Table 2).

CHALLENGES AND FUTURE PERSPECTIVES

Considering that AI is a data-driven science, the lack of standardization in collecting and storing medical data may negatively influence the interoperability of AI systems in the medical field. Data heterogeneity hinders the effective integration of AI algorithms in different clinical settings and the communication of information between healthcare systems.

Furthermore, the performance of AI algorithms in clinical practice depends heavily on the representativeness of the training data compared to the

data encountered in daily practice. In some cases, the data collected for developing AI algorithms may not be representative of the population it serves, leading to poor performance. In this sense, external validation and field testing are essential to determine the level of confidence of AI algorithms.

As artificial AI is already being integrated into clinical workflows, it is essential to demonstrate its value in patient care, support investment in these new algorithms, and encourage the adoption of new reimbursement or payment models. To achieve this on a large scale, it is essential to conduct cost-effectiveness studies of these emerging technologies.

CONCLUSIONS

When combined with intravascular imaging methods such as IVUS or OCT, AI systems significantly optimize stent implantation through a fully automated framework that identifies vascular structures and guides correct stent positioning. This facilitates the accurate selection of the stent to be implanted and the need for stent correction techniques. Additionally, it reduces both the total procedure time and interobserver variability. This could promote greater adoption of intravascular imaging techniques and ultimately reduce the incidence of adverse clinical events during follow-up.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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Artificial Intelligence in Cardiovascular Imaging and Cardiovascular Prevention

Inteligencia artificial. Aplicación en las imágenes cardiovasculares y la prevención cardiovascular

MARIANO L. FALCONI¹, MTSAC, ; MARTINA AINESEDER², ; DIEGO PÉREZ DE ARENAZA¹, MTSAC, ; MARÍA AGUSTINA RICCI LARA^{3,4,5},
SONIA BENÍTEZ^{3,5}, WALTER MASSON¹, MTSAC, 

ABSTRACT

Artificial intelligence (AI) is based on computer programs that imitate human thinking and automate certain processes. Artificial intelligence has been studied in the medical field for over 50 years, but in recent years, its growth has been exponential. The field of cardiovascular imaging is particularly attractive since AI can guide non-experts in image acquisition, automate processes and measurements, guide diagnoses, detect findings not visible to the human eye, make opportunistic diagnoses of unexpected conditions in the index test, or identify patterns of association within a large amount of data as a source of hypothesis generation. In the field of cardiovascular prevention, AI has been used for diagnostic, prognostic, and therapeutic purposes in managing cardiovascular risk factors such as dyslipidemia and hypertension. While there are limitations to the use of AI, such as cost, accessibility, compatibility of programs, external validity of results in certain populations, and ethical-legal aspects such as data privacy, this technology is rapidly growing and is likely to revolutionize current medical practice.

Key words: Images - Cardiovascular prevention - Artificial intelligence - Machine learning.

RESUMEN

La inteligencia artificial (IA) está basada en programas computacionales que pueden imitar el pensamiento humano y automatizar algunos procesos. En el ámbito médico se está estudiando hace más de 50 años, pero en los últimos años el crecimiento ha sido exponencial. El campo de las imágenes cardiovasculares es particularmente atractivo para aplicarla, dado que, guiadas por IA, personas no expertas pueden adquirir imágenes completas, automatizar procesos y mediciones, orientar diagnósticos, detectar hallazgos no visibles al ojo humano, realizar diagnósticos oportunistas de afecciones no buscadas en el estudio índice pero evaluables a través de las imágenes disponibles, o identificar patrones de asociación dentro de una gran cantidad de datos como fuente de generación de hipótesis. En el campo de la prevención cardiovascular, la IA se ha aplicado en diferentes escenarios con fines diagnósticos, pronósticos y terapéuticos en el manejo de algunos factores de riesgo cardiovascular, como las dislipidemias o la hipertensión arterial. Si bien existen limitaciones con el uso de la IA tales como el costo, la accesibilidad y la compatibilidad de los programas, la validez externa de los resultados en determinadas poblaciones, o algunos aspectos éticos-legales (privacidad de los datos), esta tecnología está en crecimiento vertiginoso y posiblemente revolucione la práctica médica actual.

Palabras claves: Imágenes - Prevención cardiovascular - Inteligencia artificial - Aprendizaje automático

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Address for reprints: Mariano L. Falconi E-mail: mariano.falconi@hospitalitaliano.org.ar



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¹ Department of Cardiology, Hospital Italiano de Buenos Aires

² Department of Diagnostic Imaging, Hospital Italiano de Buenos Aires

³ Department of Health Informatics, Hospital Italiano de Buenos Aires

⁴ Universidad Tecnológica Nacional, Ciudad Autónoma de Buenos Aires, Argentina

⁵ Department of Medical Informatics, Instituto Universitario del Hospital Italiano de Buenos Aires

INTRODUCTION

The term artificial intelligence (AI) was coined in 1956 by John McCarthy, who ventured that "every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it". (1) In this line, we can understand AI as a branch of computer science that aims to create software programs capable of automating activities related to human thinking, such as decision making, problem solving, learning, and development of concepts and abstractions. (1-3) Machine learning (ML) is a subfield of AI, that develops algorithms capable of recognizing patterns in data, to solve certain tasks without being explicitly programmed to do so. Such algorithms do not require the constant intervention of a user to solve tasks in complex environments (autonomy) and can improve their performance based through the experience gained with new data (adaptability). (4,5) Deep learning (DL) is a subfield of ML that involves the repetition of a processing block, arranged consecutively in layers to extract complex abstractions based on relatively simpler representations through a hierarchical learning process. (6-8) In general, DL models use Artificial Neural Networks (ANN) inspired by the way biological neural system works, such as the brain processes information. ANN consist of interconnected functional units called neurons that perform calculations and mathematical operations to propagate information. (7) A Deep Neural Network (DNN) is an ANN with multiple layers. A typical DNN consists of an input layer, one or more hidden layers, and an output layer; an output layer serves as input for the next one. (8-10) The performance of these methods in solving complex tasks in various fields of knowledge has led to their introduction in the medical field. Thus, the first clinical decision support systems used in Medicine, which relied on the depuration of medical knowledge databases and the formulation of robust decision rules, began to be replaced by data-driven systems, i.e., ML and DL models. (10) Implementing this type of solution has various impacts: 1) it provides professionals with a second opinion based on available data, which can improve diagnostic performance; b) it optimizes processes and workflows within the healthcare system; and c) patients benefit from an improvement in the quality of care. (9) AI has been utilized in Medicine for diagnostic, prognostic, and predictive purposes. It can automatically process various data modalities, including clinical, genetic, biomedical signals, and medical images, generated across different medical specialties. (10)

AI in cardiovascular imaging

The use of AI in Medicine has been around for over half a century. In fact, as early as 1968, Earl Hunt wrote a review article on the subject applied to the field of Psychology. (11) The number of articles published on the subject has increased slowly since then,

until about 5 years ago when the increase became exponential. In 2022 alone, nearly 39 000 articles were published on the subject, with approximately 1 in 3 articles devoted to imaging in Medicine.

The field of medical imaging is particularly attractive in this area, due to its exponential growth, complexity, and the limited availability of specialists to create and interpret such images in certain locations or at certain hours. The use of AI makes it possible to reduce acquisition and reading times, acquire and interpret images by untrained personnel, increase accuracy, and reduce the risk of diagnostic errors. On the other hand, AI has unique abilities such as detecting image features that may be difficult for humans to identify and finding unexpected patterns in an endless number of variables. These capabilities make AI a valuable tool for advancing new diagnoses and hypotheses. Combined with the ability to jointly evaluate a large amount of data beyond imaging, such as epidemiological, clinical, laboratory, genetic, and biometric data, the advances in science appear to be unpredictable. (12-14)

Optimizing timing. Image acquisition by "inexperienced" personnel. Reducing variability

Image segmentation is a well-developed tool nowadays. AI can recognize and separate anatomical structures more quickly than a trained human. Once the segmentation is complete, the software can automatically measure diameters, volumes, displacements, flows, and other parameters of the test with an accuracy similar to or better than that of an expert. (15) (Figures 1 and 2).

Variability is one of many limitations of diagnostic methods. Results-based decision-making (diameters, ejection fraction, areas) can be a challenge for those interpreting imaging tests. AI is showing promising results in this regard due to its speed and reproducibility of measurements.

In echocardiography there are programs that can evaluate the quality of the acquired images, guide inexperienced operators to enhance their quality, automatically acquire them when the section detected is suitable for analysis, and perform automatic measurements. A study found that 8 nurses, without echocardiography training, could obtain AI-guided images from 30 patients each, with diagnostic quality comparable to that obtained by 5 registered cardiac sonographers. (16)

The software can identify views and perform chambers, mass, volume, and strain measurements faster and more reproducibly than an experienced operator. Tsang et al. demonstrated the feasibility of measuring ventricular and atrial volumes, as well as ejection fraction, using 3D echocardiography with an adaptive algorithm. The automated measurements were comparable not only to manual measurements but also to those obtained by magnetic resonance imaging (MRI), with high reproducibility (zero variability when re-

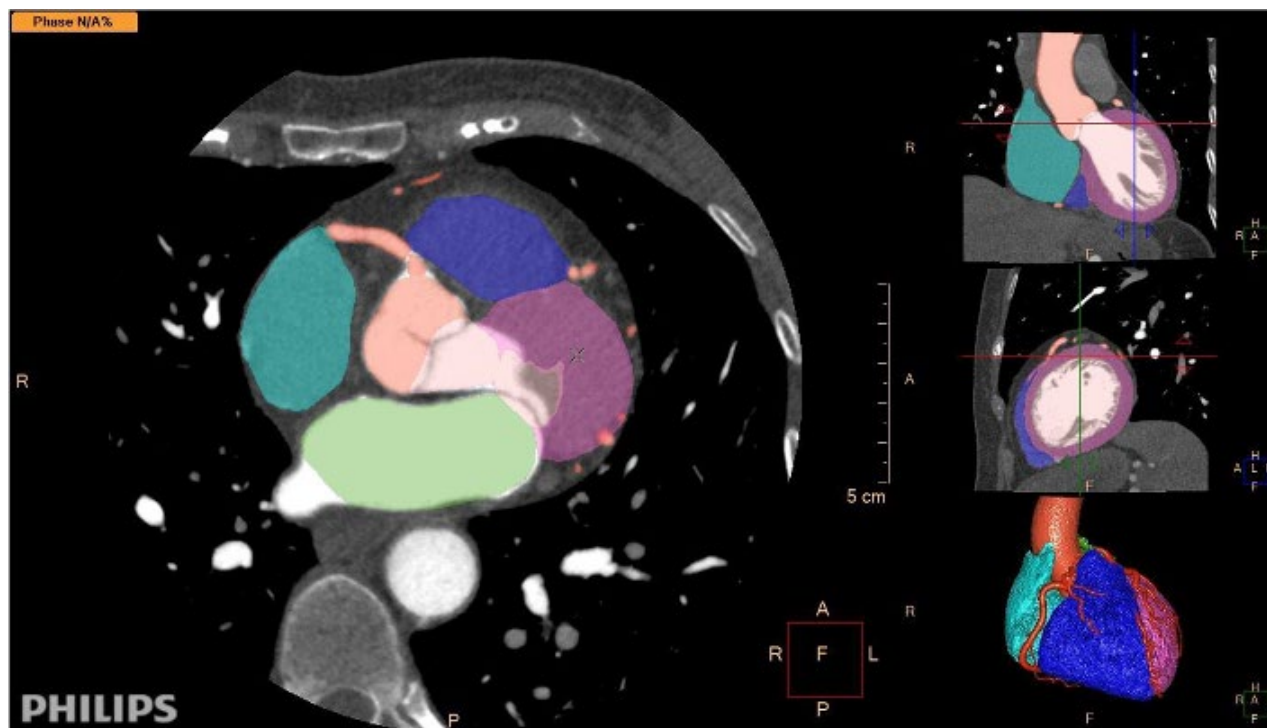


Fig. 1. Automated segmentation of a cardiovascular computed tomography scan with contrast agent. The software identifies the cardiac chambers, myocardium, coronary arteries, and ascending aorta. It provides segmentation of cardiac structures with different colors, which can be edited and corrected by professionals. Software: IntelliSpace Portal. Image and Information Management Software. Version 12.1. Philips Medical Systems Nederland B.V. Veenpluis 6, 5684 PC Best, The Netherlands



Fig. 2. A and B. Automatic cardiovascular reconstruction derived from Figure 1 (A) and with "removal" of all structures to visualize exclusively the aorta and coronary tree (B). Software: IntelliSpace Portal. Image and Information Management Software. Version 12.1. Philips Medical Systems Nederland B.V. Veenpluis 6, 5684 PC Best, The Netherlands.

peating the analysis on the same dataset). In addition, the average time per patient decreased from 144 ± 32 seconds (manual analysis) to 26 ± 2 seconds (automated analysis). (17)

A prospective study utilized an AI training program to analyze diastolic function in accordance with ASE/EACVI 2016 guidelines. The program was shown to accurately classify diastolic dysfunction patterns with 99% agreement to the guidelines. (18)

Estimating valvular heart disease severity can be difficult in some scenarios. Using AI, automated quantification of mitral regurgitation (MR) could be

performed with high diagnostic accuracy (99.52% for normal mitral valve, 99.38% for mild MR, 99.31% for moderate MR and 99.59% for severe MR). (19) In patients with aortic stenosis, an AI system utilizing echocardiographic measurements, except for left ventricular outflow tract diameter and velocity, demonstrated higher accuracy in diagnosing severe aortic stenosis than the continuity equation, even in populations with ventricular dysfunction or low flow-low gradient aortic stenosis. (20)

In cardiac MRI, planning and acquisition times, artifact correction, and automated measurements are

advancing quickly, reducing the time needed for testing and analysis. (21) Artificial intelligence analysis was quicker (20 seconds per patient) and more accurate than human (13 min). (22) The authors estimate a 46% reduction in required trial sample size with the segmentation model based on AI with left ventricular ejection fraction as the endpoint.

In computed tomography (CT), AI is being evaluated to reduce radiation dose by optimizing image acquisition, converting non-contrast scans to contrast scans and vice versa so as to detect coronary artery calcification. (13)

Improvement of diagnostic and prognostic processes: reduction of errors, opportunistic diagnoses

AI enables the identification of unexpected patterns or associations that link a condition or set of conditions to a specific finding or disease. Its use in echocardiography proved to be useful in differentiating between athlete's heart and hypertrophic cardiomyopathy, (23) between constrictive pericarditis and restrictive cardiomyopathy, (24), and in the correct identification of patients with hypertrophic cardiomyopathy, amyloidosis, and pulmonary hypertension. (25)

A multicenter study with cardiac MRI evaluated the precision of experts, trained junior physicians and ML to measure parameters of ventricular function, particularly ejection fraction, and the time required. Expert, trained junior, and ML precision were similar (coefficient of variation 6.1 [95% CI, 5.2%–7.1%], $p = 0.2581$; 8.3 [95% CI, 5.6%–10.4%], $p = 0.3653$; 8.8 [95% CI, 6.1%–11.1%], $p = 0.8620$, respectively). However, automated analysis was 186 times faster than humans (0.07 versus 13 minutes). (26)

In Nuclear Medicine imaging, the use of AI demonstrated a superior performance in diagnosing obstructive coronary artery disease compared to the commonly used total perfusion deficit (similar specificity with higher sensitivity) and required less time for the analysis (0.5 seconds per patient). (27) The use of a Support Vector Machine algorithm demonstrated better performance than the analysis of ischemic changes, total perfusion deficit or ejection fraction changes, with an area under the ROC curve (AUC) significantly better than that of two independent expert operators. (28) In another study, when clinical variables were combined with information from stress testing and perfusion imaging, AI was superior to the existing isolated images, expert medical assessment or automated quantification in predicting events in 2619 patients followed up for more than 3 years. (29)

Radiomics is another important aspect of clinically relevant information from medical imaging. Radiomics can identify tissue features that may indicate the type of tumor, characteristics of a lesion (acute or chronic), type of ventricular hypertrophy, or differences in myocardial tissue in response to risk factors by analyzing image characteristics not detectable by the human eye. (30–32)

Mannil et al. demonstrated the ability of AI in detecting myocardial infarction on noncontrast computed tomography images, with a sensitivity of 86% and specificity of 81%, which was not possible by visual assessment of two readers with experience in cardiovascular imaging. (33)

The utility of ML analysis in predicting cardiovascular events was demonstrated in the population of the CONFIRM study (10 030 patients) with 25 clinical parameters and 44 coronary computed tomography angiography parameters. ML analysis predicted 5-year mortality significantly better (AUC 0.79) than the Framingham risk score (AUC 0.61) or conventional coronary computed tomography angiography parameters (segment stenosis score, segment involvement score, or modified Duke index, AUC 0.64, 0.64, and 0.62, respectively). (34) Another analysis of 8844 patients from the same cohort revealed that a ML algorithm had greater prognostic accuracy than conventional segment analysis in predicting myocardial infarction or death at 3 years (AUC for ML 0.771, vs. AUC for conventional analysis between 0.685 and 0.701). (35)

Similarly, investigators in the PARADIGM registry demonstrated a higher predictive value of a ML framework to identify individuals at risk for rapid progression of coronary atherosclerotic plaque. (36)

In patients with newly diagnosed pulmonary hypertension, Dawes et al. used MRI to define a 3D model of right ventricular motion that more accurately predicted survival than conventional imaging and hemodynamic, functional, and clinical markers (AUC 0.73 vs. 0.60). (37)

There are many examples of opportunistic diagnoses in the literature with the use of AI. Opportunistic findings are those that are unexpected and discovered on medical imaging tests performed for other reasons. (38) Pyrros et al. detected 5% of patients with diabetes using chest radiographs with acceptable diagnostic accuracy (AUC 0.77). (39) The detection of calcium plaques in the coronary arteries on a conventional chest CT scan (score >100) has been shown to have prognostic value for predicting 10-year mortality (HR 1.51; 95% CI 1.28–1.79); death, myocardial infarction, or stroke (HR 1.57; 95% CI 1.33–1.84); and death, myocardial infarction, stroke, or revascularization (HR 1.69; 95% CI 1.45–1.98) compared with no calcium. (40) Parameters indicating osteopenia or osteoporosis can be detected in chest or abdominal CT scans, (41) or in coronary artery calcium CT scans, (42) without additional cost or radiation exposure to patients. Similarly, detection of atheromatous plaques, fatty liver disease, sarcopenia, and visceral adipose tissue can identify patients at risk of metabolic syndrome and/or long-term events such as death, cardiovascular events, and fractures. Early detection of these risks could be cost-effective. (43,44) DL-based models have been shown to improve the speed and accuracy of emphysema detection. (45)

Implementation of AI in the field of cardiovascular prevention

Multiple AI-based techniques have been implemented in different scenarios associated with cardiovascular prevention. One of them is the diagnosis of familial hypercholesterolemia (FH), the most common genetic disorder of lipid metabolism. Familial hypercholesterolemia results in exposure to very high levels of low-density lipoprotein cholesterol (LDL-C) throughout lifetime, significantly increasing the risk of cardiovascular events if left untreated. (46) The clinical diagnosis of FH (clinical scores) can be established by collecting clinical and laboratory (LDL-C) features. The diagnosis of FH can be confirmed genetically by identifying heterozygous or biallelic phenotypes, especially in genes LDLR, APOB or PCSK9. (47) However, AI techniques have the potential to improve the identification of patients with FH. In this context, several studies have demonstrated that AI-based models have an excellent predictive value to detect FH cases confirmed by genetic testing. (48-51) Furthermore, that predictive value performed better than traditional methods based on risk scores, such as the Dutch Lipid Clinic Network criteria.

Another scenario in which AI was evaluated is the calculation of LDL-C. Standard practice estimates LDL-C using the Friedewald formula. (52) However, this equation is inaccurate when triglycerides are elevated or LDL-C values are very low. (53) To improve accuracy, other formulas have been developed, such as the Martin-Hopkins formula or the Sampson equation. (54,55) Many studies have evaluated different AI-based techniques to estimate LDL-C. (56-61) In this case, the AI-based algorithms for estimating LDL-C performed similarly or better than the conventional Friedewald formula or the more contemporary Martin-Hopkins or Sampson equations.

The barriers associated with the use of statins is another field where AI has been evaluated. Statin intolerance represents a clinical challenge, and its prevalence is frequently overestimated. (62) Importantly, the nocebo effect could play a key role in this significant public health issue. (63) A recent study assessed AI-based techniques for analyzing large amounts of publicly available social media data to generate insights into people's perceptions about statins. (64) The analysis revealed predominantly neutral to negative sentiment in the discussions analyzed, with 30.8%, 66.6% and 2.6% reporting negative, neutral or positive sentiments, respectively. Sarraju et al. developed a DL-based model to identify statin nonuse and reasons for statin nonuse using unstructured electronic medical records from a large cohort of patients with atherosclerotic cardiovascular disease. (65). The model identified key patient-level reasons (side effects, patient preference) and clinician-level reasons (guideline-discordant practices) for statin nonuse. Another study used a DL-based algorithm in patients with diabetes. (66) Again, this algorithm categorized the reasons for statin nonuse based on a large dataset of

electronic medical records, including patient reasons (side effects and hesitancy to use statins), physician reasons (guideline-discordant practice), and system reasons (clinical inertia). Understanding the barriers that patients and physicians face in using statins can help reduce clinical inertia and improve treatment adherence.

AI has also been evaluated in hypertension. According to some reports, AI-based systems could help continuously monitor blood pressure using wearable technologies. (67) For example, blood pressure could be estimated from a photoplethysmography signal obtained from a smartphone or a smartwatch using DL. Furthermore, ML algorithms can help make early diagnosis of hypertension (68-70) and even of secondary hypertension. (71) In addition, ML algorithms accurately predict ambulatory blood pressure levels after treatment initiation. This could assist clinicians in personalizing antihypertensive treatment. (72,73)

Several cardiovascular risk functions or scores were developed based on large epidemiological studies. Usually, these scores can be calculated based on a few variables that are easy to obtain in the office. Although these tools are very useful in clinical practice, they have limitations related to calibration and discrimination ability. (74) In this context, many studies have incorporated AI/ML-based algorithms to optimize cardiovascular risk prediction. These studies, conducted in different regions worldwide, evaluated multiple algorithms utilizing different AI techniques. These algorithms included more variables than those typically used to stratify cardiovascular risk. (75-78) In general, these models, which utilized data from thousands of patients, have shown excellent predictive ability. In some cases, they have even outperformed traditional scores like the Framingham risk score. (75) Another AI-based model that considered the presence of subclinical atherosclerosis (qualitative analysis of atherosclerotic plaques by CT) had significant prognostic value for major cardiovascular events, and showed additional value over clinical risk factors, coronary artery calcium score, or traditional methods for evaluating CT scan images. (79)

Challenges and limitations

The usefulness of AI in Medicine is undeniable, and its implementation is rapidly expanding. However, it is not free of limitations.

Firstly, many of the programs solve some specific aspects (such as automated segmentation and/or quantification), but not others relevant to image analysis. The development cost of these programs is very high, which limits their availability.

Another important aspect is applicability. Although many AI-based results are applicable in clinical practice, some findings may lead to conclusions with limited clinical value, especially in the current stage of Medicine. This may lead professionals to disregard the results because they deviate from the usual

clinical findings of their practice. Additionally, the development of the program may have been biased by the selected population, which could limit its generalizability to other populations with different characteristics. This, in turn, limits the external validity of the program.

Similarly, some AI programs based on DL create models that are difficult or impossible to interpret due to their complexity, resulting in what is known as the "black box" effect. Professionals who must interpret the results may find it difficult to accept or reject them because they cannot understand how the model used to determine the results was constructed. This raises clinical, ethical and even legal issues when assessing responsibility in the decision-making process. (80,81)

As with previous analysis programs, it is important to obtain consistent results across different software programs to ensure that imaging tests can be analyzed using programs from different brands or generic analysis software.

And, finally, data privacy is another crucial element when considering this type of tool.

Conflicts of interest

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Should We Continue to Consider Extent of Ischemic Myocardium in Chronic Coronary Syndromes?

¿Debemos seguir considerando el monto isquémico en los síndromes coronarios crónicos?

MAGALI GOBBO^{1,2}, ALEJANDRO MERETTA¹, MARÍA VICTORIA CARVELLI¹, OSVALDO MASOLI^{1,3,4}

ABSTRACT

In the last years, new scientific evidence related to chronic coronary syndromes (CCS) has led to reconsider the diagnostic and therapeutic recommendations that historically guided our medical practice.

However, it is important to point out that the disseminated information lacks a precise critical analysis, with the risk of incorporating new algorithms in clinical practice that might not be completely applicable to our population.

The present review analyses the available scientific CCS literature to establish whether the extent of ischemic myocardium has no real clinical and prognostic significance as reported in some publications.

Key words: Chronic coronary syndromes - Ischemia - Revascularization

RESUMEN

El surgimiento de nueva evidencia científica en los últimos años en relación con los síndromes coronarios crónicos (SCC) lleva a reconsiderar las recomendaciones diagnósticas y terapéuticas que históricamente guiaron nuestra práctica médica.

Sin embargo, es importante destacar que gran parte de la información difundida carece de un análisis crítico riguroso, lo que nos expone al riesgo de incorporar nuevos algoritmos en la práctica clínica que podrían no ser completamente aplicables a nuestra población.

En esta revisión se analiza la literatura científica disponible relacionada a los SCC, para tratar de establecer si realmente el monto isquémico carece de significado clínico y pronóstico tal como se afirma en algunas publicaciones.

Palabras claves: Síndromes coronarios crónicos - Isquemia - Revascularización

INTRODUCTION

There are currently six clinical scenarios of chronic coronary syndromes (CCS): 1- Patients with stable symptoms (angina or dyspnea); 2- Patients with *de novo* heart failure (HF) or left ventricular dysfunction and suspicion of coronary artery disease (CAD); 3- Symptomatic or asymptomatic patients with <1 year acute coronary syndrome (ACS) or recent revascularization; 4- Symptomatic or asymptomatic patients with >1 year of revascularization; 5- Pa-

tients with vasospasm or microvascular disease; and 6- Asymptomatic patients with CAD findings. (1)

For almost two decades, the therapeutic conduct of CCS was ruled by the extent of myocardial ischemia found in functional tests, as recommended by the last European Society of Cardiology and the Argentine Society of Cardiology guidelines. (1,2)

This was mainly due to the contributions of the study performed by Hachamovitch et al., published in 2003, which demonstrated that early revasculari-

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Address for reprints: Magali Gobbo, magaligobbo28@gmail.com



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¹ Nuclear Cardiology Division, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina

² Nuclear Cardiology Division, Hospital JM Ramos Mejía, Buenos Aires, Argentina

³ Nuclear Cardiology Division, Hospital Cosme Argerich, Buenos Aires, Argentina

⁴ Cardio Imaging, TCba Salguero, Buenos Aires, Argentina

zation compared with optimal medical treatment (OMT) presented less risk of short-term cardiovascular mortality in patients without known CAD and moderate to severe inducible ischemia (>10%) assessed by single photon emission computed tomography (SPECT). (3,4)

Years later, the same author found again an interaction between inducible ischemia, the established treatment and all-cause mortality. He identified a benefit of greater survival with revascularization over OMT in the context of extensive ischemia, both in patients without known CAD, as among those with revascularization, but no previous infarct. (5)

The ISCHEMIA study

Recently, the ISCHEMIA trial cast doubt on this concept, since no benefit was found with an early invasive strategy in a median follow-up of 3.2 years. (6)

However, some key points of this study deserve our special attention in order to perform a critical analysis, and not fall in interpretation errors and incorrectly extrapolate their results to different populations of chronic coronary patients.

As recalled, in the ISCHEMIA study, 5179 patients with moderate or severe ischemia were randomly assigned to an initial invasive strategy (angiography and revascularization whenever possible) and medical treatment vs. an initial conservative strategy of medical therapy alone and angiography only in case of medical treatment failure. The primary endpoint was a composite of cardiovascular death, myocardial infarction (AMI) or hospitalization for unstable angina, heart failure or reanimated cardiac arrest. The secondary endpoint was cardiovascular death or AMI. (6) The study only included patients comprised in groups 1 and 4 of CCS, and did not include patients with reduced left ventricular ejection fraction (LVEF) (median value of 60%), nor those with hospitalization for heart failure or symptoms exacerbation in the last 6 months. Only patients in NYHA functional class I-II were randomized. In addition, at the time of recruitment, they did not have to present left main coronary artery disease $\geq 50\%$, refractory symptoms to OMT, nor unfavorable anatomy for revascularization. (7)

The Seattle angina scale score was 80 ± 20 in the invasive strategy group and 82 ± 19 in the OMT group, indicating that most patients were asymptomatic or slightly symptomatic at inclusion time. (8) Functional tests with imaging studies were employed in 75.5% of patients, SPECT being the most used modality (49.6%) followed by stress echocardiography (20.9%) and cardiac magnetic resonance (5%). Regarding severity, 41% of participants presented moderate ischemia defined by an extension <10%, or by an "enlarged" definition which combined 5% ischemic myocardium plus a clinical history of angina, associated with a theoretical maximum heart rate $\leq 75\%$ and less than 7 METS in the ergometric

test. Severe ischemia (>10%) was present in 45% of cases; however, the prevalence and analysis of more extended ischemia (15% or 20%) is unknown. (7)

It must be considered that as the decision to include a patient depended on the treating physician, some inclusion bias could have occurred, as for example patients with more extended severe ischemia, probably associated with higher risk of adverse events, who wouldn't had been randomized but referred directly to a revascularization procedure (Figure 1).

The slow recruitment resulted in a reduced sample size (from 8000 planned patients to 5179 effectively randomized) and to "force" the inclusion of some patients. In 14% of cases incorporated as "moderate ischemia", the central laboratory did not validate the extension. Twenty-five percent of recruited participants were included for presenting a positive ergometric test associated with an anatomical study, coronary angiography (CA) or computed tomography angiography (CTA) that demonstrated $\geq 70\%$ disease in the proximal or mid third left anterior descending artery or right coronary artery and/or proximal third of the circumflex artery. (7)

This last inclusion criteria, which incorporates anatomical information without knowledge of the ischemic extent, reflects the heterogeneity of the population.

Is the anatomy enough?

Anatomical knowledge through CTA is very useful due to its high negative predictive value (NPV); however, it has a moderate positive predictive value (PPV), close to 60-70%, if compared with CA or stress functional tests with imaging studies. This limitation is due to the difficulty in evaluating moderate lesions, the presence of coronary calcium and the interobserver variability.

To settle this inconvenience, various studies postulated as alternative the addition of the non-invasive fractional flow reserve (FFR) measurement to CTA. Nevertheless, a recent publication analyzed the usefulness and efficacy of this measurement through a multicenter audit developed in England, and the results showed that, even adding FFR, CTA PPV is still low (near 50%) and potentially more expensive than the conventional strategies that use functional tests. (9,10)

The PROMISE study included 10 003 symptomatic patients with suspected CAD and an intermediate pretest probability of 53.3%, which were randomly assigned to an initial strategy of functional tests (SPECT, stress echocardiogram and ergometry) vs. a CTA anatomical study. The initial strategy with CTA (versus functional tests) did not improve the clinical results during a median 2-year follow-up. In both arms the rate of primary events (death, AMI, hospitalization for unstable angina or severe complication of the procedure) was similar: 3.3% vs. 3%.

However, a larger number of patients assigned to the CTA group underwent cardiac catheterization within 90 days after randomization (12.2% vs. 8.1% in the functional tests arm) and a greater percentage of patients in the CTA group were revascularized (6.2% vs. 3.2%). (11)

Going back to the ISCHEMIA trial, it should be recalled that this was not designed to evaluate the clinical value of functional tests (there was no control group without ischemic evoking test or with a negative functional test), but to assess two treatment strategies. (12)

In our setting, it would be scarcely feasible and highly costly, to initiate the study of all asymptomatic or slightly symptomatic patients with suspected CAD by CTA or CA. In addition, it could needlessly and prematurely lead to perform revascularization procedures without a clear prognostic benefit, as shown by several clinical trials. (13,14)

Adding evidence

In the years after the publication of the ISCHEMIA study other studies, though with lower dissemination, were nonetheless important to complement our knowledge at the time of deciding patient management in CCS. Such is the case of the study published by Rozanski et al., who analyzed the relationship between stress-induced myocardial ischemia and all-cause mortality in patients with preserved vs. reduced LVEF. A total of 43 443 patients were evaluated with SPECT and with a long-term follow-up of 11.4 years. Patients with LVEF $\geq 45\%$ and severe myocardial ischemia and those with LVEF $< 45\%$ and moderate or severe myocardial ischemia benefitted with early revascularization. It should be pointed out that the percentage of ischemic myocardium extent in this publication differed substantially from that considered in the ISCHEMIA study: up to 5% of reversible defect was not considered ischemia, from 5-9% mild ischemia, from 10-14% moderate ischemia and $\geq 15\%$ severe ischemia. (15)

These results were similar to those reported in another retrospective trial of 16 029 patients evaluated by positron emission computed tomography (PET), where a significant interaction between ischemic extent and early revascularization was also demonstrated, so patients with larger ischemia had better survival if they underwent revascularization within 90 days after the myocardial perfusion test. (16)

In this same line, the REFINE study retrospectively analyzed a population of 19 088 patients evaluated by SPECT, in whom early revascularization decreased the rate of major events (mortality, AMI, and unstable angina) in patients with $\geq 10.2\%$ ischemia. (17)

As prior history of these works, a subanalysis of the COURAGE study analyzed 621 patients with an ischemic extent of 14-17%, and in whom a certain

benefit of revascularization was found. ($p=0.03$). However, as they were very few patients, the authors did not consider it among their conclusions, despite a statistically significant difference. (18)

Although these reports emerged from retrospective analyses, lack of treatment intervention / control and the absence of a possible inclusion bias, has perhaps turned these patients to be more similar to those we find and treat in the "real world" of cardiological practice.

Recommendations, doubts and certainties

The CCS guideline recently published by the American Heart Association (AHA) establishes that in patients with known CAD who persist symptomatic despite OMT, it is recommended to perform a functional test to detect the presence and extent of ischemia (IB recommendation), to determine the risk of major events and guide the therapeutic conduct. (19)

However, this document has generated some uncertainty among clinical cardiologists, as it also postulated guiding treatment according to anatomical findings, with the same recommendation level. Hence a new question arises: patients in whom the diagnosis is initiated by the anatomy, and severe proximal lesions are found in one or two vessels, ¿would they be amenable to receive OMT, or be revascularized without evidence that a functional involvement generating ischemia really exists?

If the diagnosis started by the anatomy, it should be considered that epicardial arteries are only 5% of the coronary tree and that anginal episodes and focal epicardial lesions do not always go hand in hand. Other pathophysiological mechanisms could generate an unbalance between myocardial oxygen offer and demand, unrelated to the atherosclerotic disease. (19-21)

Currently, a growing number of patients with CCS present with microvascular angina. (22-25) Although this is more frequent in patients without significant angiographic lesions, it can be present in patients with known CAD and in up to one third of revascularized patients that continue to manifest anginal episodes after revascularization. (26,27)

The ISCHEMIA study did not include participants with less than 12 months since the last revascularization. This group deserves a special mention, as a percentage of them can present stent or vascular graft stenosis, with no other abnormal finding than myocardial perfusion or regional wall motility. The detection of ischemia by functional tests in this group of still asymptomatic patients, worsens the prognosis. (28,29)

The evidence thus continues to be controversial, and is still not enough to confirm that the ischemic myocardium extent has lost the significance indicated more than 20 years ago. Each patient should be analyzed in his/her clinical context and socioeco-

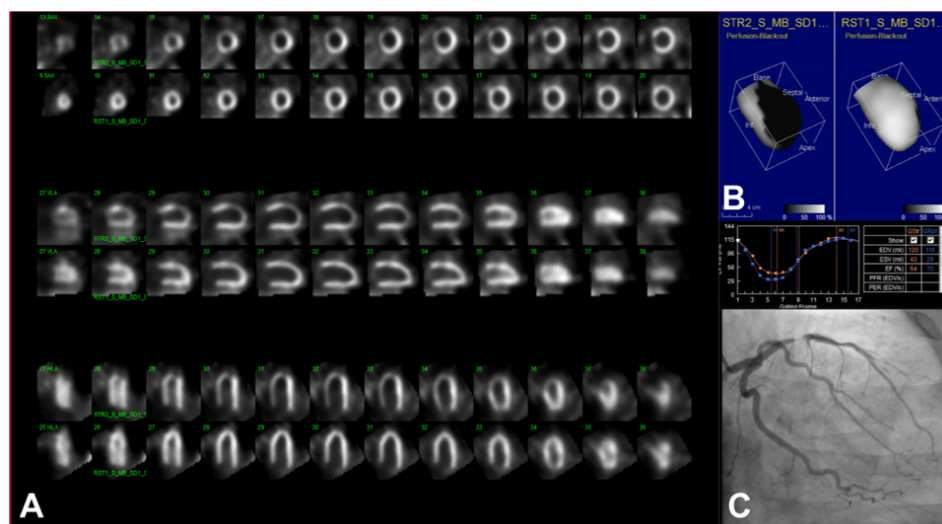


Fig. 1. Would you have enrolled this patient in the ISCHEMIA study?

51-year-old male patient, with suspected coronary artery disease due to stable angina in FC II-III. **A.** Rest-stress myocardial SPECT evidencing severe myocardial ischemia (35% in the left anterior descending (LAD) artery territory. **B.** Surface mapping showing the reversible perfusion defect and preserved left ventricular ejection fraction at rest and after exercise stress test. **C.** Coronary angiography showing subtotal lesion in the mid third of the LAD artery.

nostic environment. Functional and anatomical information should continue to be complementary and not necessarily excluding.

According to the present report, we consider that even today, knowing the presence and extent of ischemia in patients with CCS can modify their prognosis and treatment. (30)

"The mind is like a parachute... It only works if it is open",

"We are all very ignorant. What happens is that not all of us ignore the same things".

Albert Einstein.

Conflicts of interest

None declared.

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

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Coronary Angiography and Stress Myocardial Computed Tomography Perfusion: a Clinical Reality

Coronariografía y perfusión miocárdica de estrés mediante tomografía computarizada: una realidad clínica

GORKA BASTARRIKA¹, ANA EZPONDA¹

The reference standard for diagnosing coronary artery disease is conventional coronary angiography. This is an invasive and not free of complications technique, which is still performed for purely diagnostic purposes in a large number of patients who do not really require it. (1) This has led to the search for diagnostic alternatives that help in clinical management and that allow better selection of subjects requiring this procedure.

We present the case of a 70-year-old patient with hypercholesterolemia as the only cardiovascular risk factor without medical treatment, who had an active life, varied diet and occasional alcohol consumption. His brother had died of a heart attack at 55 years of age and his sister was diabetic.

He came to the clinic for cardiological evaluation due to episodes of chest tightness for the past 3 months. The tightness appeared during exertion, when walking quickly or climbing a hill, and subsided with rest. In the last week symptoms had been more serious, with greater chest tightness and dyspnea when walking.

Physical examination revealed a blood pressure of 150/85 mmHg. Cardiac and pulmonary auscultation was normal with no signs of heart failure. The ECG showed sinus rhythm of 67 beats per minute, horizontal axis, normal PR interval and narrow QRS complex. Lab test showed total cholesterol of 234 mg/dL, with an LDL cholesterol of 166 mg/dL. The chest x-ray was normal.

A coronary computed tomography angiography (CCTA) was requested to study the symptoms reported by the patient (Figure 1). The right and circumflex coronary arteries were diffusely ill, with calcified and non-calcified plaques that caused <50% stenosis. A large calcified and non-calcified plaque of about 23 mm length was observed located in the mid left anterior descending coronary artery, at the ostium of the

diagonal branches, that caused lumen stenosis of 70-99%. Given these findings, it was decided to complete the exploration using stress CT-perfusion with a vasodilator drug (regadenoson) (Figure 2). The test was positive for myocardial ischemia in the territory corresponding to the left anterior descending coronary artery. The study was classified as CAD-RADS 4A/P3/I+ (corresponding to severe stenosis with a large size plaque and demonstration of ischemia). With this result, the patient was referred to the Hemodynamics service, where a catheterization, that confirmed the serious lesions described in the CCTA (Figure 2), was performed. The first stenosis was treated with stent implantation. The most distal lesion could not be treated percutaneously because the vessel was sub-occluded. Finally, it was treated by aortocoronary bypass surgery with a graft from the left internal mammary artery to the mid left anterior descending coronary artery and from the saphenous vein to the diagonal branch.

CCTA has become the reference standard to evaluate the coronary tree in a non-invasive, reliable and accurate way. Specifically, given its ability to rule out coronary artery disease, this technique plays a very important role in the management of patients with chest pain, as demonstrated in the SCOT-HEART (Scottish Computed Tomography of the Heart), PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) and DISCHARGE (Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease) studies. Thus, the most current international guidelines and recommendations consider CCTA as the imaging technique of choice for the clinical management of patients with chest pain, especially when they have a low or intermediate pretest probability of suffering from coronary heart disease. (2,3) The great limita-

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Address for reprints: Cardiothoracic Imaging Section. Radiology Service. Clínica Universidad de Navarra. Avenida Pio XII, 36. 31008 Pamplona
E-mail: basarrika@unav.es, aezponda@unav.es



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¹ Cardiothoracic Imaging Section. Radiology Service. Clínica Universidad de Navarra.

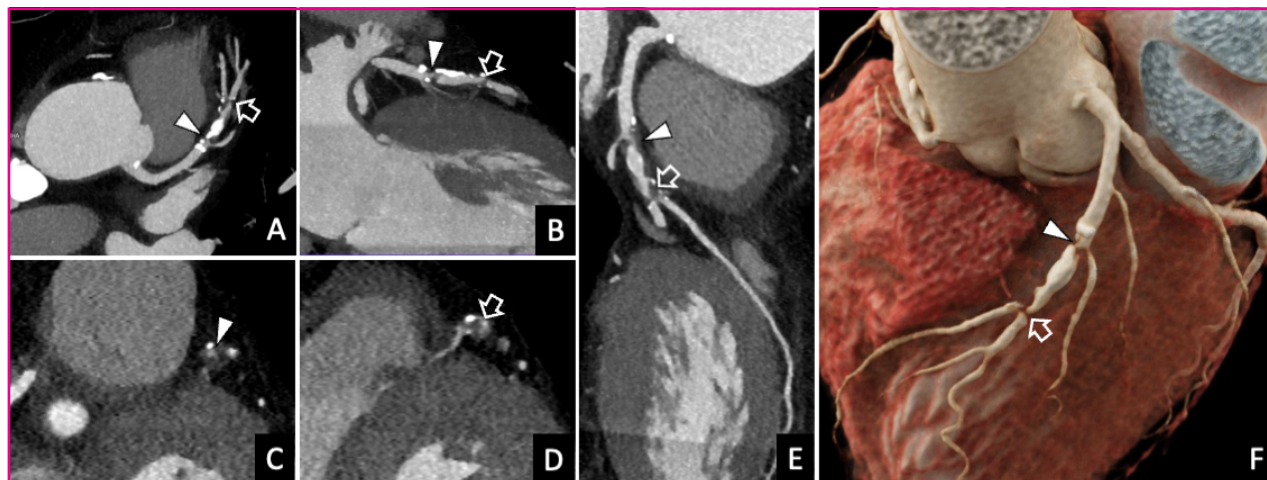


Fig. 1. Coronary CT angiography. A, B: Multiplanar reconstructions of the left anterior descending coronary artery. C, D: Reconstructions perpendicular to the long axis of the vessel. E: Curved planar reconstruction. F: Kinematic volumetric reconstruction. The study demonstrated 70-99% stenosis in the mid third of the left anterior descending coronary artery, which involves its origin (arrowhead) and second diagonal branch (hollow arrow).

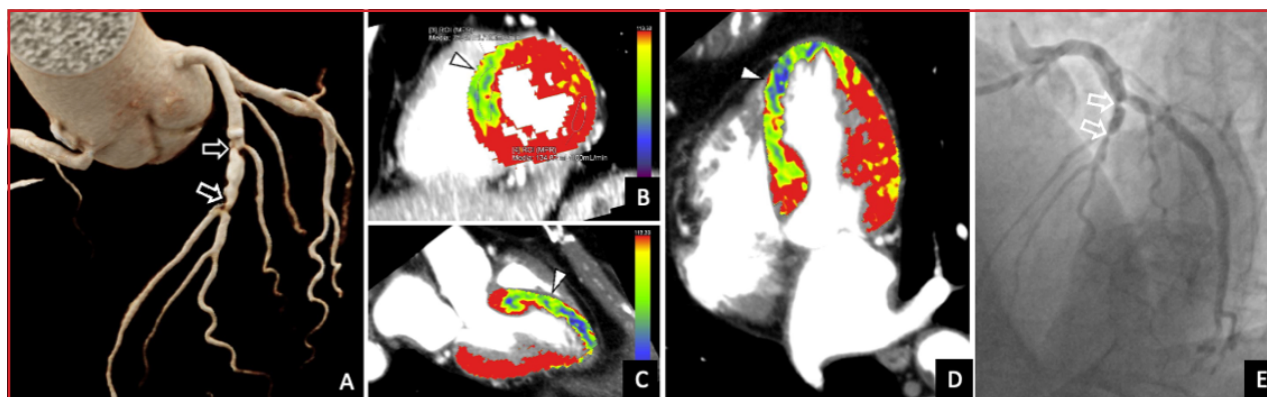


Fig. 2. Coronary CT angiography, stress CT-perfusion study and conventional coronary angiography. A: Kinematic reconstruction of the coronary tree. B, C, D: Short axis (B), three-chamber (C), and four-chamber (D) stress CT-perfusion reconstructions. E: Conventional coronary angiography. CCTA demonstrated two points of 70-99% stenosis in the mid third of the left anterior descending artery (hollow arrows in A). The study was completed with stress CT-perfusion to assess its functional significance, demonstrating inducible ischemia in septal segments (arrowheads). Based on these findings, the test was classified as CAD-RADS 4A/P3/I+. Conventional coronary angiography confirmed the CCTA findings (hollow arrows in E).

tion of the technique is its relative low specificity, for example, in patients with extensive coronary calcification or stent. In these cases, it is not uncommon to have to resort to functional techniques to complete the study and demonstrate the presence of ischemia: stress echocardiogram, stress magnetic resonance imaging, single photon emission computed tomography (SPECT) and positron emission tomography (PET).

Therefore, the most recent advances in CT have allowed for this technique, in addition to providing detailed information of the arterial coronary system, to understand the functional meaning of a coronary

stenosis, either by applying artificial intelligence algorithms and principles of computational fluid dynamics to CCTA images (known as FFR-CT) or by performing a myocardial perfusion study using the CT equipment itself (CT-perfusion) under stress induced by a vasodilator drug.

In general, compared with the rest of the ischemia detection tests, CT-perfusion provides anatomical and functional information integrated in a single examination. The acquisition is fast, has submillimeter spatial resolution and allows perfusion to be quantified with precision given the linear relationship between

the amount of iodinated contrast and the attenuation of the myocardial tissue. The limitations of perfusion-CT include the use of ionizing radiation, possible artifacts, both due to movement as hardening of the X-ray beam, and the need to use specific software to interpret the study.

In the present clinical case, the incremental diagnostic value of CT-perfusion compared with CCTA is demonstrated and it can be seen that adding CT-perfusion to CCTA allows increasing the specificity of the test. In this sense, there are several works that advocate completing CCTA with a CT-perfusion study. For example, the CRESCENT-II (Comprehensive Cardiac CT Versus Exercise Testing in Suspected Coronary Artery Disease 2) study concludes that, in patients with stable chest pain, the combination of CCTA and CT-perfusion in subjects with $\geq 50\%$ stenosis is an effective alternative to conventional traditional methods of detecting ischemia, with which a significantly higher proportion of catheterizations with an indication for coronary revascularization (88% vs. 50%; $p = 0.017$) (4) is achieved.

The results of the work carried out on CT-perfusion are incorporated into the most recent cardiac CT guidelines, which indicate that it may be appropriate to perform CT-perfusion to evaluate the functional importance of intermediate stenosis detected on CCTA (stenosis of 30-90% diameter), particularly in the context of multivessel disease, to help select patients who require conventional coronary angiography, and to plan revascularization treatment. (5) Additionally, the updated recommendations of the standardized CCTA report (Coronary Artery Disease Reporting and Data System, CAD-RADS 2.0) includes CT-perfusion assessment of ischemia as a new modifier (modifier I of ischemia), pointing out that this technique allows the exclusion of myocardial ischemia in moderate coronary stenosis (50 to 69%) or in suspected severe coronary stenosis ($\geq 70\%$) with dense calcified or mixed plaques, avoiding additional later tests. (6)

In conclusion, CCTA allows us to exclude coronary heart disease with great reliability, but has low diagnostic specificity. Taking into account that the clinical benefit of revascularization is limited to lesions causing ischemia and not only to quantify the degree of coronary stenosis, CT-perfusion plays an important role and has great added value in patients with

proven coronary stenosis demonstrated by CCTA, not only from a diagnostic point of view (by increasing the precision and predictive value of the test) but also in risk stratification, prognostic assessment and for therapeutic decisions.

Conflicts of interest

None declared.

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

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Ethical considerations

Not applicable.

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Molecular Imaging of a Cardiac Paraganglioma

Imágenes moleculares de un paraganglioma cardíaco

ROXANA CHIRICO¹, MATÍAS CIMIN¹, ALEJANDRA DE SALAZAR¹, MARÍA BASTIANELLO¹

We present a 12-year-old male patient, with no relevant medical history, who began with intense headache associated with severe arterial hypertension of unknown cause. Lab test detected elevated urinary normetanephrine. Abdominal magnetic resonance imaging (MRI) showed no specific features.

Exploratory positron emission tomography combined with computed tomography (PET-CT) with ¹⁸F-DOPA (a radiotracer analogue of L-DOPA) was requested due to suspicion of a functioning paraganglioma of unknown location.

The ¹⁸F-DOPA PET-CT showed a hyperenhancing intracardiac mass located in the right atrium, with intense enhancement in the arterial phase of intravenous contrast, as can be seen in Figure 1.

It is important to highlight the great difference that exists between the pathological uptake of the mass and the physiological fixation of the cardiac tissue, due to the presence and functionality of L-amino acid transporters (LAT) and the enzymes of the biogenic amine metabolic pathway, in relation to the neuroendocrine nature of the tumor.

The exact localization of the pathology was crucial for surgical planning. In the ¹⁸F-DOPA PET-CT performed for evaluation after surgery, the suture threads are observed after complete excision. (Figure 2)

Paragangliomas are neuroendocrine tumors that originate in paraganglionic cells derived from the neural crest. These cells form accumulations or conglomerates called paraganglia, which are located very close and related to the ganglia of the Autonomous Nervous System (ANS) in its two subdivisions and are disseminated throughout the body.

Although they can be of sympathetic or parasympathetic lineage, paraganglia have morphologically no differences. The sympathetic ones are located nearby, on the surface or embedded in the capsules of the sympathetic chain ganglia or in the fibers of the large autonomic plexuses. The adrenal medulla is a sympa-

thetic paraganglion specialized in producing epinephrine.

The parasympathetic paraganglia are located along the cranial and thoracic branches of the glossopharyngeal and vagus nerves, at the level of the head, neck, and middle and anterior mediastinum. Despite containing neurosecretory granules and having the potential to exhibit signs of physiological activity, the vast majority of paragangliomas arising from parasympathetic paraganglia are non-secreting. On the other hand, paragangliomas of sympathetic origin may or may not secrete biogenic amines. (1)

Germline mutations in more than 20 genes have been identified as responsible for more than a third of paragangliomas, thus revealing their rich hereditary nature. Depending on the mutation that causes them, they are classified into three clusters or genetic groups: pseudohypoxic, related to the kinase signal, and those related with WNT signaling. Each of these groups present distinctive differences from each other in terms of their biochemical, genetic and molecular characteristics, and each of these particular profiles has a direct impact on the clinical presentation. (2)

Less than 2% of paragangliomas are located in the thorax, and cardiac locations are extremely rare. (3)

Paragangliomas of the heart originate from the visceral paraganglia; they are described at the level of all cardiac chambers, predominantly the left atrium, and present high morbidity due to the high levels of norepinephrine they produce, with the consequent cardiovascular signs and symptoms. (4)

The most common clinical presentation of cardiac paragangliomas is, as described above, characteristically noradrenergic. Distinctive symptoms are hypertension, palpitations and arrhythmia. It may also have a silent profile, when dedifferentiation does not allow the production of biogenic amines.

The vast majority of cardiac paragangliomas are pseudohypoxic, with a starting point in mutations of

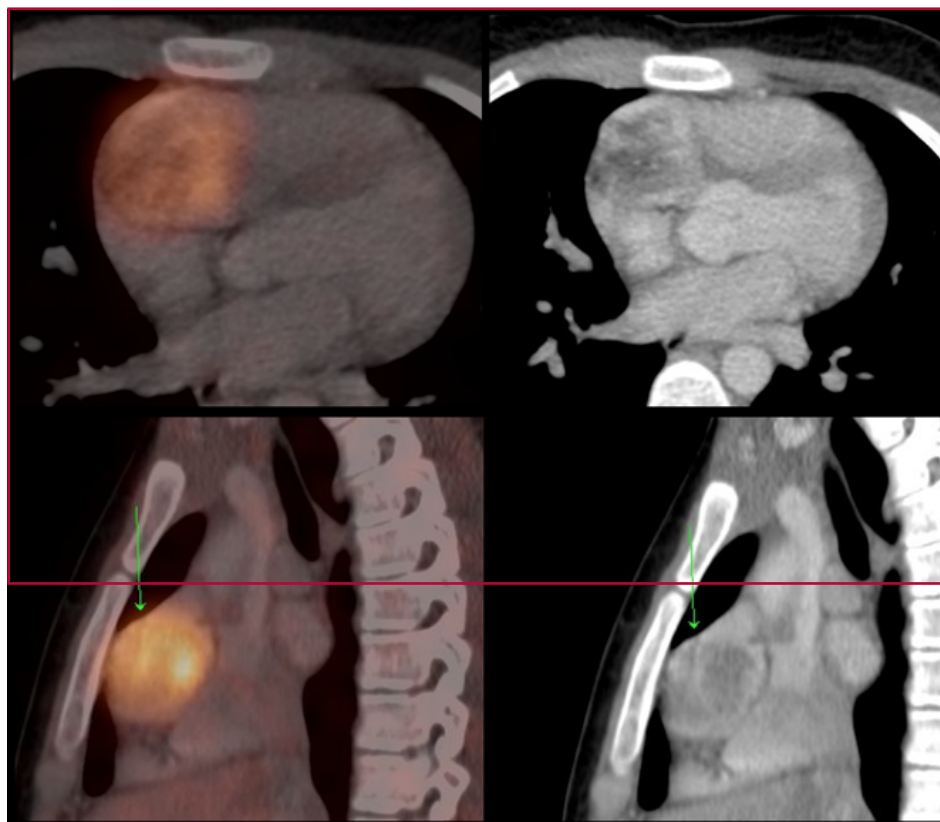


Fig. 1. ^{18}F -DOPA PET - CT showed a hyperenhancing and hypervascularized mass at the level of the right atrium.

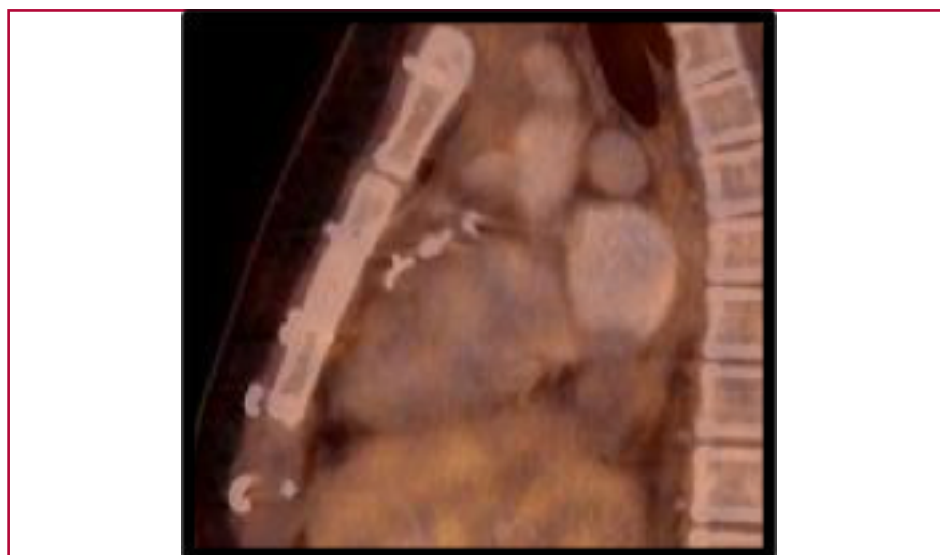


Fig. 1. ^{18}F -DOPA PET-CT treatment response assessment. The hyperenhancing mass observed in Figure 1 is no longer noticeable, and the post-surgical morphological changes are seen.

the different subunits of the mitochondrial succinate dehydrogenase (SDH) complex, predominantly SDHB, SDHC and SDHD. These paragangliomas are characterized by having a high density of somatostatin receptors and also variable presence/functionality of LAT and enzymes of the noradrenergic metabolic pathway, their vesicles housing dopamine or norepinephrine when they are functional, as occurs in most cases. (4)

The radiopharmaceuticals used to evaluate these tumors are ^{68}Ga -DOTAs (somatostatin receptor ligands) and ^{18}F -DOPA (LAT amino acid substrate). Therefore, PET-CT with ^{18}F -DOPA is one of the morphometabolic tools used for its study.

^{18}F -DOPA is a radiolabeled amino acid that is introduced into the cells through the aforementioned LAT. It is a substrate of the cytoplasmic aromatic amino acid

decarboxylase (AADC) enzyme, which transforms L-DOPA into dopamine, the first of the biogenic amines in the metabolic pathway. It will then be converted within the vesicles into norepinephrine, according to the functionality of the dopamine beta-hydroxylase enzyme. (5) These radiolabeled biogenic amines (18F-dopamine and 18F-norepinephrine), which originate from ¹⁸F-DOPA administered to the patient, are stored in the secretory granules of the paraganglioma, and constitute one of the molecular tools indicated for staging and evaluating the response to treatment.

In conclusion, molecular images are an essential tool for the correct staging and assessment of response to treatment of cardiac paragangliomas. Accurate localization is crucial for the correct pre-surgical planning, and post-surgical molecular verification must correlate with biochemical negativization, and clinical improvement.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Financing

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Malignant Type 2 Endoleak: An Already Recognized Entity, But With a More Aggressive Course

Coronariografía y perfusión miocárdica de estrés mediante tomografía computarizada: una realidad clínica

L. MARIANO FERREIRA¹, MTSAC, MIGUEL FERRER¹, LEONELA ALOY¹, OSCAR DÁVILA¹, PABLO DILUCA¹, RICARDO LA MURA¹, PEDRO LYLK¹

Current evidence indicates that endovascular aortic aneurysm repair (EVAR) is associated with a low perioperative mortality rate and high rates of medium and long-term survival related to the aneurysm. However, the rate of reinterventions is considerable, particularly due to endoleaks, the main cause of reintervention. (1) While type I and type III endoleaks require reintervention, the clinical significance of type II endoleaks (T2EL) remains controversial. (2)

Type II endoleak is defined as the presence of blood flow within the aneurysm sac after stent placement, resulting from collateral retrograde flow from the aortic branches, usually from the lumbar arteries, inferior mesenteric artery, polar renal arteries, or middle sacral artery. Most T2EL resolve spontaneously and the one-year post-operative prevalence ranges from 1–10% (defined as persistent endoleaks). However, there is evidence that persistent T2EL are associated with an increased risk of adverse outcomes (sac enlargement, aneurysm rupture, need for reintervention, conversion to open repair). A study of 832 EVAR patients found persistent T2EL accounting for 38% of secondary reinterventions. (3)

Current recommendations suggest intervention for T2EL in the presence of aneurysmal growth and/or endoleak persistence; however, the exact criteria for reintervention remain undefined. (2) Some physicians argue for aggressive management, such as prophylactic embolization of patent vessels communicating with the endoleak at the time of graft implantation (intraoperative embolization), (4) while others endorse conservative monitoring approaches. (2)

Although the discussion may focus on the sac size and its treatment, our presentation is based on the imaging tests findings of a specific type of T2EL. This type is more aggressive and resistant to conventional treatments such as embolization or laparoscopic ligation of collaterals.

The aim of this scientific letter is to describe a specific imaging pattern of these persistent "malignant" T2EL.

A 76-year-old male underwent endovascular repair of a ruptured abdominal aortic aneurysm using standard stent grafting in May 2016. The preoperative size of the aneurysm was 64 mm, and a significant retroperitoneal hematoma was present. The patient had favorable postoperative outcome. As predictors of T2EL, the patient had 3 patent lumbar arteries and 1 inferior polar artery exiting the aneurysm sac. At the six-month follow-up visit, the sac was excluded, the polar artery was thrombosed, and the two inferior lumbar arteries remained patent. The aneurysm sac size had decreased to 49 mm. However, one year later, the aneurysm sac increased to 58 mm, with a T2EL as the only attributable cause. Once type I and III endoleaks were ruled out, transarterial embolization of the T2EL was decided. In October 2019, EndoAnchors were placed due to persistent growth of the sac and dilation of the proximal neck. EndoArchs are endosutures or endovascular screws placed to reinforce the contact between the endograft and the arterial wall at the level of the infrarenal neck. However, due to persistent neck dilatation, a type IA endoleak developed, requiring repair with a physician-modified fenestrated endovascular graft (PMEG) (Figure 1) in October 2022. By that time the aneurysm sac had reached a size of 76 mm. The new postoperative control revealed a slight increase in the size of the sac (3 mm in 6 months) without type I or III endoleak, but with an image of a heterogeneous thrombus with central enhancement and distinct borders, which we have named 'malignant' T2EL. (Figure 2)

This patient should be managed with a conservative approach. If necessary, conversion to open surgery with sacotomy and partial resection of the aneurysm

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Address for reprints: Mariano Ferreira. E-mail: drferreira@yahoo.com



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¹ Clínica La Sagrada Familia. Buenos Aires. Argentina

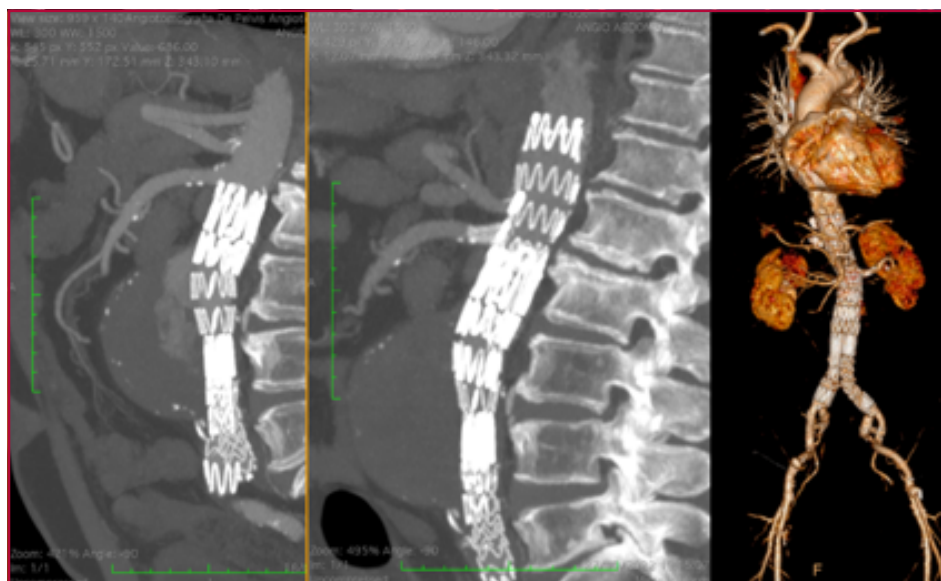


Fig. 1. From left to right. Computed tomography scan before and after placement of a fenestrated stent due to type IA endoleak. 3D reconstruction of the fenestrated endograft (right).

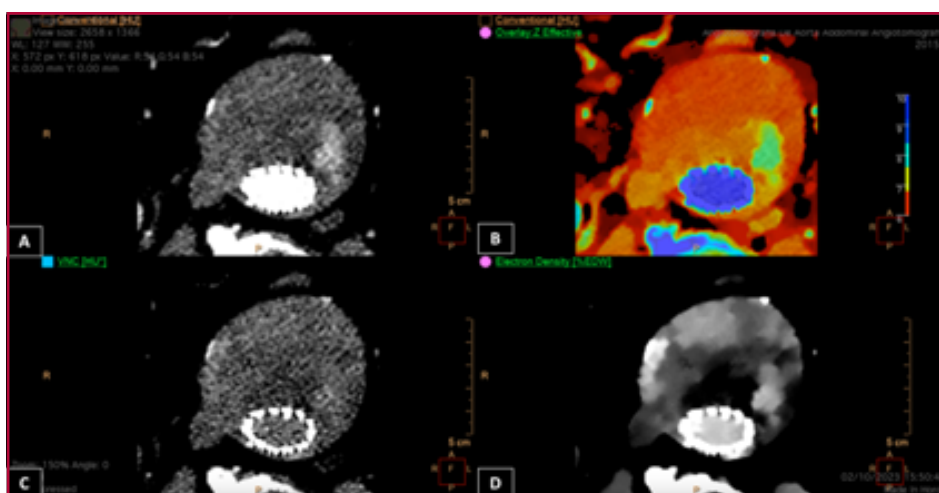


Fig. 2. Four images of the aneurysm sac acquired with spectral computed tomography (iQon Spectral CT, Philips). A) Image of conventional computed tomography angiography with iodine in the arterial phase. B) Fusion image (conventional mode and iodine map). C) Virtual non contrast (VNC) mode, where by analyzing the density of the materials it is possible to virtually extract iodine. D) Image obtained by spectral analysis of electron density (ED). Electron density values in the image are expressed in percentage relative to the ED of water; the expected ED of water is 100 (%EDW). It provides a more precise characterization of the tissue and displays various densities within the thrombus, and not just the enhanced areas, that are not visible in conventional images

sac without graft explant may be considered as a last resort.

Among endoleaks, type II is the most common and occurs in 9-30% of patients following EVAR. Those that remain patent beyond one year postoperatively are known as persistent endoleaks. Patients with persistent T2ELs are more likely to develop sac expansion and undergo reintervention during follow-up. (2)

The typical findings involve a cavity within the aneurysm, usually with one or more inflow and outflow arteries. However, the T2EL that we are describing as "malignant", has no cavity, but, on the contrary, presents irregular and diffuse contrast enhancement

of the aortic wall and thrombus on computed tomography angiography. For this reason, traditional endovascular treatments, such as embolization of the sac or its branches by transarterial, lumbar or transcaval routes, or even laparoscopically, are not very effective.

From a pathophysiological perspective, the vasa vasorum are the vessels associated with arterial microcirculation. The vasa vasorum comprise a vascular network that originate in the adventitial layer of large arteries from which smaller vessels branch. The outermost thirds of the great arteries receive nutrients from the vasa vasorum, while the innermost third is an avascular zone passively nourished by the luminal

blood flow. Several publications have shown that endovascular stenting of an artery with a covered stent caused proliferation of the vasa vasorum from the adventitia to the intima layer. The changes that occur in vasa vasorum after EVAR and the role of developed vasa vasorum in aneurysm expansion after EVAR are currently unknown. However, there have been reports of thrombosed cerebral aneurysms that continued to grow after complete endovascular occlusion due to developed vasa vasorum. Occasionally, the organized thrombus may exhibit heterogeneous contrast enhancement, as in the case described, and this expanding thrombus is referred to as chronic expansive hematoma (CEH). (5) Enhancement of the aneurysm wall is through the network of small arteries, which could correspond to vasa vasorum. The heterogeneous and patchy enhancement of the intrasaccular thrombus, without the typical endoleak cavity, was considered analogous to the findings of CEH.

The use of the IQon Spectral CT (Philips Healthcare Inc., The Netherlands) is another remarkable feature. The images in Figure 2 display the spectral analysis of electron density, highlighting the varying densities within the thrombus in contrast-enhanced CT angiography. This makes the areas of post-contrast enhancement more evident. (6)

To the best of our knowledge, these findings have not been previously reported. Although we are presenting a clinical case and our experience with ten additional cases, we believe that the imaging findings of 'malignant' T2EL may be useful for managing these cases. The visualization of the sac with heterogeneous and patchy enhancement of the thrombus could be distinctive findings in these cases.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Financing

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What Are the Potential Determinants of Favorable Long-term Outcomes Following Drug-coated Balloon Treatment? Gathering Data from a Single Observation

¿Cuáles son los posibles factores determinantes de los resultados favorables a largo plazo después del tratamiento con balón farmacoactivo? Datos procedentes de una sola observación

KAI NINOMIYA¹, ERIC K.W. POON², BERNHARD REIMERS³, YOSHINOBU ONUMA¹, PATRICK W. SERRUYS¹

Coronary angiography of a 58-year-old man with angina showed a de novo stenosis in the mid left circumflex coronary artery (LCX) with a minimum lumen diameter (MLD) and reference diameter (RD) of 1.20 and 2.44 mm, respectively. Quantitative flow ratio (QFR, Medis) was 0.80 distal to the lesion (Figure 1A and 1B). Optical coherence tomography (OCT) was performed after pre-dilatation, prior to drug-coated balloon (DCB) treatment for selection of an appropriately calibrated size DCB and to assess the extent of the barotrauma pre DCB.

The patient was loaded with prasugrel 60 mg in addition to his daily chronic aspirin therapy. Initially, pre-dilatation was performed with a semi-compliant 2.5×20 mm balloon inflated at 6 atmospheres resulting in an angiographically type B dissection without impaired distal flow. OCT disclosed a dissection with a length of 12.6 mm extending to the media; the RD was 2.55mm and the minimal lumen area (MLA) 2.36 mm² after pre-dilatation; the DCB treatment was successfully performed with SeQuent Please Neo™ paclitaxel coated balloon (PCB) (2.5 × 30 mm) inflated for 60 seconds. The transit time, duration from insertion of DCB into the sheath until DCB inflation, was 45 seconds. Acute gain was 0.6 mm (MLD pre-procedure vs MLD post-DCB: 1.20 vs 1.80 mm) and post-DCB QFR was 0.91 (Figure 1C and 1D). Dual antiplatelet therapy (DAPT) with a maintenance dose of 10 mg of prasugrel was prescribed at discharge.

The 6-month angiography showed a late lumen gain (LLG) of 0.12 mm at the site of the MLD post-DCB with a healed dissection (Figure 1E). The QFR at 6-month follow-up was 0.93 (Figure 1F).

DCB treatment in this case resulted in an expansive remodeling. Comprehensive assessments of determinants of long-term outcome, including physiological and morphological features, were retrospectively performed.

Type of drug, and drug transfer

Limus drugs are cytostatic, while paclitaxel is a cytotoxic drug, which means it essentially induces smooth muscle cell death and has potential for toxicity. Clinical data from randomized clinical trials of DCBs are primarily based on studies of PCB putatively related to their favorable pharmacokinetic properties. (1,2) It is not clear whether the effect of vessel remodeling is exclusive for paclitaxel or whether it can also be seen with sirolimus or biolimus A9. In our case, an adequate drug transfer of paclitaxel after a short transit time of 45 seconds potentially could contribute to the late lumen enlargement (LLE).

Dissection

The degree of lesion expansion will be associated with the extent of dissection. Some studies demonstrated the relationship between non-flow limiting larger dissection during PCB treatment and the LLG or enlargement. (3) The mechanism might be explained by vessel growth (expansive remodeling) induced by a direct exposure to paclitaxel delivered into the adventitia and/or plaque regression induced by an intensive lipid-lowering therapy. In this case, flap type dissection extending to the media was observed; the maximum dissection arc was 153 degrees, and the total dissection volume was 13.8 mm³ (Figure 2A).

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Address for reprints: Patrick W. Serruys, MD, Ph.D., FESC, FACC. Established Professor of Interventional Medicine and Innovation at the National University of Ireland, Galway (NUIG) and Senior Consultant of the Cardiovascular Research Centre for Advanced Imaging and Core Lab (CORRIB) Research Centre, Investigator of the Science Foundation of Ireland (SFI). University Road, Galway, H91 TK33, Ireland. Tel: +353 91 524411. E-mail: patrick.serruys@nuigalway.ie

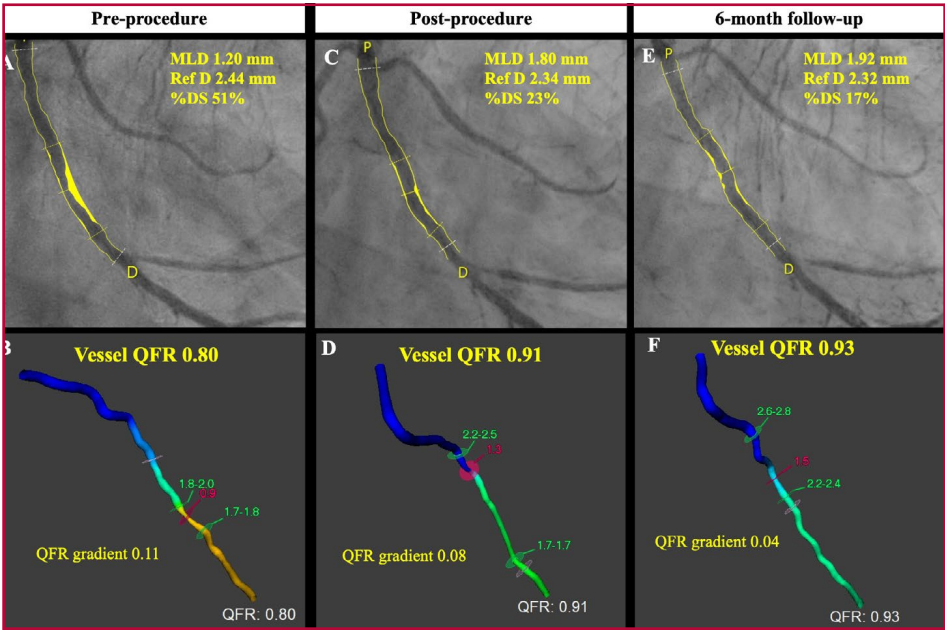


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¹ Department of Cardiology, University of Galway, Galway, Ireland

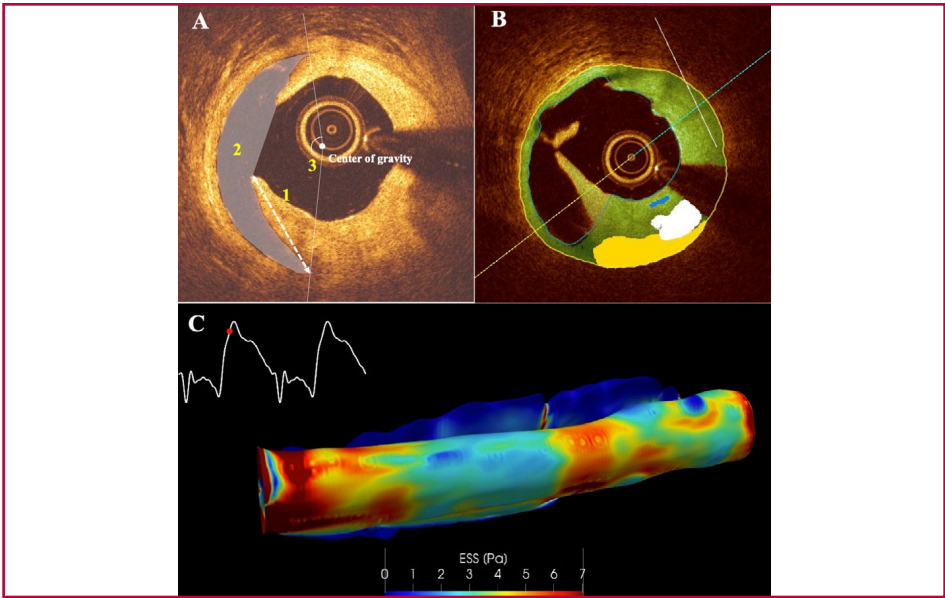
² Department of Mechanical Engineering, Melbourne School of Engineering, University of Melbourne, Victoria, Australia

³ Cardio Center, IRCCS, Humanitas Research Hospital, Rozzano, Milan, Italy



DS=Diameter stenosis; MLD= Minimum lumen diameter; QFR= Quantitative flow ratio; Ref D= Reference diameter

Fig. 1. Serial change of MLD and QFR following drug-coated balloon. MLD and QFR pre-procedure (A and B), post-procedure (C and D), and at 6-month follow-up (E and F).



DCB= drug-coated balloon; OCT= optical coherence tomography

Fig. 2. Extent of the barotrauma following DCB treatment. (A) Precise quantification of dissection volume derived from cross-sectional slices with a thickness of 100 microns. (B) OCT deep learning analysis using OctPlus software (Pulse, Shanghai). (C) Wall shear stress derived from the fusion of OCT and angiography.

Tissue composition

The tissue composition of the target lesion must have implication on the site of fracture, the extent of dehiscence of the intima from the media and adventitia, on the drug transfer at the time of the procedure, and later on the process of late lumen loss (LLL) or LLG. In this case, the tissue components of vessel wall plaque within the target lesion were identified by OCT deep learning (OctPlus, Pulse, Shanghai). (4) The distribution of fibrous, lipid, calcium plaque, and macrophage/crystal-cholesterol were 89.5%, 3.7%, 6.4%, and 0.6% (Figure 2B). The fact that fibrous plaque is predomi-

nant in this lesion may have been associated with greater dissection, adequate drug transfer and subsequent favorable outcomes.

Wall shear stress

Figure 2C shows a great heterogeneity of high and low shear stress derived from the fusion of OCT and angiography in a Computational Fluid analysis based on the Navier Stoke and Quemada equations after finite element analysis. (5) In the dissected area low shear stress dominates and is associated with high viscosity prone to thrombosis. This pattern of shear stress is

at total variance with the homogeneous profile usually seen after a well deployed stent implantation. Further investigations are warranted to understand the favorable or unfavorable impact of shear stress on outcome.

Post procedural physiological assessment

Although QFR >0.91 after stent implantation could predict a favorable vessel-oriented composite endpoint, only scarce evidence of prognostic value of QFR post procedure exists in patients treated with DCB. (6) In our case, the QFR gradually increased: 0.80 at procedure, 0.91 at post procedure, and 0.93 at 6-month follow-up.

In conclusion, the determinant of favourable outcomes following DCB treatment are multifactorial. Previous studies as well as our case report illustrate the numerous potential factors affecting outcomes after DCB treatment, and their positive and/or negative impact, as well as their complex interplay, need further study.

Ethical considerations

The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflicts of interest

Dr. Serruys reports consultancy for Merillife, Novartis, SMT (Sahajanand Medical technological), Philips/Volcano, and

Xeltis, outside the submitted work. All other authors have no conflict of interest to declare. (See conflicts of interest forms on the website).

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Non-Contrast Electron Density Detection of Pulmonary Thromboembolism and Myocardial Infarction

Detección de tromboembolismo pulmonar e infarto de miocardio por medio de densidad de electrones sin contraste

GASTÓN A. RODRÍGUEZ-GRANILLO¹, MTSAC, , JULIÁN COLLA², LUCÍA A. FONTANA¹, PABLO DILUCA³, , JUAN CIRIO⁴, , PEDRO LYLYK⁴

Most research involving spectral computed tomography (CT) has been related to its ability to improve tissue characterization in contrast-enhanced acquisitions, while preliminary investigations have suggested its usefulness for tissue characterization in non-enhanced examinations.(1,2) Dual-layer spectral CT enables the direct estimation of tissue electron density (ED) on a voxel (volumetric pixel, the minimum processable unit of a three-dimensional matrix, the equivalent of the pixel in a 2D object) basis, without modifications of acquisition protocols.(3) Previous studies have suggested improved tissue characterization using ED imaging.(4)

We report the case of a patient admitted with an acute ischemic stroke, in whom a cardiac CT requested to rule out a cardiac embolic source, identified the presence of pulmonary thromboembolism and myocardial infarction, both findings being identifiable using the non-contrast coronary artery calcium scan.

A 66-year-old man with hypertension and type 2 diabetes as coronary risk factors, and a history of coronary artery bypass grafting (left internal mammary artery to left anterior descending artery) 17 years ago, presented to the clinic with right hemianopsia, 30 hours after symptoms onset (NIHSS 2). His blood pressure was normal (129/85 mmHg) and his pulse was regular (77 bpm). A brain magnetic resonance was performed demonstrating a temporoparietal acute ischemic lesion, with occlusion of the P2 segment of the posterior cerebral artery, outside the therapeutic window for acute treatment.

Five days before he had been admitted to another institution due to a non-ST elevation myocardial in-

farction, and after percutaneous coronary revascularization with stent deployment in the left circumflex artery, he was discharged with no complications.

On admission, his daily treatment included aspirin 100 mg, clopidogrel 75 mg, bisoprolol 2.5 mg, dapagliflozin 10 mg, and rosuvastatin 20 mg.

The ECG showed sinus rhythm, with negative T waves in DIII and AvF leads. The first cardiac troponin value was 500 ng/mL, descending thereafter.

A transthoracic echocardiogram was performed, reporting a preserved global left ventricular function (left ventricular ejection fraction 58%) with inferior and inferolateral hypokinesis. A cardiac CT (IQon Spectral CT scanner, Philips Healthcare, The Netherlands) was requested to rule out an embolic source (Figure 1). Contrast-enhanced images identified the presence of pulmonary thromboembolism (Figure 1, panel a, arrow), and a severe perfusion defect of the basal inferior left ventricular wall (Figure 1, panel b, arrows). A patent stent was detected in the left circumflex artery, whereas a severe irregular lesion was identified at the distal (large and dominant) right coronary artery (Figure 2). Of note, using ED imaging, the pre-contrast coronary artery calcium scan (32 x 0.625 mm collimation, 2.5 mm thickness, 120 kV, 80 mAs, rotation speed 0.33 seconds, triggered at 75% of the RR interval), enabled the detection of both the pulmonary thromboembolism (Figure 1, panel c, arrow) and the inferior basal myocardial infarct (Figure 1, panel d, arrows). The ED value measured at the high-density area corresponding to the pulmonary thrombus was 107.9 %EDW (mean percentage ED relative to water), compared with values of 104.3%EDW at the main pul-

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Address for reprints: Gastón A. Rodríguez-Granillo: grodriguezgranillo@gmail.com.

Instituto Medico ENERI, Clínica La Sagrada Familia. Av. Libertador 6647 (C1428ARJ), Buenos Aires, Argentina.



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¹ Department of Cardiovascular Imaging, Instituto Medico ENERI, Clínica La Sagrada Familia, Buenos Aires, Argentina

² Department of Cardiology, Instituto Medico ENERI, Clínica La Sagrada Familia, Buenos Aires, Argentina

³ Department of Radiology, Instituto Medico ENERI, Clínica La Sagrada Familia, Buenos Aires, Argentina

⁴ Stroke Unit, Instituto Medico ENERI, Clínica La Sagrada Familia, Buenos Aires, Argentina

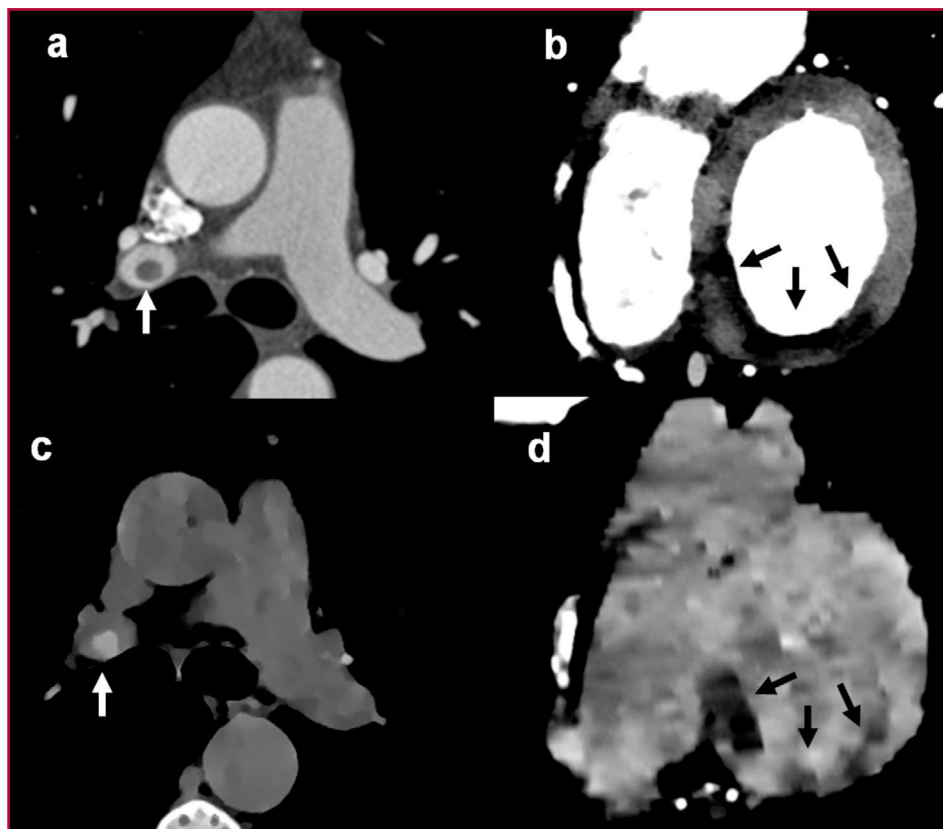


Fig. 1. Contrast-enhanced cardiac computed tomography (panels a and b) showing a pulmonary thromboembolism (panel a, arrow) and a myocardial perfusion defect of the inferior wall (panel b, arrows). Non-contrast electron density images derived from coronary calcium scoring scan (panels c and d) showing the same findings without contrast administration. Thrombus displayed as white, related to high electron density values (panel c), whereas the perfusion defect is displayed as an area with low electron density values (panel d).

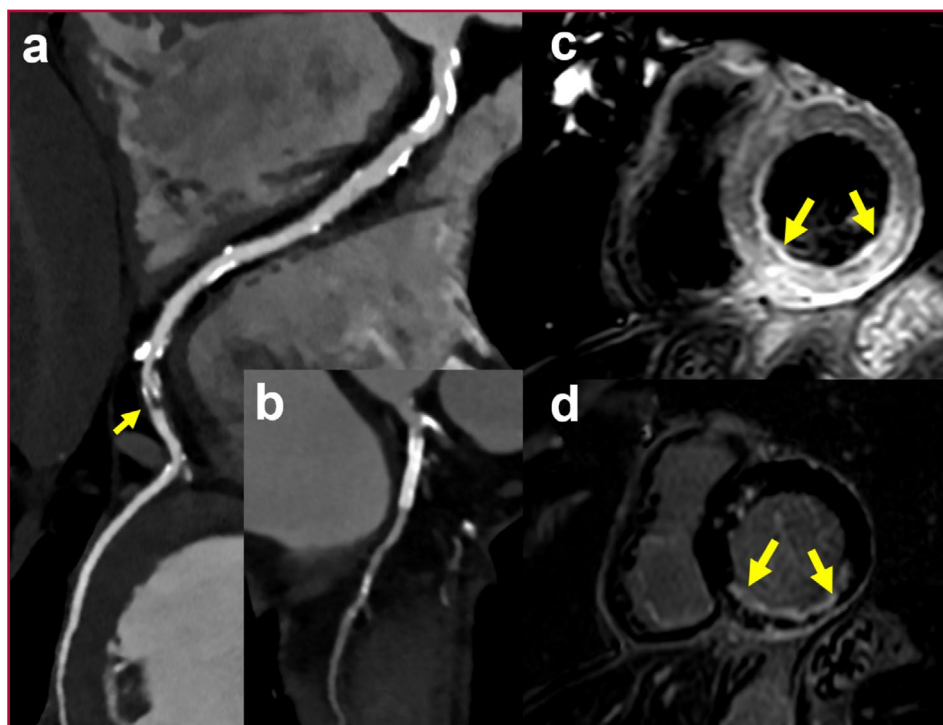


Fig. 2. Coronary CT angiogram, showing a large and dominant right coronary artery with a severe distal lesion (panel a, arrow), and a patent stent in a small left circumflex artery (panel b). Cardiac magnetic resonance (panels c and d) images displayed in basal short axis views, demonstrating an inferior-wall myocardial infarction (panel c: T2-weighted imaging, panel d: late enhancement).

monary artery and of 103.9 %EDW at the ascending aorta. The ED value measured at the low-density area corresponding to the myocardial infarct was 101.9 %EDW, compared with values of 104%EDW at the remote myocardium.

Cardiac magnetic resonance confirmed the findings (Figure 2), showing transmural myocardial edema using T2-weighted imaging, and a predominantly subendocardial inferior myocardial infarction.

The case was interpreted as an ischemic stroke in

the context of an acute myocardial infarction. Given the presence of pulmonary thromboembolism, he received enoxaparin 60 bid for seven days, and oral apixaban 5 mg bid thereafter. The patient evolved stable and was discharged.

The assessment of acute myocardial infarction and pulmonary thromboembolism requires contrast-enhanced examinations. Although dual energy CT improves tissue characterization, with an incremental value among diverse clinical settings, particularly involving cardiothoracic imaging, most research about dual energy CT involves the ability of iodine density maps and low monoenergetic imaging to enhance tissue discrimination. On the contrary, the potential usefulness of spectral imaging for non contrast examinations remains widely unexplored, especially the role of ED imaging.

Coronary artery calcium scoring (CAC) has been extensively validated for atherosclerotic cardiovascular disease risk assessment among asymptomatic patients. Nonetheless, the role of CAC testing as a gatekeeper within the Emergency Department remains uncertain if not discouraged. In this regard, a recent large registry including patients presenting to the emergency department with acute chest pain at low to intermediate risk for acute coronary syndrome, who underwent CAC and coronary CT angiography, identified a 99% negative predictive value of CAC for ruling out obstructive coronary artery disease and revascularization.

To the best of our knowledge, this is the first case to report that CAC might potentially be able to detect, aside from the presence and extent of coronary artery calcifications, pulmonary artery thromboembolism and early tissular changes associated with myocardial infarction. CAC is an unsophisticated, non-contrast, fast, and safe (associated with low radiation dose) tool. While performed in a dual-layer configuration CT scanner, CAC allows the simultaneous acquisition of spectral data such as ED imaging without affecting routine workflow.⁽⁴⁾ In this regard, in a previous study ED imaging had the lowest deviation from phantom tissue-equivalent inserts compared to other spectral parameters.⁽⁵⁾

Our findings are in line with those from a recent preliminary report including non-gated chest CT examinations, showing the potential of ED imaging to improve the detection of low contrast structures, in part due to the almost absence of noise in ED images.⁽⁶⁾

The clear identification of pulmonary thromboembolism using unenhanced scans shown in our case might warrant further research in the field of pulmonary and cardiac embolic detection. Indeed, pul-

monary embolism is one of the major complications of stroke, with high rates of death. Furthermore, the possible identification of myocardial infarction without the requirement of contrast administration might provide added value among non-enhanced examinations, which is conceivably relevant for patients with impaired renal function or for those at risk for contrast-induced nephropathy.

In conclusion, we present the first report showing the potential of CAC performed in a dual layer spectral CT scanner to identify, aside from the presence and extent of coronary artery calcifications, pulmonary artery thromboembolism and signs of myocardial infarction.

Ethical considerations

Not applicable.

Conflicts of interest

Pedro Lylyk is Consultant of Philips Healthcare. Gastón Rodríguez Granillo is Consultant of MultiplAI Health, Caristo Diagnostics, and Fundación INICIAR.

None of the other authors have conflicts of interest to declare related to the content of the manuscript.

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

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Pulmonary Embolism and Takotsubo Syndrome as Causes of Cardiopulmonary Arrest

Tromboembolismo pulmonar y Síndrome de Takotsubo como causantes de paro cardiorrespiratorio

EDWIN A. RODRÍGUEZ¹, JAIME TABOADA¹, SANDRA P. SWIESZKOWSKI¹, MTSAC.

Venous thromboembolism (VTE), with pulmonary embolism (PE) as its most serious manifestation, is the third leading cause of in-hospital mortality. The thrombus usually comes from the veins of the lower limbs. Virchow's triad of venous stasis, hypercoagulability and endothelial injury usually triggers the pathophysiologic cascade that contributes to the development of venous thrombosis. (1)

Stress cardiomyopathy or takotsubo syndrome presents as an acute, transient and reversible left ventricular dysfunction, often related to an emotional or physical stressful event producing a reduction in cardiac output. Most cases occur in postmenopausal women > 55 years. Patients may be asymptomatic or present serious symptoms due to heart failure. (2,3)

Pulmonary embolism has been reported as a physical and psychological trigger for stress cardiomyopathy. The combination of these two factors, which have been extensively described and studied in the literature, can be catastrophic for the patient and result in a high mortality rate. (2)

This situation is of the utmost interest due to the combination of these factors, the severity of the condition, the high clinical suspicion, and the role of bedside echocardiography in identifying this type of event and enabling prompt intervention to minimize consequences and mortality.

We present a 65-year-old female patient with a history of hypertension, hypothyroidism, smoker of 20 packs-year, and dermatomyositis with involvement of the skin, joints and lungs.

She was admitted with fractures on the left side, one in the femoral shaft and the other in the proximal humerus. During hospitalization, the patient evolved with septic shock due to urosepsis and was transferred to the critical care unit. Four days after being admitted, she developed cardiac arrest with ventricular fibrillation and required basic and advanced cardiopulmonary resuscitation for four minutes.

Thereafter, an echocardiogram was performed, which showed akinesis of the mid and apical segments with hypercontractility of the basal segments, and severe left ventricular dysfunction (left ventricular ejection fraction 33%). The right ventricle was slightly dilated with decreased systolic function and tricuspid annular plane systolic excursion (TAPSE) of 10 mm (Figure 1). There was a mobile hyperechogenic image in the right atrium swinging between the inferior vena cava and the right atrium, which could correspond to a thrombus in transit.

She was managed with Alteplase and anticoagulation, and the hemodynamic status improved. (Figure 2) The patient underwent coronary angiography and left ventriculography. The coronary arteries showed no significant obstructions but the ventriculography evidenced apical ballooning (Figure 3). The cause of cardiac arrest was interpreted as pulmonary embolism combined with stress cardiomyopathy. The patient had a favorable clinical course. An echocardiogram performed 10 days later revealed complete improvement of the systolic function in both ventricles, normal wall motion and absence of thrombus in transit.

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Address for reprints: Edwin A. Rodríguez Arias, Unidad de cuidados críticos cardiovasculares - Hospital de Clínicas José de San Martín. Av. Córdoba 2351, Buenos Aires, Argentina, CP 1120 - e-mail: edwin2721rodriguez@gmail.com



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¹ Cardiovascular Critical Care Unit, Hospital de Clínicas José de San Martín Buenos Aires, Argentina.

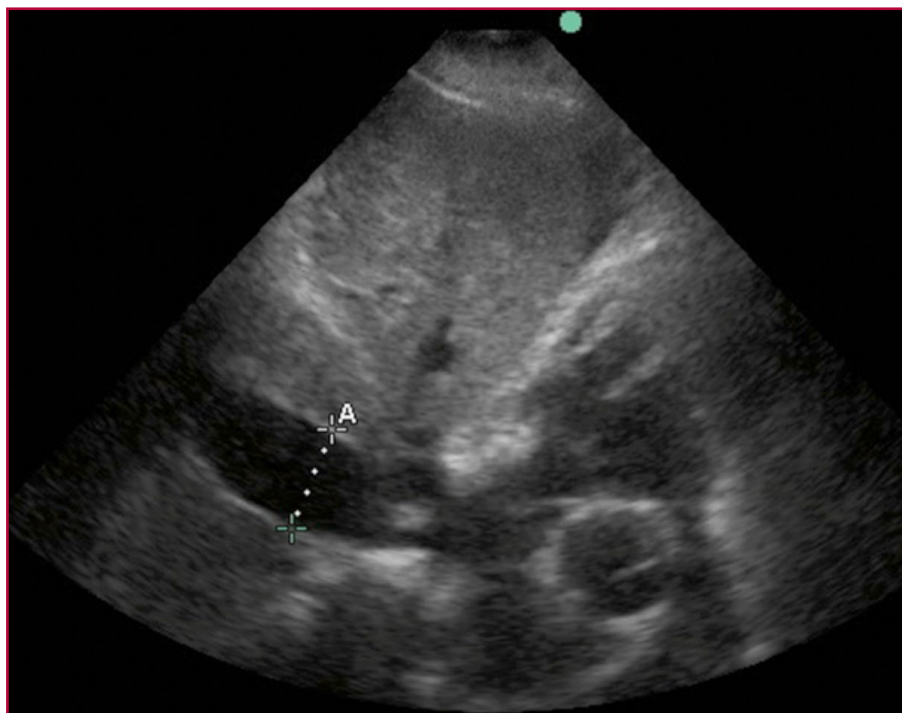


Fig. 1. Four-chamber apical view. Depressed contractility in mid-anterior segments with normal wall motion in basal segments. The right chambers are dilated and the septum is flattened.

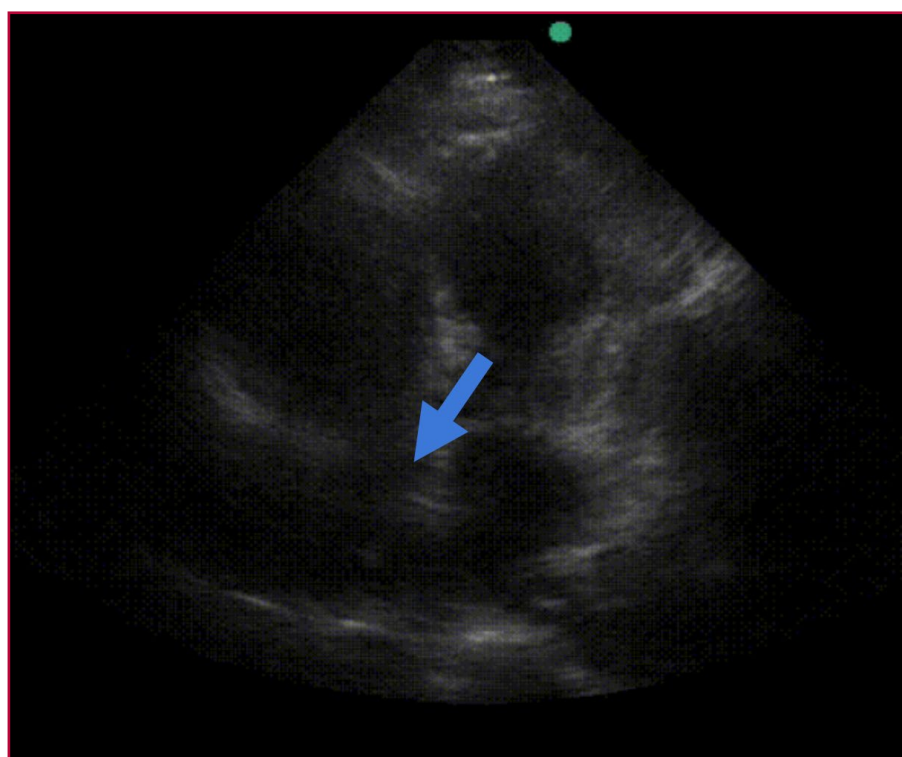


Fig. 2. Subcostal view. The arrowhead shows a hyperechogenic image in transit between the inferior vena cava and the right atrium, suggestive of a thrombus in transit.

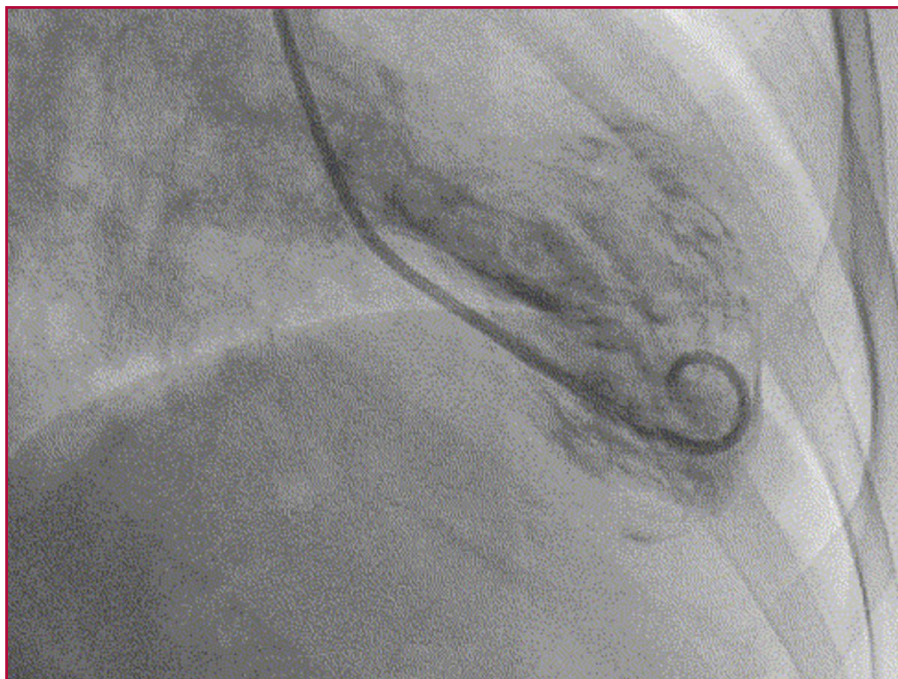


Fig. 3. Ventriculography with typical apical ballooning.

Conflicts of interest

None declared.

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William Harvey (III) De Motu Cordis (Second Part)

JORGE C. TRAININI ^{MTSAC}, 

We continue with the analysis of De Motu Cordis, and each of its chapters

Chapter I. "The Author's Motives for Writing"

Harvey describes the difficulties he encountered in proving his theory. "*I came to think, [he says] with Fracastoro, [a Renaissance epidemiologist], that the motion of the heart was only to be comprehended by God.*" Because the heart moved so fast, Girolamo Fracastoro (Verona, 1478-1553) had expressed this concept in his book *De sympathia et antipathia rerum* (Venezia, 1546).

His own words certify that Harvey had been teaching the concepts of circulation since 1616, in the lectures of anatomy of Praelectiones Anatomiae of the London Medical College, a fact that is recorded in the manuscripts made for those classes. He explains that he wrote De Motu Cordis due to conflicting views on this circulatory description. His teacher, Fabrizio d'Acquapendente, did not cover this topic in depth in his work, making it necessary for him to do so.

Chapter II. "The Motion of the Heart as Seen in the Vivisection"

To better understand cardiac motion, he observes the motion of the heart in cold-blooded animals (toads, snakes, frogs, and fish) because their heartbeats are slow. Here, he demonstrates the different phases of the organ's function, providing an understanding of systole and diastole. With this view he opposes the doctrine of Galen, who believed that the activity of the heart was manifested in dilatation, by means of the "*vis pulsifica*."

Chapter III. "Of the Motion of Arteries as Seen in the Vivisection"

He considers that the arterial pulses are directly related to the activity of the heart that pushes the fluid. Therefore, once again, Galen's theory of "*vis pulsifica*" is disproved. Harvey spoke of the synchrony between

cardiac systole and peripheral pulsation, but he did not notice the delay in the arterial pulse, which was related to the location of the vessel being examined. It is important to remember that during that time, clocks only had one hand that marked the hours. It was not until 1707 that the Englishman John Floyer (1649-1734) published *Physicians' Pulse Watch* where he described the use of a watch to measure the pulse. The first to refer to this time difference was Weibrecht in 1734. In 1834, E. H. Weber found a delay in the submaxillary artery of 1/6 or 1/7 seconds, corresponding to an average velocity of blood propagation of about 8.5 meters/second.

Regarding this topic, he refers to Aristotle who mentions in his books *De animalibus* and *De respiratione* the simultaneous occurrence of arterial pulsation and cardiac activity.

Chapter IV. "Of the Motion of the Heart and its Auricles as Seen in the Vivisection"

Harvey made distinctions between the atria and the heart, which is why this chapter is titled as such. This differentiation was a legacy of Galen, who considered the atria to be mere dilatations of the vena cava, while the ventricles formed the structure of the heart.

Rebutting Jean Riolo, author of *Anthropographia* (1649), and Gaspar Bauhin (Switzerland, 1550-1624), he mentions that there are two movements of the heart and not four, emphasizing that the heartbeat is initiated in the atria. In one paragraph, he states: "*Dividing them into fragments is also futile as each fragment continues to contract and relax even after being separated*". This concept constitutes a description of what was later called cardiac automatism. He also mentions that the atrium is the first to beat, "*primum movens*", and the last to die, "*ultimum moriens*".

Chapter V. "Of the Motion, Action, and Function of the Heart"

In this chapter, Harvey explains how blood circulates



due to the movements of the heart and mentions that the "*vena arteriosa*" is an artery in both function and structure. Regarding the heart sounds, he explains that "*each time the heart delivers blood from the veins to the arteries, it produces a pulse that can be heard within the chest*". Many detractors denied this sound. Later, although these sounds were not disregarded, they were considered to be unimportant. It was not until 1819 that the Frenchman René Téophile Hyacinthe Laennec (1781-1826) interpreted this semiological finding, in his text *Traité de l'auscultation*.

He argues that the lack of understanding of the close relationship between the heart and the lungs "has been the main cause of doubt and error" in the understanding of cardiac physiology. He refutes the idea of blood passing through the septum "*as I have previously disproved*".

Chapter VI. "Of the Course by Which the Blood is Carried from the Vena Cava into the Arteries, or From the Right into the Left Ventricle"

He admirably describes fetal circulation, mentioning the "*ductus arteriosus*" and the foramen ovale. He provides a reasonable explanation based on the fact that the obliteration of fetal passages coincides with the initiation of pulmonary function and relates this fact to blood flowing from the right ventricle to the left ventricle through the lungs.

Harvey asks himself: "*Why does Nature, which always does what is best, [Aristotelian reference] completely close the various open routes after birth which she had formerly made use of in the embryo and fetus, and still uses in all other animals?*". It was necessary to wait until 1660 to understand this problem when Robert Boyle (Englishman, 1626-1691) described the chemistry of respiration. At that time, Harvey interpreted that the blood was sent through the lungs to be tempered according to the prevailing Galenic concept. In any case, his statement "*about the need and uses of air*" left the question open to later knowledge. The chapter ends with an emphatic and clear description of the pulmonary circulation.

Chapter VII. "Blood Passes Through the Lung Parenchyma from the Right Ventricle of the Heart to the Venous Artery and the Left Ventricle"

He categorically affirms that blood passes through the pulmonary tissue. He even reminds the Galenists that Galen himself admitted the circulation of a small portion of blood from the "*vena arteriosa*" to the "*arteria venosa*". In Harvey's exact words: "*The very words of Galen fully confirm as a truth that blood can be transmitted from the vena arteriosa to the arteria venosa and from there to the left ventricle*". He also acknowledges Colombo, whom he calls "*the most expert and erudite anatomist*", as the discoverer of the passage of blood through the lungs.

In reference to the usefulness of the sigmoid valves, that Galen had already described in *De usu partium*,

he wrote: "*If our Maker had not instituted these supplementary membranes [the valves], an inconvenience would result...The valves have all a common use: preventing matter from returning into the opposite direction.*"

The concept of the importance of the right ventricle in animals with lungs is extremely valuable. This represents evolutionary reasoning prior to the development of phylogenetic theories. Literally, he writes: "*Nature, when she ordained that the same blood should also pass through the lungs, saw herself obliged to add the right ventricle.*" By the end of the chapter, he links this idea to that of the pulmonary blood course: "*The right ventricle was made for the sake of the lungs, and for the transmission of the blood through them, not for their nutrition.*"

Chapter VIII. "Of Quantity of Blood Passing Through the Heart from the Veins to the Arteries and of the Circular Motion of the Blood"

From the quote "*Alea jacta est!*" (the die is cast), taken from Julius Caesar, he expresses his concern. This is supported by numerous experiments conducted on circulation to gather the necessary evidence. His statement, "*I began to think whether there might not be a motion, as it were, in a circle*", establishes his concept of the circulation of the blood.

Harvey relates his circular theory of the perpetual return of the blood to Aristotle's cosmology and the motions of the stars, which he mistakenly also considered circular. From the historical process, let us recall that as early as 1609, Johann Kepler (Germany, 1571-1630) described that planets move in elliptical orbits and obey fundamental laws.

Chapter IX. "The existence of a circular movement of blood based on the confirmation of a first hypothesis"

In the search for truth through demonstration, he considers three key items to reach truth:

- 1) The volume of blood that flows from the vena cava to the right ventricle, then to the left ventricle through the lungs, and finally through the aorta into the body is too great to be solely derived from ingested food, as Galen had imagined.
- 2) The body sends blood to its various parts in larger quantities than necessary. Therefore, it is incorrect to assume that blood is continuously produced.
- 3) The veins return this blood to the heart.

Harvey begins his deductive process within this general scheme. Regarding the amount of blood needed, Galen claimed that the blood expelled by the heart was constantly consumed by tissues. To refute this concept, which Harvey calls the "*first hypothesis*", he introduces the "*more mathematico*" method (Desiderio Papp), which involves quantitative reasoning in medicine. He calculates that the heart beats between 1000 and 3000 times - on average 2000 - every half an hour. Considering that the left ventricle has a capacity of

one and a half ounces* (47 g) and sends no less than one-eighth of that volume to the aorta with each systole, which is equivalent to one to two drachms* (6 g), we can infer that in that time interval, it ejects 3000 drachms of blood (about 12 kg). This large amount of blood cannot be continuously produced from the

food in the liver. As a consequence of this quantitative analysis, he writes: "*Blood could not move if it did not walk out and return making a circuit*".

In a second demonstration of this first hypothesis, he turns to vivisection by means of arteriotomy, stating: "*The whole of the blood may be withdrawn in the course of half an hour, until it is exhausted*". He clarifies that the arteries only receive blood from the heart and not from the veins.

* An ounce is equal to 8 drachms, and a drachm is equal to 3.89 grams.

JORGE THIERER^{MTSAC} 

Surprising result, or not so much? In frail elderly people with atrial fibrillation, the routine switching of vitamin K antagonists to direct oral anticoagulants is not advisable. FRAIL-AF Study

Joosten LPT, van Doorn S, van de Ven PM, Kohlen BTG, Nierman MC, Koek HL et al. Safety of Switching From a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients With Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial. *Circulation* 2024;149:279-89. <https://doi.org/10.1161/CIRCULATIONAHA.123.066485>

The incidence and prevalence of atrial fibrillation (AF) increase with increasing age and the presence of comorbidities. It is well known that AF is a risk factor for the occurrence of stroke, heart failure (HF), kidney failure, cognitive impairment, and cardiovascular and all-cause mortality. Specifically, in patients with AF, stroke prevention is a primary objective, and oral anticoagulant treatment aims to achieve this. Oral Vitamin K antagonists (VKAs) have been surpassed in the last two decades by direct oral anticoagulants (DOACs), which in large clinical trials were shown to be more effective in preventing stroke, with a decrease in the rate of bleeding attributable to anticoagulation. DOACs also offer the advantage of their use not requiring periodic coagulation tests, and greater stability in the therapeutic range. However, a high proportion of elderly patients continue to use VKAs instead of DOACs. The causes are varied, but the presence of frailty (a condition that involves biological vulnerability, dependence on care and a diminished capacity to resist stressors) is one of marked importance. We know that frailty is a condition that, like AF, increases with age, and that the coexistence of both conditions obscures the prognosis. The prevalence of each one increases in the presence of the other; frail patients have been underrepresented in large DOAC trials, and therefore there is no conclusive evidence regarding the superiority of these agents in frail patients with AF.

The FRAIL-AF clinical study, multicenter, randomized, open-label, pragmatic, was designed to demonstrate the superiority of DOACs over VKAs in elderly, frail patients with AF, already anticoagulated with VKAs, and in which a strategy of switching to treatment with DOAC was compared to remaining on usual anticoagulation. They had to be at least 75 years old and have a Groningen Frailty Indicator (GFI) val-

ue ≥ 3 . This indicator includes 4 questions on mobility limitations, 2 on visual or hearing impairment, one on unintentional weight loss, 6 on cognitive impairment and psychosocial limitation and one on global physical fitness. Each question answered positively adds one point, the maximum is 15, and a higher score means greater frailty. Patients with AF of valvular origin and those with glomerular filtration rate < 30 mL/Min/1.73m² were excluded. In the crossover arm to a DOAC, it was proposed that after suspending the VKA, the new treatment could be started with an international normalized ratio (INR) value < 2 , but when certain excess bleeding was verified, it was decided that the DOAC could be started with an INR < 1.3 . In the VKA arm, a target INR between 2 and 3 was set. The primary end point was the occurrence of major bleeding or non-major but clinically relevant bleeding (NMCR). Major bleeding was defined as fatal bleeding, bleeding that occurred in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular that led to a compartment syndrome), bleeding which generated a drop in hemoglobin ≥ 2 g./dL or required a transfusion of at least 2 units of blood or red blood cells. NMCR bleeding was defined as bleeding that required an in-person medical consultation, an intervention by health personnel, hospitalization, or an increase in the level of care. It was assumed that with an annual incidence of major bleeding or NMCR between 11% and 15% in the VKA arm, for a two-tailed p value < 0.05 and a power of 80%, 1250 patients in each arm would be necessary to demonstrate a risk reduction of 20% to 30% in the DOAC arm. The analysis was done by intention to treat.

Between 2018 and 2022, 2621 patients underwent screening, but 662 were finally included in the DOAC arm and 661 in the VKA arm. The mean age of the patients was 83 years, and the median GFI was 4; 38.7% were female, just over 50% of the cases were permanent AF and almost 30% were paroxysmal AF; the median CHA₂ DS₂ -VASc score was 4. The DOAC used was at the discretion of the general practitioner: in just over one half of the cases it was rivaroxaban, and the rest was mainly divided between apixaban, edoxaban and dabigatran.

During a mean follow-up of 344 days, 6.7% of the DOAC arm and 7% of the VKA arm patients died. The incidence of the primary endpoint was 15.3% in the DOAC arm and 9.4% in the VKA arm (HR 1.69, 95% CI 1.23-2.32; p = 0.0011). In the DOAC arm

there was more gastrointestinal (2.6% vs 0.6%) and urogenital (3% vs 1.7%) bleeding. There was no difference in intracranial bleeding. The significant difference in the incidence of bleeding between both arms was verified after 100 days of follow-up: HR 1.17 (95% CI 0.79-1.96) until day 100, and 2.10 (95% CI 1.40-3.16) then. The difference between both arms was in the incidence of NMCR bleeding: 12.7% vs 7.4%. On the other hand, the incidence of major bleeding was similar: 3.6% vs 2.4%. The incidence of thromboembolic events was also similar: 2.4% vs 2%.

When deciding anticoagulant treatment in an elderly patient with AF, we often lean towards DOACs. The reduction in embolic events and hemorrhagic stroke compared to the use of VKAs is a compelling reason. To this we add that it is not necessary for the patient to undergo frequent tests to control the INR, which facilitates anticoagulation and makes transfers unnecessary in patients who often lack adequate family support, or with mobility limitations. In the 4 large, randomized trials of DOACs vs warfarin (RE-LY with dabigatran, ARISTOTLE with apixaban, ROCKET-AF with rivaroxaban and ENGAGE AF with edoxaban), with 71 683 patients included, the use of DOACs was associated with a decreased risk of major bleeding or NMCR regardless of age. However, older patients had a higher risk of major bleeding with DOACs than younger patients: each 10-year increment marked an increase of 10.2% with the standard dose and 17.6% with the reduced dose (although it could seem like a contradiction, let us remember that patients with a reduced dose per se have more comorbidities and risk than patients with a usual dose). In both ROCKET-AF and ARISTOTLE trials, polypharmacy entailed a greater risk of bleeding. Why do we emphasize these aspects? Because age and comorbidities are generally considered the greatest predictors/indicators of frailty. Frail patients were under-represented in the trials we mentioned, as is generally the case across the spectrum of clinical research. In FRAIL-AF, however, there was a decision to focus on this type of patient, and the criteria for considering frailty (included in the GFI) were much broader, as corresponds to an entity with multiple layers of meaning. We must remember that the included population consisted of patients who were already treated with VKAs and had tolerated them. So, there was undoubtedly an initial advantage for patients who remained on VKA: the chance of experiencing significant bleeding was lower, because they were already treated and there had been no indication to stop treatment until now. The results of the FRAIL-AF study go against the general indication. They demonstrate, in an increasingly large subgroup of patients with a high prevalence of AF (elderly, with a high rate of comorbidity) an increased risk of non-major, but clinically relevant, bleeding. A more detailed analysis of the data would be necessary to detect higher risk groups, but with the information available, caution is neces-

sary when deciding to cross from a VKA to a DOAC in this population. Each case must be analyzed individually. It should be clear, however, that these results do not automatically apply to anticoagulation-naïve patients in whom initial treatment must be decided, and that frail elderly patients with VKA intolerance were not represented in the study.

Combination of non-steroidal mineralocorticoid receptor antagonists, gliflozins and glucagon-like peptide-1 receptor agonists (GLP-1 RA) in diabetes with albuminuria: the new standard of care?

Neuen BL, Heerspink HJL, Vart P, Claggett BL, Fletcher RA, Arnett C et al. Estimated Cardiovascular Lifetime, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria. *Circulation* 2024;149:450-62. <https://doi.org/10.1161/CIRCULATIONAHA.123.067584>

The presence of albuminuria in the context of diabetes indicates renal compromise and endothelial dysfunction. The prognostic impact of this combination is fearsome: accelerated deterioration of renal function, need for dialysis, marked increase in cardiovascular morbidity and mortality and mortality from all causes. For a long time, therapeutic alternatives in this context were scarce: demanding control of risk factors, reduction of sodium intake, and meeting strict glycemic goals were postulated. Regarding specific pharmacological treatment, there was only room for inhibitors or antagonists of the renin-angiotensin system. In the last decade, new therapeutic agents have appeared: sodium-glucose cotransporter 2 inhibitors (SGLT2i, or gliflozins), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and non-steroidal mineralocorticoid receptor antagonists (nsMRA), mainly finerenone. Each of these drugs has been shown to improve vital prognosis in patients with diabetes and albuminuria. Very few patients in these trials were treated with the combination of at least 2 of the families, and until now we do not know the results of ongoing clinical trials that explore these combinations. Until these results arrive, we can ask ourselves if, with the data from the studies that evaluated each drug separately, there is sufficient reason to use a treatment in which the three families of drugs coincide.

To answer this question, an actuarial analysis was carried out that took into account a) the individual data from two trials with SGLT2i, both with canagliflozin: CREDENCE, in patients with type 2 diabetes, renal failure and albuminuria, and CANVAS, in patients with diabetes and established cardiovascular disease or multiple risk factors; in total 14 543 patients; b) data from a meta-analysis of 8 studies with GLP-1 RA in the context of type 2 dia-

betes with or without established cardiovascular disease: ELIXA with lixisenatide, LEADER with liraglutide, SUSTAIN-6 and PIONEER-6 with semaglutide, EXSCEL with exenatide, Harmony Outcomes with albiglutide, REWIND with dulaglutide, and AMPLITUDE-O with efpeglenatide; in total 60 080 patients; and c) combined data from 2 studies with finerenone in type 2 patients, renal failure and albuminuria, FIDELIO-DKD and FIGARO-DKD, in total 13 026 patients. The primary endpoint was considered the incidence of major adverse cardiovascular events (MACE), but also the incidence of hospitalization for heart failure (HHF), progression of renal failure, cardiovascular mortality (CVM), and all-cause mortality. The placebo arm of CANVAS and CREDENCE was taken as the control group (patients with type 2 diabetes and urinary albumin-creatinine ratio > 30 mg/g), and the effect of the combination of 2 of the three families, and of the 3 combined (which we call triple therapy, TT), on those end points was defined through indirect comparisons.

In a median follow-up of 2.5 years, among patients in the placebo arm of CANVAS and CREDENCE trials, incidence of MACE was 12.6%, HHF 5.8%, progression of renal failure 7.2%, CVM 6.7% and all-cause death 9.5%. Regarding MACE, each of the treatments in isolation implied HR between 0.83 and 0.90; the combination of two of them, depending on the case, HR between 0.72 and 0.77; and TT an HR 0.65 (95% CI 0.55-0.76). For HHF, isolated interventions had HR between 0.64 and 0.78; the combinations of two of the three, HR between 0.50 and 0.69; TT an HR 0.45 (95% CI 0.34-0.58). For the progression of renal failure, one intervention was associated with HR between 0.63 and 0.67, two interventions with HR between 0.49 and 0.66, and TT, an HR of 0.42 (95% CI 0.31-0.56). For CVM, the HR ranged between 0.84 and 0.88 for one treatment, between 0.74 and 0.77 for two, and the HR was 0.64 (95% CI 0.51-0.80) for TT. Finally, for all-cause death, the HR of one intervention varied between 0.85 and 0.89, those of 2 interventions between 0.76 and 0.78, and TT implied an HR of 0.67 (CI 95 % 0.55-0.80). In terms of absolute risk reduction, 3-year TT involved 4.4% for MACE, 3.4% for HHF, 4.4% for progression of renal failure, 2.4% for CVM, and 3.1% for all-cause death. This implied for a 50-year-old patient an event-free survival gain of 3.2 years for MACE and HHF, 5.5 years for the progression of renal failure, 2.2 years for CVM and 2.4 years for all-cause death. The benefits were greater the younger the patients.

The combination of diabetes and albuminuria (a condition we usually call diabetic nephropathy) is, as we said, one of the most ominous in the context of cardiovascular disease. The appearance in the last 10 years of various therapeutic alternatives undoubtedly implies a renewed hope for these patients. Perhaps the simultaneity of the emergence of these drugs has caused that, in the clinical trials of each of them,

the others were underrepresented or directly absent. Thus, for example, in the FIGARO study (finerenone vs placebo) only 7.5% of patients were treated with GLP-RA and 8.4% with SGLT2i. The different mechanisms of action (which include, but are not limited to, promotion of autophagy and attenuation of glomerular hyperfiltration in the case of SGLT2i, anti-inflammatory action and correction of metabolic alterations for GLP-1 RA and the antifibrotic action of nsMRA) allow us to understand an additive action when two of these drugs are combined. It has already been demonstrated in animal models or in mechanistic studies. This synergistic effect remains to be verified when considering randomized trials with clinical endpoints, which are being carried out. In this sense, the analysis we present seems to predict what will happen. But certain limitations must be considered: adherence to the combined treatment is assumed, which must be verified in practice; It is understood that the clinical effect represents a sum of what was achieved with each drug separately, when it is possible that there is some overlap (since some biological effects are coincident) and the magnitude of the observed reduction in risk is less than predicted. On the other hand, the issue of tolerance also arises, and the possible appearance of adverse effects due to the various combinations. In any case, a quadruple therapy for diabetic nephropathy (TT plus the use of inhibitors or antagonists of the renin-angiotensin system) appears on the horizon, as there is a quadruple therapy in heart failure with reduced ejection fraction... and let's note the similarity of the components in both cases. And, as we have said so many times, it is impossible to forget the issue of access to the best treatment, so that what we discuss can actually be good news for the majority of patients.

Women obtain greater prognostic benefit than men from physical activity, and with less effort

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Although clinical practice guidelines emphasize the importance of physical activity (PA), with at least 150 minutes of moderate PA or 75 minutes of vigorous PA per week, without differentiating between sexes, it has been reported that participation and commitment of women with PA are lower than those of men. Reasons range from differences in tolerance to PA, to different physiological responses and, of course, sociocultural factors. This gender gap should be closed, especially in light of the findings of a recent observational study.

For more than 20 years, the Centers for Disease Control and Prevention (CDC) has been collecting data in the USA, in a health survey that is carried out

in all 50 states and the District of Columbia. For this study, data from 646 279 participants surveyed between 1997 and 2017 were considered. Those with a previous diagnosis of cardiovascular disease, stroke, respiratory disease, or cancer, those unable to perform PA, data not available and those with who had presented events within 2 years of being surveyed were excluded. This finally left a sample of 412 413 participants available. All of them provided data on the PA they developed, its frequency, type, and duration. In this way, the number of weekly minutes of PA could be calculated, and how much of it corresponded to moderate to intense PA. We examined the association of PA with cardiovascular and all-cause mortality in men and women, adjusting for age, ethnicity, body mass index (BMI), cardiovascular risk factors, alcohol consumption, socioeconomic factors, access to the health system, marital status, self-perceived health status and chronic health conditions. Participants were considered inactive when moderate/vigorous PA did not reach 150 minutes per week, and active when it was at least 150 minutes. Similarly, they were considered inactive if PA involved less than 2 weekly muscle strengthening sessions, and active if it involved at least 2.

The average age of the participants was 44 years, 54.7% were women. Compared to men, they were slightly older, had a lower BMI, had a lower prevalence of smoking and alcohol consumption, and had a worse socioeconomic status. Among men, 43.1% practiced aerobic PA regularly, compared to 32.5% of women; 15.2% of men and 10.3% of women carried out moderate PA for at least 150 minutes weekly, and 38.9% of men and 28.3% of women carried out intense PA for at least 75 minutes weekly. The average follow-up was almost 12 years. In women, carrying out regular moderate/vigorous PA was associated, compared to being inactive, with a reduction in all-cause mortality of 24% (HR 0.76; 95% CI 0.73-0.80). Among men, the same behavior was associated with a 15% reduction in all-cause mortality (HR 0.85; 95% CI 0.82-0.89), $p < 0.001$ compared to the reduction in women. Among men, the maximum benefit was achieved with 300 minutes of moderate/intense PA per week, with a reduction in total mortality of 18%; Among women, this reduction was achieved with 140 minutes per week, and with moderate/vigorous PA for 300 minutes per week the reduction was 24% ($p = 0.002$ compared to men). Regarding vigorous PA, in men the maximum benefit (a 19% reduction in the risk of overall mortality) was achieved with 110 minutes per week. In women, this reduction was achieved with 57 minutes per week, and with 110 minutes the reduction was 24%. Regarding moderate PA, the maximum benefit in men (20% mortality risk reduction) was seen with 90 minutes per week; In women, the same reduction was achieved with 50 minutes per week. Regular PA also decreased cardiovascular mortality more in women (36%) than in

men (14%), and the same thing happened specifically with muscle strengthening activities (30% vs. 11%).

Regarding muscle strengthening exercises, 27.8% of men and 19.9% of women reported actively carrying them out. This translated into a reduction of 11% in men and 19% in women in the risk of all-cause mortality ($p = 0.005$). Men achieved the greatest reduction, 14%, with 3 weekly muscle-strengthening PA sessions; women achieved the same reduction with just one weekly session.

When it comes to doing PA, men and women have differences. The effort capacity is greater in men, hand in hand with greater muscle mass, heart size, diameter of the airways, and gas diffusion capacity in the alveolus-capillary membrane. In men the ability to do strength exercises is greater, in women those linked to flexibility. However, women have a greater possibility of improving their performance: they have greater capillary density per unit of skeletal muscle mass and a greater supply of oxidative muscle fibers. For the same dose of PA focused on increasing muscle strength, the increase achieved is greater in women, and it is known that muscle strength is a better predictor of survival than mass. So it is that PA seems to offer more advantage in women than in men.

The findings of this large observational study are not unexpected. A meta-analysis of 33 prospective cohort studies demonstrated that PA generates a greater reduction in the incidence of coronary artery disease in women (RR 0.66) than in men (RR 0.79). The current data add up to a reduction in global and cardiovascular mortality. What could be the reason for this different decrease in the risk of coronary artery disease and death? It may be that women start from a more disadvantaged physical condition, so the opportunity for improvement with training is greater. We should not rule out that the difference in the physiological response to PA also implies more favorable changes in women, with greater repercussions. It is striking that this difference in the beneficial effect of PA tends to attenuate with increasing age, suggesting interaction with the estrogenic effect.

The exclusion of events recorded in the first 2 years of follow-up aims to attenuate the effect of reverse causality: a present illness that will trigger an upcoming death may be responsible for lower PA, and not the other way around. Because it is an observational study, there may be, as always, residual confusion: factors unequally distributed between men and women, truly responsible for the observed phenomenon. In any case, the large number of observations and follow-up time (more than 4 million person-years) seems to exclude this possibility. In summary, the evidence presented strongly impels us to advise women to engage in PA, traditionally understood as an area of male domain. As in so many other things, the gender gap must be closed. Women have an advantage that they should not waste.

Microvascular dysfunction and a change in the

diagnostic yield of exercise electrocardiographic stress testing.

Sinha A, Dutta U, Demir OM, De Silva K, Ellis H, Belford S et al. Rethinking False Positive Exercise Electrocardiographic Stress Tests by Assessing Coronary Microvascular Function. *J Am Coll Cardiol* 2024;83:291-9. <https://doi.org/10.1016/j.jacc.2023.10.034>

For decades, the exercise electrocardiographic stress testing (EST) was considered the fundamental test for diagnosing obstructive coronary artery disease in patients who reported angina pectoris or equivalents. The gold standard to define its sensitivity and specificity was, then, coronary angiography, which certified the presence or absence of significant coronary artery disease. Little by little, EST was displaced by other imaging methods (exercise echocardiography, pharmacological stress testing, nuclear cardiology studies) that exhibit greater diagnostic yield. But in recent years we have witnessed notable progress in the pathophysiological understanding of angina pectoris and its substrate, myocardial ischemia. We learned that up to a third of patients with angina present the condition called ANOCA (angina with non-obstructive coronary artery disease), and that a coronary angiography without significant lesions in no way excludes the presence of ischemia. Coronary microvascular dysfunction (CMD) assumes a predominant role in ANOCA, and is also present as a contributing mechanism in angina with obstructive coronary artery disease. If this is so, the concept of a “false positive” when an EST is positive due to ST segment depression in a patient without significant coronary obstruction is called into question. The authors of the article we present dedicated themselves to exploring this concept.

Patients with ANOCA, defined by a fractional flow reserve (FFR) > 0.80, were included; with left ventricular ejection fraction (LVEF) > 50%. Patients with glomerular filtration rate <30 mL/min/1.73 m², significant valvular disease, history of acute coronary syndrome, left bundle branch block, poor quality or uninterpretable ECG tracings, limitation due to non-anginal symptoms, and patients with pacemaker rhythm were excluded. Coronary angiography was performed, and distal coronary pressure and average peak flow velocity (APV) were measured in the left anterior descending artery. Microvascular function was defined in two forms: a) endothelium-independent, with intravenous infusion of adenosine, and b) endothelium-dependent, with intracoronary infusion of acetylcholine. Coronary flow reserve was defined as the ratio between the APV with adenosine and the baseline APV: the presence of endothelium-independent CMD was established if this ratio was < 2.5. The presence of endothelium-dependent CMD was explored with acetylcholine infusion: a flow reserve with acetylcholine (AFR), ratio between coronary flow

with acetylcholine and in basal conditions ≤ 1.5 , was considered an expression of CMD. After a median of 29 days, an EST with Bruce protocol was performed in all patients, and sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for the development of ECG changes in the presence of endothelium-dependent, endothelium-independent CMD or any of them interchangeably were defined.

Of 262 patients initially considered, after excluding those free of symptoms, those who did not have angina, and those who presented some of the aforementioned exclusion criteria, 102 patients were finally included. Of them, 32 developed ischemia in the EST (ischemic group, IG) and 70 did not (non-ischemic group, NIG). There was no difference between them in age, sex, coronary risk factors or functional class. IG patients had a higher prevalence of typical angina (91% vs 73%, $p = 0.04$) and lower hemoglobin values (13 vs 13.7 g/dL, $p = 0.008$). There was no difference between both groups in the development of angina during EST, the prevalence of risk factors, exercise time or mean FFR. All patients in the IG had CMD, compared to 66% in the NIG ($p < 0.001$). The difference was mainly based on the AFR (ratio of 1.2 in the IG and 1.5 in the NIG, $p < 0.001$), the maximum heart rate in the EST (mean of 145 bpm in the IG vs 136 bpm in the NIG, $p = 0.015$) and the product of heart rate and maximum systolic blood pressure (27 662 vs 24 678, $p = 0.039$). Ninety seven percent of the IG patients had AFR ≤ 1.5 , and therefore endothelium-dependent CMD, compared to 56% in the NIG, $p < 0.001$. Regarding endothelium-independent CMD, it occurred in 63% of the IG versus 43% of the NIG, $p = 0.066$. In multivariate analysis, AFR (OR 0.82; 95% CI 0.72-0.93), hemoglobin (OR 0.93; 95% CI 0.89-0.99) and maximum heart rate (OR 1.03; 95% CI 1.00-1.06) were independent predictors of positive EST due to changes in the ECG.

EST had low Sn for detecting endothelium-independent (40%), dependent (44%) or any of them (41%) CMD, hence its poor NPV for any of these forms of CMD. On the other hand, although Sp was also poor for endothelium-independent CMD (77%, with PPV 63%), it was on the contrary very high for endothelium-dependent CMD (97%, with PPV 97%) and absolute for the indistinct diagnosis of one form or another of CMD: 100%, with PPV 100%.

This interesting study allows us to advance in the pathophysiological understanding of the ECG changes evidenced in an EST. Up to this point, in the absence of coronary artery disease, a positive ECG response in EST is interpreted as a false positive. In this specific case, of the 102 patients without obstructive coronary artery disease finally selected, 32 (31%) presented ischemic changes. According to the traditional criterion, they are false positives, and this indicates a specificity of 69%, poor for a stress test. If the true criterion is no longer the presence of obstructive coronary disease, but

of endothelium-independent CMD, the specificity rises to 77%, but if we consider a decreased AFR, expression of endothelium-dependent CMD, we are on the verge of a specificity of 100 %, which is achieved when we accept any form of CMD. What changes, then? What we want to demonstrate. Specificity increases because our true criterion for accepting ischemia is no longer the presence of macrovascular disease but that of CMD. And the gold standard is no longer coronary angiography alone but accompanied by acetylcholine infusion.

Very rich from a pathophysiological point of view, at the moment these findings add little to the usual therapy. It should be made clear that the aforementioned specificity is achieved in a selected group of patients: those with coronary angiography that excluded obstructive coronary disease, and in whom the usual sources of false positive EST results were previously ruled out. Therefore, the interpretation that can be made when these conditions are present is not as precise.

2024 Opening Speech by the President of the Argentine Society of Cardiology

Discurso inaugural de la presidencia de la Sociedad Argentina de Cardiología 2024

Dear colleagues, family, and friends.

Today is the most important day in my professional life, as I am greatly honored and proud to have been appointed President of our house, the Argentine Society of Cardiology.

And I feel even prouder to know that my colleagues have valued my work and my career by selecting me for this position.

I had the tremendous luck and pleasure to have worked for the past 2 years for the board led by Héctor Deschle and Claudio Majul. As I have once said, I think a good leader knows how to create a work environment based on freedom and trust, and both these colleagues share that virtue. Therefore, I want to express my gratitude to both.

The progress made by the SAC throughout its 86 years of history has not just been the result of the work by some visionary. It was due to the generous and committed contribution of each of the presidents; the members of our different boards and commissions; the Argentine Journal of Cardiology (RAC); the Argentine Cardiology Foundation; the districts, councils, and local departments that are part of SAC País; the lecturers delivering courses; technicians, nurses, and non-medical staff, and particularly, every member of our society. I also want to say thank you very much to all of them.

Today I have the duty of representing them all, and in order to grow, we need to continue to recreate that work ethic that makes us proud to be part of the SAC. Personally, I am committed to that goal and certain that each member of our Society agrees with me, as the SAC makes us all better because of our effort and merit.

Nowadays, the paradigm implies living with no role model to look up to. Forty years ago, I attended case conferences every Wednesday and took my first steps in our Councils hoping to be inspired by and

learn from this or that head of department, dreaming that one day I might be able to follow their steps. Personally, that worked for me.

Today relationships tend to be more fluid and transversal. Fortunately, technology has made knowledge highly accessible, and the utopia of resembling someone else has been lost in time. This new reality, in turn, has made us more disconnected and sometimes leads to a deep feeling of personal and professional loneliness.

And what do we receive from the SAC? The answer to this question may be personal. I would like it to be the place where you belong, a place open to dialogue, the frame for your professional development sharing ideas and experiences, your possibility in this ethereal universe of becoming an inspiration yourself, an environment where you can bond with colleagues to defend your interests and the interests of your community. It is truly amazing to witness the SAC grow despite the conditions in our country. I believe we are ALL making a great contribution.

Those of us who have had the honor to preside this Society never intended to redefine our institution, but rather to do our best for the SAC to continue to expand its brilliant and prolific history.

My proposal has several parts:

1. We shall continue to provide resources and work hard to meet all the Index Medicus requirements so that our Journal is admitted, as it certainly deserves to be.
2. We shall continue to reinforce our bonds with every international association, giving rise to a space of integration and cooperation. We are about to sign an agreement with the Uruguayan Society of Cardiology (SUC) that, starting next year, will turn our biannual course into their cardiology training platform, including Uruguayan cardiologists as lecturers.



3. We are going to renew the Young SAC Department, encouraging their involvement in personal and collaborative projects with other departments and councils, and foster bonds with similar departments from different international associations. We will make every effort for members to be able to take part in international congresses, submit papers, and become more active in other activities by the Society. We also aspire to a closer relationship with the Argentine Council of Cardiology Residents (CONAREC). Always respecting individual needs and expectations, we need to promote participation among our younger members so that they continue to work and grow in our Society, as they will eventually become our leaders.
4. We would like to issue the first "SAC Practical Handbook of Cardiology" providing simple and practical answers to the most common clinical situations in the medical office or hospital. This project will become real thanks to the deep involvement of every area in our Society.
5. We shall work more closely with the Argentine Cardiologic Foundation, as we are certain that our goals can be boosted by this collaboration.
6. We are organizing the first Congress on Cardiometabolic Prevention and Hypertension, designed by the Councils of cardiometabolism, hypertension and cardiovascular prevention and sure to become a success. This is in addition to our traditional and consolidated Imaging Congress, for which we intend to find a more attractive venue.
7. Ten inter-district conferences and various other workshops have been planned. SAC País has developed a cardiology course for non-cardiologist physicians starting next year. We are also working to organize and support rotations around sites in Buenos Aires for residents in training from other parts of the country and taking the Biannual SAC Course to be able to select one rotation based on their merit. A central policy of our Society is to offer any means needed to consolidate the SAC throughout the country.
8. We have created the National Intersocietal Relations Department to coordinate exchanges and activities with local scientific societies, as we need to improve our perspective with a more comprehensive view on cardiovascular conditions. We are also announcing a new Council called Cardiac Ecology and Healthy Habits, important for the promotion of cardiovascular health.
9. We shall encourage the role of the Research Department and seek financial support for our registries. We need to be aware of our reality. Applications will be opened throughout the country to grant scholarships for original papers and will continue to provide the best paper published in the last year with the RAC Award.
10. We have signed an agreement with the Argentine Catholic University (UCA) for a Higher University degree on Nuclear Cardiology (UCA-SAC) next year, in addition to the existing postgraduate degree on Hypertension, Cardiometabolism and Dyslipidemia that we have successfully been teaching together for 2 years.
11. Five additional ongoing virtual courses will be added to the 39 courses we already offer. Next year we shall use a percentage of the revenue to pay for the fees of our colleagues who prepare the lectures. We will also deliver a choice of 3 SAC courses at half their price to every department, every Council and every district in SAC País, and the relevant authorities shall decide which members are receiving the benefit. We are aware that this is merely symbolic in this context, considering the huge effort that has been made, but it is critical to invest in our human resources, the most valuable and essential resource for our Society.
12. Next year we are holding and enjoying our 50th Argentine Congress of Cardiology. We will do our best to make it a very special event.
This year our Society has worked hard to protect our professional practice and shall continue to do so. In the past, and maybe to this date, many believed that the Society had to focus only on scientific activities. Times have changed. We are healthcare workers and should be able to highlight the value of the work we do. The SAC cannot be indifferent to the economic reality affecting our cardiologists. We are not a labor union. We have the Argentine College of Cardiology for that. However, we are joining forces with other scientific societies to open any necessary means of communication with fund providers in order to defend our medical fees. We intend to submit a proposal to the relevant political authorities regarding any actions needed to ensure proper medical practice and to protect our professional rank. We cannot just be witnesses to this overwhelming reality. We have the responsibility of being protagonists and protecting the wellbeing of our cardiologic community and patients. We have already made some progress in this sense. To conclude, it is now time to express my gratitude to others, as we always need others to become who we are.
I would like to thank the more than 100 residents who have come to our clinics since 1993, renewing day after day my desire and joy to continue to learn and teach. I thank my colleagues and friends Adrian Charask and Enrique Fairman for creating a respectful work environment where each of us has been able to develop as a group and as individuals.
I also thank Carlos Bertolasi, Carlos Tajer and Carlos Barrero for their relevant involvement in my professional development. My deepest

thanks to Carlos Barrero: my boss, my friend, and a brother I was given as a gift of life. Thanks to Enrique Abramovich for helping me see my strengths and understand my weaknesses. Thanks to my siblings in law, nieces, and nephews. Thanks to my three children,

Luli, Mica, and Rocco, for letting me transcend through them every single day in my life, and a big thank you to Yanina, for everything.

Víctor Mauro ^{MTSAC, }

President of the Argentine Society of Cardiology