ARGENTINE JOURNAL OF CARDIOLOGY

SCIENTIFIC ORGAN OF THE ARGENTINE SOCIETY OF CARDIOLOGY

Argentine Journal of Cardiology is property of the Sociedad Argentina de Cardiología.
ISSN 2314-2278 ISSN electronic version 2314-2286 - Trademark registry N° 5198451
Indexed en SciELO, Scopus, Embase, LILACS, Latindex, Redalyc, Dialnet y DOAJ. Included in the U.S. National Library of Medicine (NLM)
VOL 93 N° 1 FEBRUARY 2025
Scientific and administrative address
Azcuénaga 980 - (1115) Buenos Aires - Argentina / Tel.: +54-11-4961-6027/8/9 / Fax: +54-11-4961-6020 / e-mail: revista@sac.org.ar
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VOL 93 Nº 1
FEBRUARY 2025

Summary

EDITORIAL

Prognosis After Myocardial Infarction: Should we Still Use the Calculator or Just Measure a Biomarker?

Pronóstico del infarto: ¿seguimos con la calculadora o basta con un biomarcador?

MARCELO TRIVI[1, 2, 3, MTSAC]

"Simplicity is the ultimate sophistication"
Leonardo da Vinci

One of the great challenges of cardiology has been and continues to be to accurately establish the immediate and long-term prognosis of patients with acute coronary syndromes (ACS), particularly in cases of acute myocardial infarction (AMI). This is an imperative question for the patient and family once the hyperacute phase of the first hours of the event is over.

Significant advances in medicine do not occur in a continuous fashion; rather, they follow a step-by-step pattern. Undoubtedly, the incorporation of troponins in the biochemical diagnosis of ACS represents a breakthrough, one of those that mark a milestone. Indeed, this incorporation has forced a redefinition of the diagnosis of AMI. (1,2)

But the advent of high-sensitivity cardiac troponins also allows for an accurate quantitative measurement of myocardial injury size. Thus, one can detect from microscopic infarcts to large ones. As there is a significant correlation between the infarct size and prognosis after AMI, one may feel inclined to use troponin values to predict patients' outcome. (3,4)

Among the multiple risk scores that have been used to measure the prognosis of patients with ACS, the GRACE score and the CRUSADE score are the most widely used tools to estimate risk of ischemic events or bleeding, respectively. (5) These scores include clinical, biochemical and electrocardiographic data, among other variables. The original GRACE score used elevated biomarkers as categorical variables (yes-no). A recent modification has incorporated high-sensitivity cardiac troponin as a quantitative variable, thus improving its prognostic value. (6) The extensive use of these scores makes it possible to compare different populations for statistical, demographic, and scientific purposes.

Could troponin measurement at presentation compete with these well-established scores? An additional problem exists: there are no universal high-sensitivity troponin values. Cardiac troponins I and T have different cut-off values, so it is recommended to use the 99th percentile to differentiate between normal and pathological values. Beyond the controversy regarding the superiority of one over the other, there appear to be negligible disparities in their prognostic significance. (7)

The article published in this issue of the Journal by Kersten et al. (8) proposes a highly innovative solution to this problem: the utilization of a score derived from the troponin value at presentation as multiple of the 99th percentile value to balance the measurements of the various types of troponins. To validate this new score, they compare it with the performance of the GRACE and CRUSADE scores by analyzing ROC curves, using the ReSCAR registry, published in this Journal by Mirza Rivero et al. in 2022, with about 1000 patients from Argentina, and where the present study was a pre-specified analysis. (9)

The results show that the predictive ability is similar to that of traditional scores for non-fatal events, and somewhat lower for fatal in-hospital events and at 1-year follow-up. Interestingly, the area under the ROC curve of 0.79 (95% CI 0.73-0.85) for 1-year mortality of the GRACE score in this study is very similar to the one published by Lucrecia Burgos et al. (0.76, 95% CI 0.70-0.82) from a similar registry of the National Council of Cardiology Residents, CONAREC XVII,(10) which supports the reliability of the data obtained.

A study conducted in Israel by Loutati R et al. with non-ST-segment elevation MI patients demonstrated a clear association between high-sensitivity troponin I quartiles at presentation and mortality at 1 year. (11) Unlike the Argentine study, this study only measured

Rev Argent Cardiol 2025;93:1-2. https://doi.org/10.7775/rac.v93.i1.20860

SEE RELATED ARTICLE: Rev Argent Cardiol 2025;93:25-30. https://doi.org/10.7775/rac.v93.i1.20852

Correspondence: Marcelo Trivi. Blanco Encalada 1543. CABA. E-mail: mstrivi@icba.com.ar

[1] Instituto Cardiovascular Buenos Aires, Autonomous City of Buenos Aires
[2] Head of Cardiovascular Medicine. Instituto Cardiovascular Buenos AIres, Autonomous City of Buenos Aires, Argentina
[3] Director of the Consensus on Non-ST-Segment Elevation Acute Coronary Syndromes of the Argentine Society of Cardiology

troponin I and the selection of the population was more homogeneous, although it supports the same hypothesis.

Which are the clinical values of these findings? In my opinion, a single determination of troponin levels at presentation, which is standard practice in our country and worldwide in all types of hospitals (at least we wish it were so), can be used to estimate the prognosis of patients quite reliably, revaluing the extent of myocardial injury as the main prognostic value in AMI. The addition of the score derived from the troponin value at presentation as multiple of the 99th percentile value is extremely valuable to balance the different types of troponins and standardize its value.

Obviously, the addition of clinical data further improves the predictive ability. These findings underscore the idea that, although troponin is a key biomarker in the evaluation of ACS patients, its interpretation should not be performed in isolation. (12) Integration with other clinical factors, such as those contemplated in GRACE and CRUSADE scores, remains essential for more accurate risk stratification. In this sense, the score based on the 99th percentile troponin value could be considered a complementary tool but should not replace the traditional risk prediction models.

In a time when randomized studies are held in high regard and registries are criticized, this publication serves as a model for obtaining valuable scientific information from a registry. It employs ideas prior to conducting the registry, as recommended by the scientific research methodology.

In fact, this study received the Dr. Raúl Borracci award at the last SAC Congress. The lack of sponsorship for this study, which is common in our environment and rare in other countries, is a credit to the authors and also to the researchers who made its execution possible.

Conflicts of interest

None declared

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

Ethical considerations

Not applicable.

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EDITORIAL

New Genetic Variants Associated with Acquired Dilated Cardiomyopathy

Nuevas variantes genéticas asociadas a miocardiopatía dilatada adquirida

MARIANNA GUERCHICOFF

BASIS OF THE POLYGENIC RISK SCORE

In 2003, the Human Genome Project revealed the first sequence of the human genome: an 'instruction manual' contained in the deoxyribonucleic acid (DNA), a molecule present in the nucleus of all cells, made up of 4 nucleotides or bases, cytosine (C), guanine (G), thymine (T) and adenine (A), in a sequence of 3300 million of them, which determines the genetic code. (1). Thus the era of genomic medicine was born.

Genomics is the scientific study of DNA. All the information to "manufacture" a human being and maintain its functions represents only 1% of the DNA. "Segments" of DNA with instructions for making proteins are called genes. We believe that humans have 25 000 genes separated by large amounts of intergenic DNA. Genetics is the study of each gene.

Next Generation Sequencing (NGS) technology has significantly reduced costs and increased efficiency, allowing its use in what is now known as the era of post-genomic medicine.

Post-genomic medicine uses DNA information from thousands of individuals of different races to create "reference patterns" of "normal" sequences, currently based on European population data.

In 2017, the HapMap Project revealed that humans share 99.9% of the genetic sequence, i.e., they are "nearly identical."

There are different types of genetic variants. The most common is the substitution of one nucleotide for another. If this variant has a frequency greater than 1% in the population, it is called a Single Nucleotide Polymorphism (SNP).

Some genetic variations in DNA determine appearance, others the response to drugs, some protect or predispose to suffer from certain conditions, or are directly responsible for causing disease. For many we still do not know the implications.

Genetic cardiology studies the association between a genetic variant in a patient or population with gene expression or phenotype. If the variant is associated with the phenotype, genetic causation of the disease is demonstrated. These variants are known as mutations; however, the correct name is "pathogenic genetic variants".

This "model gene+mutation=disease" can follow a pattern of expression and autosomal dominant Mendelian inheritance; in this case a carrier of the mutation will generally develop the disease with varying degrees of severity, and has 50% risk of transmitting it to his or her offspring regardless of gender. These mutations are rare and are responsible for autosomal dominant monogenic diseases, the most studied and important in cardiology, especially within the group of genetic dilated cardiomyopathies formerly called "idiopathic or non-ischemic" cardiomyopathies.

Genome Wide Association Studies (GWAS) incorporated a different paradigm configured according to the "polygenic risk" scheme. This risk contemplates many SNPs, in different genes, frequent in the general population, that combined can have an additive large effect on the expression of a condition. (2)

The combination of the effects of all these SNPs captures much of the genetic heritability and can be used to construct predictive models or polygenic risk scores (PRS), which are considered a quantitative measure of genetic susceptibility to estimate an "individual probability". (Figure 1)

Since the germline genotype does not change, this

Rev Argent Cardiol 2025;93:3-5. https://doi.org/10.7775/rac.v93.i1.20869

SEE RELATED ARTICLE: Rev Argent Cardiol 2025;93:14-24. https://doi.org/10.7775/rac.v93.i1.20851

Correspondence: Marianna Guerchicoff. E-mail: mguerchicofflemcke@gmail.com

Former Director of the Council of Genetic Cardiology. Argentine Society of Cardiology.
Chief of Pediatric Arrhythmias and Electrophysiology. Hospital Italiano de Buenos Aires.
External Genetic Cardiology Consultant, Instituto Cardiovascular de Buenos Aires

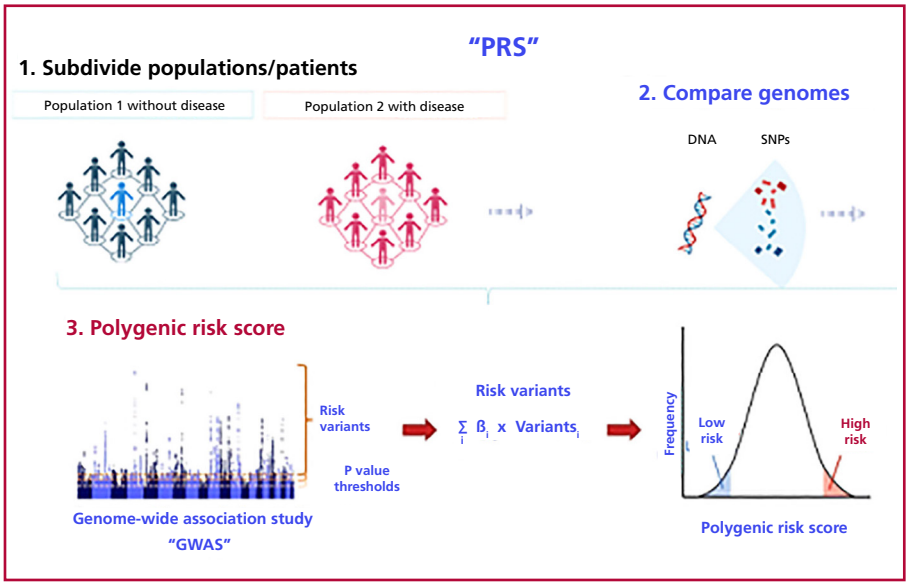

Fig. 1. Polygenic risk score

precludes reverse causality, indicating that PRSs ideally represent a stable measure unaffected by age and environment. They can be estimated on a one-time basis at any point in time and overcome many obstacles associated with other biomarkers or risk modifiers. Most include hundreds and sometimes thousands of SNPs. (3)

POLYGENIC RISK SCORE IN PRIMARY PREVENTION

An ideal PRS will allow predicting a condition with an interindividual variability in accordance with the variability of the trait studied, defining the endophenotype, an intermediate position in the pathway "genotype-endophenotype-phenotype", reflecting the individual genetic predisposition. An ideal PRS discriminates endophenotypes into low, moderate or high risk. (4)

Understanding the highly polygenic architecture of disorders with an inherent etiological complexity may allow for changes as in those with high interaction between environmental factors and lifestyle, or early pharmacological treatment in those with a high-risk endophenotype. (5) (Figure 2)

POLYGENIC RISK SCORE IN SECONDARY PREVENTION

The value of PRS in secondary prevention is gaining much interest. (6) As in the work of Principato et al. is left ventricular systolic function, (7) the challenge is to identify clearly the outcome against which to measure the prognostic value of the score. The authors use left ventricular ejection fraction, which is highly dependent on both the ventricular geometry and the operator. However, in the future, assessment by magnetic resonance imaging and the use of artificial intelligence may mitigate this pitfall. It is worth mentioning the importance that this work, which,

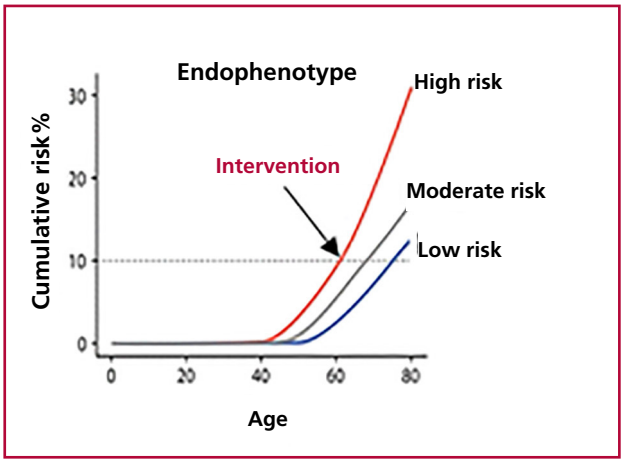

Fig. 2. Endophenotype

in addition to incorporating PRS, includes artificial intelligence algorithms. However, it would be desirable to expand the criteria used in the selection of the SNP studied.

In this population with ethnicity from southern Bolivia and northern Argentina, diverse allelic frequencies should be expected, whose future consideration would improve the estimation, allowing statistical adjustment with ancestral information. (8) In addition, the inclusion of other risk factors such as obesity, smoking, dyslipidemia, socioeconomic environment and access to health care of the population could optimize uniformity within the sample. Further multicenter studies with randomized selection of participants for external validation will be required to assess the fit of the model in other populations.

CHALLENGES AND PERSPECTIVES

The use of PRS to predict causal propensity genetically determined and independent of traditional risk factors that have so far not demonstrated detection power in presymptomatic or preclinical stages is bringing important insight to cardiovascular disease research, especially cardiomyopathies

There are no precedents for studies of PRS in chagasic cardiomyopathy, and this highlights the importance of this work performed with the intention of having local data and accurately detecting individuals who could benefit from early intervention.

The potential of PRS has recently led to position papers from the American Heart Association (9) and the European Society of Cardiology, (10) both of which advise against the routine use of PRS as there are still many challenges. For example, current scores only assess "common" SNPs, without investigating the potential to include rare variants such as those responsible for monogenic diseases.

It is essential to carry out prospective studies in heterogeneous populations, ensuring compliance with strict quality standards in processing and reporting data, with rigorous control protocols and uniform reference frameworks that ensure the validity and reproducibility of the results.

Genetic information, because of its unfamiliar language to cardiologists is less intuitive than any of the traditional risk factors, clinical or imaging data, but its proper incorporation into our predictive models can influence the strength and direction of shared decisions to improve the quality of medical care in the era of personalized and precision medicine.

Conflicts of interest

None declared

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

Ethical considerations

Not applicable.

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ORIGINAL ARTICLE

Detection of Subclinical Cardiac Damage by Echocardiography in a Hypertensive Population with a High Prevalence of Obesity: Discrepancies According to the Indexing Method Used

Detección de daño cardíaco subclínico mediante ecocardiografía en una población de hipertensos con alta prevalencia de obesidad: discrepancias observadas según el método de indexación empleado.

CAROLINA M. TRAVETTO[1], LAURA V. ARGENTO[1, MTSAC]

ABSTRACT

Background: Allometric height-based indexing improves the detection of cardiac target organ damage in overweight/obese hypertensives versus body surface area-based indexing; however, its use is not common in daily practice.
Objective: To compare the prevalence of left ventricular hypertrophy and/or left atrial enlargement according to the echocardiographic indexing method used, and to estimate the level of agreement and the percentage of reclassified subjects.
Methods: Descriptive, observational and prospective study. We included 150 adults with hypertension. Left ventricular mass was indexed to body surface area and height^{2,7}. Maximum left atrial volume was indexed to body surface area and height^{2}. Subgroup analysis was performed according to body mass index categories. The degree of agreement between methods was evaluated with the Kappa index (k).
Results: Mean age was 57.1 years, 62.7% were women, 58.7% were obese. The prevalence of ventricular hypertrophy and left atrial enlargement was higher with height-based indexing. The level of agreement for the detection of left ventricular hypertrophy with both indices was considerable (k=0.76) but poor for the detection of left atrial enlargement (k=0.23). The discrepancy between the methods was greater at higher body mass index. One third of the subjects were reclassified regarding the presence of cardiac target organ damage by using height-based indexing.
Conclusion: Cardiac structures indexed to body surface area underestimate the presence of target organ damage in overweight/obese hypertensive subjects. We suggest considering the systematic use of height-based indexing in hypertensive subjects.

Key words: Obesity - Hypertension - Echocardiography - Indexing methods - Left ventricular hypertrophy - Cardiovascular diagnostic techniques

RESUMEN

Introducción: Los índices alométricos basados en la altura mejoran la detección de daño de órgano blanco cardíaco en hipertensos con sobrepeso/obesidad versus la indexación por superficie corporal; sin embargo su uso no es habitual en la práctica diaria.
Objetivo: Comparar la prevalencia de hipertrofia ventricular izquierda y/o agrandamiento auricular izquierdo según el método de indexación ecocardiográfico empleado, y estimar el nivel de concordancia observado y el porcentaje de individuos que resulta reclasificado.
Material y métodos: Estudio descriptivo, observacional y prospectivo. Se incluyeron 150 adultos con hipertensión arterial. La masa ventricular izquierda se indexó por superficie corporal y altura^{2,7}. El volumen auricular izquierdo máximo se indexó por superficie corporal y altura^{2}. Se realizó análisis por subgrupos según categorías de índice de masa corporal. El grado de concordancia entre métodos se evaluó con el índice Kappa (k).
Resultados: Edad media 57,1 años, 62,7% mujeres, 58,7% con obesidad. La prevalencia de hipertrofia ventricular y agrandamiento auricular izquierdo fue mayor con la indexación basada en la altura. El nivel de concordancia para la detección de hipertrofia ventricular izquierda con ambos índices fue considerable (k=0,76) y pobre para la detección de agrandamiento auricular izquierdo (k=0,23), con mayor discrepancia entre métodos a mayor índice de masa corporal. Un tercio de los sujetos
fue reclasificado respecto de la presencia de daño cardíaco empleando la indexación basada en la altura.
Conclusión: La indexación de estructuras cardíacas por superficie corporal subestima la presencia de daño de órgano blanco en hipertensos con sobrepeso/obesidad. Sugerimos considerar el uso sistemático de la indexación basada en la altura en sujetos con hipertensión arterial.

Palabras claves: Obesidad - Hipertensión - Ecocardiografía - Métodos de indexación - Hipertrofia ventricular izquierda - Técnicas de diagnóstico cardiovascular

Rev Argent Cardiol 2025;93:6-13. https://doi.org/10.7775/rac.v93.i1.20852

Received: 01/16//2025– *Accepted:* 02/03/2025

Correspondence: Carolina M. Travetto, RO del Uruguay 224, Morón, Provincia de Buenos Aires, Argentina. E-mail: carolinatravetto@hotmail.com
Financing: The study was conducted without external financing.
This article won the Dr. Oscar Orías Award - special mention "Accesit" at the 50th Argentine Congress of Cardiology.

[1] Cardiology Department, Sanatorio Clínica Modelo de Morón, Province of Buenos Aires, Argentina

INTRODUCTION

Early detection of subclinical cardiac target organ damage (TOD) is essential for the stratification of the overall cardiovascular risk in hypertensive patients and has a direct impact on the appropriateness of treatment, the target blood pressure (BP) value and the time to achieve it, as well as the choice of the drug class expected to provide the greatest therapeutic benefit. (1,2)

Normalization of cardiac chambers measurements using allometric height-based indexing (AHI) improves the detection of TOD in subjects with hypertension (HT) and overweight or obesity compared to body surface area-based indexing (BSAI). Although this has been included in international guidelines, (3-8) its use in clinical practice is not widespread. This may be due to different factors, including lack of knowledge, habit or technical difficulties because of the lack of suitable calculation packages for this population in most echocardiography equipment.

Both HT and obesity promote left ventricular remodelling and hypertrophy (LVH) independently and synergistically. (9-12) Increased ventricular mass in non-hypertensive subjects is related to weight and body mass index (BMI), (13, 14) and the presence of obesity-related LVH is an independent predictor of cardiovascular events. (15) Likewise, obesity per se may promote atrial chamber enlargement. In a subanalysis of the MONICA/KORA study, obesity was the most important independent predictor of the incidence of left atrial enlargement (LAE) after aging. (16)

In view of today's obesity pandemic, which in some regions has reached a prevalence of almost 60% in populations over 20 years old, (17) and in which 75% of the incidence of HT is directly related to overweight, (18) we wondered how often the use of AHI, compared to BSAI leads to the reclassification of subjects in terms of the presence of TOD according to their degree of obesity. This knowledge is important to measure the degree of error that results from failing to use the appropriate indices.

OBJECTIVES

To compare the prevalence of TOD, defined as LVH and/or LAE, according to the echocardiographic indexing method used, and to estimate the level of agreement between the methods and the percentage of subjects who are reclassified according to their degree of obesity.

METHODS

Between January 2020 and December 2021, adults over 18 years old with a diagnosis of HT either under drug treatment or non-drug treatment and referred to a Doppler echocardiography were prospectively assessed. Subjects with any other cardiovascular history or relevant comorbidity were excluded, except for cardiovascular risk factors, known secondary HT, pregnancy, echocardiographic findings consistent with significant valvular heart disease, structural heart disease of other origin or systolic dysfunction. A complete medical history was taken from all patients and weight, height (H) and BP were recorded. Body surface area (BSA) was estimated using the Du Bois and Du Bois formula: BSA (m^2) = 0.007184 x H (cm)$^{0.725}$ x weight (kg)$^{0.42}$. BMI was calculated according to the formula: BMI (kg/m^2) = Weight (kg) / [H (m)]^2. BP was measured in a seated position, after a 5-minute rest, with an automatic sphygmomanometer (Omron MODEL Hem 7142, Omron Corporation). Two consecutive measurements were obtained, with an interval of 2 minutes between each one, and the values were averaged. Controlled BP at the time of the study was defined as the presence of systolic BP <140 mmHg and diastolic BP <90 mmHg. Doppler echocardiography was performed immediately after BP measurement.

Echocardiography

A Mindray M9 equipment with SP5-1s probe was used. Cardiac chambers diameters and remodelling patterns were evaluated according to the recommendations of the American Society of Echocardiography Guidelines. (3, 4) M-mode was used to measure left ventricular (LV) diameters. LV ejection fraction (LVEF) was estimated using the biplane Simpson method. Left ventricular mass (LVM) was calculated with the Devereux formula and indexed to BSA and $H^{2.7}$. Relative wall thickness (RWT) was calculated with the formula 2 x LV posterior wall thickness in diastole/LV end-diastolic diameter (LVEDD), and a value ≥ 0.42 was considered increased RWT. Left atrial (LA) volumes were assessed by using the modified biplane Simpson's method from apical 2- and 4-chamber views. In each case, 2 measurements were obtained and averaged. Absolute values were indexed to BSA and H^2. Table 1 shows the cut-off values used for each determination. The choice of these allometric indices over others was based on the evidence supporting their use and the recommendations of international guidelines. (5-8)

Statistical analysis

Qualitative variables are presented as absolute frequency and percentage, and quantitative variables are presented as median and interquartile range (IQR 25-75) or mean and standard deviation (SD), according to data distribution. The distribution of variables was analysed in the total population and by BMI subgroups (<25, 25-29.9, 30-34.9, ≥35 kg/m^2). Comparison of discrete variables was performed with the chi-square test with Fisher's correction. Comparison of continuous variables was performed with Kruskal-Wallis or ANOVA method, as appropriate. Comparison of the prevalence of LVH/LAE/TOD between both methods was performed with the paired binomial test. The degree of agreement for the classification of presence/absence of subclinical cardiac TOD between different indexing methods was evaluated with Cohen's Kappa index (k), considering that a value of 1 represents perfect agreement in the classification of each case and a value of 0 indicates agreement no better than that expected by chance. A statistical significance level of 0.05 (bilateral test) was used in the hypothesis tests. Data processing was performed with EpiInfo version 7.2.5.0 (CDC, Atlanta) and EpiDat version 4.2 (Consellería de Sanidade, Xunta de Galicia, Spain; PAHO, Washington; Universidad CES, Colombia. Available at: http://www.sergas.es/Saude-publica/EPIDAT).

Ethical considerations

The study was evaluated by an independent Research Ethics Committee. Informed consent was obtained from participants prior to enrolment. The research was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1. Cut-off limits used in indexed echocardiographic measurements

Variable	Men	Women	Reference
LVM/BSA (g /m^2)	≤ 115	≤ 95	3, 4
LVM/H$^{2.7}$ (g/m$^{2.7}$)	≤ 50	≤ 47	5-8
LAV/ BSA (mL/m^2)	≤ 34	≤ 34	5-8
LAV/H^2 (mL/m^2)	≤ 18.5	≤ 16.5	5-8

BSA: body surface area; H: height; LAV: maximum left atrial volume; LVM: left ventricular mass

RESULTS

A total of 150 subjects were included. Mean age was 57.1 years (SD 12.6); 62.7% were women, 58.7% were obese; 94% were receiving drug treatment. Tables 2 and 3 show the clinical and echocardiographic characteristics of the population. Non-indexed and H^{2,7}-indexed LVM, and non-indexed or H2- indexed maximum left atrial volume (LAV) presented higher values in the groups with higher obesity, while BSA-indexed LVM and LAV showed no differences between the groups according to BMI.

The presence of LVH ranged from 22% using BSAI to 25.3% using AHI (p= 0.266), with a greater difference between the methods at higher BMI (Figure 1). The overall agreement for classification according to the presence or absence of LVH was substantial (k= 0.76), with the highest level of agreement in the group with BMI 25-29.9 and the lowest level of agreement in the group with BMI 30-34.9 (Table 4 and Figure 2). The use of LVM indexed to H^{2,7}, compared to BSAI, resulted in the reclassification regarding the presence of LVH in 13 subjects (8.6%).

The greatest discrepancy between the methods was recorded in the detection of LAE, which ranged from 11.3% using BSAI to 49.3% using AHI (p < 0.001), with a greater difference in prevalence between the groups at higher BMI (Figure 1). The overall agreement between the methods for LAE detection was low (k= 0.23), with the exception of the group with BMI ≤ 25, which showed a substantial level of agreement (k= 0.85). In the rest of the groups, the level of agreement was poor and the greatest discrepancy was observed in the group with BMI ≥35 (Table 4 and Figure 2). Using AHI for LAV resulted in the reclassification of 57 subjects (38%). In all discordant cases, by using AHI, LAE was identified in subjects classified as not having LAE according to BSAI.

When comparing the prevalence of TOD (LVH and/or LAE) using either BSAI or AHI, a detection rate of 26% and 56%, respectively, was observed (p<0.001), with a greater difference between methods in the higher BMI subgroups (Figure 1). The overall level of agreement between the methods for the detection of TOD was moderate (k= 0.38); the group with BMI ≤25 showed a substantial level of agreement (k=0.85), in the remaining groups the level of agreement was low, and the greatest discrepancy was observed in the group with BMI ≥35 (Table 4 and Figure 2).

DISCUSSION

The results of this study show that the presence of subclinical cardiac TOD may remain undetected in a high proportion of overweight or obese hypertensive subjects when using BSAI instead of AHI. The level of agreement between both methods for the detection of TOD was poor, lower for the detection of LAE than LVH, and with greater discrepancies at higher BMI. In the group of subjects without overweight, the level of agreement between the two methods was high, both for the detection of LVH and LAE, which leads us to believe that in hypertensive populations with a high prevalence of overweight or obesity, such as the one included in the present study, the global use of AHI may be convenient.

Numerous studies have evaluated the impact of the indexing methods used to detect LVH, both in selected cohorts of subjects with HT and in population-based studies. The frequencies reported vary considerably depending on the characteristics of the population included and the cut-off values used to define LVH. When reviewing the studies that compared BSAI and AHI, a consistent finding was the higher detection rate of LVH using AHI, and the difference was greater when the proportion of obese subjects in the included sample was higher. (19-22) Using AHI for LVM has shown to be more predictive of cardiovascular events than BSAI at follow-up in overweight or obese hypertensive subjects (19,22,23). Gosse et al. reported in a cohort of 763 hypertensive subjects that LVM (g/H^{2,7}) before the initiation of treatment was the strongest predictor of cardiovascular events at follow-up, above other risk factors, such as age, systolic BP, and smoking, as well as the second strongest predictor of all-cause death, after age. Detection of LVH at follow-up had a similar predictive value, whereas regression of LVH was associated with lower cardiovascular risk. (23) In the study by Kuznetsova et al., the presence of LVH according to the H^{2,7} method had the highest prognostic value for fatal or non-fatal cardiovascular events compared to other indexing methods. (19) That study also evaluated the level of agreement for the detection of LVH using different indexing methods according to the degree of obesity. Similar to this study, the difference in the detection of LVH between the two methods was small in the subgroup of non-overweight, but it increased sharply in the subgroups of overweight or obese subjects, with a difference in

Tabla 2. Clinical characteristics of the population included in the study by body mass index (BMI) categories

	Global n = 150	<25 kg/m² n = 21	25-29.9 kg/m² n = 41	30-34.9 kg/m² n = 58	≥35 kg/m² n =30	p
Age (years)	57.10 (12.66)	60.57 (15.35)	56.00 (11.40)	57.84 (12.84)	54.73 (11.88)	0.389
Women	94 (62.67%)	16 (76.19%)	23 (56.10%)	32 (55.17 %)	23 (76.67%)	0.097
Diabetes mellitus	39 (26.00%)	1 (4.76%)	9 (21.95%)	17 (29.31%)	12 (40.00%)	0.034
Current or past smoking	65 (43.33%)	7 (33.33%)	17 (41.46%)	24 (41.38%)	17 (56.67%)	0.365
Dyslipidemia	78 (52.00%)	16 (76.19%)	17 (41.46%)	33 (56.90%)	12 (40.00%)	0.028
Weight (kg)	84.37 (16.33)	61.23 (8.31)	77.31 (9 .12)	88 .87 (11.08)	101.48 (12.88)	< 0.001
Height (m)	1.64 (0.09)	1.63 (0.09)	1.66 (0.09)	1.66 (0.10)	1.60 (0.08)	0.039
BSA (m²)	1.90 (0.21)	1.66 (0.16)	1.85 (0.17)	1.96 (0.18)	2.01 (0.16)	< 0.001
BMI (kg/m²)	31.22 (5.62)	22.94 (1.57)	27.7 (1.27)	32.3 (1.48)	39.7 (3.20)	< 0.001
Diagnosis of HT older than 1 year	115 (76.67%)	16 (76.19%)	19 (70.73%)	47 (81.03%)	23 (76.67%)	0.698
Drug treatment	141 (94.00%)	19 (90.48%)	36 (87.80%)	57 (98.28%)	29 (96.67%)	0.138
SBP (mmHg)	136.14 (15.53)	138.66 (19.80)	135.78 (13.09)	136.06 (14.89)	135.00 (17.05)	0.866
DBP (mmHg)	85.61 (9.03)	85.38 (9.22)	86.31 (8.69)	85.03 (9.70)	85.93 (8.35)	0.912
MBP (mmHg)	102.38 (9.45)	103.10 (10.51)	102.77 (7.88)	101.91 (9.97)	102.25 (10.05)	0.952
Pulse pressure (mmHg)	50.52 (14.39)	53.28 (18.56)	49.46 (14.26)	51.03 (13.3)	49.06 (13.67)	0.715
Controlled BP	65 (43.33%)	9 (42.86%)	16 (39.02%)	25 (43.10%)	15 (50.00%)	0.836
HR (bpm)	73.88 (13,31)	72.14 (10,38)	71.73 (12.73)	75.08 (15.21)	75.7 (11.98)	0.486

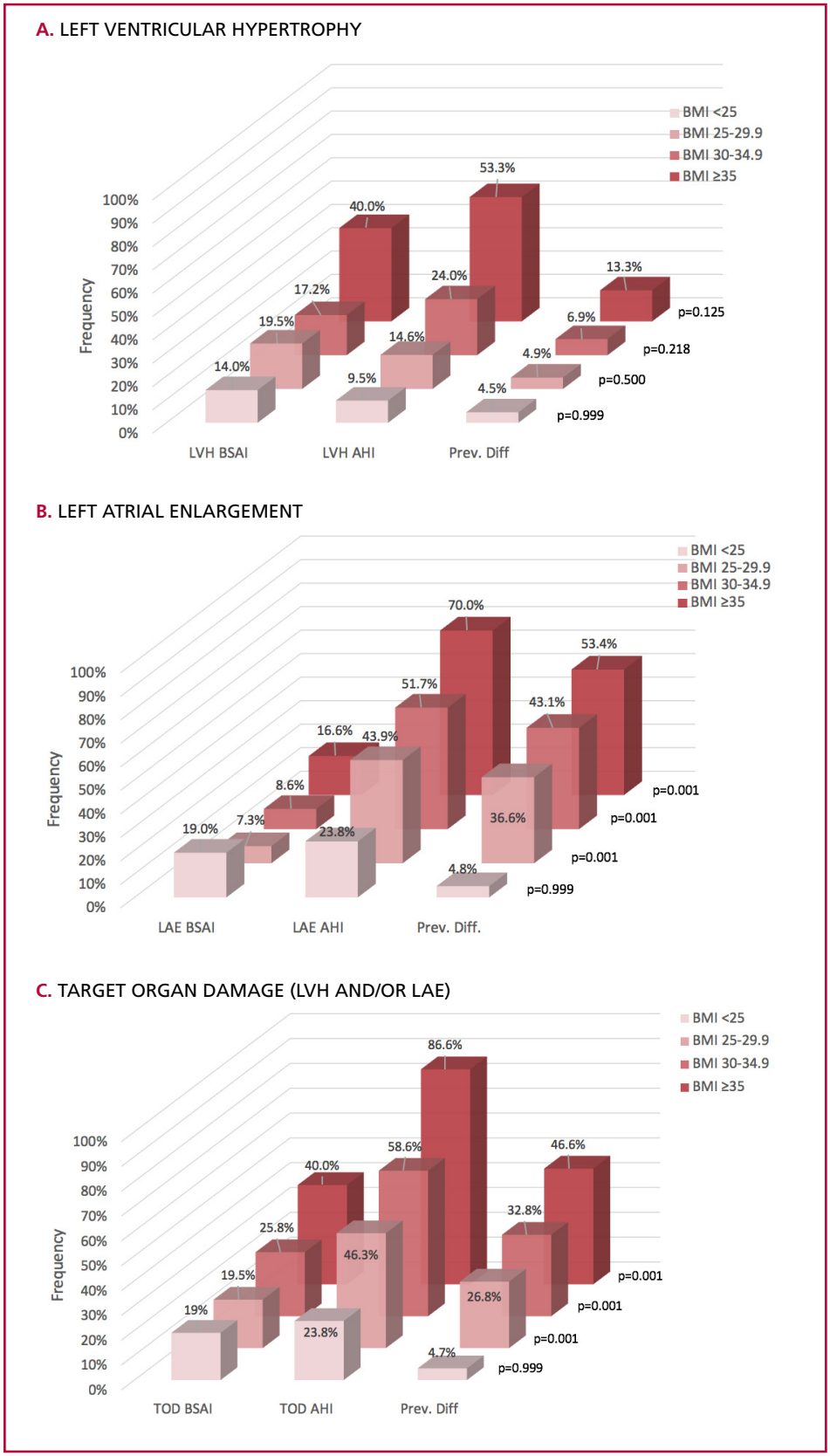
BMI: body mass index; BP: blood pressure; BPM: beats per minute; BSA: body surface area; DBP: diastolic blood pressure; HR: heart rate; HT: hypertension; MBP: mean blood pressure; SBP: systolic blood pressure.
Quantitative variables are expressed as mean (SD) and categorical variables as absolute frequency (%).

Tabla 3. Echocardiographic characteristics of the population included in the study by body mass index categories

	Global n = 150	<25 kg/m² n = 21	25-29.9 kg/m² n = 41	30-34.9 kg/m² n = 58	≥35 kg/m² n =30	p
LVDD (cm)	4.63 (4.34-4.99)	4.44 (4.30-4.76)	4.59 (4.23-4.94)	4.64 (4.40-4.90)	4.89 (4.50-5.57)	0.032
IVS (cm)	1.03 (0.20)	0.87 (0.19)	1.05 (0.19)	1.05 (0.20)	1.07 (0 .18)	0.001
PW (cm)	0.89 (0.16)	0.77 (0.18)	0.88 (0.16)	0.93 (0.15)	0.91 (0.15)	0.001
RWT	0.38 (0.07)	0.34 (0.07)	0.39 (0.07)	0.40 (0.08)	0.37 (0.06)	0.004
LVM (gr)	150.03 (124.22-192.02)	115.87 (90.97-152.15)	139.19 (129.10-177.78)	159.23 (125.67-192.02)	171.49 (135.33-221.08)	< 0.001
LVM/ BSA (g/m²)	78.05 (66.60-98.64)	67.68 (58.16-84.32)	76.71 (68.58-98.64)	80.43 (65.68-93.30)	80.25 (69.74-110.54)	0.117
LVM/H$^{2.7}$ (g/m$^{2.7}$)	38.80 (33.04-48.47)	29.02 (24.94-38.78)	36.19 (32.71-44.44)	39.38 (34.33-47.74)	48.30 (39.08-63.71)	< 0.001
LVEF (%)	63.06 (4.47)	62.55 (3.54)	64.37 (4.66)	62.04 (4.10)	63.68 (5.10)	0.065
LAV (mL)	47.80 (12.30)	41.16 (11.63)	46.40 (10.86)	49.18 (12.49)	51.84 (12.64)	0.013
LAV/BSA (mL/m²)	25.28 (6.19)	25.38 (8.15)	25.09 (5.22)	25.15 (6.34)	25.74 (5.85)	0.973
LAV/H² (mL/m²)	17.64 (4.48)	15.42 (4.53)	16.65 (3.19)	17.92 (4.64)	20.07 (4.67)	< 0.001

BSA: body surface area; H: height; IVS: interventricular septum; LAV: maximum left atrial volume; LV DD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; PW: posterior wall; RWT: relative wall thickness.
Quantitative variables are expressed as mean (SD) or median (IQR 25-75) and categorical variables as absolute frequency (%).

Fig. 1. Prevalence of left ventricular hypertrophy (A), left atrial enlargement (B) or subclinical cardiac target organ damage (C) by indexing method and body mass index category

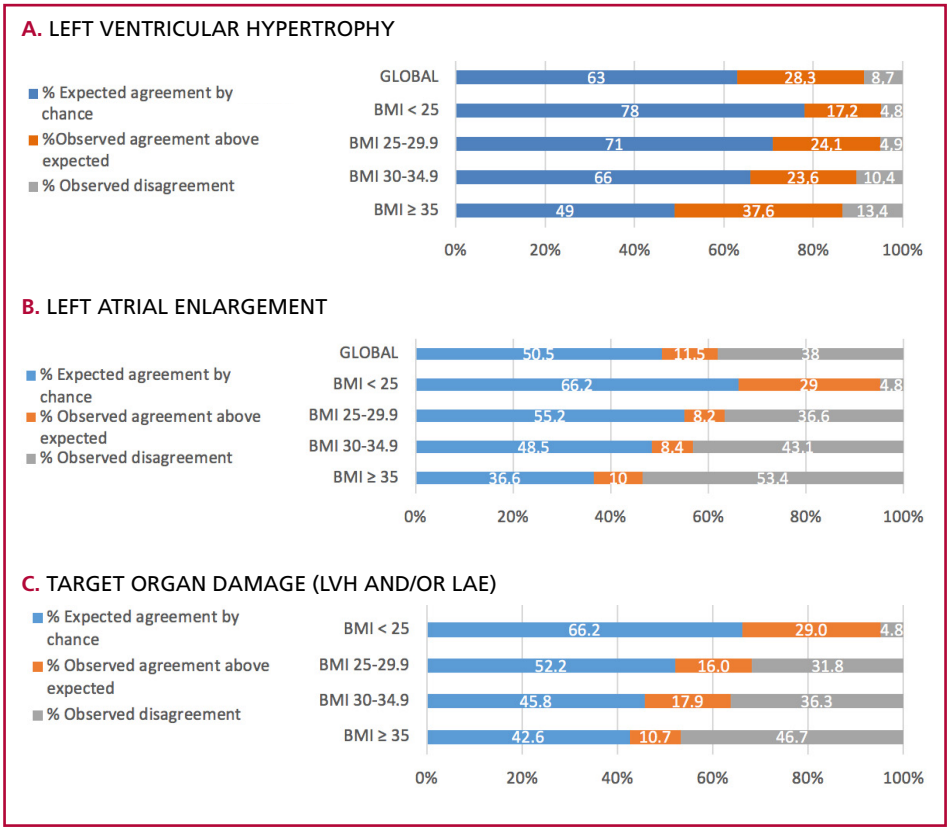


AHI: allometric height-based indexing; BMI: body mass index; BSAI: body surface indexing; LAE: left atrial enlargement; LVH: left ventricular hypertrophy; Prev diff: difference in prevalence between indexing methods; TOD: subclinical cardiac target organ damage (LVH and/or LAE). The p value presented to the right of each row corresponds to the comparison of the prevalence observed between both methods in the paired analysis by body mass index subgroup.

Tabla 4. Level of agreement for the determination of presence or absence of subclinical cardiac target organ damage using body surface area-based indexing or allometric height-based indexing

BSAI vs AHI measurement	BMI subgroup	Agreement	k	95% CI	Maximum k value
LVH	Global	91.3%	0.76	0 .63-0.88	0.82
	<25 kg/m²	95.2%	0.77	0.35 -1	090
	25-29.9 kg/m²	95.1%	0.82	0.60-1	0.90
	30-34.9 kg/m²	89.6%	0.68	0.45-0.91	0.79
	≥35 kg/m²	86.6%	0.73	0.5-0.96	0.73
LAE	Global	62%	0.23	0.13-0.33	0.33
	<25 kg/m²	95.2%	0.85	0.59-1	0.90
	25-29.9 kg/m²	63.4%	0.18	-0.006-0.37	0.35
	30-34.9 kg/m²	56.9%	0.16	0.02-0.29	0.27
	≥35 kg/m²	46.6%	0.15	0.005-0.30	0.16
TOD	Global	67.3%	0.38	0.26-0.49	0.40
	<25 kg/m²	95.2%	0.85	0.59-1	0.90
	25-29.9 kg/m²	68.2%	0.33	0.09-0.58	0.42
	30-34.9 kg/m²	63.7%	0.33	0.14-0.51	0.35
	≥35 kg/m²	53.3%	0.18	0.005-0.36	0.23

AHI: allometric height-based indexing; BMI: body mass index; BSAI: body surface area indexing; H: height; k: Kappa index;LAE: left atrial enlargement; LVH: left ventricular hypertrophy; TOD: subclinical cardiac target organ damage (LVH and/or LAE)



BMI: body mass index; LAE: left atrial enlargement; LVH: left ventricular hypertrophy.

Fig. 2. Graphical representation of the Kappa index for the determination of presence or absence of left ventricular hypertrophy (A), left atrial enlargement (B) and subclinical cardiac target organ damage (C) between body surface area-based indexing or allometric height-based indexing

prevalence of almost 20% in the latter group. In that study, the level of agreement for the detection of LVH between BSAI and AHI (k= 0.72) was similar to that observed in this study. In contrast to our study, the level of agreement in the subgroups for BMI was not compared in that study.

It is worth noting that the use of AHI for LVM has predictive value not only at individual level but also at population level. De Simone et al. compared the population attributable risk of LVH defined by different indexing methods in the Strong Heart Study cohort and found that normalization of LVM to $H^{2,7}$ had the highest population attributable risk of cardiovascular events at follow-up, both in the total population and in the subgroup of subjects with HT. (24)

Similarly, using AHI for LAV was also shown to be superior to BSAI for the detection of LAE and prediction of events at follow-up in overweight or obese subjects. (25-27) In a sample of 127 overweight or obese subjects, of which 50% had HT, Ilijevska et al. observed that the frequency of LAE ranged from 15.7% to 70.1% depending on whether BSAI or AHI was used. AHI led to reclassification from normal LAV to enlarged LAV in 52.8% of subjects, with variations from 38.9% in the group with overweight to 88.2% in the group with BMI >40 kg/m^2. (25) Similar results were reported by Airale et al. in a study that included 441 hypertensive subjects; the frequency of LAE ranged from 23.4% to 50.6% using either BSAI or AHI, with a level of agreement for the detection of LAE between the two methods of k= 0.46. (26) In the study by Davis et al. LAE detected by AHI was independently predictive of death and cardiovascular events in all BMI groups and showed an overall performance, in terms of sensitivity and specificity, superior to BSAI across all BMI categories, including the group with BMI <25 kg/m^2. (27) The reclassification rate from normal to enlarged LA using AHI was 28.5% in the total sample and reached 55.4% in the group with BMI >40 kg/m^2. The subgroup of reclassified subjects showed an increased risk of death and cardiovascular events across all BMI categories, including those with normal or near-normal BMI. (27)

CONCLUSIONS

Overweight and obesity are growing public health issues worldwide. In Argentina, results from the most recent Cardiovascular Risk Factor Survey showed that 61.6% of the adult population is overweight, (28) and this proportion is likely to be higher in the population with HT.

Although it has been known since the 1980s that the use of weight-related parameters, such as BSA, to index cardiac structures in overweight or obese subjects has a deficit in detecting LVH and LAE compared to AHI, BSAI is still widely used in daily practice either for reasons of tradition or simplicity.

In addition to what has already been reported in the literature, the results of this study highlight the significant discrepancy in the classification of subjects according to the presence or absence of TOD when using one indexing method or the other, which is more evident in subjects with severe obesity.

In view of the evidence provided, we must increase efforts to adapt practice to the characteristics of the population we treat. To this end, we consider it essential to include in the echocardiography equipment a calculation package appropriate to this population in order to allow the application of AHI in the parameters above mentioned, and to recommend its implementation in local clinical practice guidelines. Besides, we suggest considering the systematic use of AHI in all hypertensive subjects.

LVM and LAV indexed to BSA underestimate the presence of TOD in hypertensive overweight or obese patients, leading to an incorrect assessment of their cardiovascular risk and the therapeutic implications of this underdiagnosis. We hope this study will help to bring this issue to the forefront.

Limitations

Prevalence of LVH in our sample was lower than in other studies, probably because all subjects were on treatment and most had BP values near to normal. Reclassification of LV morphological patterns and ventricular enlargement was not evaluated due to sample size limitations. The value of the k- statistic is influenced by the prevalence of the phenomenon under study, so caution should be exercised when extrapolating the data to populations with different characteristics.

Conflicts of interest

None declared.

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

Acknowledgments

We thank Bárbara Lux and María Fernanda Ramírez Serrano for their collaboration in data collection.

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ORIGINAL ARTICLE

New Genetic Variants Associated with Acquired Dilated Cardiomyopathy. Towards a New Predisposing Polygenic Panel

Nuevas variantes genéticas asociadas a miocardiopatía dilatada adquirida. Hacia un nuevo panel poligénico predisponente

MARIO B. PRINCIPATO[1, MTSAC], ANALÍA G. PAOLUCCI [1], ROCÍO DEL CIELO VILLA FERNÁNDEZ[1], M. VICTORIA CARVELLI[1, MTSAC], PAOLA SETTEPASSI[1], ALEJANDRO TOMATTI[1], M ALEJANDRA VON WUFFEN[1], MANUEL LAGO[1], JUSTO CARBAJALES[1, MTSAC]

ABSTRACT

Background: Heart failure with reduced left ventricular ejection fraction (HFrEF) is one of the cardiovascular pathologies with the highest mortality. The existence of a genetic predisposition for the development of this pathology in the presence of a noxa is still uncertain.
Objectives: The aim of this study was to identify associations between genetic variants in polymorphic alleles, single nucleotide polymorphisms (SNPs) with the presence of rEF and intraventricular conduction disorders (IVCD) in a model of acquired cardiomyopathy such as chagasic cardiomyopathy.
Methods: A study model including patients seropositive for Chagas disease with a history of infection of more than 20 years, one group with rEF (≤35%) and another group with preserved LVEF (pEF, ≥50%). A blood collection was performed and processed to obtain deoxyribonucleic acid (DNA), which was sent to an international genotyping laboratory. A panel of gene SNPs was prepared using the international TheGenomeAggregationDatabase (GnomAD), choosing SNPs with a frequency in the population of 10% to 40%. The SNPs chosen are related to genes responsible for the process of ventricular contraction and relaxation (TTN, BAG3, MTSS1), myocardial metabolism (PPARGC1A, SIRT1, AKT1 mTOR, AMPK), adrenergic receptor beta 1 (ADRB1), cholinergic receptor muscarinic 2 (CHRM2), angiotensin II type 1 receptor(AGTR1B), and atrial natriuretic peptide (NPPA) Using various artificial intelligence models for supervised learning (Logistic Regression, Support Vector Machines, Artificial Neural Networks, NaiveBayes, Classification Trees, and RandomForest) 68 SNPs were evaluated as predictors of the presence of two phenotypes: rEF, and IVCD. The performance of the models for the prediction of rEF was evaluated by cross-validation technique, with the F1 metric as a measure of accuracy to select the best model.
Results: One hundred and eighty-two patients were included, with a median age of 62 years, 39.6 % men. Thirty-one percent had rEF and 53% had some IVCD. The model with the best performance was logistic regression (F1=0.85), so it was used to express the association by Odds Ratio and its 95% CI. It was observed that the variants rs2076300, rs61772962 and rs7071853 were independent predictors of rEF, whereas the only predictor for IVCD was the SNP rs72840788. The SNP rs61772962 corresponds to the PRKAA2 gene, which encodes the alpha-2 catalytic subunit of 5'-AMP-activated protein kinase. On the other hand, rs7071853 and rs72840788 correspond to the gene encoding the BAG3 protein (chaperone regulator 3). Finally, the SNP rs2076300 corresponds to the DSP gene encoding a desmoplakin, a protein of the desmosome binding plate.
Conclusions: In this derivation model, in a set of patients with positive serology for Chagas disease, 3 SNPs predictive of rEF and one SNP predictive of IVCD were identified. The reproducibility of these results should be confirmed in a validation model with a larger sample of individuals. Furthermore, this finding could be useful in dilated cardiomyopathies of other etiologies.

Key words: Cardiomyopathy, Dilated - Heart Failure - Genetics - Chagas Disease

RESUMEN

Introducción: La insuficiencia cardíaca con fracción de eyección ventricular izquierda reducida (FEVIr) es una de las patologías cardiovasculares con mayor mortalidad. La existencia de una predisposición genética para el desarrollo de esta patología ante la presencia de una noxa es aún incierta.

Rev Argent Cardiol 2025;93:14-24. https://doi.org/10.7775/rac.v93.i1.20851

SEE RELATED ARTICLE: Rev Argent Cardiol 2025:93:3-5. https://doi.org/10.7775/rac.v93.i1.20869

Received: 10/27/2024 – *Accepted:* 01/03/2025

Correspondence: Mario B. Principato. Correo electrónico: mbprincipato@yahoo.com.ar
This article won the Dr. Pedro Cossio award at the 50th Argentine Congress of Cardiology

[1] Hospital General de Agudos JM Ramos Mejía, Autonomous City of Buenos Aires, Argentina

Objetivos: El objetivo de este estudio fue identificar asociaciones entre variantes genéticas en alelos polimórficos, polimorfismos de nucleótido único (SNPs) con la presencia de FEVIr y de trastornos de conducción intraventricular(TCIV), en un modelo de miocardiopatía adquirida como es la chagásica.
Material y métodos: Se incluyó como modelo de estudio a pacientes seropositivos para enfermedad de Chagas con data de infección de más de 20 años, un grupo con FEVIr(FEVI ≤35%) y otro con FEVI preservada, FEVIp(≥50%). Se realizó una toma de sangre que fue procesada para la obtención del ácido desoxirribonucleico (ADN), que se envió a un laboratorio internacional de genotipado. Se preparó un panel de SNPs de genes utilizando la base internacional TheGenomeAggregationDatabase (GnomAD), eligiendo SNPs con una frecuencia en la población del 10% al 40%. Los SNPs elegidos están relacionados con genes responsables del proceso de contracción y relajación ventricular (TTN, BAG3, MTSS1), el metabolismo miocárdico (PPARGC1A, SIRT1, AKT1 mTOR, AMPK), receptor adrenérgico beta 1 (ADRB1), receptor colinérgico muscarínico 2 (CHRM2), receptor de angiotensina II tipo 1 (AGTR1B), y el péptido natriurético auricular (NPPA) Mediante diversos modelos de inteligencia artificial para aprendizaje supervisado (Regresión Logística, Máquinas de Vectores de Soporte, Redes Neuronales Artificiales, NaiveBayes, Árboles de Clasificación y RandomForest) se evaluaron 68 SNPs como predictores de la presencia de dos fenotipos: FEVIr, y TCIV. El desempeño de los modelos para la predicción de la FEVIr se evaluó mediante la técnica de validación cruzada (*cross-validation*), con la métrica F1 como medida de precisión para seleccionar el mejor modelo.
Resultados: Se incluyeron 182 pacientes, con una mediana de edad de 62 años, el 39,6 % hombres. El 31 % presentó FEVIr y el 53 % algún TCIV. El modelo con el mejor desempeño fue la regresión logística (F1 = 0,85), por lo que se la utilizó para expresar la asociación mediante el Odds Ratio y su IC del 95%. Se observó que las variantes rs2076300, rs61772962 y rs7071853 fueron predictores independientes de reducción de la FEVI. Mientras que, para la presencia de TIVC, el único predictor fue el SNP rs72840788. El SNIP rs61772962 corresponde al gen PRKAA2, que codifica a la subunidad catalítica alfa-2 de la proteína quinasa activada por 5'-AMP. Por su parte el rs7071853 y el rs72840788 corresponden al gen que codifica a la proteína BAG3 (regulador 3 de chaperona). Finalmente el SNP rs2076300 corresponde al gen DSP que codifica una desmoplaquina, proteína de la placa de unión de los desmosomas.
Conclusión: En este modelo de derivación, en un conjunto de pacientes con serología positiva para Chagas se identificaron 3 SNPs predictores de reducción de la FEVIr y un SNP predictor de TCIV. La reproducibilidad de estos resultados debería ser confirmada en un modelo de validación con una mayor muestra de individuos. Además, este hallazgo podría ser de utilidad en miocardiopatías dilatadas de otras etiologías.

Palabras claves: Miocardiopatìa dilatada - Insuficiencia cardíaca - Genética - Enfermedad de Chagas

INTRODUCTION

Heart failure with reduced left ventricular ejection fraction (LVEF) represents one of the pathologies with the highest mortality. Among its main etiologies is dilated cardiomyopathy (DCM). The predictors of DCM development and prognosis are subject to ongoing research. Despite advances in understanding the underlying pathophysiological mechanisms, the reasons why certain conditions predispose to the progression of dilated cardiomyopathy are still not fully understood. (1)

Genotypic (familial) alterations that are responsible for a small group of cases with the ventricular dilatation phenotype have been identified.

A notable aspect is that the same noxa can generate variable effects among different patients. This suggests the possible existence of a genetic predisposition that would influence a differentiated clinical evolution. In this context, single nucleotide polymorphisms (SNPs) could play a key role in the variability of patients' response to the same noxa.

To investigate the existence of genetic variants associated with the predisposition to DCM, we used Chagas disease as model. (2) Chagas disease is responsible for DCM with the highest morbidity and mortality. It presents two clinical phases: an acute phase, which is usually asymptomatic in 95% of patients, and a chronic phase, with a long latency period of 10-30 years. In this group, between 25% and 30% of individuals develop signs or symptoms of cardiac involvement (Chagas cardiomyopathy). (3)

Chronic Chagas cardiomyopathy (CCM) has been considered the most frequent cause of non-ischemic cardiomyopathy in Argentina. However, there is no consensus on the risk indicators for the development of this condition and other cardiovascular events, regardless of the effect of traditional risk factors. (4)

OBJECTIVE

The aim of our study was to determine the genetic variants related to the presence of DCM by performing an association analysis with SNPs.

METHODS

Prospective single-center study that included patients from June 2016 to January 2020.

Patients from 21 to 80 years of age, seropositive for Chagas disease with DCM, from the provinces of northwestern Argentina and southern Bolivia, and other serologically positive patients of similar age, from the same geographic areas without DCM, were included as a control group.

All patients should have a known history of infection of more than 20 years certified by the treating physician, serological analysis, and abandonment of the endemic area for more than 20 years as well as a LVEF measured within 12 months prior to inclusion, ≤ 35% or ≥ 50%.

Patients who refused to sign the informed consent form, those with known serious pathologies (excluding cardiovascular) that generate a life expectancy of less than one year, and those who were participating in research protocols in the 30 days prior to sample collection were excluded. Those in whom personal or telephone contact could not be assured, with alcohol or drug abuse in the last 6 months, with clinical and laboratory evidence of liver failure (transaminase value x3 and total bilirubin >2 mg/dL), with LVEF between 36% and 49% (the objective was to separate the groups avoiding patient crossover), and those receiving drugs with a known

action on cardiovascular parameters (immunosuppressants, nitrates, estrogens) were also rejected. Patients with acute or chronic coronary artery disease, with an indication for revascularization or with coronary angioplasty or myocardial revascularization surgery in the previous 6 months, patients with renal failure (serum creatinine >2.5 g/dL), with severe obstructive pulmonary disease, with DCM of other etiologies (e.g. rheumatoid arthritis, diabetes, hypertension), with significant valvular diseases (except those secondary to mitral and/or tricuspid valve annulus dilatation), with pacemakers with stimulation greater than 50%, or with autoimmune pathologies (lupus, scleroderma, hepatitis C, etc.) were also excluded.

Patients who met the inclusion criteria and did not present exclusion criteria were divided into 2 groups:

- Group 1: patients with LVEF≤ 35%.
- Group 2: individuals with LVEF≥50%.

After signing the informed consent, a complete clinical history and physical examination were performed, according to their underlying pathology and the corresponding diagnostic and prognostic procedures.

An echocardiogram to confirm the LVEF value and a 12-lead ECG were performed. According to the ECG results, patients were classified into two groups: with intraventricular conduction disorders (IVCD), when they had one or more of the following criteria: right bundle branch block, left bundle branch block, left anterior hemiblock and left posterior hemiblock; or without IVCD.

Patients were coded with an alphanumeric system to ensure the identity of the groups.

A 10 mL blood sample was taken by trained personnel for genomic determination. The sample was placed in tubes with the presence of ethylenediaminetetraacetic acid (EDTA) according to ISO standards to prevent coagulation and stored at -20ºC until processing. This sample was processed to obtain the corresponding deoxyribonucleic acid (DNA) in a specialized center in our country, leaving safety samples.

The DNA was sent via a courier authorized by international legislation for this purpose to the international laboratory Xenética Cardiovascular, Instituto de Investigación Sanitaria de Santiago, laboratory nº1, Complexo Hospitalario Universitario de Santiago de Compostela, where genotyping and analysis were performed (Table 1). The laboratory remained blind to which group the patients belonged. This was only known by the statistical team at the time of the analysis.

An SNPs panel of genes was prepared related to the following:

- Ventricular contraction and relaxation process (TTN, BAG3, MTSS1). (5-7)
- Myocardial metabolism (PPARGC1A, SIRT1, AKT1 mTOR, AMPK, PRKAA2).
- Beta 1 adrenergic receptor (ADRB1). (8-11)
- Cholinergic receptor muscarinic 2 (CHRM2).
- Angiotensin II type 1 receptor (AGTR1B).
- Atrial natriuretic peptide (NPPA).
- Cell cycle regulators (CDKN1A, RYR2)
- Sarcomeric structure (ATP2A2, DSP, JUP)
- Cellular energy (PRKAB2, PRKAB1)
- Mitochondrial activity (SOD 2)
- Apoptosis (AKT1)
- Cellular hypoxia regulator (HIF1A)
- Respiratory chain (LDHA, lactate dehydrogenase (LDH))
- Nitric oxide (NOS1, NOS2P3)
- Growth and inflammation factors (SH2B3)

The international database TheGenomeAggregationDatabase (GnomAD) was used, choosing SNPs with a frequency of 10% to 40% in the population incorporated into this database.

Finally, 68 SNPs, detailed in Table S1, were selected for analysis.

The technology used was iPLEX Gold. The script was created in SNPassoc to evaluate whether the entire population met the H-W equilibrium condition.

The association between these two phenotypes was evaluated as binomial variables coded as YES=1 and NO=0, with the SNPs coded as an ordinal variable according to the following convention: 0 for homozygotes of the wild-type allele, 2 for homozygotes of the alternative allele and 1 for heterozygotes.

To evaluate the relationship between the different SNPs under study and the presence of reduced LVEF, various artificial intelligence models for supervised learning were used. The performance of 1) Logistic Regression, 2) Support Vector Machines, 3) Artificial Neural Networks, 4) Naive Bayes, 5) Decision Trees and 6) Random Forest was evaluated, with the collaboration of the genomIT Artificial Intelligence team.

The performance evaluation of the different models for the prediction of rEF was carried out using the cross-validation technique, using F1 score as a measure of precision to select the best model.

To evaluate the relationship between each SNP and the presence of IVCD, a univariate logistic regression model with the presence of reduced LVEF and IVCD as outcomes and each SNP as a predictor was evaluated. SNPs with an associated p value<0.05 were selected for evaluation of their effect using a multivariate logistic regression model, selecting those SNPs with a p value<0.05 using the backward selection strategy with stepwise regression method. The magnitude of the association between each SNP and the outcome under study was expressed as the Odds Ratio and its respective 95% confidence interval (95% CI). The predictive performance of the model was evaluated using the area under the curve (AUC). The same procedure was applied using logistic regression of the SNPs with reduced LVEF.

The analyses were performed with the R ® software (version 4.1.1, R Development Core Team/R Foundation for Statistical Computing, Vienna, Austria).

A Manhattan plot was also generated with different inheritance models for all SNPs, analyzing the nominal level of significance and the Bonferroni level.

Ethical considerations

The study was developed in accordance with the ethical principles of the Declaration of Helsinki and approved by the Teaching and Research Committee of the institution.

RESULTS

One hundred and eighty-two patients with positive serology for Chagas disease from southern Bolivia and northwestern Argentina were studied.

The median age of the population was 62 years, 39.6% were men. Fifty-seven of them (31%) had rEF and 95 (53%) had some IVCD (Table 1).

Among the different supervised classification models evaluated, the model that uses 7 K folds and a logistic regression classifier obtained a score of F1=0.85, being the best model obtained; therefore its results are reported.

The univariate analysis of the relationship between each SNP (on the horizontal axis) and the presence of a reduced LVEF and IVCD respectively performed by logistic regression is presented in Figures 1 A and 1 B. A multivariate analysis that revealed the association of reduced LVEF phenotype and IVCD was performed. (Figures 2 A and B, Tables 2 and 3).

It was observed that the variants rs2076300, rs61772962 and rs7071853 were independent predictors of reduced LVEF; whereas, for the presence of blocks, the only predictor was the SNP rs72840788, as is seen in the univariate analysis.

In each of the three SNPs predicting DCM, the proportion of homozygous wild-type, heterozygous and each homozygous variantof the alternative allele was analyzed, according to the presence or not of a reduced LVEF and IVCD. (Figures 3 A, B and C, Figure 4)

The predictive performance of the model for the presence of reduced LVEF is evidenced by the area under the ROC curve (0.662) and its corresponding 95% CI (0.580-0.745) (Figure 5)

Regarding the performance of the neural network for the prediction of reduced LVEF with the three identified SNPs, the best model was that of a neural network with 2 hidden layers of 6 and 3 neurons respectively, with an error rate (proportion of prediction failures) of 0.33 and an accuracy rate (proportion of prediction successes) of 0.67, (Figure 6).

DISCUSSION

Heart failure (HF) is a disease of epidemic proportions, representing the final stage of various pathologies. Its prevalence increases two to three times when including patients with asymptomatic systolic dysfunction. (12-14)

Initially, 60-70% of patients with HF had a high mortality within five years after diagnosis, accompanied by a high rate of hospitalization for decompensated HF. However, with the advent of new drugs, a significant decrease in morbidity and mortality has been seen. (15-21)

Heart failure with reduced LVEF is a progressive disorder that usually begins after a noxa or damaging event that affects the heart muscle, resulting in the loss of functional myocytes or a decrease in the contractile capacity of the myocardium. In most cases, an asymptomatic phase initially occurs due to compensatory mechanisms that are activated and modulate LV function within physiological limits for a certain period of time. However, the sustained activation of the neurohormonal and cytokine systems causes a series of changes in the myocardium, leading to ventricular remodeling and the eventual appearance of symptomatic HF.

Neurohumoral systems include the sympathetic nervous system (SNS), through the activation of the Beta 1 receptor, and the renin-angiotensin system (RAS), mediated by the persistent action of angiotensin II (AT2) and aldosterone on the myocardium.

Parasympathetic inhibition also contributes to HF pathogenesis by reducing nitric oxide (NO) concentrations with the consequent increase in inflammation and ventricular remodeling. (22)

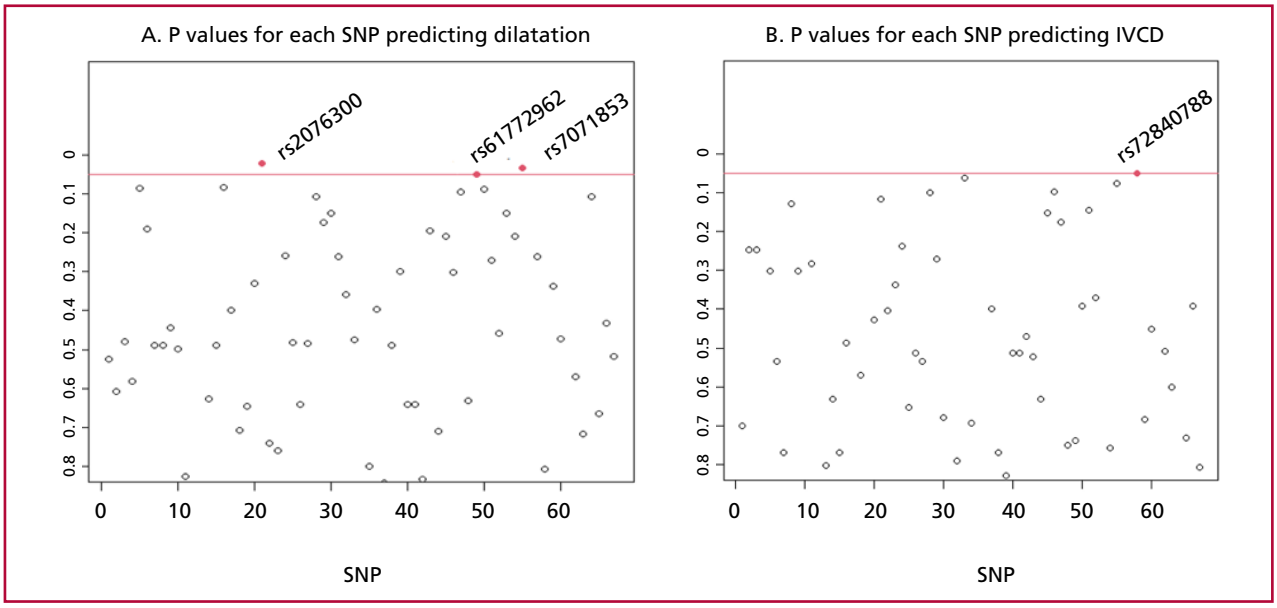
Most of the genes involved in the development of DCM and HF are involved in energy production and regulation processes, as well as calcium signaling and transcription regulation. The genes described are mainly those of sarcomere proteins (MYH7, TNNT2, TNNI3, TNNC, TPM1, MYBPC3, TTN, ACTC, MYL3, MYL2), Z-disc proteins (VCL, LDB3, TCAP, MYOZ2), cytoskeletal or cell membrane proteins (DES, DAG1, SGCA, LMNA, FLNC), desmosomal proteins (JUP, DSP, DSG2, DSC2, PKP2, RYR2, PLN), sodium channel (SCN5A), metabolic proteins (PRKAG2, GLA, LAMP2, GAA) and regulatory proteins (RMB20, BAG3, TGFB3) among others.

Through genome-wide association studies (GWAS), certain SNPs associated with the risk of developing HF have been described.

Table 1. Baseline characteristics

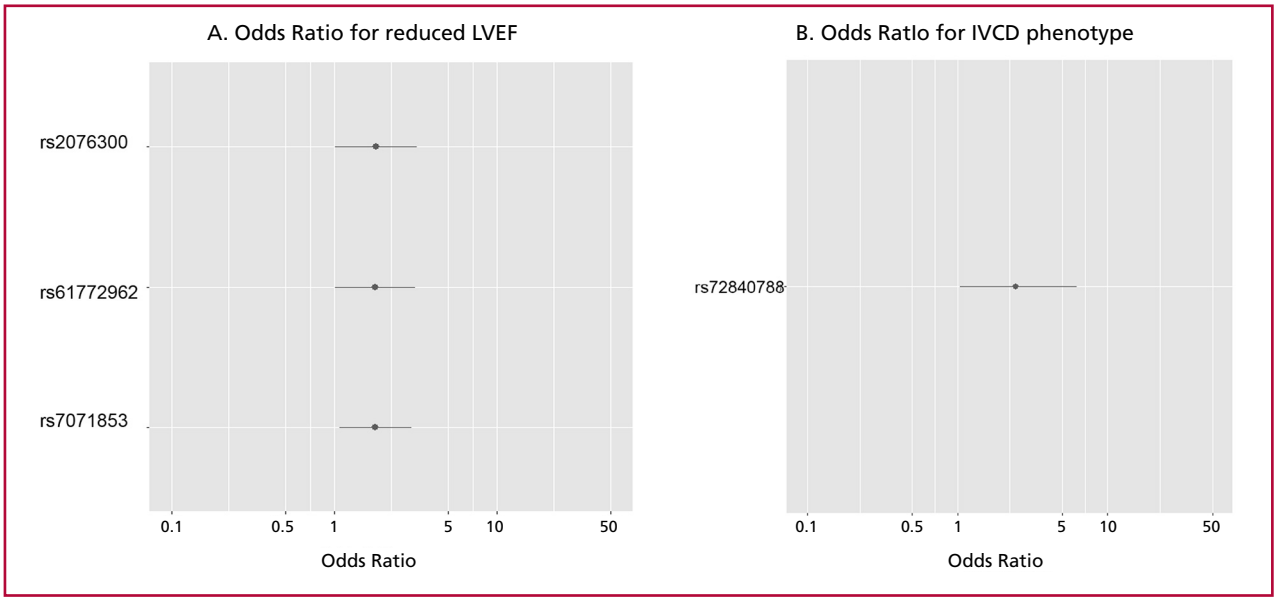
	Preserved LVEF	Reduced LVEF
N	125	57
Age (years)	59.44 (11.25)	64.68 (10.09)
Male gender	39 (31.2)	33 (57.9)
HTN	38 (30.4)	13 (22.8)
DM		
• No	116 (92.8)	51 (89.5)
• Type I	3 (2.4)	0 (0.0)
• Type II	6 (4.8)	6 (10.5)
HF	4 (3.2)	34 (59.6)
Arrhythmias	21 (16.9)	28 (50.0)

DM: diabetes mellitus; HF: heart failure; HTN: hypertension; LVEF: left ventricular ejection fraction
Quantitative variables are presented as mean and standard deviation, qualitative variables as frequency and percentage.



IVCD: intraventricular conduction disorder; SNP: single nucleotide polymorphism

Fig. 1. A and **B**: The vertical axis expresses the p values for each SNP, the red line marks a p = 0.05 significance level, and the red dots correspond to the SNPs that presented a p value < 0.05



95% CI: 95% confidence interval; IVCD: intraventricular conduction disorder; LVEF: left ventricular ejection fraction; SNP: single nucleotide polymorphism

Fig. 2. A and **B**. Odds ratio and 95% CI for SNPs predicting A) reduced LVEF and B) IVCD phenotype

Table 2. Multivariate analysis. Odds ratio and 95% CI and p-value for each of the three SNPs independently associated with reduced LVEF

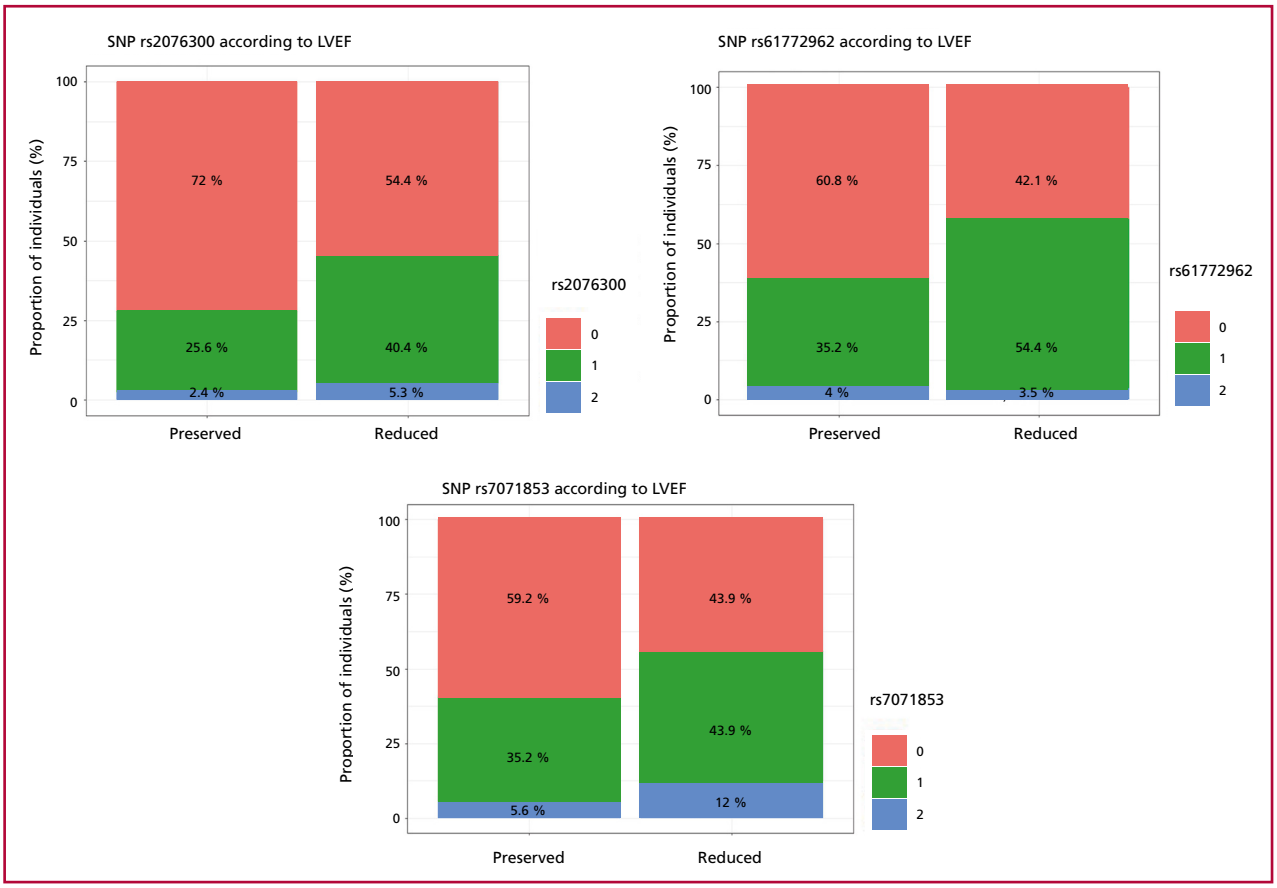
	Reduced LVEF		
Predictor	**Odds ratio**	**95% CI**	**p value**
rs2076300	1.79	1.01 – 3.21	0.046
rs61772962	1.77	1.00 – 3.14	0.049
rs7071853	1.77	1.07 – 2.96	0.026

95% CI: 95% confidence interval; LVEF: left ventricular ejection fraction; SNP: single nucleotide polymorphism

Table 3. Odds Ratio, 95% CI and p value for the only SNP associated with the presence of intraventricular conduction disorders

	Reduced LVEF		
Predictor	**Odds ratio**	**95% CI**	**p value**
rs72840788	2.44	1.04 – 6.22	0.048

95% CI: 95% confidence interval; SNP: single nucleotide polymorphism



LVEF: left ventricular ejection fraction; SNP: single nucleotide polymorphism
0: homozygous for the wild-type allele 1: heterozygous 2: homozygous for the alternative allele.

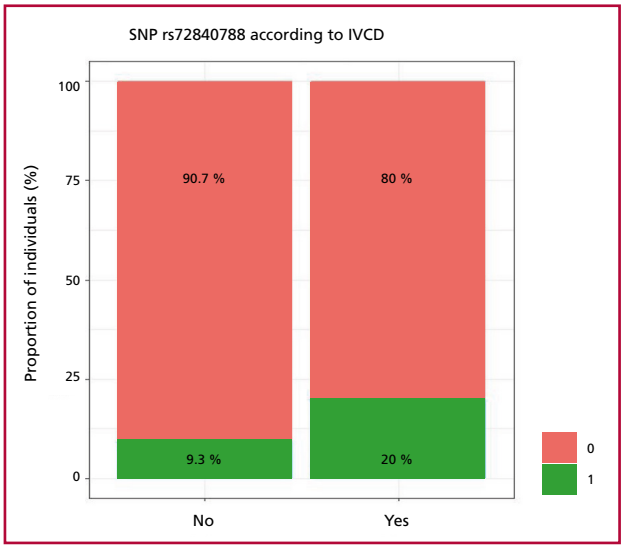
Fig. 3. Proportion of homozygous wild-type (0), heterozygous (1) and homozygous alternative allele (2) variants of SNP rs2076300 (3 A), rs61772962 (3 B) and rs7071853 (3 C), according to the presence of reduced or preserved LVEF

One of the most widely studied SNPs is the variant responsible for the change of arginine to glycine (Arg-389Gly) in the Beta 1 receptor. In the general population, Arg389Gly polymorphism was not significantly associated with HF, but in the subgroup analysis according to ethnicity, the presence of Gly389 in Asian patients was shown to increase the risk of HF by 35% compared to Arg389 carriers (RR 1.35; 95% CI: 1.16-1.57; $p < 0.001$). In a more detailed subgroup analysis, Arg389 homozygotes were associated with an improvement in LVEF in East Asians (95% CI 1.85-3.40; $p < 0.001$) and mixed population (95% CI 0.72-2.91; $p < 0.001$); while among white patients, Arg389 homozygotes had an improvement in LV systolic diameter. The improvement was significantly greater than that of Gly389 (95% CI 0.04-0.36, p=0.001). (23-26)

In the case of renin genes, G/AI 9-83 polymorphisms were analyzed in patients with DCM. The heterozygous form was found in only 37.5% of control subjects. This study did not show involvement of renin A/G polymorphisms in HF pathogenesis. (27)

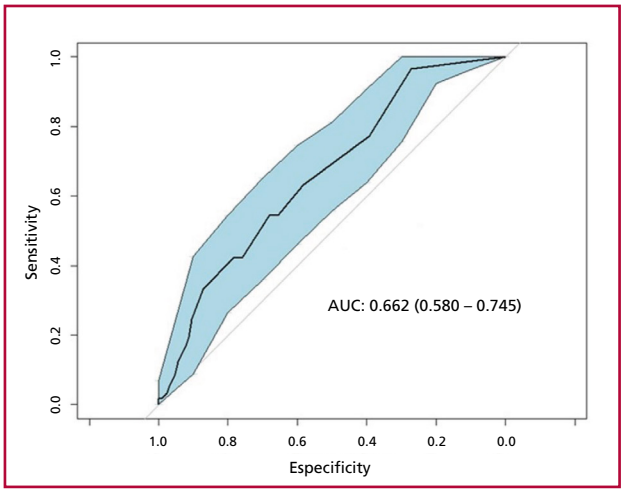
Patients with DCM may present hypertrophy and fibrosis. An association of the angiotensin II type 1 receptor and gene polymorphisms (AGTR1, A1166C) was observed in angiotensin converting enzyme (ACE)-mediated left ventricular hypertrophy (LVH) in endurance athletes, that would be a variant for future study in DCM. (28)

On the other hand, in several studies, two SNPs (rs763361 and rs727088) in the last exon of CD226



IVCD: intraventricular conduction disorder; SNP: single nucleotide polymorphism
0: homozygous for the wild-type allele 1: heterozygous

Fig. 4. Proportion of homozygous wild-type, heterozygous and homozygous variants of the alternative allele of SNPrs72840788, according to the presence of IVCD



AUC: area under the curve; LVEF: left ventricular ejection fraction; 95% CI: 95% confidence interval

Fig. 5. Predictive performance of the model for the presence of reduced LVEF: area under the ROC curve (0.662) and its 95% CI (0.580-0.745)

have been reported in the Titin gene (TTN), as associated with an increased risk of DCM. (29)

Another gene to consider is MMP2. This gene SNPs were analyzed to evaluate their association with the development of DCM and three of them were found to be related both to the risk of suffering from it as to its worse prognosis. (30)

Since there is no consensus on the variants that could predispose to the development of DCM in response to harmful factors affecting the myocardium, we decided to establish an analysis panel. This includes structures related both to neurohumoral systems as to aspects of energy metabolism that could be involved in the development of DCM. The international database TheGenomeAggregationDatabase (GnomAD) choosing SNPs with a frequency of 10% to 40% in the world population. The SNPs used are detailed in Table S1.

In our analysis we were able to observe that the variants rs61772962, rs7071853 and rs2076300 were independent predictors of reduced LVEF in our population of patients with chronic Chagas cardiomyopathy.

The SNP rs61772962 corresponds to an intronic variant of the PRKAA2 gene. This gene encodes the alpha-2 catalytic subunit of the 5'-AMP-activated protein kinase. This AMPK protein, is an important cellular energy-sensing enzyme. In response to cellular metabolic stress, AMPK is activated and thus phosphorylates and inactivates acetyl-CoAcarboxylase (ACC) and beta-hydroxy beta-methylglutaryl-CoAreductase (HMGCR) key enzymes involved in the regulation of de novo biosynthesis of fatty acids and cholesterol. (31) The AMPKα2 variant is required for energy metabolism in cardiomyocytes. (32)

The RNF207 and PRKAA2 genes, known for their involvement in cardiac action potentials, energy homeostasis and morphology, have been postulated as candidates for DCM models after study in dogs and follow-up in humans. (33)

Dominant mutations in the γ2 regulatory subunit of AMP-activated protein kinase (AMPK), encoded by the PRKAG2 gene, cause glycogen storage cardiomyopathy in mutant mice. (34)

The rs7071853 corresponds to the gene for the BAG3 regulatory protein (position chr10:119552094 (GRCh38.p14). On the other hand, rs72840788 was associated with the prediction of conduction disorders and corresponds to the intronic position of that protein. The BAG3 protein plays an important role in maintaining myocardial homeostasis and excitation-contraction coupling and is an adaptive mechanism to maintain cellular homeostasis under stress. It is most prominently expressed in the heart, skeletal muscle, and in many forms of cancer. In the heart, it acts as a chaperone for heat shock proteins to facilitate autophagy. Mutations in BAG3 have been associated with the development of a variety of phenotypes, including hypertrophic/restrictive and dilated cardiomyopathy. (35-40)

The rs2076300 is part of the DSP gene that encodes for desmoplakin, a calcium-dependent protein of the cadherin family essential for desmosomes, multiprotein structures involved in signal communication between cells and in the coordination of cardiac muscle contractions. Desmosomes are critical intercellular junctions for the mechanical and electrical integrity of tissues, specially in the myocardium and epithelial tissues. Mutations in the DSP gene are typically associated with arrhythmogenic cardiomyopathy. However,

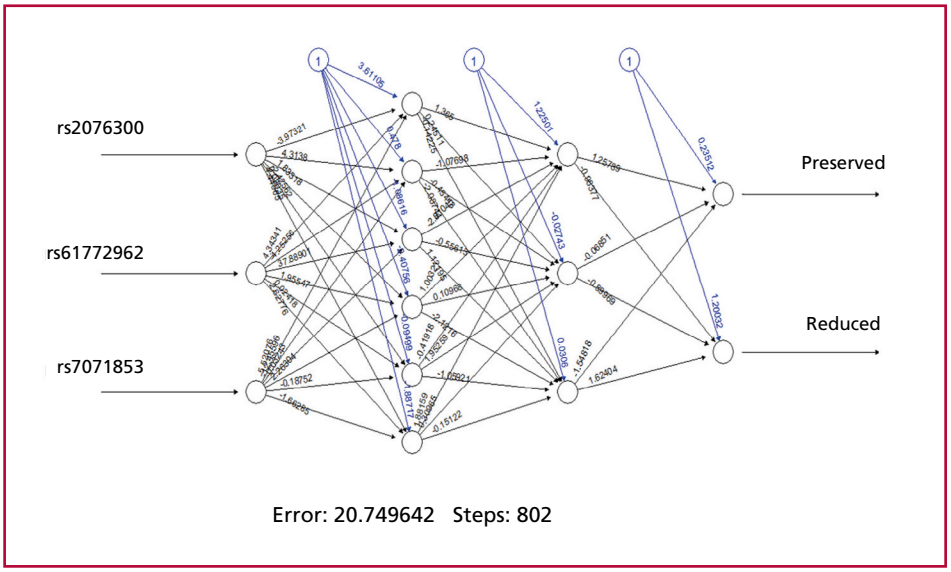


Fig. 6. Neural network to assess the predictive power of reduced LVEF of the three identified SNPs

LVEF: left ventricular ejection fraction SNP: single nucleotide polymorphism

they can also cause dilated cardiomyopathy, which presents with a higher incidence of ventricular arrhythmias and an increased risk of sudden death. This finding is significant, as it demonstrates that a proportion of patients with a clinical diagnosis of dilated cardiomyopathy harbor mutations in genes encoding intercalated disc proteins. (41-45)

Attempting to confirm these results with other statistical methods using the "Bonferroni threshold" did not yield reproducible results. Since most effects of a single SNP are in the range of a 10 to 15% modification of the baseline risk of presenting a certain phenotype, the Bonferroni adjustment for the evaluation of 70 SNPs, maintaining the global alpha level of 0.05 and a power of 80%, determines that the rejection of the null hypothesis for each test could be carried out only with a p value <0.0007, which implies, under the most optimistic effect of a 15% increase in risk (RR = 1.15), the need to recruit 6280 individuals. This is why we believe that the results could not be confirmed with other tests, due to the sample size used.

CONCLUSION

In this derivation model, in a group of patients with positive serology for Chagas, 3 SNPs were identified as predictors of reduced LVEF (rs2076300, rs61772962 and rs7071853) and one predictor of conduction disorders (SNP rs72840788).

When trying to confirm these results with other statistical methods using the "Bonferroni threshold" the results could not be reproduced, due to the sample size used. This reinforces the idea that we must continue in this line of analysis, increasing the number of patients. It is essential to continue exploring the hypothesis that, even in the absence of a family history of DCM and pathogenic variants in genetic studies, there may be polymorphisms that predispose to the development of ventricular dilatation.

This approach would be very useful in the future, not only for early identification of patients predisposed to present DCM and HF, but also for anticipating treatment, thus improving both morbidity and mortality in our patients. We believe that this could open new perspectives in pharmacogenomics applied to HF.

This study aims to be a starting point to promote future research and strategies. Its intention is to establish a line of research that, by incorporating a larger number of patients and continuing with the analysis, will make it possible to achieve greater statistical power.

Conflicts of interest

None declared.

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

Acknowledgments

The authors would like to thank Engineer Roberto Bunge (Director of Artificial Intelligence Engineering, Universidad San Andrés) and Engineer Trinidad Monreal (Research and Development, Artificial Intelligence and Robotics Laboratory, Universidad San Andrés) for their contributions and expertise in artificial intelligence and neural networks.

Financing

The authors declare they have not received any funding for this work.

Policy on the use of artificial intelligence

Artificial intelligence resources have not been used to write the text or to create the tables or graphs.

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SUPPLEMENT 1

Table S1. Analyzed SNPs

GENE	SNP	
ADRB1	rs12414657	Upstream variant
	rs1801252	Missense variant
	rs1801253	Missense variant
	rs3813719	Downstream variant
	rs3813720	Downstream variant
CHRM2	rs13247260	Upstream intron
	rs6962027	Prime UTR variant
	rs6967953	Prime UTR variant
NOS1	rs12811583	intron
	rs1875140	intron
	rs3741475	Synonymous variant
TTN	rs2042995	Missense variant
	rs2255167	intron
PRKAA2	rs17848595	Synonymous variant
	rs61772962	Intron
	rs17848596	Missense variant
MTOR	rs1034528	Intron
	rs11581010	Intron
	rs17036350	Intron
	rs74225573	Intron
RYR2	rs10802607	Intron
	rs67622164	Intron
	rs10925391	Intron
	rs16835818	Intron
JUP	rs1126821	Missense
	rs8067890	Intron
	rs7405731	Missense variant
	rs7216034	Intron
SOD2	rs11752345	Intron
	rs4880	Missense variant
PRKAB2	rs1348316	Intron
	rs72708505	Intron
CDKN1A	rs146170154	Intron
ZNF592	rs149369954	non coding transcrip tvariant
BAG3	rs1831018	BAG cochaperone 3
	rs72840788	Intron
	rs7071853	
ATP2A2	rs1860561	Intron
DSP	rs2076300	Synonymous variant
	rs926411	Intron
SIRT1	rs2236318	Intron
	rs2273773	Synonymous variant
PPARGC1A	rs2290604	Intron
	rs3755863	Synonymous variant
AGTR1	rs275653	Upstream variant
	rs5186	3 Prime UTR variant
	rs387967	Upstream variant
	rs422858	Upstream variant
SOD2	rs2758332	Intron
	rs5746094	Intron
PRKAB1	rs278145	intron
	rs278149	intron
PPARGC1A	rs2946385	Stop gained
	rs8192678	Missense variant
PRKAB2	rs34838459	Synonymous variant
LOC105375743	rs34866937	intron
AKT1	rs3730346	intron
	rs3730358	intron
	rs3803304	intron
HIF1A	rs373909145	intron
NPPA	rs5063	Missensevariant
	rs5064	Intron
	rs5065	stop loss
DERL32KB	rs6003909	Upstream variant
NOS2P3	rs62066941	Intron
LDHA	rs6498	Synonymous variant
SH2B3	rs7310615	Intron
SIRT1	rs7896005	Intron
CHRM2	rs8191992	3 Prime UTR variant
CLCNKA2KB	rs945425	Upstream variant

SNP: single nucleotide polymorphism

ORIGINAL ARTICLE

Performance of a Multiplier Score of the 99th Percentile of Troponin Level to Predict In-Hospital Events and one-year Mortality in Acute Coronary Syndrome

Rendimiento de un score multiplicador del percentilo 99 de troponina para predecir eventos intrahospitalarios y mortalidad a 1 año en el síndrome coronario agudo

SOL KERSTEN, ALAN R. SIGAL, MIRZA RIVERO[MTSAC], JUAN F. FURMENTO, DIEGO CONDE, MAYRA MEZA, ANA SPACCAVENTO, GASTÓN PROCOPIO, JUAN PABLO COSTABEL[MTSAC], REPRESENTING THE BOARD OF CARDIOVASCULAR EMERGENCIES AND CRITICAL CARDIOLOGY "DR. RAFAEL BULLRICH"

ABSTRACT

Background: In Argentina, high-sensitivity troponin is widely used to evaluate patients with chest pain. However, variability between assays (troponin I or T) and their different cut-off points and percentiles may hinder uniform interpretation.
Objective: This study assessed the performance of a multiplier score based on the 99th percentile of troponin level to predict in-hospital and one-year mortality, as well as ischemic and bleeding events in patients with acute coronary syndrome (ACS).
Methods: We used the ReSCAR registry, a prospective multicenter study that included patients with ACS. A total of 917 cases were analyzed: 291 with troponin I measurement and 626 with troponin T measurement. The multiplier score was calculated as the ratio of the troponin concentration to the 99th percentile of the corresponding assay. The area under the ROC curve of this score was evaluated regarding its ability to predict in-hospital ischemic and bleeding events, as well as in-hospital mortality and mortality at one-year follow-up.
Results: In-hospital mortality was 3.9%, while at one-year mortality was 7.2%. In-hospital ischemic events occurred in 8.2% of patients and bleeding events in 2.9%. The median score was 5.4 (IQR 1.2-48.2). The area under the ROC curve of the score to predict ischemic events was 0.64. No significant differences were observed when compared to the GRACE score (0.67). For bleeding events, the area under the ROC curve of the score was 0.63, comparable to that of the CRUSADE score (0.67). The discriminative ability of the score to predict in-hospital and one-year mortality was lower than that of the GRACE score (0.59 vs. 0.77 and 0.62 vs. 0.79, p <0.01 for both).
Conclusion: The multiplier score based on the 99th percentile of troponin level is a simple and potentially useful tool for standardizing risk assessment in different centers which have diverse laboratories. Although its performance to predict in-hospital ischemic and bleeding events is comparable to that of the GRACE and CRUSADE scores, it showed lower accuracy to predict mortality.

Key words: Troponin – Score – Mortality – Acute Coronary Syndrome

RESUMEN

Introducción: En Argentina, la troponina de alta sensibilidad es ampliamente utilizada para evaluar pacientes con dolor torácico. Sin embargo, la variabilidad entre ensayos (troponina I o T) y sus diferentes puntos de corte y percentilos puede dificultar su interpretación uniforme.
Objetivo: Este estudio evaluó el desempeño de un score multiplicador basado en el percentilo 99 de troponina para predecir mortalidad intrahospitalaria y al año, así como eventos isquémicos y hemorrágicos en pacientes con síndrome coronario agudo (SCA).
Material y métodos: Se utilizó el registro ReSCAR, un estudio multicéntrico prospectivo que incluyó pacientes con SCA. Se analizaron 917 casos: 291 con troponina I y 626 con troponina T. El score multiplicador se calculó como la relación entre el dosaje de troponina y el percentilo 99 del ensayo correspondiente. Se evaluó el área bajo la curva ROC del score para predecir eventos isquémicos y hemorrágicos intrahospitalarios, al igual que para mortalidad intrahospitalaria y al año de seguimiento.
Resultados: La mortalidad hospitalaria fue 3,9% y al año 7,2%. Los eventos isquémicos intrahospitalarios ocurrieron en el 8,2% y los eventos hemorrágicos en 2,9% de los pacientes. La mediana del score fue 5,4 (rango intercuartílico 1,2-48,2). El área bajo la curva ROC (ABC ROC) del score para predecir eventos isquémicos fue 0,64, sin diferencias significativas con el score GRACE (0,67). Para eventos hemorrágicos, el score mostró un ABC ROC de 0,63, comparable a la del score CRUSADE (0,67). La capacidad discriminativa del score para mortalidad intrahospitalaria y al año fue menor que GRACE (0,59 vs. 0,77 y 0,62 vs. 0,79, p <0,01 para ambos casos).

Rev Argent Cardiol 2025;93:25-30. https://doi.org/10.7775/rac.v93.i1.20852

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Received: 11/03/2024 – *Accepted:* 01/07/2025

Correspondence: Juan Pablo Costabel. Libertador 6302. Capital Federal. Argentina. E-mail: juanpablocostabel@gmail.com
This article won the Dr. Raúl Borracci Award in the 50th Argentine Congress of Cardiology

Conclusiones: El score multiplicador basado en el percentilo 99 de troponina es una herramienta simple y potencialmente útil para estandarizar la evaluación del riesgo en diferentes centros con distintos laboratorios. Aunque su desempeño es comparable al de GRACE y CRUSADE para eventos isquémicos y hemorrágicos intrahospitalarios, mostró menor precisión para predecir mortalidad.

Palabras claves: Troponina - Score - Mortalidad - Síndrome Coronario Agudo.

INTRODUCTION

Since its introduction around 2010, high-sensitivity troponin has become the biomarker of choice to diagnose acute myocardial infarction (AMI). (1-3) Both troponin T and I are integral components of myocardial cells, released from necrotic tissue, and exhibit high specificity for the diagnosis of AMI. (4) High-sensitivity assays offer improved sensitivity compared to other diagnostic tests, which increases their usefulness in emergency departments. (2, 3, 5)

Different studies have demonstrated that both troponin T and I provide high diagnostic accuracy for AMI, little variability in terms of symptom onset and multiple sampling, as well as high predictive value. (2, 3, 6-10) Today, most medical centers have access to these tests, but the distribution of assays and manufacturers is heterogenous, and the centers use different cut-off points and percentiles. As a result, the collection of these values in multicenter studies has become a challenge that hinders the interpretation and correct analysis of data in acute coronary syndrome (ACS). Therefore, we propose a new system that uses the 99th percentile of the high-sensitivity troponin to standardize the different assays and assess their predictive ability.

METHODS

We performed a prespecified analysis of the patients included in ReSCAR (11), a multicenter, prospective, observational registry performed in Argentina, which included patients with ACS from several centers of the country and collected data from history, ACS characteristics and treatment, as well as hospital events and patient status at one-year follow-up. ReSCAR included 984 patients with ST-elevation ACS or non-ST-elevation ACS from 15 centers in Argentina from January to August 2022.

Generation of a new score using the 99th percentile of troponin level

We transformed the high-sensitivity troponin value at admission, both troponin T assays and troponin I assays, into multiples of its 99th percentile, generating a new score. Only values at admission were included, regardless of whether they were the highest during hospital stay. For example, in a center, if a 99th percentile of troponin is 14 and the patient had a troponin of 28, his multiplier score (MS) is 2.

Comparison

To evaluate the effectiveness of the percentile, we compared its ability to predict ischemic and bleeding events with that of the GRACE (12) and CRUSADE (13) scores, analyzing the areas under the ROC curves. In addition, we evaluated the score ability to predict in-hospital and one-year follow-up mortality, again comparing it with the GRACE score, and analyzing the ROC curve. Ischemic events were defined as AMI, stent thrombosis, stroke/transient ischemic attack (CVA/TIA) or post-infarction angina. Bleeding events were defined as those that were BARC 2 or greater. (14)

Data collection and inclusion criteria

As previously mentioned, we analyzed data from ReSCAR, an observational, cross-sectional, multicenter registry that included patients ≥18 years with ACS from several hospitals in Argentina, which had a coronary care unit, 24-hour hemodynamics service and ability to measure high-sensitivity troponin, from January to August 2022. Follow-up was carried out by telephone calls, and the information was complemented with data from medical records. Inclusion criteria were age ≥18 years, ST-elevation ACS or non-ST-elevation ACS, and a signed informed consent, whereas the only exclusion criterion was being lost to follow-up.

Data collected included history and ACS characteristics (type of ACS, Killip-Kimball scale, ECG findings), invasive or conservative strategy, time to coronary angiography (CA), treatment strategy, CA findings, ischemic, electrical and mechanical complications, requirement for mechanical ventilation and ventricular assistance, bleeding complications, in-hospital mortality and length of hospital stay.

Statistical analysis

Statistical analysis was performed with the IBM SPSS 25.0 software (for Mac iOS). Continuous variables were expressed as median and interquartile range (IQR) or mean and standard deviation, according to their distribution. Categorical variables were presented as frequencies and percentages. Normality analysis was performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests.

The ROC curves were plotted using the sensitivity (true positive rate) and 1-specificity (false positive rate) of the 99th percentile of the high-sensitivity troponin for different endpoints: in-hospital ischemic events, in-hospital bleeding events, and in-hospital and one-year follow-up mortality. The area under the ROC curve (AUC ROC) was then calculated for each of these determinations, allowing the diagnostic threshold for the test to be calculated and compared with the traditional scores. Statistical significance was achieved when an alpha error <5% was obtained.

Ethical considerations

All study participants signed an informed consent form prior to enrollment. This form explained the purpose of the study, the confidential nature of the information and the mechanisms used to protect the patient's identity. Participation was voluntary, and patients could refuse to take part in the study with no impact on their health care. Patients had the right to withdraw from the study at any time, according to their wishes.

Informed consent was submitted to the ethics committees of all medical centers for its approval, in accordance

with the regulations of the central Ethics Committee. This study was performed in compliance with the Argentina's Personal Data Protection Act No 25326. The identity of the patients and their personal data were anonymized. Only the investigators, the members of the teaching staff and the research ethics committees (if required) had access to data.

The study was conducted in accordance with the Argentine ethical standards: Act No. 3301, National Law on Clinical Research on Human Subjects, Declaration of Helsinki, (15) among others.

RESULTS

One hundred and eighty-two patients with positive serologA total of 917 patients were included in the analysis, 291 with troponin I measurement and 626 with troponin T measurement, while 67 values could not be collected. Table 1 shows the baseline characteristics of the patients. The median age was 66 years, 25% of the patients were women, and the median left ventricular ejection fraction (LVEF) was 56%. Regarding medical history, 68% had a diagnosis of hypertension, 57% had dyslipidemia, 26% had diabetes, and 37.7% of patients were smokers. The median GRACE score was 131.2 (IQR 128.8-133.6), and the median CRUSADE score was 24.7 (IQR 23.7-24.7), while the median MS was 5.4 (IQR 1.2-48.2).

Regarding events, 38 patients (3.9%) died during hospitalization, and 71 (7.2%) died during the one-year follow-up. Eighty-one patients (8.2%) had an ischemic complication during initial hospitalization, 28 had an AMI and 8 had a CVA/TIA, while 29 patients (2.9%) had a bleeding event (BARC ≥2). During follow-up, 55 patients (5.5%) had ischemic complications, including 14 (1.4%) who presented an AMI and 38 (3.9%) who required revascularization. Table 2 shows detailed ischemic and bleeding events.

When comparing our score with the GRACE score to predict ischemic events, the AUC ROC of our score was 0.64 (95% CI 0.57-0.71), while that of the GRACE score was 0.67 (95% CI 0.61-0.75), p=0.512. To evaluate the ability to predict bleeding events, we compared our score with the CRUSADE score and obtained an AUC ROC of 0.63 (95% CI 0.53-0.73) versus 0.64 (95% CI 0.57-0.78), p=0.526. Regarding mortality, when comparing the performance for in-hospital mortality, our score had an AUC ROC of 0.59 (95% CI 0.49-0.68), while that of the GRACE score was 0.77 (95% CI 0.68-0.86), p=0.005, demonstrating the superiority of the latter as a predictive factor. However, when analyzing the ability to predict mortality during follow-up, our score had a slightly better value, with an AUC ROC of 0.62 (95% CI 0.55-0.69), but still lower than the GRACE score, 0.79 (95% CI 0.73-0.85), p=0.002. Figure 1 shows the mentioned curves.

DISCUSSION

The heterogeneous distribution of the troponin assays has resulted in a variety of data for troponin levels in ACS. Therefore, unification and interpretation

Table 1. Baseline Characteristics (n=984)

Characteristic	Values
Age, years - median (IQR)	66 (56.5-74)
Female sex - n (%)	243 (24.7)
Hypertension - n (%)	671 (68.1)
Diabetes mellitus - n (%)	255 (25.9)
Dyslipidemia - n (%)	560 (56.9)
Smoking - n (%)	377 (37.7)
CKD - n (%)	69 (7)
Unstable angina - n (%)	219 (22.2)
STEMI - n (%)	236 (24)
NSTEMI - n (%)	385 (39.1)
Type II infarction - n (%)	40 (4.1)
Heart rate, bpm- median (IQR)	77 (70-88)
Systolic blood pressure, mmHg- median (IQR)	130 (120-150)
LVEF, %- median (IQR)	56 (45-60)
Troponin T - n (%)	626 (63.6)
Troponin I - n (%)	291 (29.6)
GRACE score - median (IQR)	131.2 (128.8-133.6)
CRUSADE score - median (IQR)	24.7 (23.7-24.7)
Multiplier score - median (IQR)	5.4 (1.2-48.2)

BPM: beats per minute; CKD: chronic kidney disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

Event	Value
In-hospital AMI - n (%)	28 (2.7)
In-hospital stroke - n (%)	8 (0.8)
In-hospital bleeding (BARC ≥2) - n (%)	29 (2.9)
In-hospital mortality - n (%)	38 (3.9)
AMI at follow-up - n (%)	14 (1.4)
Stroke at follow-up - n (%)	3 (0.3)
Revascularization at follow-up - n (%)	38 (3.9)
HF at follow-up - n (%)	22 (2.2)
Mortality at follow-up - n (%)	33 (3.7)
Total AMI - n (%)	42 (4.1)
Total stroke - n (%)	11 (1.1)
Total mortality - n (%)	71 (7.2)

AMI: acute myocardial infarction; BARC: Bleeding Academic Research Consortium; HF: heart failure.

Table 2. Ischemic and bleeding events

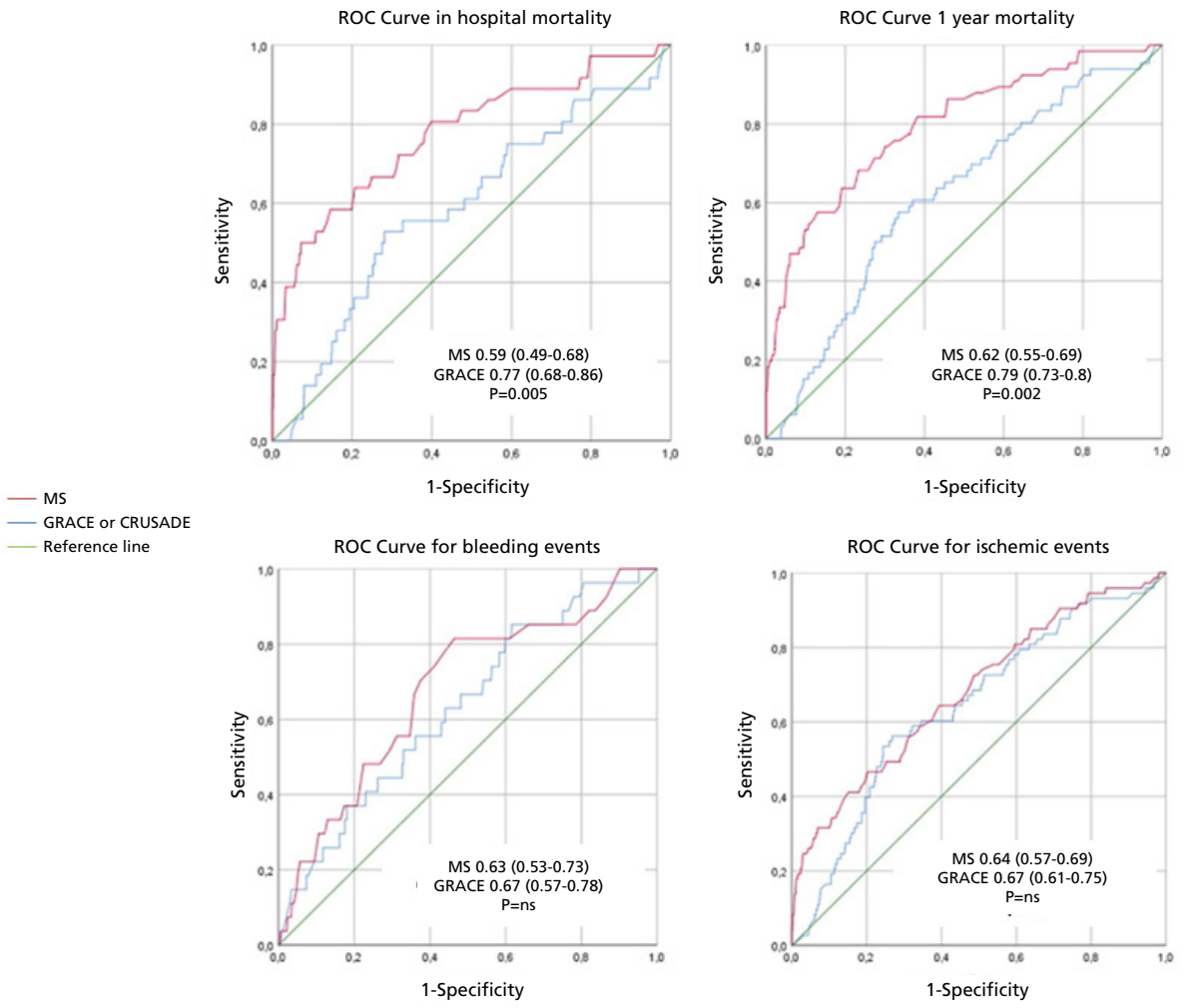
of those results, as well as their use in multicenter studies is challenging. The use of the MS of the 99th percentile of troponin could harmonize the different assays and mitigate those differences. To assess its predictive ability, we compared it with conventional score systems for ischemic events, bleeding events, and mortality. We highlight four findings in our work.

First, for bleeding events, the AUC ROC was 0.63, demonstrating a moderate predictive ability for this endpoint, which was not statistically different from that of the CRUSADE score, 0.64. (13) Other studies have already demonstrated the predictive value of the troponin for bleeding events, such as the study by Mathews et al., which demonstrated an increasing risk based on the troponin level on admission. (16) Iser et al. showed an increased risk of gastrointestinal bleeding in patients with elevated troponin, (17) while Al-Mallah et al. observed an increased overall bleeding risk according to the peak troponin value in acute coronary syndromes. (18) Furthermore, in terms of predictive value, the ABC score to predict bleedings in patients with atrial fibrillation, including biomarkers such as the high-sensitivity troponin, was shown to be superior to that of the HAS-BLED and ORBIT scores. (19) These results could be attributed to the elevated troponin levels generally observed in patients with chronic kidney disease, diabetes or advanced age, among others, where the risk of bleeding is usually higher.

Second, the predictive ability of the MS for ischemic events was modest. The AUC ROC was 0.64, which does not differ significantly from the values from the GRACE score (AUC ROC 0.67), which is the usual predictive tool to calculate ischemic risk in ACS. The ability of the troponin to predict ischemic events has been previously documented in the study by Blankenberg et al., where the troponin I was a predictor of cardiovascular and overall disease and mortality, (20) or in the study by Lindahl that showed similar results. (21,22)

Third, for in-hospital mortality, the MS had limited ability as a predictive factor. The AUC ROC was 0.59 compared with 0,77 of the GRACE score. Although the marker could indicate higher risks, as above mentioned, the GRACE score also includes crucial patient parameters, such as cardiac arrest on admission, the Killip-Kimball assessment, and the incorporation of the patient's hemodynamic status into the equation. (23) Regarding mortality at one-year follow-up, our test showed an improved area under the curve (0.62), although this value was lower than that of the GRACE score (0.79). The above cited Blankenberg study showed that although the troponin is a predictor of mortality, the addition of this biomarker to other risk scores did not significantly modify the area under their ROC curves. (20) The same was documented by Meune et al. in their study, where it was shown that the GRACE score remains useful for determining in-hospital and long-term mortality in patients with ACS in the era of the high-sensitivity troponin, and that its addition, or the addition of the B-type natriuretic peptide (BNP) value to the score did not increase its predictive value. (24) In contrast, the study by Ordoñez et al. showed that troponin T was superior to the GRACE and TIMI scores when predicting adverse events and in-hospital mortality. However, in that study, AUC ROC was 0.52 for the GRACE score, clearly lower than that obtained in our population and that published in the literature, and ST-elevation infarctions were excluded. (25)

Finally, our results highlight that the MS could be a useful tool for data standardization in multicenter settings and for risk assessment in ACS. However, its ability to predict mortality is inferior to that of the established scores, such as GRACE and CRUSADE.



MS: multiplier score

Fig. 1. ROC curves for hospital events and per year.

This underscores the need to use the troponin to complement, rather than to replace, more comprehensive predictive tools in clinical practice.

Limitations

The retrospective characteristics of the analysis generate biases inherent to the type of study. In addition, the number of events was relatively low, which may make the results unrepresentative. We understand that the wide interquartile range of the MS contrasts with the narrower ranges of the GRACE and CRUSADE scores, although we do not believe that this influences the results. Besides, although centers from all over the country participated, only those centers of medium and high complexity with 24-hour access to hemodynamics were included, so the applicability of the score to patients from centers of lower complexity may be lower.

CONCLUSION

The use of the MS of the 99th percentile of troponin level in ACS may be a useful tool for harmonizing the vast and variable amount of assays and data available today, which hinders the accurate interpretation of information. As a simple tool, this new score system could help to standardize information worldwide and encourage new multicenter studies. Its predictive value is not inferior to that of the conventional risk scores, such as GRACE and CRUSADE, for both in-hospital ischemic and bleeding events.

Conflicts of interest

None declared.

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

Financing

No funding was required for this study..

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ORIGINAL ARTICLE

Events Prediction Ability in Patients with Hypertension using Artificial Neural Network Analysis of Ambulatory Blood Pressure Monitoring Compared to Clinical Risk Stratification

Capacidad predictiva de eventos en pacientes con hipertensión arterial mediante el análisis con redes neuronales artificiales del monitoreo ambulatorio de presión arterial en comparación con la estratificación de riesgo clínica

FEDERICO P. DI GENNARO[1], MARÍA P. CATALANO[1], ALEJANDRO GARCÍA AGUIRRE[1], MARÍA L. FERNÁNDEZ[1], ROMINA LLANOS[1], SANTIAGO PÉREZ LLORET[2], CLAUDIO HIGA[1, MTSAC]

ABSTRACT

Background: There is no available evidence comparing the predictive value of an artificial neural network (ANN)-based analysis method that integrates ambulatory blood pressure monitoring (ABPM) variables versus clinical risk stratification (CRS) for serious events in hypertensive patients at follow-up.
Methods: We analyzed ABPM studies that included 27 measurements each one. The variables were daytime, nighttime and 24-hour mean, systolic and diastolic blood pressure, pulse pressure and heart rate; hypertensive load; standard deviations of pressures and heart rate; circadian rhythm. The dependent variable was the combined endpoint of death, stroke, acute myocardial infarction, heart failure and kidney disease. For clinical risk stratification, the Argentine Consensus on Hypertension was used as a model. We evaluated the discriminative ability to predict the endpoint using ANN-ABPM and CRS by logistic regression through the analysis of the area under the receiver operating characteristic curve (AUC-ROC). Both AUC-ROC were compared by De Long test. SPSS 23.0 Statistics was used for statistical analyses and ANN modelling.
Results: Data from 491 ABPM studies were analyzed. Mean age was 69 ± 14 years; 53% of population was female; 11.6% had diabetes; 51% had dyslipidemia; mean body mass index was 26 ± 4 kg/m^2; 14.3% were smokers. Median follow-up was 6.6 years (interquartile range 4.5-8). The best predictive ANN model was the Multilayer Perceptron one with a hidden layer; neuronal architecture (27/7/2). Nocturnal systolic blood pressure (SBP) had 100% independent normalized importance for modelling. The AUC-ROC for the combined endpoint was 0.81 (95% CI 0.77-0.90) using neural network analysis with ABPM variables, and 0.67 (95% CI 0.56-0.77) using CRS; De Long's test $p < 0.001$.
Conclusion: We observed a higher discriminative ability to predict events at follow-up using ANN analysis with ABPM variables compared to conventional CRS. This observation raises a research hypothesis to be validated prospectively to optimize risk stratification and treatment in hypertensive patients.

Key words: Risk assessment - Artificial neural networks - Hypertension.

RESUMEN

Introducción: No hay evidencia disponible sobre la comparación del valor predictivo de eventos graves en el seguimiento de pacientes hipertensos mediante el análisis con redes neuronales artificiales (RNA) de las mediciones del monitoreo ambulatorio de presión arterial (MAPA) en comparación con la estratificación de riesgo clínica (EC).
Material y métodos: Se analizaron estudios de MAPA que incluyeron 27 mediciones cada uno: presión arterial media sistólica, diastólica, presión del pulso y frecuencia cardiaca de 24 hs, diurnas y nocturnas; carga hipertensiva; desvíos estándar de presiones y frecuencia cardíaca; ritmo circadiano. La variable dependiente fue el punto final combinado de muerte, accidente cerebrovascular, infarto agudo de miocardio, insuficiencia cardíaca e insuficiencia renal. Para la EC de cada paciente se utilizó como modelo el Consenso Argentino de Hipertensión Arterial. Se evaluó la capacidad discriminativa para predecir el punto final con RNA-MAPA y con EC por análisis de regresión logística a través del análisis del área bajo la curva ROC (ABCR). Se compararon ambas ABCR mediante test de De Long. Para los análisis estadísticos y el modelaje de las RNA se usó el programa SPSS 23.0 Statistics.
Resultados: Se analizó la información de 491 estudios de MAPA; edad media: 69 ± 14 años, 53 % mujeres, 11,6 % diabéticos, 51% dislipidémicos, media de índice de masa corporal 26 ± 4 kg/m^2, 14,3 % fumadores. La mediana del seguimiento fue 6,6 años (rango

Rev Argent Cardiol 2025;93:31-40. https://doi.org/10.7775/rac.v93.i1.20854

Received: 12/10/2024 – *Accepted:* 01/12/2025

Correspondence: Federico Di Gennaro, Hospital Alemán, Av. Pueyrredón 1640 (1112), Buenos Aires, Argentina. E-mail: fpdigennaro@hospitalaleman.com

[1] Arterial Hypertension Area, Cardiology Service, Department of Internal Medicine, Hospital Alemán de Buenos Aires 2 Health Observatory, Universidad Católica Argentina, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)

intercuartílico 4,5-8). El modelo de RNA con mejor capacidad predictiva fue el Perceptrón Multicapa con una capa oculta; arquitectura neuronal (27/7/2). La presión arterial sistólica nocturna presentó una importancia normalizada independiente del 100 % para la determinación del modelo. El ABCR para la discriminación del punto final fue, con el análisis con RNA del MAPA, 0,81 (IC 95% 0,77-0,90); con la estratificación de riesgo clínico fue de 0,67 (IC 95% 0,56-0,77); test de De Long p < 0,001.
Conclusión: Observamos una mayor capacidad discriminativa en la predicción de eventos mediante el análisis con RNA de las variables del MAPA vs. la estratificación de riesgo clínico, lo cual constituye una hipótesis de investigación a validar prospectivamente..

Palabras claves: Estratificación del riesgo - Redes neuronales artificiales - Hipertensión

INTRODUCTION

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide. Prediction of cardiovascular (CV) events is essential for early identification of individuals at risk and implementation of more appropriate preventive interventions. (1,2)

Therefore, it is recommended that all hypertensive patients be assessed to determine their overall cardiovascular risk (CVR) in order to define therapeutic and cardiovascular risk factor control measures. The information from medical history, physical examination, office blood pressure (BP) measurements and the results of recommended complementary studies will determine the presence of associated risk factors, target organ damage, and history of cardiovascular events. With this data it is possible to stratify the overall CVR of hypertensive patients and classify their risk as low, moderate, high and very high. Knowledge of an individual patient's overall CVR stratification provides important predictive information, a global approach to prevention and the appropriate drug therapy. (3,4)

A series of formulas or risk scores have been proposed to calculate CVR. The calculators arising from them are a heterogeneous group with various limitations (qualitative variables, complementary studies that are not used in daily clinical practice). Many of them have not been validated in our population. (3-5)

The Argentine Consensus on Arterial Hypertension proposes an approach similar to that used by the European Society of Hypertension and adapted to our setting. (5)

Although office blood pressure measurement is currently the recommended diagnostic method, it is not free of significant variability and bias due to the inaccuracy of the measurement technique. Thus, several national and international guidelines recommend the use of out-of-office measurements by means of ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension (HT) and provide more accurate predictive information. (5-7)

In recent years, ABPM has become a useful adjunctive study for the diagnosis and prognostic assessment of CV events in hypertensive patients compared to isolated office measurements. In addition, ABPM can provide additional data, such as blood pressure variability, blood pressure dipping patterns, and mean blood pressure values at different periods of the day. (8-10)

Although the accuracy of cardiovascular risk prediction models has improved over the years, some uncertainty still remains in the estimates. At present, the hemodynamic variables provided by the ABPM are not considered for cardiovascular risk stratification in hypertensive patients. (11,12)

In this regard, it is important to highlight the need for more accurate predictive tools that incorporate the different blood pressure variables derived from ABPM.

One of the most widely used methodological tools for predictive analysis in different areas of medicine, currently in full development, is artificial neural network (ANN). Analysis with ANN as an artificial intelligence (AI) model has shown to be superior in terms of prognostic accuracy (especially in the presence of non-linear associations) to the statistical tools we usually use, such as multivariate analysis and logistic regression. (13-15)

ANNs can recognize relevant features in the data and adjust their synaptic weights and connections to improve their predictive performance, which depends on the number of input variables and their training. This allows ANN to make more accurate predictions. (16-18)

The application of different machine learning models has been aimed at early detection and screening to identify those who will develop hypertension. (19-22)

The ANN-based analysis model which integrates ABPM variables could improve the predictive ability and provide information to design a more accurate and complete stratification of CVR compared to the existing models.

This study aimed to evaluate the ability to predict serious events in hypertensive patients at follow-up using an ANN-based analysis model which integrates ABPM variables compared to conventional clinical risk stratification (CRS).

METHODS

A database with measurements from ABPM studies was analyzed according to the following inclusion criteria: adult patients (over 18 years of age), with a diagnosis of essential arterial hypertension under drug therapy, who underwent ABPM studies to evaluate treatment efficacy. They were required to have complete follow-up through electronic medical records and clinical visits to a community hospital.

Consecutive ABPM studies performed between September 2013 and April 2020 with complete clinical follow-up

until November 2022 were included. Data from the ABPM study reports (the averages of each of the variables were considered) were transferred to a spreadsheet and processed using Visual Basic and SQL softwares.

Cardiovascular risk stratification was performed using the variables proposed by the Argentine Consensus on Arterial Hypertension (Argentine Society of Cardiology, Argentine Society of Arterial Hypertension, Argentine Federation of Cardiology) as a model. (5)

The variables considered were the following: a) Risk factors: age, gender, history of dyslipidemia, diabetes, smoking, obesity; b) Target organ damage: diagnosis of left ventricular hypertrophy (LVH) confirmed by echocardiogram, chronic renal failure (stages 1 and 2); c) Associated clinical conditions or history of cardiovascular events: acute myocardial infarction (AMI), heart failure (HF), stroke and/or transient ischemic attack (stroke/TIA), coronary artery disease, myocardial revascularization, chronic kidney disease (stages 3, 4 and 5).

Low risk was defined as patients with one associated risk factor; moderate risk: patients with two associated risk factors; high risk: patients with three or more associated risk factors and/or diabetes and/or target organ damage; very high risk: patients with history of cardiovascular events or associated clinical conditions. (4,5)

A combined endpoint of serious events (SE) was defined as the occurrence of death and/or non-fatal AMI and/or stroke and/or TIA and/or HF and/or chronic renal failure validated in the electronic medical record by specialists in Internal Medicine and Cardiology according to current national and international guidelines. (3-5)

Neural network algorithm models were developed including the ABPM variables as independent cofactors for input to the ANN, and SE as the dependent event (output layer). An NN algorithm is a special type of non-linear regression that has multiple local minimum values. Therefore, every time the training algorithm runs, it will converge in a different model. To choose the best model, the training process was repeated 50 times. Only models showing the best discriminative power by logistic regression or ANN were selected for comparison.

SPSS 26.0 Statistics was used for statistical analysis and ANN modelling. Different models, architecture and activation functions were compared to select the one with the best performance in terms of discrimination to predict the endpoint.

Categorical variables were expressed as percentages with 95% CI and continuous variables were expressed as means and their respective standard deviation or median and interquartile range (IQR) according to their distribution (parametric or non-parametric).

The discriminative ability of ABPM vs. CRS to predict SE was assessed with the area under the receiver operating characteristic curve (AUC-ROC) analysis. For the comparison of the AUC-ROC, the De Long test was used with the MEDCALC program, version 23.0.9.

In order to identify the variables with the greatest weight and usefulness in the development of the ANN, a sensitivity analysis was performed to determine their normalized importance in the model.

Ethical considerations

The study was reviewed and approved by the institutional and independent Ethics Committee. Due to the observational nature of this analysis, informed consent was not required. According to the Declaration of Helsinki of the World Medical Association, (23) every precaution was taken to protect the privacy and confidentiality of all personal information.

RESULTS

We analyzed data from 491 ABPM studies that included 27 numerical variables from each study: means of 24-hour systolic blood pressure (24-h mSBP), 24-hour diastolic blood pressure (24-h mDBP), 24-hour mean blood pressure (24-h mMBP), 24-hour pulse pressure (24-h mPP), 24-hour heart rate (24-h mHR), daytime systolic blood pressure (day mSBP), daytime diastolic blood pressure (day mDBP), daytime mean blood pressure (day mMBP), daytime pulse pressure (day mPP), daytime heart rate (day mHR), nighttime systolic blood pressure (night mSBP), nighttime diastolic blood pressure (night mDBP), nighttime mean blood pressure (night mMBP), nighttime pulse pressure (night mPP), nighttime heart rate (night mHR); variability of 24-hour systolic blood pressure (24-h SBPsd), 24-hour diastolic blood pressure (24-h DBPsd), 24-hour pulse pressure (24-h PPsd), 24-hour mean blood pressure (24-h MBPsd), 24-hour heart rate (24-h HRsd); daytime SBP load (day SBPL), daytime DBP load (day DBPL), nighttime SBP load (night SBPL), nighttime DBP load (night DBPL); daytime blood pressure ≥135/85 mmHg (day HT), nighttime blood pressure ≥120/70 mmHg (night HT), circadian rhythm with nocturnal SBP and/or DBP fall <10% (*non-dipping pattern*).

Table 1 details the mean values of each variable from the ABPM studies used for ANN modelling for the combined endpoint.

The mean age of the population was 64 ± 14 years, 47% were women, 12% had diabetes, 11% were active smokers, 52% had dyslipidemia and the mean body mass index was 26 ± 4 kg/m2.

The median patient follow-up was 6.6 years (IQR 4.5-8). The endpoint incidence at follow-up was 2.6%. Table 2 details the best ANN models with their neuronal activation functions of the hidden and output layers and their AUC-ROC.

The best performing models were the Multilayer Perceptron of a hidden layer (activation function of the hidden layer neurons of hyperbolic tangent type) and those of the output layer of *softmax* type with a neural architecture (27/7/2) describing the nodes of each of the layers (Figure 1). Table 3 describes the synaptic weights with which the neural network is constructed and trained to predict the endpoint. The hyperbolic tangent function was used as the activation function for the input layer and the *softmax* for the hidden layer. The sample was split with a segmentation of 70% training group and 30% validation of the algorithms. The estimated synaptic weights were considered for the development and testing of a multilayer perceptron model for the combined endpoint based on the input of the 27 variables from the ABPM studies.

The AUC-ROC of the analysis of ABPM variables using neural networks was 0.81 (95% CI 0.77-0.90)

Table 1. Description of the mean values of the ABPM variables

ABPM variables	Value
24-h mSBP	126.16 ± 11.65 mmHg
24-h mDBP	79.22 ± 9.30 mmHg
24-h mMBP	94.87 ± 9.4 mmHg
24-h mHR	75.21 ± 8.5 bpm
24-h mPP	46.93 ± 7.62 mmHg
24-h SBPsd	17.92 ± 5.6 mmHg
24-h DBPsd	14.52 ± 4.2 mmHg
24-h PPsd	16.9 ± 6.1 mmHg
24-h MBPsd	13.51 ± 3.8 mmHg
24-h HRsd	11.59 ± 3.1 bpm
day mSBP	130.13 ± 12.2 mmHg
day mDBP	82.35 ± 9.9 mmHg
day mMBP	98.17 ± 10.14 mmHg
day mHR	78.85 ± 9.1 bpm
day mPP	47.77 ± 8.08 mmHg
night mSBP	117.34 ± 13.47 mmHg
night mDBP	72.23 ± 9.90 mmHg
night mPP	48.10 ± 8.99 mmHg
night mMBP	87.27 ± 10.50 mmHg
night mHR	67.47 ± 9.2 bpm
day SBPL	34.86%
day DBPL	42.25%
night SBPL	39.47%
night DBPL	49.68%
night HT	58.4% (95% CI 55-72)
day HT	43.9% (95% CI 40-56)
Non-dipping	42.6% (95% CI 39-55)

24-h DBPsd: 24-hour diastolic blood pressure variability; 24-h HRsd: 24-hour heart rate variability; 24-h mMBP: mean of 24-hour mean blood pressure; 24-h MBPsd: 24-hour mean blood pressure variability; 24-h mDBP: 24-hour mean diastolic blood pressure; 24-h mHR: 24-hour mean heart rate; 24-h mPP: 24-hour mean pulse pressure; 24-h mSBP: 24-hour mean systolic blood pressure; 24-h PPsd: 24-hour pulse pressure variability; 24-h SBPsd: 24-hour systolic blood pressure variability; ABPM: ambulatory blood pressure monitoring; day DBPL: daytime DBP load; day HT: daytime blood pressure ≥135/85 mmHg; day mDBP: daytime mean diastolic blood pressure; day mHR: daytime mean heart rate; day mMBP: mean of daytime mean blood pressure: day mPP: daytime mean pulse pressure; day mSBP: daytime mean systolic blood pressure; day SBPL: daytime SBP load; night DBPL: nighttime DBP load; night HT: nighttime blood pressure ≥120/70 mmHg; night mDBP: nighttime mean diastolic blood pressure; night mHR: nighttime mean heart rate; night mMBP: mean of nighttime mean blood pressure: night mPP: nighttime mean pulse pressure; night mSBP: nighttime mean systolic blood pressure; night SBPL: nighttime SBP load; non-dipping: circadian rhythm with nocturnal SBP and/or DBP fall <10%.

compared to clinical risk stratification, 0.67 (95% CI 0.56-0.77), for the combined endpoint; De Long's test $p < 0.001$ (Figure 2).

The variables with the greatest weight and usefulness in the development of the neural network or normalized importances in this model were: nighttime mean systolic blood pressure (night mSBP) with a value of 100%, followed by 24-hour mean systolic blood pressure (24-h mSBP), BMI, mean of 24-hour mean blood pressure (24-h mMBP), nighttime mean blood pressure (night mMBP) and 24-hour mean pulse pressure (24-h mPP) (Figure 3).

DISCUSSION

To our knowledge, this analysis is the first to report the predictive ability of the analysis of variables from ABPM studies using ANN and their superiority compared to clinical risk stratification for long-term events in hypertensive patients.

The importance of stratifying hypertensive patients according to their estimated risk of a cardiovascular events allows treatment to be adapted to this risk rather than to the office BP levels alone. Among the most widely used risk scales are the Framingham equation, the SCORE (Systematic Coronary Risk Evaluation) system, the QRISK, calculators from different United States medical societies and from the World Health Organization, the latter adapted to different geographical areas. In our country, the stratification recommended by the Argentine Consensus on Arterial Hypertension is applied. (3-5)

However, the scores have several limitations that may affect their accuracy and applicability, such as differences between populations according to geographic regions, environmental and socioeconomic characteristics, underestimation of the risk in young patients, qualitative difference in risk factors in many cases, and failure to identify patients with a diagnosis of masked hypertension. Most scores do not consider antihypertensive treatment to reduce o predict risk in the short term. (15,16)

In contrast to the conventional multivariate analysis methods, the trained ANN algorithm is presented as a powerful tool to predict events, as it includes all the variables available in the ABPM studies which avoids bias in the selection of variables.

Multi-layer Perceptron neural networks are among the most powerful and popular network architectures. They consist of an input layer, an arbitrary number of hidden layers, and an output layer. Each of the hidden or output neurons receives an input from neurons in the previous layer (backward connections), but there are no lateral connections between neurons within each layer. The input layer contains as many neurons as categories corresponding to the independent variables (categorical and continuous). The output layer corresponds to the response variable, which in this case is a categorical variable (combined endpoint).

Radial basis neural networks are those whose activation functions at the hidden nodes are radially symmetric. A function is said to be radially symmetric if its output depends on the distance between a vector that stores the input data and a vector of synaptic weights, which is called the center or centroid. (17-20)

Previous studies using machine learning have

Table 2. Neural network models with best performance (multilayer perceptron with one hidden layer, two hidden layers and with radial basis model) with their neural activation functions of the hidden layer and the output layer, the neural architecture, and their area under the ROC curve.

Model	Hidden layer activation function	Output layer activation function	Neural architecture	Area under the ROC curve
Multilayer perceptron with a hidden layer	Hyperbolic tangent	Softmax	27/7/2	0.81 (95% CI 0.77-0.90)
Multilayer perceptron with two hidden layers	Hyperbolic tangent	Softmax	27/20/15/2	0.75 (95% CI 0.68-0.80)
Radial basis	Softmax	Identity	27/6/2	0.68 (95% CI 0.61-0.70)
De Long's test	Multilayer perceptron 1 hidden layer vs. 2 hidden layers	Multilayer perceptron 1 hidden layer vs. radial basis	Radial basis vs. multilayer perceptron 2 hidden layers	
p-value	0.040	0.002	0.001	

95% CI: 95% confidence interval

studied its usefulness as a method to screen and early detect hypertension in different populations around the world, while other research groups have used it to predict events in hypertensive patients. (21, 22, 24-26)

Other authors have reported the usefulness of learning machines to optimize decision making in order to improve the treatment of hypertensive patients based on clinical data, and to achieve high accuracy when predicting the individual probability of achieving office blood pressure targets with different treatments. The AUC-ROC were very close to 0.90, indicating high prediction accuracy, and the Kappa coefficients were close to 0.8, showing high levels of agreement between observed and predicted target outcomes. (27,28)

The AUC-ROC shows that the ANNs detect nonlinear relationships between independent and dependent variables beyond the scope of logistic regression. These results support the usefulness of the ANN as a method of analysis in the prediction of serious events in hypertensive patients. (24,27)

ANN-based prediction models prove to be robust and reliable and could be implemented in clinical practice as decision support tools. This method would early identify those hypertensive patients at higher risk of developing serious events and would allow more effective preventive interventions. (22, 24-26)

We highlight that nighttime mean systolic blood pressure (night mSBP) presented an independent normalized significance for the determination of the model. Nocturnal blood pressure has been shown to be an independent risk variable in the prediction of cardiovascular events in hypertensive patients, associated with a higher incidence of stroke, myocardial infarction, heart failure and renal failure. (29)

During nighttime hours, blood pressure follows a characteristic circadian pattern, with a physiological decrease. In hypertensive patients, this decrease may be insufficient or even reversed, known as non-dipping or reverse dipping pattern. These abnormal nocturnal blood pressure patterns have been associated with increased cardiovascular risk and events. (29-31)

Different publications have described that increased nighttime mSBP is associated with higher risk of cardiovascular events in hypertensive patients, even after adjusting for other known risk factors. (30-38)

Considering previous observations and the results of this study using the ANN analysis, nighttime mSBP could be considered a useful marker for cardiovascular risk stratification in hypertensive patients. Its evaluation would help to identify patients at higher risk of complications and would allow their reduction by clinical interventions.

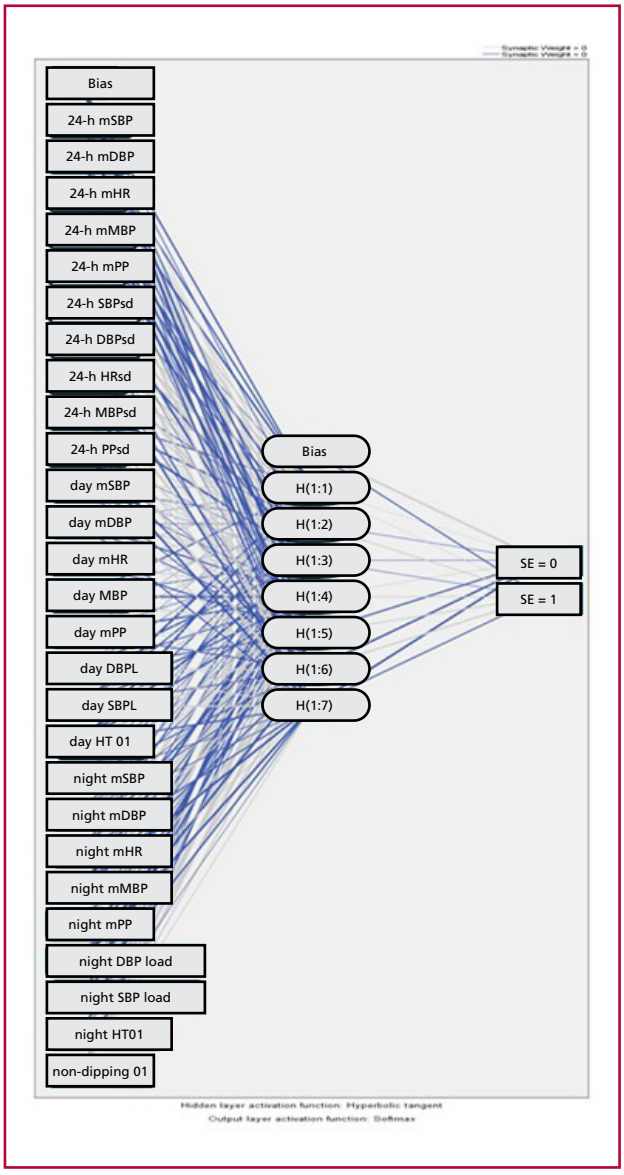
The effective implementation of the current neural network models can be done using software or hardware systems. Thus, the synaptic weights of the proposed architectures can be trained and calculated through a Python algorithm. In turn, this algorithm should be able to automatically read data sets from electronic study records.

The present study shows that the analysis of ABPM variables using ANNs has a significant predictive value of serious events in hypertensive patients. This suggests the importance of considering ABPM variables for risk stratification in hypertensive patients and shows that the ANNs are an effective tool for the predictive analysis of cardiovascular events with adequate accuracy.

Limitations

Although several clinical and ABPM variables were used, the inclusion of other measurements, such as microalbuminuria or peripheral vascular disease, may provide additional information to improve the predictive capacity. Risk stratification was performed using all data available in the electronic medical record.

In our opinion, the retrospective nature of the



24-h DBPsd: 24-hour diastolic blood pressure variability; 24-h HRsd: 24-hour heart rate variability; 24-h mMBP: mean of 24-hour mean blood pressure; 24-h MBPsd: 24-hour mean blood pressure variability; 24-h mDBP: 24-hour mean diastolic blood pressure; 24-h mHR: 24-hour mean heart rate; 24-h mPP: 24-hour mean pulse pressure; 24-h mSBP: 24-hour mean systolic blood pressure; 24-h PPsd: 24-hour pulse pressure variability; 24-h SBPsd: 24-hour systolic blood pressure variability; day mDBP: daytime mean diastolic blood pressure; day DBPL: daytime DBP load; day mHR: daytime mean heart rate; day HT: daytime blood pressure ≥135/85; day mMBP: mean of daytime mean blood pressure; day mPP: daytime mean pulse pressure; day mSBP: daytime mean systolic blood pressure; day SBPL: daytime SBP load; night DBPL: nighttime DBP load; night HT: nighttime blood pressure ≥120/70; night mDBP: nighttime mean diastolic blood pressure; night mHR: nighttime mean heart rate; night mMBP: mean of nighttime mean blood pressure; night mPP: nighttime mean pulse pressure; night mSBP: nighttime mean systolic blood pressure; night SBPL: nighttime SBP load; Non-dipping: circadian rhythm with nocturnal SBP and/or DBP <10%; SE: serious event

Fig. 1. Architecture of the multilayer perceptron type neural network with a hidden layer with 27 neurons in the input layer, 7 neurons in the hidden layer and 2 neurons in the output layer.

analysis is a limitation due to the associated biases that affect the quality of the evidence. The single-center nature of this study limits the transfer of our results to the real world.

A larger sample size with a prospective analysis, external validations in different cohorts of hypertensive patients and the participation of various healthcare centers would optimize the robustness of this study hypothesis.

Neural network algorithms have been criticized on several occasions for being "black boxes" with limited ability to identify possible causal relationships. In the present study we identify the most influential factors in the algorithm modelling using standardized importance values.

The performance quality of learning machines and their algorithms is associated with a larger proportion of events and a higher volume of cases in the total population compared to this study. It should be noted that the incidence of events registered in our work is consistent with that reported in the literature for the outpatient hypertensive population. (39-41)

CONCLUSIONS

The novelty of this study is that it was the first to publish the use of ANNs integrating the ABPM variables to predict long-term events compared to currently recommended cardiovascular risk stratification.

Of additional interest, we observed that nighttime mean SBP was the variable with the greatest weight in the performance of the ANN.

In our view, this analysis is a generator of a research hypothesis to be evaluated in future multicenter studies using adequate power and real-world representativeness to transfer its results.

These algorithms can be integrated into the results of each ABPM study to automatically calculate the probability of risk of serious events in hypertensive patients at follow-up, thus supporting physician's decision making.

Conflicts of interest

None declared.

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

Acknowledgments

The authors would like to thank Engineer Roberto Bunge (Director of Artificial Intelligence Engineering, Universidad San Andrés) and Engineer Trinidad Monreal (Research and Development, Artificial Intelligence and Robotics Laboratory, Universidad San Andrés) for their contributions and expertise in artificial intelligence and neural networks.

Financing

The authors declare they have not received any funding for this work.

Policy on the use of artificial intelligence

Artificial intelligence resources have not been used to write the text or to create the tables or graphs.

Table 3. N Description of the synaptic weights with which the neural network is constructed and trained to predict the endpoint.

		Predicted									
		Hidden layer 1							Output layer		
Predictor+A1:L42		O (1:1)	O (1:2)	O (1:3)	O (1:4)	O (1:5)	O (1:6)	O (1:7)	PF	[PF = 0]	[PF = 1]
Input	(Bias)	0.526	0.579	-0.457	-0.125	-0.394	-0.600	0.459			
layer	non-dipping 0	0.560	0.134	-0.105	-0.501	-0.245	0.258	0.314			
	non-dipping 1	0.293	-0.190	0.180	-0.293	-0.418	-0.298	-0.112			
	night HT 0	-0.018	-0.055	0.410	-0.073	0.170	-0.531	0.356			
	night HT 1	0.046	0.100	-0.270	0.251	-0.128	-0.358	0.424			
	day HT01 0	0.209	-0.108	-0.165	-0.299	0.332	-0.427	0.505			
	day HT01 1	0.459	-0.275	0.110	0.368	0.169	-0.669	0.200			
	24-h mSBP	0.119	-0.452	-0.159	0.315	0.005	-0.141	0.388			
	24-h mDBP	0.334	-0.166	0.080	-0.167	0.241	0.417	-0.365			
	24-h mHR	0.228	-0.080	0.435	-0.323	0.136	-0.457	0.551			
	24-h mMBP	0.486	0.475	0.216	0.019	0.036	-0.313	0.321			
	24-h mPP	-0.361	-0.470	-0.308	-0.269	-0.080	0.020	-0.005			
	24-h SBPsd	-0.179	-0.346	-0.027	0.319	-0.312	0.002	0.427			
	24-h DBPsd	-0.275	0.037	-0.240	0.050	-0.378	0.697	-0.199			
	24-h HRsd	-0.184	0.178	-0.381	0.133	0.228	-0.230	-0.109			
	24-h MBPsd	-0.208	0.170	-0.290	0.268	-0.269	0.153	-0.023			
	24-h PPsd	0.088	0.233	-0.445	0.141	-0.167	0.184	0.347			
	day mSBP	-0.089	-0.398	0.480	0.291	0.325	0.331	-0.216			
	day mDBP	-0.330	0.307	-0.107	0.391	0.243	-0.350	0.110			
	day mHR	-0.427	0.294	-0.401	-0.089	-0.330	-0.263	0.154			
	day mMBP	-0.470	0.010	0.345	0.318	-0.147	-0.041	-0.604			
	day mPP	0.053	0.222	0.373	0.179	0.133	-0.169	-0.001			
	day SBP load	0.476	0.488	-0.056	-0.249	0.460	-0.051	0.265			
	day DBP load	0.265	0.474	0.331	-0.092	0.126	0.365	0.372			
	night mSBP	-0.266	-0.077	-0.196	-0.281	-0.514	0.146	-0.317			
	night mDBP	0.134	0.278	-0.099	0.426	-0.488	0.554	0.269			
	night mHR	-0.429	-0.124	-0.280	-0.184	0.066	0.307	-0.257			
	night mMBP	-0.260	0.253	0.435	0.511	-0.116	-0.308	-0.046			
	night mPP	0.313	-0.343	-0.294	0.278	-0.272	-0.245	-0.196			
	night SBP load	-0.376	-0.294	0.233	-0.010	-0.285	-0.195	-0.305			
	night DBP load	0.189	-0.134	-0.062	-0.336	0.122	-0.123	0.276			
Hidden	(Bias)								-1.302	1.206	-0.093
layer 1	O (1:1)								-0.348	0.844	0.712
	O (1:2)								-0.230	0.008	0.005
	O (1:3)								0.121	-0.058	-0.129
	O (1:4)								0.158	-0.023	-0.129
	O (1:5)								-0.031	0.045	-0.504
	O (1:6)								0.589	-0.891	-0.178
	O (1:7)								-0.553	0.691	-0.168

24-h DBPsd: 24-hour diastolic blood pressure variability; 24-h HRsd: 24-hour heart rate variability; 24-h mMBP: mean of 24-hour mean blood pressure; 24-h MBPsd: 24-hour mean blood pressure variability; 24-h mDBP: 24-hour mean diastolic blood pressure; 24-h mHR: 24-hour mean heart rate; 24-h mPP: 24-hour mean pulse pressure; 24-h mSBP: 24-hour mean systolic blood pressure; 24-h PPsd: 24-hour pulse pressure variability; 24-h SBPsd: 24-hour systolic blood pressure variability; day DBPL: daytime DBP load; day HT: daytime blood pressure ≥135/85 mmHg; day mMBP: mean of daytime mean blood pressure; day mDBP: daytime mean diastolic blood pressure; day mHR: daytime mean heart rate; day mPP: daytime mean pulse pressure; day mSBP: daytime mean systolic blood pressure; day SBPL: daytime SBP load; night DBPL: nighttime DBP load; night HT: nighttime blood pressure ≥120/70 mmHg; night mMBP: mean of nighttime mean blood pressure; night mDBP: nighttime mean diastolic blood pressure; night mHR: nighttime mean heart rate; night mPP: nighttime mean pulse pressure; night mSBP: nighttime mean systolic blood pressure; night SBPL: nighttime SBP load; non-dipping: circadian rhythm with nocturnal SBP and/or DBP fall <10%.

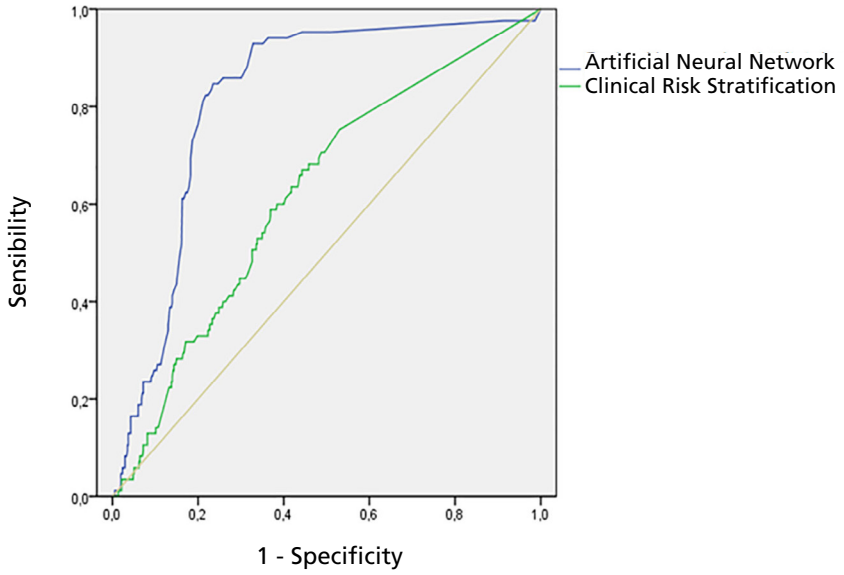
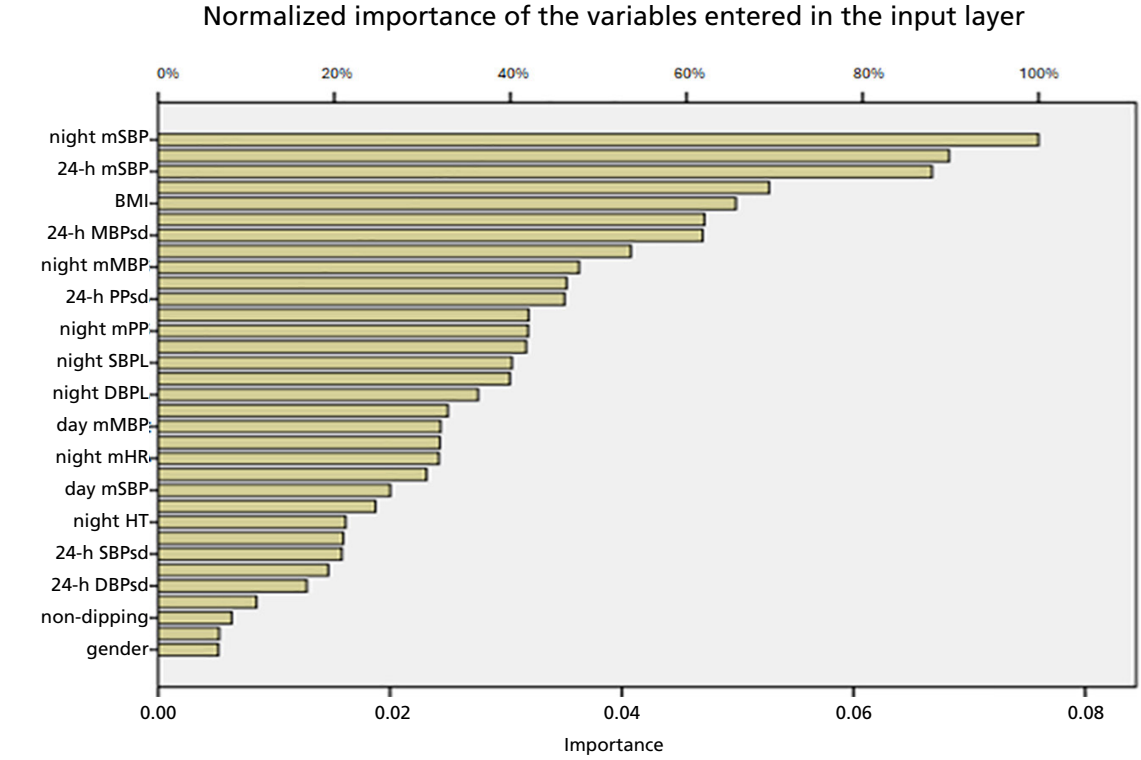


Fig. 2. Comparison of the areas under the ROC curve; ABPM variables analyzed with artificial neural networks: 0.81 (95% CI 0.77-0.90) versus clinical risk stratification: 0.67 (95% CI 0.56-0.77); De Long's test p < 0.001



24-h DBPsd: 24-hour diastolic blood pressure variability; 24-h MBPsd: 24-hour mean blood pressure variability; 24-h mSBP: 24-hour mean systolic blood pressure; 24-h PPsd: 24-hour pulse pressure variability; 24-h SBPsd: 24-hour systolic blood pressure variability; BMI: body mass index; day mMBP: mean of daytime mean blood pressure; day mSBP: daytime mean systolic blood pressure; night DBPL: nighttime DBP load; night HT: nighttime blood pressure ≥120/70 mmHg; night mMBP: mean of nighttime mean blood pressure; night mHR: nighttime mean heart rate; night mPP: nighttime mean pulse pressure; night mSBP: nighttime mean systolic blood pressure; night SBPL: nighttime SBP load; Non-dipping: circadian rhythm with nocturnal SBP and/or DBP <10%.

Fig. 3. Bar graph representing the variables with the highest normalized importance for the development of the artificial neural network in this model

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ORIGINAL ARTICLE

Properties of the Cardiac Fulcrum

Propiedades del fulcro cardíaco.

JORGE TRAININI[MTSAC, 1,2], MARIO BERAUDO[3], MARIO WERNICKE[3], EFRAÍN HERRERO[3], ALEJANDRO TRAININI[1], OSCAR FARIÑA[2], JESÚS VALLE CABEZAS[5], JORGE LOWENSTEIN[MTSAC, 5], ROBERTO LÓPEZ SANTORO[2]

ABSTRACT

Background: Taking into consideration the sequential movements of the myocardium, the cardiac fulcrum is subject to a functional requirement that indicates its role as support and stabilizer of the myocardium, as well as being modeled in its morphology by the tensions that occur in its structure. Could the myocardium function without the cardiac fulcrum?
Methods: Thirty five bovine, porcine and human hearts from the slaughterhouses and the morgue were used in this research.
Results: As the fulcrum is subject to the forces of the myocardial segments attached to its structure, it obviously registers tensions that model its morphology. This concept is explained given that myocardial movements are sequential and overlap in the myocardial segments, developing asymmetric tensions that act with their epicenter in the fulcrum. The myocardium inevitably needs this support in order not to destabilize its structure due to the unequal movements generated by its forces.
Conclusions: The fulcrum constitutes the support enabling the myocardium to exert the necessary power, but due to the sequential cardiac movements, it acts as a stabilizer of the entire heart, absorbing the alternating ascending, descending and torsional tractions. This interplay poses not only a limit to the movements of the heart, but also models the shape of the fulcrum through the torque to which it is subjected. Its properties of stability, resistance, elasticity and plasticity allow the myocardium to fulfill its function.

Key words: Fulcrum - Helical myocardium - Cardiac movements

RESUMEN

Introducción: Teniendo en consideración los movimientos secuenciales del miocardio, el fulcro cardíaco se halla sometido a una exigencia funcional que implica que sea soporte y estabilizador miocárdico, y que sea modelado en su morfología por las tensiones que ocurren en su estructura. ¿Podría el miocardio cumplir su función sin el fulcro cardíaco?
Material y Métodos: En la investigación se han utilizado corazones de bovino, porcino y humano. Fueron utilizados 35 corazones provenientes de la morgue y matarifes.
Resultados: Al estar sujeto el fulcro a las fuerzas de los segmentos miocárdicos amarrados a su estructura, registra tensiones que lo llevan a modelar su morfología. Este concepto se explica dado que los movimientos miocárdicos son secuenciales y se superponen en los segmentos miocárdicos, determinando tensiones asimétricas que actúan con epicentro en el fulcro. El miocardio necesita inevitablemente ese soporte para no desestabilizar su estructura ante los movimientos desiguales que generan sus fuerzas.
Conclusiones: El fulcro constituye el soporte para que el miocardio pueda ejercer la potencia necesaria, pero debido a los movimientos cardíacos secuenciales, actúa como estabilizador de todo el corazón, absorbiendo las tracciones ascendentes, descendentes y torsionales alternantes. En este juego implica no solo un límite a los movimientos del corazón, sino que también el mismo fulcro es modelado en su forma por dichos movimientos a través del torque a que es sometido. Sus propiedades de estabilidad, resistencia; elasticidad y plasticidad, permiten que el miocardio pueda cumplir con su función.

Palabras clave: Fulcro - Miocardio helicoidal - Movimientos cardíacos

Rev Argent Cardiol 2025;93:41-47. https://doi.org/10.7775/rac.v93.i1.20862

Received: 10/04/2024 – *Accepted:* 02/01/2025

Correspondence: Jorge Carlos Trainini. E-mail: jctrainini@hotmail.com

[1] Hospital Presidente Perón, Buenos Aires, Argentina.
[2] Universidad Nacional de Avellaneda, Argentina.
[3] Clínica Güemes, Luján, Argentina.
[4] Real Academia de Ingeniería, Madrid, España.
[5] Investigaciones Médicas, Buenos Aires, Argentina.

INTRODUCTION

The contraction and distension of the continuous myocardium fibers, whose ends must be attached to a "fixed point" to have a mechanical effect, would not be effective without the existence of the cardiac fulcrum. This structure is found at the beginning and end of the myocardium, ensuring the functionality of the cardiac system, (1) and allowing the forces to be adequately distributed, not only to support but also to stabilize the sequential and asymmetrical cardiac movements. To comply with this mechanism of being subjected to traction in a magnitude of about one hundred thousand cardiac cycles per day, the fulcrum must meet certain conditions: stability, resistance, elasticity, and plasticity. As it is subjected to loads, these faculties allow the fulcrum to reach a certain level of stress, modify its spatial location with the variation of these loads, and then recover when the loads are removed (Figure 1).

Cardiac mechanics is complex, because it must integrate its ejection, suction and filling properties under different successive and concatenated phases through the continuous helical myocardium. (2) The function of cardiac fibers is described as a homogeneous and synchronous faculty, and little attention is paid to the disposition adopted in the helical construction and the sequence of contraction. It is impossible to interpret cardiac function without taking into account its morphology and activation circuit with the corresponding sequential movements. (3) Cardiac activation is a consequence of the propagation of stimuli through its helical muscular structure. (4) The mechanism of suction and ejection requires a structure-function integration that interprets various aspects of its dynamics consistent with the propagation of excitation. (4,5)

It was classically considered that both mechanical contraction and electrical activation of the heart were homogeneous processes. Thus, contraction would occur "en bloc" during systole and relaxation would occur homogeneously during diastole. Thus, systole would be synonymous with cardiac contraction and diastole with relaxation. At this stage of knowledge, more complex mechanisms should be considered. (5) Although various aspects of electrical stimulus propagation in the heart have long been known, the advent of three-dimensional navigators and electroanatomical mapping have allowed more detailed studies of myocardial activation. It was thus evidenced that endocardial activation "occupies" approximately 60% of the initial surface QRS. The "rest" of the QRS corresponds to myocardial and epicardial activation. The beginning of ventricular activation evidenced by the QRS is then exclusively endocardial; during the intermediate phase both activations coexist and the end, during suction, in the so-called protodiastolic phase of myocardial contraction (PPMC) of both ventricles, there is an active process whose activation is exclusively myo-epicardial. (4)

In this study, the structural properties of the cardiac fulcrum were analyzed in relation to the movements of the myocardial segments during the cardiac cycle. Considering the sequential movements of the myocardium, the cardiac fulcrum is subjected to a functional requirement that implies its role as support and stabilizer of the myocardium, as well as being modeled in its morphology by the stresses occurring in its structure.

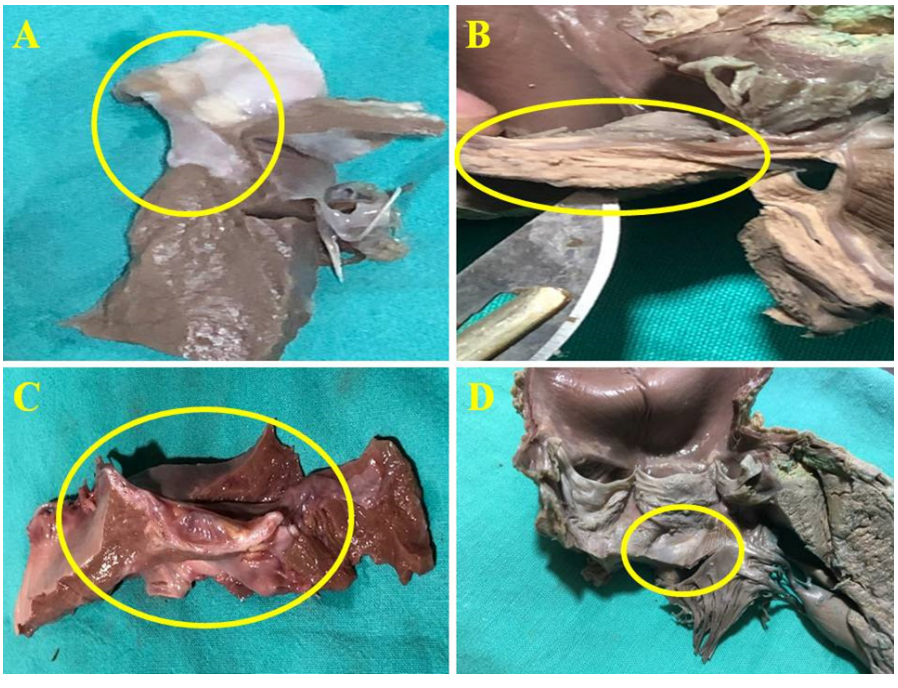

Fig. 1. Cardiac fulcrum (yellow circle) in porcine (A), adult human (B and D), and bovine (C) hearts.

METHODS

Thirty-five bovine, porcine and human hearts from the slaughterhouses and the morgue were used in this research: a) 18 two-year-old bovine hearts weighing 800-1000 g; b) 16 human hearts (two from 16 and 23-week gestation embryos; four from 30- and 36-day and 10- and 27-week infants; one from 4-year-old child; one heart from a 10-year-old child weighing 116 g and eight adult hearts with an average weight of 300 g); and c) one porcine heart (400 g). Histology was performed with hematoxylin-eosin (H&E) and Masson's trichrome staining techniques and four-micron sections. Formalin 10% was used as buffer. Immunostaining (s100-neurofilaments) was also performed.

The single continuous and helical myocardium was deployed according to a previously published technique. (6) The conjunction of the origin and end of the continuous myocardium in a support that we call cardiac fulcrum constitutes a meeting point that allows the heart to adopt the spatial arrangement of a set of fibers twisted unto themselves, like a laterally flattened rope forming a double helix that defines the two ventricular chambers. This research on the properties of the cardiac fulcrum complements previous findings on the myocardium, the cardiac fulcrum and ventricular activation studies with the Carto system. (2,4,6,7).

RESULTS

The microscopic analysis of the bovine cardiac fulcrum shows a trabecular osteochondral matrix with segmental lines. Its general structure resembles the metaphyseal growth of long bones. The same histological findings have been found in the chimpanzee, buffalo, sheep, goat, antelope, deer, giraffe, camel, dog, cat, pig, sea lion, horse and elephant fulcrum. Until our research, no function or sense of its presence was ever assigned to it, nor was it described in humans (8).

The histology of the fulcrum in adult humans (approximately 25 mm long and 15 mm wide) has shown a chondroid-tendinous matrix, which needs further clarification. In principle, there is similar consistency in the detection, location and morphology of the fulcrum in all the hearts analyzed. They present myocardial insertion in the fulcrum, integrating a cardiomyocyte-matrix unit, independently of the osseous, cartilaginous or tendinous nature of the fulcrum in the different specimens. This difference corresponds to the higher power developed in bovids, which makes it necessary to have a more rigid support. This point of fixation implies that, as in all muscle, it acts as a support and also as a bearing, preventing the ventricular rotation force, either by torque (twisting force) or torsional effort, from extending to the great vessels, thus dissipating the energy produced by the movement of the muscular helix. In all the hearts, the myocardium was found to be tethered to the fulcrum, which we can symbolize as "the ivy to the stone", integrating a cardiomyocyte-matrix unit, either osseous, cartilaginous or tendinous.

If a force is applied at one end of the fulcrum, this is displaced, since it is a semi-floating structure, but if a force F2, equal and opposite to F1, is applied at the insertion point P2, at the end opposite to point 1 (P1), as can be seen in the Figure 2 inset, the fulcrum is not destabilized. As both forces are produced by the same myocardial muscle fiber, which originates at P1, and ends at P2, the action and reaction effects compensate for the displacements. The same can be applied to the totality of myocardial muscle fibers along the lines of insertion. The forces in the myocardial muscle fibers compensate each other and with the reactions in the fulcrum, which is elastic enough to bear them.

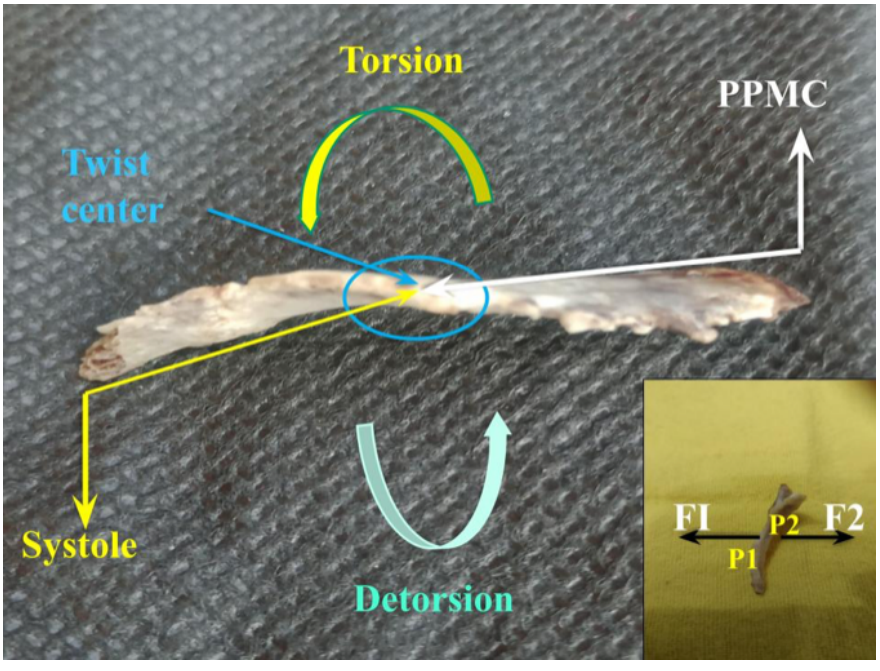

Fig. 2. The yellow arrows show the orientation of the cardiac fulcrum movements during systole; the black arrows during suction (protodiastolic phase of myocardial contraction –PPMC). The inset shows that if only one force is applied to the fulcrum, it would be displaced; on the contrary, if a force F2 equal and opposite to F1 is applied at the insertion point P2, opposite end to P1, the fulcrum does not destabilize.

The histological conformation of the bovine fulcrum shows a less dense area in its center (marrow) in relation to the cortical area (Figures 3, I and II). These characteristics, compared with the human and porcine fulcrum (Figures 3, III and IV), explain what is shown in relation to the body weight and the absolutely osseous characteristics in the former and cartilaginous in the rest, associated to the power developed. In analogy, the bovine fulcrum has defined cortical and marrow areas in order to absorb much higher tensions due to its weight, compared with mammals such as man and swine, which present a greater homogeneity in the cartilaginous structure. These differences with the bovine fulcrum do not prevent them from dissipating the powers generated by the myocardium, contributing to the stability and organization of the heart.

The system of forces to which the fulcrum is subjected is compensated with respect to a central point, but the fulcrum does not remain static in the thoracic cavity but shows small movements due to the different compensations of these forces. For an observer located at the center of the fulcrum all the forces of the cardiac muscle are compensated, but for an external observer the compensation involves fulcrum movement.

As the fulcrum is subject to the forces of the myocardial segments attached to its structure, it obviously registers tensions that even lead to modeling its morphology. This concept is explained by the fact that myocardial movements are sequential and superimposed in the myocardial segments, (9) producing asymmetric stresses that act with their epicenter in the fulcrum. The myocardium inevitably needs this support in order not to destabilize its structure in the face of the unequal movements generated by its forces.

Cardiac activation through the myocardium (Figure 4), whose segments are helically arranged and therefore superimposed, determines sequential stimulation. The contraction is not global or homogeneous but by sectors. Therefore, the contraction, during the 400 ms of the cardiac cycle (systole and suction), is paced. In the face of this asymmetric muscular move-

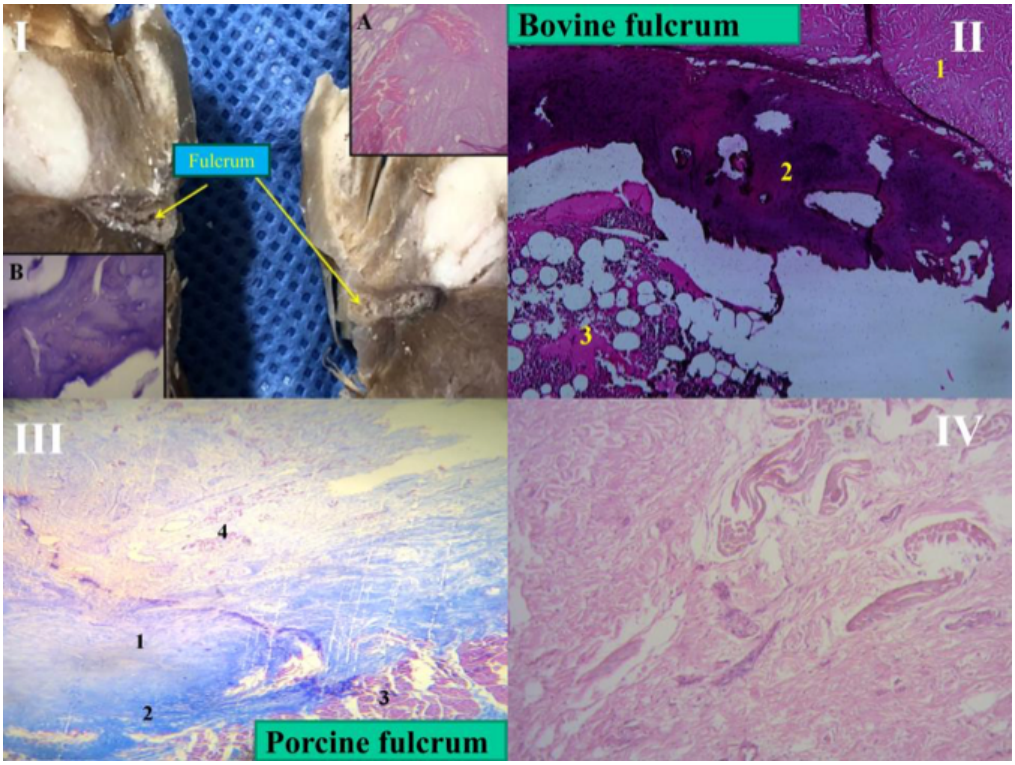

Fig. 3. I. Cardiac fulcrum in the bovine heart. The cortical and marrow areas of the fulcrum are well defined. A: The insertion of the myocardial fibers in the chondroid tissue is shown. B: H&E at high magnification (40x) showing an osseous trabecula with osteoblasts and segmental lines. The structure forms the scaffold of trabecular osseous tissue similar to the metaphyseal growth zones of long bones. Osseous trabeculae with osteoblasts and segmental lines secondary to bone apposition are visualized.
II. Bovine fulcrum, cortical and marrow areas. Partially calcified osteochondral tissue is observed in the cortex and osteochondral trabeculae in the marrow that results in a spongy structure with elements of bone marrow in the space. **1**: myocardium. **2**: fulcrum cortex. **3**: fulcrum marrow.
III. Porcine fulcrum: 25x, Masson's staining. **1**: porcine cartilaginous fulcrum. **2**: peri-fulcrum fibrous tissue. **3**: septum. **4**: intermingled conduction cardiomyocytes, nerves, and ganglia reaching the fulcrum.
IV. Central area of a human heart fulcrum. Fibrous tendon and cardiomyocytes, H&E (25x). H&E: hematoxylin-eosin staining.

ment, the fulcrum plays a supporting role so that the heart can have the necessary power to eject and draw out the blood volume. In the face of these displacements generated by the anisotropic activation of the myocardial fibers, the fulcrum acts as a stabilizer since the continuous myocardium originates and ends in this structure. In this way it avoids an accentuation of the displacements so that the cardiac structural scaffolding is not lost. (10)

The orientation of the continuous myocardium fibers and their activation implies a concatenation of muscular movements in cardiac mechanics. These follow one another, giving rise to three active phases according to the segments stimulated: narrowing (right and left segments), shortening-torsion (descending and ascending segments), lengthening-detorsion (cubic segment).

DISCUSSION

During systole, the different segments of the continuous myocardium contract sequentially. Activation begins in the right segment, tethered to the right and anterior sector of the cardiac fulcrum, with continuation in the left, descending and ascending segments. The fundamental peculiarity of this activation is that although at the beginning it is unidirectional, upon reaching the junction of the descending and ascending bands, simultaneity is produced -by transversal activation- in both bands, generating a helical movement essential for the myocardium to expel the ventricular contents at a speed of 200 cm/s (Figure 4).

At the beginning of myocardial activation in the right segment (free wall of the right ventricle), the right end of the fulcrum (where the right segment inserts) moves downward due to the predominantly downward orientation of its fibers. Conversely, the opposite end, where the ascending segment ends, undergoes an upward displacement as it is still relaxed (Figure 2).

The continuation of activation by the left segment (mitral orifice) determines, together with the right segment, the narrowing phase. The right and left segments constitute the basal loop. This contraction defines an external sheath within which the apical loop (descending and ascending segments) will contract. Actually, the right ventricular crescent-shaped free wall is *ad latere* to the rest of the ventricular mass (septum and left ventricle), since the left segment constitutes part of the posterior epicardial wall of the left ventricle in its superior portion, while the rest of the left ventricular wall is covered externally by the ascending segment.

In this sheath, stimulation runs from the subepicardium to the subendocardium. It then runs through the descending segment and, in our investigation, at an average of 25.8 ms after activation in this segment, the ascending segment contracts (at an average of 38.2 ms from the start of myocardial activation) (Figure 4). This probably occurs because the subendocardial fibers of the descending segment, on the anterior aspect of the left ventricle, pass deep into the mesocardium crossing obliquely with those of the ascending segment, thus facilitating transverse stimulation between the two segments.

At this moment of systolic activation, longitudinal shortening of the myocardium occurs with circular narrowing and the torsion that characterizes its helical function, which implies that the fulcrum undergoes a downward displacement, accompanied by a torque from its right end to the opposite end due to

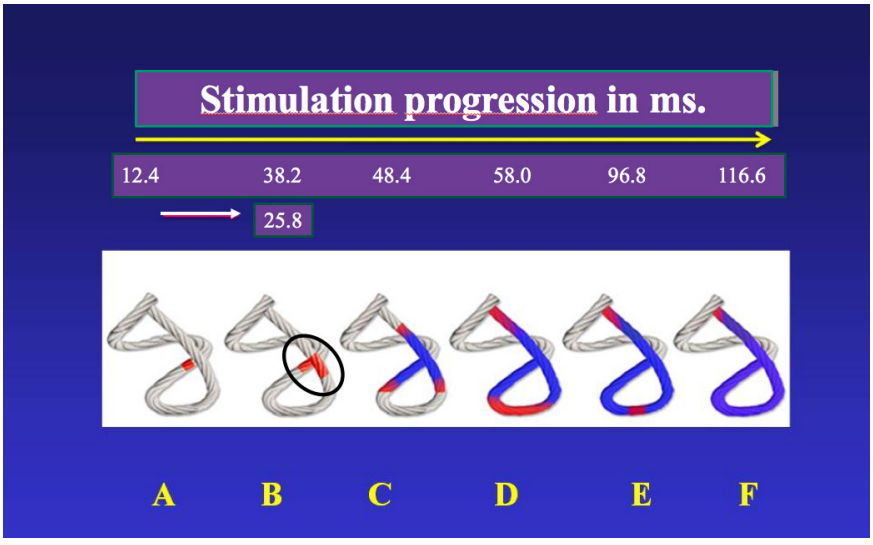

Fig. 4. Chord model. Activation sequence (A-F) in the continuous myocardium according to our investigation. The propagation times are observed. The 25.8 milliseconds in **B** represent the delay of the stimulation to pass from the descending band in **A** to the ascending band in **B** (detailed in the black circle). In red: depolarization; in blue: zones already activated.

torsion (Figure 2).

When the ejective period ends, the terminal part of the ascending segment remains in the active process of contraction, that is, in its attachment to the cardiac fulcrum, which occurs fundamentally in the antero-inferior portion and posterior face of the latter. This phase occupies about 80-100 ms and is intermediate between systole and diastole. We have called it the protodiastolic phase of myocardial contraction (PPMC) and is the cause of the process of generating negative intracavitary ventricular pressure, resulting in the opening of the atrioventricular valves and the precipitous entry of blood into the ventricles by a suction mechanism. During this phase the myocardium lengthens, narrows and detorsions. (11) Under these tensions the fulcrum at its left end undergoes an upward displacement and generates a torque opposite to the one it had during systole, due to myocardial detorsion. Obviously, this continuous torque in coupling models the fulcrum with a torsion that is well observed in a profile view. The torque is a demonstration of the opposing and unaligned forces that stress the fulcrum; thus, the continuous myocardial ascent and descent together with the torsion-detorsion effect shape its morphology.

The section of the fulcrum is not axisymmetric (symmetrical in relation to its axis); therefore, the torsion-detorsion it undergoes in each cardiac cycle determines deformations in its structure. Thus, the torque (Figure 2) applied at each of its ends during the cardiac cycle causes the free ends of the bar to rotate at an angle Φ, which is called the twist angle. In this deformation the maximum shear strain is produced in the middle of the fulcrum faces and around the axis in which it rotates, thus producing a rotation effect, without achieving an overt translation. In diástole, the fulcrum returns to its position (Figure 5).

Could the myocardium function without the cardiac fulcrum? With its helical configuration, but without the fulcrum, the myocardium would be a Moebius band modified so that the beginning and end of the same fiber would be closed. The closed fibers would determine that their stresses are established as in an elastic band, but without an anchor point or support. The non-existence of the anchor point would not allow the adequate sliding of the fibers between them, losing the correct sequence of their efforts. Physically, we would speak of free and unfixed vectors, losing the correct sequence of their efforts, and the myocardium itself would be exposed to undesired displacements, due to asynchronous movements.

The existence of the fulcrum is inevitable. Also, it has been proven in published research that the fibers are lubricated with hyaluronic acid in order to reduce the friction between them and the loss of energy, so that most of it is transformed into motion. (12)

The upper edge of the fulcrum has a ledge that adapts to the aortic annulus, providing evidence of the pattern of organization of the helical heart. The cardiac fulcrum, in order to maintain stabilization

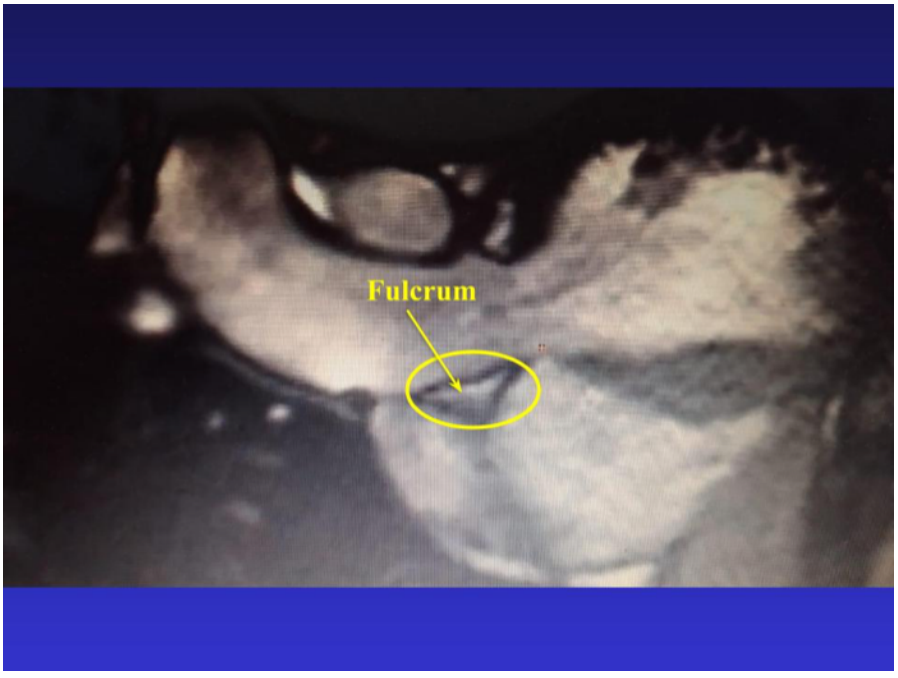

Fig. 5. Cardiac fulcrum in diastole. Magnetic resonance image in adult human.

of the myocardium, which originates and ends in its structure, is subjected to sequential tractions by the cardiac movements. These forces exerted on its structure must have practically zero resultant to maintain the equilibrium of the cardiac system, which with its movements generates tensions that are absorbed by the fulcrum, preventing them from being transferred to the aorta. In this way, it avoids the aorta from traction and rotation, which would produce resistance to ejection.

In addition to the contractions that generate myocardial shortening and lengthening, the cardiac fulcrum is subjected to clockwise and counterclockwise rotational movements in its posterior and anterior regions respectively, given the helical constitution of the cardiac fibers and the consequent myocardial torsion-detorsion. The torque force rotates the cardiac descending and ascending segments in opposite directions until their forces are equalized at point 0 (center or twist). In this interplay the fulcrum is modeled around the axis of rotation in which it is located, with its maximum shear strain being produced in the middle of its faces and around the axis of rotation.

CONCLUSIONS

The fulcrum constitutes the support for the myocardium to exert the necessary power, but due to the sequential cardiac movements, it acts as a stabilizer of the whole heart, absorbing the alternating ascending, descending and torsional tractions. This interplay implies not only a limit to the movements of the heart, but also that the fulcrum itself is shaped in its form by these movements through the torque to which it is subjected. Its properties of stability, resistance, elasticity and plasticity allow the myocardium to fulfill its function.

Conflicts of interest

None declared.

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

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BRIEF ARTICLE

Basal Glucose and HbA1c Associated with Carotid Plaques in non-Diabetics: an Approach with CHAID Trees

Glucemia basal y HbA1c asociados a placas carotídeas en no diabéticos: un enfoque con árboles CHAID

ALBERTO GUEVARA-TIRADO[1]

ABSTRACT

Background: Carotid plaques are significant markers of risk for stroke.
Objective: The aim of this research was to analyze the association between baseline glycemia and glycated hemoglobin (HbA1c) with the presence of carotid plaques in non-diabetic adults.
Methods: We conducted a cross-sectional analytical study using a secondary database. The variables considered included carotid plaque score, baseline glycemia and HbA1c. The CHAID decision tree was utilized in this analysis.
Results: The CHAID tree classified baseline blood glucose levels > 104 mg/dL along with HbA1c values > 6%. as the most decisive variables associated with the presence of carotid plaques at risk for stroke. The odds of presenting with a high-risk carotid plaque score was 3.69 times higher for these patients when compared to those with lower glucose and HbA1c levels (OR 3.69; 95% CI, 2.59-5.28). Patients with the aforementioned blood glucose levels and HbA1c had greater probability of a true positive result for high-risk carotid plaque (LR+ 3.29; 95% CI, 2.38-4.54). In these patients, the median carotid plaque score was 1.60 compared to 0.25 in those with lower values (p=0.001). The median number of plaques was also greater (1.20 vs. 0.30; p < 0.001).
Conclusions: Baseline blood glucose levels >104 mg/dL and HbA1c >6% were associated with the presence of high-risk carotid plaques in non-diabetic patients.

Keywords: Plaque, Atherosclerotic - Ultrasonography, Carotid Arteries - Glycated Hemoglobin - Blood Glucose - Primary Health Care

RESUMEN

Introducción: La presencia de placas carotídeas es un importante marcador de riesgo de accidente cerebrovascular (ACV).
Objetivo: Analizar la asociación entre valores de glucemia basal y hemoglobina glicosilada (HbA1c) con la presencia de placas carotídeas en adultos no diabéticos.
Material y métodos: Estudio analítico de corte transversal con la utilización de una base de datos secundaria. Las variables consideradas incluyeron: puntaje de placas carotídeas, glucemia basal y HbA1c. Se empleó el árbol de decisiones CHAID.
Resultados: El árbol CHAID identificó que una glucosa basal de 104 mg/dL con HbA1c >6 % es la característica principal asociada a presencia de placas carotídeas de riesgo para ACV. Los pacientes con estas características tuvieron 3,69 veces más a menudo placas carotídeas de riesgo que aquellos con valores menores de glucosa y HbA1c (OR 3,69; IC95% 2,59-5,28). Los valores citados de glucemia basal y HbA1c tuvieron probabilidad significativamente mayor de corresponder a un verdadero positivo que a un falso positivo para señalar la presencia de placas de riesgo (LR+ 3,29; IC95% 2,38-4,54). La mediana de puntaje de placas carotídeas fue de 1,60 en estos pacientes, comparado con 0,25 en aquellos con valores menores (p=0,001). También tuvieron una mediana mayor de número de placas (1,20 vs. 0,30; p<0,001).
Conclusiones: Valores de glucemia basal >104 mg/dL con HbA1c >6 % se asociaron a mayor presencia de placas carotídeas de riesgo en pacientes no diabéticos.

Palabras clave: Placa Aterosclerótica - Ultrasonografía carotídea - Hemoglobina Glicosilada - Glucemia - Riesgo cardiovascula

Rev Argent Cardiol 2025;93:48-52. https://doi.org/10.7775/rac.v92.i6.20855

Received: 11/13/2024 – *Accepted:* 02/12/2025

Correspondence: Calle Doña Delmira manzana E lote 4 Urbanización Los Rosales, Santiago de Surco, Lima, Perú (15048).
E-mail: albertoguevara1986@gmail.com

[1] Universidad Científica del Sur, Lima, Perú

INTRODUCTION

Atheromatous plaques are accumulations of macrophages, T cells, dendritic cells, calcium, lipids, and fibrous connective tissue in the inner layer of arteries. (1) These plaques narrow the arterial lumen and cause micro-ruptures, increasing the risk of thromboembolic and ischemic events such as myocardial infarction and stroke. (2) Atherosclerosis, a chronic inflammatory disease, is influenced by factors such as dyslipidemia, dysglycemia, smoking, diets high in fat and carbohydrates, sedentary lifestyle, age and genetic predisposition. (3)

Carotid artery stenosis due to atherosclerosis causes about 10-20% of all ischemic strokes by two main mechanisms: hemodynamic impairment in case of significant stenosis, and thromboembolism from an atherosclerotic plaque regardless of the degree of stenosis. (4) Stroke is the second leading cause of death and the third leading cause of morbidity and mortality worldwide, (5) especially ischemic stroke, which accounts for 85% of cases. (6) Hyperglycemia, mainly in type 1 and 2 diabetes mellitus, promotes atherosclerosis through mechanisms such as the formation of advanced glycation end-products, oxidative stress and alteration of endothelial growth factor. (7)

Given that the relationship between glycemia and atherosclerosis is not limited to patients with diabetes or prediabetes, it is crucial to understand the glycemic profile associated with carotid artery atherosclerosis in subjects without dysglycemia. The use of the chi-squared automatic interaction detection (CHAID) decision tree analysis can help to identify this profile. The aim of this research was to analyze the association between baseline blood glucose levels and HbA1c with the presence of carotid plaques in non-diabetic adults.

METHODS

Study design and population

We conducted an analytical and cross-sectional study, based on an international database registered in the Dryad repository (https://datadryad.org). The research was triggered after reading the article "Mathematical modeling for the prediction of cerebral white matter lesions based on clinical examination data", (8) which refers to the prediction of white matter lesions using routine medical examinations and complex mathematical algorithms. (9)

From a total population of 1904 adults, 1775 were intentionally selected. Patients taking antidiabetic medications and those with baseline blood glucose levels ≥ 126 mg/dL were excluded.

Baseline determinations included systolic blood pressure (SBP), diastolic blood pressure (DBP), baseline blood glucose levels in mg/dL and glycated hemoglobin (HbA1c).

During the carotid ultrasound procedure, the presence of plaques in the common carotid artery, its bifurcation and, the internal carotid artery was evaluated. Carotid intima-media thickness was measured.

The dependent variable in the CHAID decision tree was the carotid plaque score, assessed by ultrasound and dichotomized into values > 1.20 mm and ≤ 1.20 mm. (10) The carotid plaque score is a measurement used to assess the presence and severity of atherosclerotic plaques in the carotid arteries. This score is obtained by carotid artery ultrasound, which measures the maximum carotid plaque thickness. A value >1.20 mm is associated with increased cardiovascular risk.

Statistical analysis

We used the CHAID decision tree technique, based on a chi-square measurement metric, to segment the data into homogeneous groups and construct a predictive model. This method identifies patterns in the relationship between a dependent variable and multiple independent variables, using both quantitative and categorical data. (11)

CHAID iteratively divides the sample into nodes, creating branches based on the categories of the explanatory variables. In each branch the most significant cut-off points are selected according to the chi-square test, generating mutually exclusive subgroups. (12) For example, in the case of the carotid plaque score the nodes represent differentiated categories according to their association with the variable of interest.

Finally, the terminal node with the strongest strength of association with the root node was selected, which was the presence or absence of carotid plaques > 1.20 mm.

Diagnostic tests were performed to estimate the odds ratio (OR), degree of association (Phi coefficient), sensitivity (S), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR). All the statistical calculations were performed using SPSS Statistics 25.0® software package. (13)

Ethical considerations

The database was voluntarily uploaded to Dryad (https://datadryad.org/) under Creative Commons license (CC0). (14) The study was conducted following the recommendations of the Declaration of Helsinki. The database is available at: https://datadryad.org/stash/dataset/doi:10.5061/dryad.73bh2q8.

RESULTS

The characteristics of the selected population are described in Table 1.

Of the 1775 patients, 565 (31.8%) had high-risk carotid plaque score. These patients had significantly higher number of plaques, higher HbA1c and baseline blood glucose levels, and higher systolic and diastolic blood pressure values compared with those without high-risk carotid plaque score ($p < 0.001$). However, there were no significant differences in BMI between both groups ($p = 0.071$). This highlights the association between high-risk carotid plaque score and elevated metabolic and cardiovascular markers (Table 2)

The decision tree with the carotid plaque score as the dependent variable included 2 depth levels and a total of 8 nodes of which 5 were terminal nodes. The tree classified baseline blood glucose levels > 104 mg/dL along with HbA1c values > 6%. as the most decisive variables associated with the presence of high-risk carotid plaques. The main characteristic associated with the absence of high-risk carotid plaque score was the presence of HbA1c values ≤ 5.30% (Figure 1). The association between the presence of baseline blood glucose levels >104 mg/dL and HbA1c >6 % (node 7

Table 1. Baseline characteristics of the population (n=1775)

Variable	
Male sex, n (%)	891 (50.2%)
Age group, n (%)	
18-39 years	164 (9.2%)
40-59 years	838 (47.2%)
≥ 60 years	773 (43.5%)
Carotid plaque score, n (%)	
High risk (> 1.2 mm)	565 (31.8%)
No risk	1210 (68.2%)
Carotid plaque score, median (IQR)	0.40 (0.10-1.00)
Blood glucose levels (mg/dL), mean ± SD	99.86 ± 8.98
HbA1c (%), mean ± SD	5.61± 0.38
BMI (kg/m2), mean ± SD	22.91± 3.28
SBP (mm Hg), mean ± SD	123.14± 18.29
DBP (mm Hg), mean ± SD	73.74± 12.17
Number of plaques, median (IQR)	0 (0-1)
TG (mg/dL), mean ± SD	111.82 ± 69.55
HDL (mg/L), mean ± SD	61.12 ± 15.39

BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IQR: interquartile range; SD: standard deviation; SBP: systolic blood pressure; TG: triglycerides

Table 2. Biological markers in patients with high-risk carotid plaque score

	High risk score (n=565)	No pathological risk score (n=1210)	p
Number of plaques, median (IQR)	2 (0.50-2.50)	0.35 (0.10-1.12)	<0.001
HbA1c (%), mean ± SD	5.67 ± 0.30	5.58 ± 0.29	<0.001
Blood glucose levels (mg/dL), mean ± SD	101.33 ± 9.02	99.22 ± 8.23	<0.001
SBP (mm Hg), mean ± SD	128.64 ± 18.34	120.76 ± 17.72	<0.001
DBP (mm Hg), mean ± SD	75.49 ±12.19	72.98 ± 12.18	<0.001
BMI (kg/m2), mean ± SD	23.13 ± 3.18	22.82 ± 3.26	0.0710

BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation

of the CHAID decision tree) with carotid plaque score >1.2 mm was moderate (Phi = 0.182). The odds of presenting with high-risk carotid plaque score was 3.69 times higher for patients with elevated blood glucose levels and HbA1c when compared to those with lower blood glucose levels and HbA1c. The sensitivity was low (15%), the specificity high (95%), and the positive and negative predictive values were 61%, and 71%, respectively. The likelihood ratio indicates that patients with blood glucose levels > 104 mg/dL and HbA1c > 6% exhibited a 3.29 times greater probability of a true positive result for high-risk carotid plaque score in comparison to a false positive result (Table 3). Patients with the predominant feature of node 7 of the CHAID decision tree (blood glucose levels > 104 mg/dL and HbA1c > 6%), had a median carotid plaque score of 1.60, while patients in the other nodes had a median carotid plaque score of 0.25 (p = 0.001). In addition, the median number plaques in patients in node 7 was 1.20, while the median number plaques in patients in the other nodes was 0.30 (p < 0.001) (Table 4).

DISCUSSION

The CHAID decision tree classified and divided the continuous variables HbA1c and baseline glucose levels into segments. Baseline blood glucose levels >104 mg/dL and HbA1c >6% were associated with the presence of high-risk carotid plaque score, consistent with prediabetes. This was confirmed with diagnostic tests which demonstrated a significant influence on carotid intima-media thickness, similar to the findings by Zhou et al. (15) The association between HbA1c and carotid plaques has been observed in patients with chronic diseases, as in the studies by Dodos et al. (16) and Cheng et al. (17)

Elevated HbA1c promotes carotid artery atherosclerosis through mechanisms such as the formation

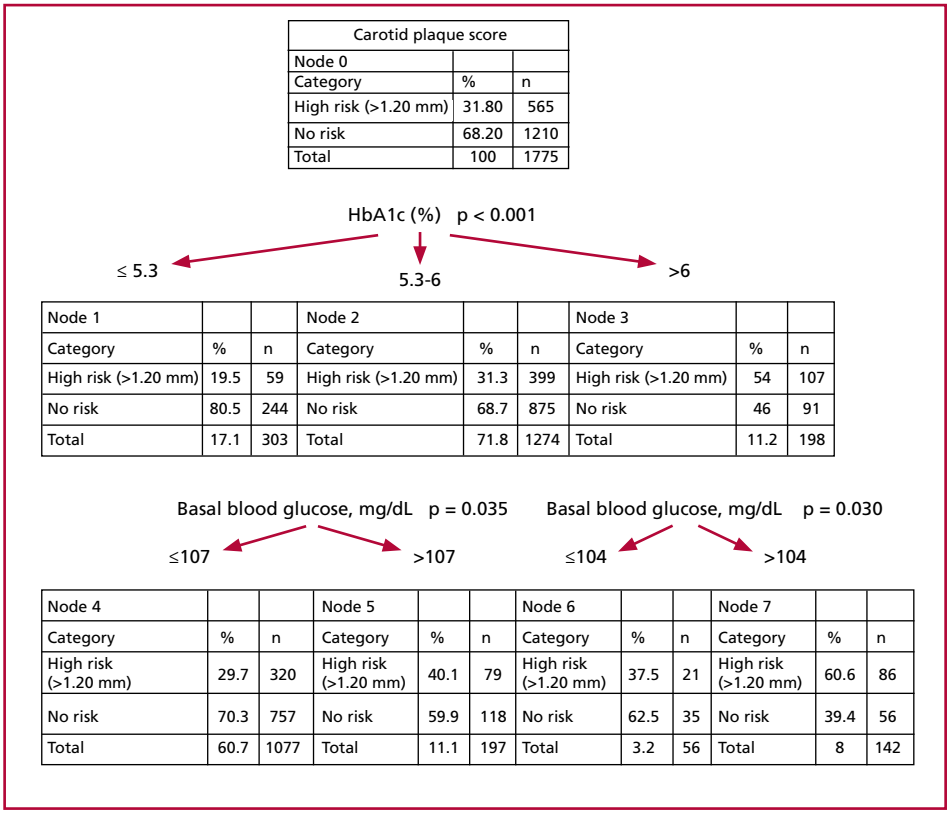

Fig. 1. CHAID decision tree for glycemic profile associated with carotid plaques in non-diabetic adults.

Table 3. Measurements of association between node 7 of the CHAID decision tree and the presence of carotid plaques detected by ultrasound in non-diabetic adults

Phi	0.182
OR (95% CI)	3.69 (2.59-5.28)
S	15%
Sp	95%
PPV	61%
NPV	71%
LR+ (95% CI)	3.29 (2.38-4.54)
LR- (95% CI)	0.89 (0.85-0.93)

LR: likelihood ratio; NPV: negative predictive value; OR: odds ratio; Phi: Phi coefficient; PPV: positive predictive value; S: sensitivity; Sp: specificity

of advanced glycation end-products, oxidative stress and endothelial dysfunction. (18-20) These mechanisms may have an impact on non-diabetic adults who exhibit HbA1c and baseline blood glucose values indicative of prediabetes. suggesting that carotid plaque formation may be a prodromal sign.

The decision tree also identified that HbA1c ≤ 5.30% is associated with absence of high-risk carotid plaques. While these findings suggest an association between HbA1c and the presence of high-risk carotid plaques, further studies and additional evidence are needed to make a strong recommendation for the adoption of HbA1c targets or the routine measurement of HbA1c to prevent cerebrovascular events related to carotid atherosclerosis.

The limitations of this study include the sample size (n=1775), which may not be representative of larger populations, and potential reporting biases due to the retrospective nature of the data collection. In addition, information on other key risk factors, such as dietary habits, physical activity, and family history, which could influence glycemia and atherosclerosis, is lacking. The absence of longitudinal follow-up precludes the establishment of a definitive causal relationship, and the study does not consider individual variability or the use of multiple biomarkers, which could provide a more complete assessment of cardiovascular risk.

CONCLUSIONS

Baseline blood glucose levels >104 mg/dL and HbA1c >6% were associated with the presence of high-risk carotid plaques in non-diabetic adults. Despite the CHAID decision tree excluded triglycerides and HDL as relevant factors, and the observation that baseline blood glucose levels >104 mg/dL and HbA1c levels >6% were associated with a higher prevalence of high-risk carotid plaques in nondiabetic adults, the absence of data on additional potential risk factors, such as total cholesterol or genetics, hinders the inter-

Table 4. Comparison of mean anthropometric, hemodynamic and laboratory tests values according to the presence of baseline blood glucose levels >104 mg/dL and HbA1c >6% in non-diabetic adults (node 7 of the CHAID decision tree).

Variable	Node 7 (n=142)	Nodes 1 to 6 (n= 1633)	p
Carotid plaque score, median (IQR)	1.60 (0.50- 3.70)	0.25 (0.10-0.50)	0.001
Number of plaques, median (IQR)	1.20 (0.80-1.55)	0.30 (0.10-0.50)	< 0.001
BMI (kg/m^2), mean ± SD	24.36 ± 4.18	22.85 ± 3.17	< 0.001
SBP (mm Hg), mean ± SD	127.34 ± 18.64	123.03 ± 18.22	0.007
DBP (mm Hg), mean ± SD	73.65 ± 11.85	73.70 ±12.20	0.962
HbA1c (%), mean ± SD	6.46 ± 0.45	5.59 ± 0.28	<0.001
Blood glucose levels (mg/dL), mean ± SD	114.58 ± 5.86	99.21 ± 8.11	<0.001

BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation

pretation of these findings. Nevertheless, the routine assessment of HbA1c in nondiabetic adults could be useful in identifying the risk of carotid atherosclerosis, though further research is necessary to ascertain the validity of this association and its implications for disease prevention.

Conflicts of interest

None declared.

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

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CONTROVERSY

Triglyceride Levels Should be Lowered to Reduce Cardiovascular Risk

Se debe disminuir el nivel de triglicéridos para reducir el riesgo cardiovascular

AGONIST

PABLO CORRAL[MTSAC,]

INTRODUCTION

Hypertriglyceridemia is defined as fasting and postprandial triglyceride (TG) levels greater than 150 and 175 mg/dL, respectively. This elevation results from either increased TG production, decreased catabolism of TG-rich lipoproteins (TRL) or impaired clearance. The estimated prevalence of hypertriglyceridemia is 25% worldwide. (1)

The role of TG as a risk factor for cardiovascular disease (CVD) has been the subject of debate within the medical and scientific communities for many years. (2) The residual atherosclerotic risk, as previously defined, is attributable to the persistence of atherogenic particles with apolipoprotein B (ApoB). These particles are not exclusively present in low-density lipoprotein cholesterol (LDL-C); they are also found in other very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and cholesterol remnants. These particles are characteristically present in patients with type 2 diabetes, metabolic syndrome and insulin resistance.

The following discussion will present the arguments in favor of considering TG, expressed as absolute value, non-high-density lipoprotein cholesterol [total cholesterol (TC) minus high-density lipoprotein cholesterol (HDL-C)] or cholesterol remnants, as a significant risk factor for CVD. It will be demonstrated that lowering TG values contributes to lowering CVD risk. This argument is supported by recent evidence from epidemiological, genetic, and interventional studies. (Figure 1). (3,4)

ARGUMENTS IN FAVOR OF THE ROLE OF TRIGLYCERIDES AS CVD RISK FACTOR

1. Epidemiological evidence:

Population-based studies: Several observational studies, including the PREDIMED study and the Copenhagen General Population Study, have consistently demonstrated a correlation between elevated TG levels and an increased risk of cardiovascular events (CVE) such as myocardial infarction and coronary artery disease. (5-7)

Follow-up data: Longitudinal studies have observed that individuals with hypertriglyceridemia have a higher incidence of CVE, independently of other risk factors such as LDL-C levels. (8)

2. Biochemical mechanisms:

Atherosclerotic plaque formation: TG contribute to atherosclerotic plaque formation from their remnants, which are cholesterol-rich particles that infiltrate the arterial wall, contributing to the development of atherosclerotic plaques. When these particles become trapped in the vascular subendothelium, they trigger a retention process, leading to the generation of atherosclerotic plaque and subsequent complications, such as rupture. This is the classic pathophysiological process of atherosclerosis. (9)

Endothelial dysfunction and inflammation: Elevated TG levels are associated with endothelial dysfunction and with the production of inflammatory mediators and cytokines within the vascular subendothelium. These mediators can contribute to the progression of atherosclerosis. This raises the double effect or impact in terms of vascular damage derived from these lipoproteins, not only capable of internalizing in the subendothelium but also of generating local inflammation that enhances the deleterious mechanism. (9)

3. Genetic and intervention studies:

Mendelian randomization: Studies using the Mendelian randomization technique have found a causal relationship between genetic variants that elevate TG levels and an increased risk of CVD. (10)

INTERVENTION CLINICAL TRIALS:

Therapeutic agents for the treatment of elevated TG levels include statins, fibrates, peroxisome prolifera-

Rev Argent Cardiol 2025;93:53-57. https://doi.org/10.7775/rac.v93.i1.20865

Internist. Lipidologist. Professor, School of Medicine, FASTA University, Department of Pharmacology. Clinical Researcher, Clinical Research Institute (IIC). Mar del Plata. Argentina

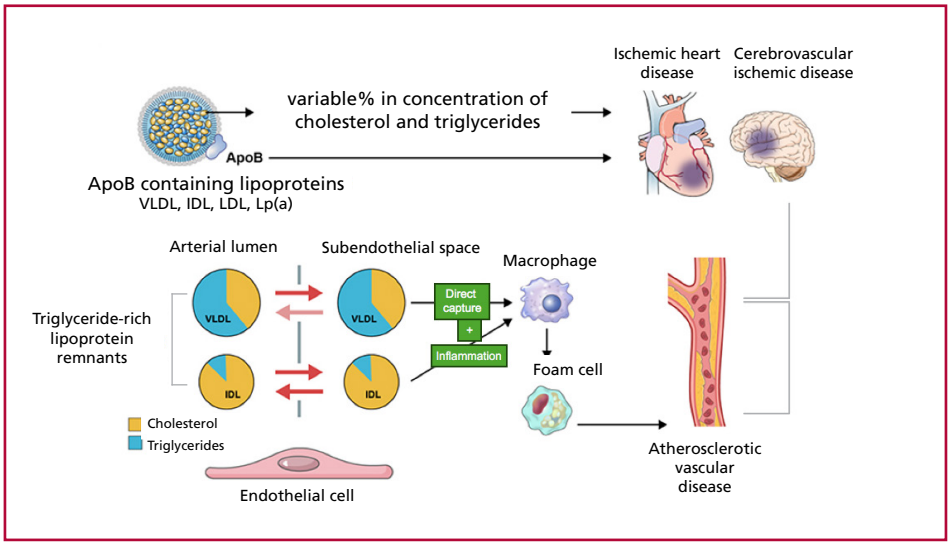

Fig. 1. Triglycerides, remnants and cardiovascular disease

IDL: intermediate-density lipoproteins; LDL: low density lipoproteins; Lp(a): lipoprotein(a); VLDL: very low density lipoproteins

tor-activated receptor alpha (PPAR-α), and omega-3 polyunsaturated fatty acids. Fibrates have the greatest power to reduce TG (a reduction between 30-50%, depending on baseline plasma concentrations) and non-HDL cholesterol (between 6-16%). In patients with severe hypertriglyceridemia, the use of fibrates can lead to an increase in LDL levels. Eicosapentaenoic acid (EPA) is less effective than fibrates at reducing TG levels, but it has several other notable benefits, such as improving vascular endothelial function, inhibiting platelet aggregation, and having anti-inflammatory properties.

Subgroup analysis of pharmacological interventions to lower TG, such as fibrates, has been shown to reduce the risk of CVEs in patients with elevated TG levels. Additionally, the legacy effect, evidenced in the long-term follow-up of patients who received fenofibrate, shows a clear benefit with these drugs. (11,12) High-dose omega-3 fatty acids (specifically EPA), demonstrated a clear benefit on CVD risk in the REDUCE-IT trial in those patients with high TG levels. The impact on TG levels is proposed to be one of the mechanisms that explains this benefit. (13)

CONCLUSIONS

While TG have historically been overshadowed by the focus on LDL-C, the cumulative evidence suggests that they should not be ignored as a risk factor for CVD and should clearly be taken into account when assessing atherosclerotic residual risk. TG and their remnants have direct implications in the pathogenesis of atherosclerotic CVD and their management could represent an additional therapeutic strategy in the global effort to combat the epidemic of CVD. However, further research is needed to optimize treatment strategies and to establish clear guidelines on the appropriate timing and manner for intervention in cases of hypertriglyceridemia.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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ANTAGONIST

AUGUSTO LAVALLE COBO[MTSAC]

"To be or not to be—that is the question" is perhaps one of the most famous quotes in world literature. It is also the opening line of Hamlet's soliloquy in William Shakespeare's eponymous play. With all the respect that the play and its author deserve, I will borrow it to argue my position on this interesting controversy.

The association between lipids, particularly cholesterol, and the risk of developing CVD began to be robustly established in 1953 with the publication by Ancel Keys. (1) Since then, the role of cholesterol in the development of atherosclerotic CVD and the impact of lowering cholesterol levels, particularly LDL-C, on reducing cardiovascular risk have been clearly demonstrated. (2)

There is also evidence of the association between TG levels and increased risk of atherosclerotic CVD. (3,4) However, in my role as an antagonist in this controversy, it is necessary to analyze why I should not focus on reducing TG levels to reduce CV risk. I bring up a phrase that I have heard repeatedly from Dr. Corral, who acts as an agonist in this debate: "Correlation does not imply causation". Returning to the opening quote of the text, the key question is: are TGs a causal factor or simply a marker of cardiovascular risk? This distinction is fundamental and extends beyond a mere semantic difference. While a marker allows for identifying those individuals or populations at greater risk of developing an event (in this case, a CVE), treatment cannot modify this risk. In contrast, a risk factor is a condition that, when modified, reduces the chance of an event occurring, thereby becoming a therapeutic target.

From a physiological point of view, lipids circulate in the bloodstream bound to proteins, forming particles called lipoproteins, whose content varies from one particle to another. TG are primarily transported in particles that originate in the liver (VLDL and IDL) and in chylomicrons, which originate in the intestine. Although these particles are rich in TG, it is estimated that they carry approximately one third of circulating cholesterol (remnant cholesterol), (5) and their constitutive protein is ApoB, as in LDL-C. (6) Consequently, the question arises as to whether the increased CV risk observed in patients with elevated TG levels is directly associated with this elevation (causation) or with the concomitantly transported cholesterol (correlation). Although this analysis focuses on lipid particles, the common factor in atherogenic risk associated with both lipid fractions seems to be more related to the number of ApoB particles than to the mass of cholesterol within ApoB particles. (7)

It is also relevant to consider what happens in patients with extremely high TG values due to genetic alterations in their metabolism. Although this brief pathophysiological review might suggest that TGs are not the main cause of the problem, different research groups have evaluated strategies to reduce cardiovascular risk by lowering TG levels.

In this context, I will focus on the two most widely used pharmacological groups for the treatment of mild and moderate hypertriglyceridemia: fibrates and omega-3 fatty acids.

The most prominent studies on fibrates are the BIP (Bezafibrate Infarction Prevention) study, (8) the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study (9) and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. (10) In these studies the use of bezafibrate (BIP) and fenofibrate (FIELD and ACCORD) did not result in a significant reduction in CVE, despite achieving reductions in TG levels of 21%, 29% and 25.6%, respectively. However, a meta-analysis that included 45 048 patients with hypertriglyceridemia and low HDL-C levels showed significant reductions of 10% in major CVEs and 13% in coronary events. (11) This suggests that the impact of TG may have clinical relevance in patients with low HDL-C. It also raises questions about the adequacy of the populations evaluated in the aforementioned studies to confirm causation of hypertriglyceridemia in atherosclerotic disease.

The PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study was conducted to answer this question. (12) This trial included patients with diabetes, plasma TG levels between 200 and 499 mg/dL and HDL-C levels ≤ 40 mg/dL who were randomly assigned to receive pemafibrate or placebo. Despite a 26.2% reduction in TG levels in the treated group, the incidence of the primary CV endpoints was not significantly lower. This finding could be attributed to

Head of the Department of Cardiology, Sanatorio Otamendi, Former Director of the Councils of Epidemiology and CV Prevention and Cardiometabolism, SAC.

the increase in ApoB levels observed in the pemafibrate-treated group, which reopens the debate: "TG or ApoB, that seems to be the question".

With regard to omega-3 fatty acids, I will voluntarily omit the GISSI-Prevenzione study. The omission is not due to any personal convenience in my role as antagonist; rather, the decision is based on the fact that the baseline treatment used in the study does not align with the current concept of cardiovascular risk management. (13) The JELIS (Japan EPA Lipid Intervention Study) deserves to be mentioned in first place. This study evaluated the use of EPA in subjects with hypercholesterolemia who were receiving statins and who had mean TG levels of 154 mg/dL (111 mg/dL - 224 mg/dL). (14) Patients treated with EPA 1800 mg daily experienced a 19% reduction ($p = 0.048$) in the incidence of major coronary events compared with those receiving statins alone. However, the difference in TG reduction between the two groups was only 4% (9% vs. 5%), suggesting that this modest decrease alone would not fully explain the observed benefit. More recently, the REDUCE-IT study evaluated the use of icosapent ethyl in patients with CVD or diabetes associated with other risk factors treated with statins, with TG levels between 135 and 499 mg/dL. (15) Patients treated with 4 g/day of icosapent ethyl had a 25% reduction (HR 0.75, $p < 0.001$) in the risk of presenting the composite ischemic events (nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) and CV death, and the risk of the secondary end point was also lower. Contrary to the findings of the JELIS study, a greater reduction in TG levels was observed in this case, reaching 18.3%. Is this 18.3% reduction sufficient to justify the CV benefit? I believe not, and I support my position with two arguments. First, the STRENGTH (Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial, which evaluated a combination of EPA with docosahexaenoic acid (DHA) in a similar population, found no reduction in CVD despite a reduction in TG levels that was virtually identical to that reported in the REDUCE-IT trial. (16) Second, in the REDUCE-IT trial subgroup analysis, the benefit was similar in patients with baseline TG levels < 150 mg/dL versus those with levels ≥ 150 mg/dL, or < 200 mg/dL versus ≥ 200 mg/dL. Additionally, TG levels at one year after randomization were not predictive of CV benefit. The study was favorable even in the subgroup of patients with TG levels < 150 mg/dL, (17) suggesting that other mechanisms may be responsible for the CV benefit observed in the REDUCE-IT study. (18)

Considering the aforementioned points, it can be concluded that lowering TG levels should not be considered a primary strategy for reducing CV risk. In this context, hypertriglyceridemia should be regarded as a risk marker rather than a therapeutic target, given its association with elevated levels of remnant cholesterol and ApoB-rich particles, which appear to be the primary contributors to the observed increase in CV risk. Therefore, the therapeutic approach should focus on reducing ApoB-rich particles.

Furthermore, certain treatments, such as icosapent ethyl, could offer an alternative approach due to their pleiotropic effects that extend beyond the mere reduction of TG levels.

To conclude, I would like to reiterate and adapt to the context the famous phrase from Hamlet with which I began this post of this controversy: "To be or not to be a lipid fraction causative of atherosclerosis, that is the question.".

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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AGONIST REPLY

First, I would like to express my gratitude to my friend, Dr. Augusto Lavalle Cobo, for facilitating this exchange and for his clear exposition and review of the available evidence, primarily from pharmacological intervention studies.

However, I must point out that if it is suggested that TG levels should not be measured and treated, neither non-HDL-C nor ApoB (which is recommended in all national and international guidelines) should be used as a therapeutic target. This is because the representation of blood TG levels is provided by the remnant TG-rich particles containing ApoB, and these particles have the dual capacity to cause damage, infiltrate the subendothelium, and create an inflammatory phenomenon that speeds up and enhances the development of atherosclerosis.

Despite what has been previously mentioned, we must understand and re-examine the physiology and pathophysiology of lipids, wherein LDL particles emerge as a consequence of the catabolism and degradation of VLDLs secreted by the liver. This continuous metabolic process (from VLDL, traversing IDL, culminating in LDL) is distinctive and linear, and the presence of elevated TG levels clearly evidences increased cardiovascular risk.

In my daily practice, I ask myself: why would I order determination of ApoB or estimation of non-HDL-C in a patient? The answer to this question is simple: because that patient has elevated TG levels, residual risk attributable to TRL and cholesterol remnants, and it has been demonstrated that, in that context, measuring LDL-C alone is not sufficient for risk assessment (in my patient with TG levels of 70 mg/dL, measuring ApoB or calculating non-HDL-C does not provide more information for management).

In conclusion and referring to the initial point of the controversy (lowering TG to reduce cardiovascular risk), it is crucial to acknowledge that TGs are not merely a "marker" of CV risk (as are, for example, troponin T or NT-proBNP). The futility observed in various pharmacological studies conducted to date should not make us ignore the fact that my patient, with TG levels of 300 mg/dL, should be "treated", which is not the same as "medicated", because they have an evident risk with interventions (diet, exercise, future ApoC3 inhibitors?) that can modify this biomarker and improve cardiovascular prognosis.

Pablo Corral

ANTAGONIST REPLY

It is a pleasure to share this controversy with Dr. Pablo Corral, with whom, in addition to a great interest in lipids, I have a deep friendship. I congratulate Dr. Corral for the clear and precise explanation offered during his intervention as a proponent of the agonist position in this controversy. In his presentation, he highlights the evidence from various types of studies demonstrating the relationship between elevated TG levels and increased risk of atherosclerotic cardiovascular events.

As the saying goes: "Tell me who you hang out with and I will tell you who you are". In this regard, it is noteworthy to mention that TG, as previously indicated, circulate in the bloodstream in particles that contain ApoB as a constituent protein. In most of these particles, TG are associated with other lipid fractions, such as cholesterol, which justifies measuring ApoB or estimating non-HDL-C to assess an individual's residual lipid risk.

Personally, when I see a patient with moderate hypertriglyceridemia, I ask myself the following question: should I focus on lowering TG or be more aggressive in lowering ApoB? After all that has been said, you can probably imagine my approach.

I would like to conclude with a reflection that may seem obvious, but which is always important to emphasize when we talk about cardiovascular risk: the necessity of a comprehensive approach. This is even more relevant when we refer to hypertriglyceridemia, since, in many cases, this condition reflects a poor "cardiometabolic" state. In such cases, lifestyle interventions (e.g., weight control, improved diet, and increased physical activity) have been shown to not only positively impact cardiovascular risk but also reduce plasma TG levels.

Augusto Lavalle Cobo

REVIEW ARTICLE

Cardiovascular Disease and Depression

Enfermedad cardiovascular y depresión

IGNACIO DÁVOLOS[1,2,MTSAC], OMAR PRIETO[3,4, MTSAC], ALEJANDRA ÁVALOS ODDI [3,4, MTSAC]

ABSTRACT

Depression and cardiovascular disease (CVD) are two leading causes of disability, impacting quality of life and increasing healthcare costs. There is a bidirectional relationship between them: depression is a risk factor for developing CVD and worsens prognosis in CVD patients. CVD in turn increases the incidence of depression and worsens its prognosis. Biological factors involved in both pathologies include autonomic dysfunction, chronic inflammation, and increased platelet reactivity. It is recommended to screen for depression during cardiology consultations, using tools such as the Patient Health Questionnaire (PHQ-2). Treatment should be comprehensive, combining antidepressants, psychotherapy, physical exercise, and mindfulness practices. Initially focused on exercise, cardiovascular rehabilitation (CR) has evolved to encompass lifestyle modification, which has been shown to improve depression and overall well-being in CVD patients.

Keywords: Cardiovascular disease - Depression - Health care quality.

RESUMEN

Existe una relación bidireccional entre ambas: la depresión es un factor de riesgo para desarrollar ECV y empeora el pronóstico en pacientes con ECV. La ECV a su vez aumenta la incidencia de depresión y empeora su pronóstico. Los factores biológicos implicados en ambas patologías incluyen la disfunción autonómica, la inflamación crónica y una mayor reactividad plaquetaria. Se recomienda la detección de la depresión en la consulta cardiológica, usando herramientas como el cuestionario de salud del paciente (PHQ-2). El tratamiento debe ser integral, y combinar antidepresivos, psicoterapia, ejercicio físico y prácticas de mindfulness. Inicialmente centrada en el ejercicio, la rehabilitación cardiovascular (RCV) ha evolucionado para abarcar la modificación del estilo de vida, lo cual ha demostrado mejorar la depresión y el bienestar general en pacientes con ECV..

Palabras claves: Enfermedades cardiovasculares - Depresión - Calidad de la atención médica.

INTRODUCTION

Depression is characterized by persistent sadness and loss of interest in activities normally enjoyed, as well as the inability to carry out daily activities, for at least two weeks (WHO, 2021). (1) According to the World Health Organization, cardiovascular disease (CVD) and depressive disorders are the most common causes of disability, affecting 1 in 5 adults during their lifetime. (2) Major economic and health system indicators reveal rising medical costs, increased utilization of health services, and loss of productivity in patients with these pathologies. (3-6) Furthermore, CVD and depression profoundly impact overall quality of life; (7,8) depression being probably the most important determinant of overall quality of life. There is a bidirectional relationship between CVD and the development of depressive disorders. (9) Depression is a major cause of morbidity and poor quality of life among patients with CVD and is also considered an independent risk factor for major adverse cardiovascular events. (10) Therefore, it is imperative to know that depression is considered a risk factor for the development of CVD in healthy individuals, and implies worse outcomes in those with a diagnosis of CVD .

Rev Argent Cardiol 2025;93:58-65. https://doi.org/10.7775/rac.v93.i1.20864

Received: 06/06/2024 – *Accepted:* 08/02/2024

Correspondence: Cardiovascular rehabilitation unit. Hospital Cuenca Alta, Cañuelas. E-mail: ignacio.davolos@hotmail.com

[1] Cardiovascular Rehabilitation Unit, Hospital Cuenca Alta, Cañuelas, Cañuelas, Argentina
[2] Council on Epidemiology and Vascular Prevention SAC
[3] Heart and Women Area SAC
[4] Council on Psychosocial Aspects SAC

Since 2008, the American Heart Association (AHA) has recommended systematic screening for depression in patients with established CVD, and in 2014, the same cardiological society added that depression should be considered a risk factor for poor outcome in patients with acute coronary syndromes. (1) Currently, the presence of depression after myocardial infarction is independently associated with a 2- to 4-fold increased risk of cardiovascular events at follow-up. (11,12) This risk is directly proportional to the severity of depression. (13) The risk is higher in patients refractory to antidepressant treatment. (14) Similarly, depression is associated with a higher rate of cardiovascular events after coronary artery bypass grafting (CABG). (15)

A recent study among patients who suffered out-of-hospital cardiac arrest showed that those diagnosed with depression or anxiety had higher long-term mortality rates, suggesting that psychological and neurological rehabilitation intervention for survivors may improve long-term survival. (16)

Like chronic noncommunicable diseases, depression is considered a systemic and multidimensional pathology, affecting both body and mind, relationships, work performance and social insertion, with a strong tendency to chronicity and recurrence. (17,18)

METHODS

A review was carried out by selecting the most significant papers related to this topic. The PubMed, Lilacs and Scielo search engines were used, employing the following word combinations in the title and abstract: "depression AND cardiovascular health"; "depression AND cardiology"; "depression AND cardiovascular disease", and their equivalents in Spanish. In addition, the search was supported by the use of the tool offered by Open Alex.

The Consensus on Psychosocial Aspects of Cardiovascular Disease written by the Council on Psychosocial Aspects of the Argentine Society of Cardiology (SAC) was used as reference. (19) In addition, the Position Document for Stress Management written by the working group of the Council on Psychosocial Aspects of the SAC was used. (20)

RESULTS

Pathophysiology

Multiple biological mechanisms have been identified as contributing to the less favorable prognosis observed in patients with both CVD and depression. Among these factors are the influence of unhealthy lifestyle habits, alterations in the autonomic nervous system, imbalance in the neuroendocrine axis, chronic inflammatory processes, insulin resistance, and increased platelet activity. These mechanisms are not only present simultaneously, but also interact with each other in a complex manner, jointly affecting cardiac function and neuropsychiatric condition. Consequently, the co-occurrence of depression and CVD represents a multifactorial interaction that exacerbates the risk of adverse health outcomes. (21)

Patients with depression are more susceptible to engage in behaviors that impair health, such as smoking, physical inactivity, and poor diet, which, together with low adherence to recommended therapeutic interventions, enhances CVD progression and decreases recovery probability. (22,23) Depression and prevalent forms of CVD, such as heart failure and ischemic heart disease, share a strong relationship with autonomic dysfunction, which acts as a trigger for adverse cardiovascular events. This autonomic dysfunction manifests itself through increased sympathetic activity and decreased parasympathetic activity, which, in depressed patients, translates into increased resting heart rate, reduced heart rate variability, and increased blood pressure. These autonomic alterations contribute to structural and functional pathologies such as left ventricular hypertrophy, increased risk of ventricular arrhythmias and endothelial dysfunction, in addition to mismatches in myocardial tissue oxygen supply and demand, factors that increase the risk of myocardial ischemia. (24,25)

On the other hand, depression is closely related to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which responds to stress with the release of glucocorticoids, such as cortisol. In depressed individuals, overstimulation of the HPA axis leads to chronic hypercortisolemia, which is implicated in the development of arterial hypertension and early atherosclerosis. Excess cortisol elevates the risk of thrombotic cardiovascular events and the development of diabetes mellitus, complications that may accelerate CVD progression. (26-28)

Platelet function is also abnormal in depressed patients, who tend to exhibit increased platelet reactivity, reflected in the release of mediators such as platelet factor 4 and beta-thyroglobulin. This intensified platelet activation could act as an additional factor in the predisposition to acute cardiovascular events, by promoting a prothrombotic environment and, consequently, favoring the occurrence of events such as acute myocardial infarction. (29)

Regarding the inflammatory profile, patients with depression usually reveal elevated levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), in addition to other inflammatory markers such as C-reactive protein (CRP) and adhesion molecules. This chronic inflammatory condition is considered an intermediate factor of great relevance in the pathogenesis of CVD, as it promotes endothelial dysfunction, contributes to the development of atherosclerosis, and increases the risk of major cardiovascular events. Inflammation, then, emerges as a key link between depression and CVD, standing out as one of the most influential pathological mechanisms in this association. (30) This confluence of factors suggests that the relationship between depression and CVD is not merely additive

but rather responds to a complex interaction that exponentially increases cardiovascular risk in these patients. In this context, intervention in both physical and psychological factors is crucial to improve the prognosis of these patients and reduce the risk of adverse health outcomes.

Diagnosis

Detection of depression in the cardiology consultation

In recent decades, clinical practice guidelines on CVD prevention suggest that depression should be screened for and treatment offered to patients with clinically significant depression. (31)Similarly, the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure suggest that it is good practice to routinely screen for depression using a validated questionnaire. (32) However, most cardiologists do not believe they have a role in screening for depression in their patients and understand that it is the responsibility of someone else, such as a nurse, rehabilitation program, or family physician. (33) Given that depression is the main factor of quality of life in cardiac patients, cardiologists should not shirk their responsibility to ensure that depression is detected.

Individuals who have had an acute coronary syndrome have a prevalence of depression two to three times higher than that of the general population. Depression is often repressed or suppressed in the hospital because of the initial denial of affect. Therefore, patients should be re-screened for depression one to two months after the acute event. In studies as early as 50 years ago, non-deniers seemed to shed their fears more slowly and let down their guard more quickly than deniers. As discharge approached, the trajectories of anxiety and depression scores increased. (34,35) Patients with chronic heart failure have a frequency of depression 3 to 5 times higher than that of the normal population. Therefore, all these patients should be examined at least once a year.

Most studies have focused primarily on major depression or on a self-report scale intended to "diagnose" major depression. Scales are tools to evaluate and assess the severity of the depressive condition, adding the impact of the depression on the patient's life to the subjective impression of the professional. They will also enable to monitor symptoms and evaluate response to treatment. Some are used as a first screening step requiring a subsequent "clinical diagnosis". Others have satisfactory psychometric properties to "diagnose" major depressive disorder in a single step. Self-report questionnaires include the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Cardiac Depression Scale (CDS), and the Center for Epidemiologic Studies Depression Scale-10 (CES-D). Most of these scales are available and have been validated in many different languages. (36-40) Currently, their use as diagnostic tools is not recommended.

An AHA scientific advisory group suggested that the PHQ-2 may be the most useful questionnaire for screening patients with CVD. (41) The PHQ-2 consists of two items that ask about patients' mood and their experience of anhedonia in the last 2 weeks. (Figure 1) Patients who screen positive (score ≥ 3) should be evaluated with the 9-item patient health questionnaire (PHQ-9). The PHQ-9 expands the PHQ-2 to include seven additional DSM-IV symptoms of depression. (42,43) Those who are tested positive for depression in the PHQ-9 should be treated with a multidisciplinary, team-based approach that includes primary care providers and mental health clinicians. (44)

Treatment

Interventions in patients with cardiovascular disease

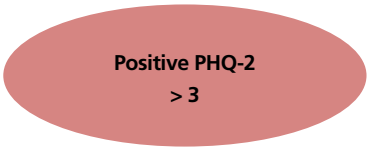
Treatment of depressive disorders in patients with CVD includes primary prevention and secondary prevention strategies. Primary prevention focuses on identifying possible risk factors for depression. These are clinical and symptomatic factors that should alert the treating professional to the existence of a possible depressive disorder. (45,46) (Table1) There are a series of recommendations for these patients that range from the application of selective physical activity programs, healthy diet, sleep hygiene, control of exposure to screens, to meditation and/or mindfulness (which promotes focusing exclusively on the present)

The approach to depression in adults with CVD should be comprehensive and include all psychotherapeutic, psychosocial and pharmacological interventions that contribute to improving well-being and functional capacity. (21) Antidepressants are used more frequently than psychological or social interventions, although mild depression usually responds positively to psychotherapy and other therapeutic alternatives. The search for immediacy and quick resolutions leads to the use of pharmacotherapy as the first measure, although studies have shown that the combination of psychotherapy, antidepressants, physical exercise and meditation or mindfulness practices provide better results in the short and long term.

Non-pharmacological treatment of depression

The effectiveness of psychological and behavioral interventions in improving cardiovascular outcomes has shown variability, reflecting the complexity of the interaction between psychological treatment and cardiac health outcomes. Science-based therapies, such as cognitive-behavioral therapy (CBT), have shown superior results compared with usual care in reducing the intensity of depressive symptoms in patients with heart failure and a diagnosis of depression, suggesting a benefit in the co-management of both conditions. (47) During a 2-year follow-up period, a meta-analysis that included clinical trials focused on psychological and behavioral interventions revealed that psychotherapy is associated with a significant reduction in mortality, up to 28% lower compared to

How often have you had discomfort due to the following problems?	Never	Several days of the week	More than half the days of the week	Most days of the week
Little interest in the last 2 weeks	0	1	2	3
Negative feelings, depression or unhappiness in the last 2 weeks	0	1	2	3



In case of a positive PHQ-2, continue with the PHQ-9 questionnaire.

Fig. 1. Two-item Patient Health Questionnaire (PHQ-2).

Clinical factors	Symptomatic factors
-History of unexplained depression	-Chronic pain
-Family history of mood disorder	- Fatigue
-Psychosocial adversity. Complex grief	-Sleep disorders
-Chronic diseases (DM, CVD, neurological)	-Anxiety
-Psychiatric pathology	-Peripartum period
-Hormonal changes in women	

Source: Parikh SV, et. al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder. The Can J Psychiat. 2016; 61(9):524-39. (45). CVD: cardiovascular disease; DM: diabetes mellitus

Table 1. Clinical and symptomatic factors leading to suspicion of possible depressive disorder.

control groups. (48) Furthermore, the benefits of psychological intervention were more evident in patients who started treatment within the first 2 months after an acute cardiac event, highlighting the importance of the time of intervention in treatment efficacy (49-51).

The ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) study was a randomized clinical trial that explored the effects of CBT in post-myocardial infarction patients with symptoms of depression or low social support. Patients were assigned to receive either conventional care or a CBT intervention, and the results showed significant improvements in psychosocial indicators, such as a reduction in levels of depression and an increase in perceived social support in the treated group. However, these psychosocial benefits did not translate into improved event-free survival, suggesting that although CBT improves certain aspects of quality of life, its impact on mortality or recurrent cardiovascular events in this specific setting may be limited. (52)

Physical exercise has emerged as an effective additional therapy against depression in patients with CVD. In a secondary analysis of the ENRICHD study, patients with depression who maintained adherence to regular physical exercise 6 months after acute myocardial infarction had 38% to 52% lower rates of major events (fatal and nonfatal) during a 4-year follow-up compared with those who did not exercise consistently. These findings highlight the potential value of exercise as an adjunctive measure to reduce mortality and the incidence of new infarctions in post-infarction patients, especially in those at increased risk of adverse events due to depressive symptoms or lack of social support. (53)

In addition, practices such as meditation and mindfulness, specifically mindfulness-based cognitive therapy, have been recommended to prevent the recurrence of depressive symptoms. Several studies have shown that the latter can help patients manage recurrent depressive symptoms and reduce emotional reactivity, which could offer additional benefits in emotional regulation of patients with CVD, although the evidence regarding its direct impact on cardiovascular health is still under study. (54-67)

Altogether, these interventions suggest that a comprehensive approach including psychological treatment, physical exercise, and mindfulness practices may contribute to the improvement of mental condition and reduce the risk of recurrent cardiac events, although further studies are required to fully understand the magnitude of their effects on mortality and CVD progression in this group of patients.

Role of cardiovascular rehabilitation

Although cardiovascular rehabilitation (CVR) was initially introduced as an exercise-focused intervention, its scope was subsequently broadened to become a more comprehensive lifestyle intervention, with

exercise as the main component and four additional elements including dietary modification, risk factor management, stress reduction, and patient education. This development is relevant because of the growing evidence available suggesting that lifestyle change, including sleep hygiene, either individually or in combination with exercise, can contribute to improving depression. (68-70) Even in countries with limited medical resources, the virtual (home-based) modality has demonstrated positive impact on both quality of life and psychological well-being. (71) In a recent experience in our country, it was observed that the positive effects of referral to Mental Health complemented the benefits of CVR. (72) Undoubtedly, the improvement in the individual's mood favors adherence and compliance with rehabilitation treatment

Pharmacological treatment of depression

When addressing psychopharmacological treatments for depression in patients with CVD, it is essential to rely on sound clinical guidelines to guide daily medical practice. These include the Canadian Network for the Management of Mood and Anxiety Disorders (CANMAT) Guidelines for the Management of Depression and the UK National Institute for Health and Care Excellence (NICE). (45,46) The NICE guidelines are particularly valuable because of their comprehensive review of scientific evidence. They recommend the use of antidepressants in cases of moderate to severe depression or when symptoms persist without improvement. Within the antidepressants, they suggest selective serotonin reuptake inhibitors (SSRIs) as the preferred option for efficacy, although no SSRI has demonstrated superiority over another in general terms. (73-77) However, the characteristics of each drug allow choosing the most appropriate one for each patient's profile. (78)

The effectiveness of SSRIs in patients with CVD has been supported in clinical trials. The SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) trial led by Glassman et. al., evaluated their use in 369 post-ACS patients with major depression. Although the Hamilton Depression Scale (HAM-D) scores showed no significant differences between the sertraline and placebo groups, sertraline-treated patients had higher response rates and clinical improvement in the overall group. In addition, participants with a history of depressive episodes or with depressive disorders of greater severity experienced a more pronounced improvement in their HAM-D scores. (74) Pizzi et. al. also observed that sertraline, compared with placebo, produced a significant improvement in depression scores in patients with coronary artery disease after 20 weeks. (75) In the UPBEAT (Understanding Prognostic Benefits of Exercise and Antidepressant Therapy for Persons with Depression and Heart Disease) study, sertraline, aerobic exercise, and placebo were compared in a sample of 101 patients with coronary artery disease and depressive symptoms. Both the sertraline and exercise groups showed significant improvements in depressive symptoms compared to placebo, with no considerable difference between the effects of sertraline and exercise, reinforcing the value of exercise as an adjunct in the treatment of depression in this population. (77)

Another recent study with an extended follow-up of 8.1 years and a sample of 300 patients showed that escitalopram reduced the incidence of major adverse cardiac events after acute coronary syndrome (ACS) compared to placebo (40.9% vs. 53.6%) after 24 weeks, confirming its benefit in this context. (79)

The EsDEPACS (Escitalopram for Depression in ACS) trial, which evaluated 300 patients with ACS and depression, showed that escitalopram was superior to placebo in reducing depressive symptoms at 24 weeks and up to 1 year of follow-up. (80) These results reinforce the safe and effective profile of SSRIs for the treatment of depression in patients with recent ACS and stable coronary artery disease, making them suitable for the management of depression in this high-risk group. In conclusion, the evidence supports the use of sertraline and escitalopram as treatments of choice in patients with depression and cardiovascular disease, providing a benefit both in the reduction of depressive symptoms and in the reduction of adverse cardiac events.

CONCLUSION

The relationship between depression and cardiovascular health is an area of growing interest in medical research, with an extensive body of evidence supporting its bidirectional link. Depression can exacerbate morbidity and mortality associated with cardiovascular disorders, in addition to affecting the quality of life and prognosis of these patients. It is imperative to adopt a multidimensional approach that includes mental health assessment and treatment strategies in the context of cardiovascular care. The search for immediacy and quick resolutions leads to the use of pharmacotherapy as the first treatment measure, although studies have mostly evidenced that the combination of psychotherapy, antidepressants, physical exercise and contemplative practices, provide better short- and long-term outcomes. Overcoming mental health disparities and barriers involves health policy interventions, education, training, innovation in medical care, and diversification of cardiology.

In conclusion, recognition of the interaction between depression and cardiovascular health is essential to improve outcomes and encourage a multidisciplinary approach to care appropriately integrating mental and cardiovascular health.

"*Every affection of the mind accompanied by pain or pleasure, hope or fear, produces an agitation whose influence extends to the heart.*"

Willam Harvey

Conflicts of interest

None declared.

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

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LETTER TO THE EDITOR

Cardiomyopathy and Obstructive Coronary Artery Disease: Causality or Chance?

Miocardiopatía y enfermedad coronaria obstructiva: ¿causalidad o casualidad?

LUCAS SAN MIGUEL[1], ENRIQUE SODOR[1], OSVALDO H. MASOLI[1, MTSAC]

Detection of coronary artery disease is essential in the evaluation of patients with dilated cardiomyopathy and is a common practice in our setting. However, it is important to emphasize that the presence of obstructive coronary artery disease, even if extensive, does not necessarily indicate the presence of ischemic cardiomyopathy, as both conditions may coexist without a causal relationship. (1)

Bawaskar et al. recently published a registry of 3023 patients with documented obstructive coronary artery disease defined as ≥ 70% stenosis in ≥ 1 of the left anterior descending coronary artery (LAD), circumflex artery, or right coronary artery and/or ≥50% stenosis of the left main coronary artery identified on invasive coronary angiography, who underwent cardiac magnetic resonance (CMR) imaging. In this study, 9.3% of patients had non-ischemic cardiomyopathy, and this subgroup had higher risk of cardiovascular events during follow-up. (2)

STUDIES EVALUATING REVASCULARIZATION IN ISCHEMIC CARDIOMYOPATHY

In the STICH study published in 2011, patients with left ventricular ejection fraction (LVEF) less than or equal to 35% and extensive coronary artery disease amenable to coronary artery bypass grafting were randomly assigned to revascularization surgery or medical treatment, with no significant differences in death from any cause at 56 months. (3) The possible causes of the lack of response to revascularization identified in the viability sub-study were the use of methods other than CMR imaging for the assessment of viability, and the probable inclusion of patients with ventricular remodeling with a low probability of reversal, as evidenced by the high ventricular volumes recorded. (4)

In the REVIVED study published in 2022, patients with LVEF less than or equal to 35%, extensive coronary artery disease amenable to percutaneous coronary intervention and viability in at least 4 segments, were randomly assigned to percutaneous coronary intervention or optimal medical treatment with no significant differences in the composite end point of death from any cause or heart failure at 41 months. Although viability was assessed using CMR imaging in 70% of the cases, again patients with excessively high volumes were not excluded and any dysfunctional segment with less than 25% late gadolinium enhancement was considered viable. (5)

A CASE THAT POSES A DISTURBING QUESTION

In a patient with 3-vessel disease and a dilated left ventricle with global hypokinesia and severe systolic dysfunction, the absence of necrotic tissue on CMR imaging (Figure 1) suggests that the myocardium is entirely viable. However, ventricular function is unlikely to improve after revascularization because the likelihood of ischemic cardiomyopathy is very low.

Let us now imagine that we are recruiting patients for the REVIVED study. Are there any inclusion or exclusion criteria to consider this patient not eligible? This case represents a clear example of a patient with non-ischemic cardiomyopathy who could have been included in the study.

CLARIFYING BASIC CONCEPTS

Cardiomyopathy, ischemic heart disease or dual mechanism?

By definition, cardiomyopathy is a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease that may explain the cardiac dysfunction. (6) It is essential to emphasize that cardiomyopathies can coexist with ischemic heart disease, valvular heart disease or hypertension and, therefore, the presence of one condition does not exclude the other. Therefore, it is essential not only to assess the presence of obstructive coronary artery disease, but also to demonstrate that it explains the extent of left ventricular dysfunction.

Rev Argent Cardiol 2025;93:66-69. https://doi.org/10.7775/rac.v93.i1.20856

Received: 10/20/2024 – *Accepted:* 11/28/2024

Correspondence: Lucas San Miguel. Jerónimo Salguero 560. (C1177AEJ). Autonomous City of Buenos Aires, Argentina. E-mail: lucasanmiguel@gmail.com

[1] Especialidad transversal Cardioimagen. TCba, Autonomous City of Buenos AIres, Argentina

What do we mean when we talk about viability?

Viable myocardium is defined as myocardial tissue with reversible dysfunction caused by coronary artery disease. (7) Two main mechanisms are responsible for dysfunctional myocardium at rest with viability: stunning and hibernation. (8,9) Myocardial stunning is a phenomenon of reversible myocardial contractile dysfunction after a short period of ischemia followed by restoration of perfusion. Myocardial stunning occurs during the transient period when perfusion has normalized but myocardial contractile dysfunction persists. (10) A common example in clinical practice is the transient ventricular dysfunction that occurs after reperfusion during an acute coronary syndrome.

On the other hand, the hibernating myocardium results from prolonged hypoperfusion at rest associated with myocardial metabolic demand that surpasses the coronary flow reserve. This type of myocardium presents persistent dysfunction at rest due to chronic insufficient coronary artery flow and may be partially or fully reversible following revascularization procedures. (11) A typical example of hibernation in clinical practice can be observed in chronic coronary artery occlusions with collateral circulation and minimal necrotic tissue.

Can we talk about viable myocardium in the absence of hibernation or stunning?

This question leads us to one of the conceptual errors with the greatest impact on both daily practice and the establishment of criteria for the selection of populations in randomized studies: ischemic myocardium is not usually considered in the search for viable myocardium. Ischemic myocardium is characterized by normal wall motion, metabolism and perfusion at rest; however, it becomes dysfunctional under stress conditions due to vascular impairment. If we understand this concept, it is evident that a non-necrotic myocardial segment can be ischemic. The only way to determine this is to perform a stress protocol to induce myocardial ischemia, either by stress CMR, gated SPECT or stress echocardiography.

Consequently, if the STICH and REVIVED studies did not quantify ischemia, how can we differentiate ventricular dysfunction due to coronary artery disease from cardiomyopathy with associated obstructive coronary anatomy?

Can we speak of alive but non-viable myocardium?

Hibernation and stress-induced ischemia represent different spectra of myocardial involvement due to chron-

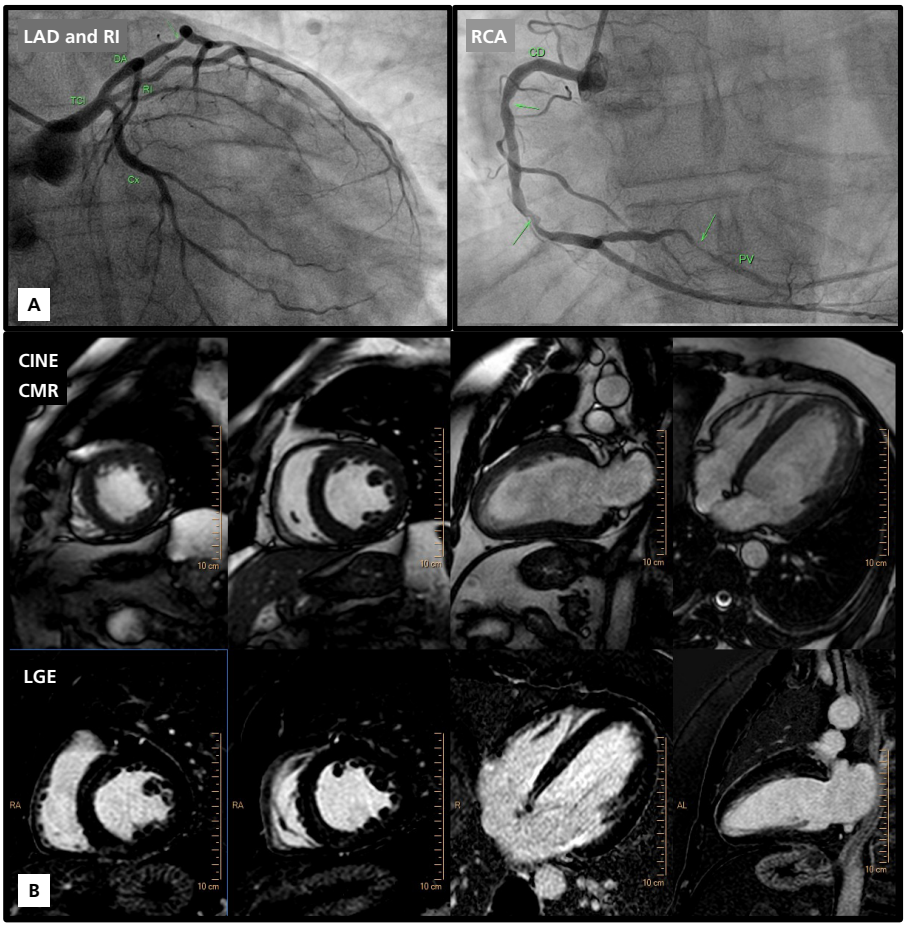

Fig. 1. Images of a 64-year-old patient hospitalized for congestive heart failure. A) Coronary angiography (CA) showing three-vessel disease: severe involvement of the left anterior descending artery (LAD) , ramus intermedius (RI) and right coronary artery (RCA). B) Cardiac magnetic resonance (CMR) revealing a dilated left ventricle with global hypokinesia, normal wall thickness and absence of late gadolinium enhancement (LGE), interpreted as non-ischemic necrotic cardiomyopathy.

ic coronary artery disease. (12) Therefore, they should be considered within the spectrum of what we call clinically significant viability. In other words, a mass of myocardium worthy of revascularization. Therefore, in the context of a dilated and globally dysfunctional left ventricle, the presence of significant percentages of myocardium without necrosis, but with neither hibernation nor ischemia, indicates that we are dealing with alive (non-necrotic) but non-viable myocardium. This is because the etiology of this dysfunction is not coronary artery disease, and therefore revascularization will not improve ventricular function.

A PROPOSAL TO FACILITATE DAILY PRACTICE

According to the Argentine National Registry of Cardiac Resonance (RENAREC), viability evaluations account for approximately 5% of CMR imaging requests in our country. (13) To ensure the maximum utility of this resource, which is difficult to access in our environment, we propose the adoption of a unified terminology that is simple to implement. This terminology could help clinical cardiologists who refer patients for cardiovascular imaging tests intended to assess myocardial viability to understand this concept. We suggest referring to clinically significant viability which means hibernating or ischemic myocardium, excluding myocardium that is alive but not affected by coronary artery disease (Table 1).

As previously mentioned, it is imperative to clarify that, with certain exceptions, stunning is a phenomenon predominantly associated with post-reperfusion dysfunction following acute coronary syndrome. This phenomenon is uncommon in cases of chronic coronary ventricular dysfunction. Consequently, myocardial viability in an outpatient setting primarily refers to situations of hibernation or ischemia.

FINAL COMMENT

When referring to viable myocardium or clinically significant viability, we assume that ventricular dysfunction results from coronary artery disease. As with other medical specialists, cardiologists formulate diagnostic interpretations that are subject to debate. Therefore, we propose to talk about viable myocardium only under the suspicion of underlying coronary artery disease. It is essential to have data derived from clinical examination and imaging tests that support our hypothesis of myocardial dysfunction due to obstructive coronary artery disease (causality) and that it is not a mere coincidence between the two conditions.

For this purpose, we believe that a proper diagnostic approach should include the assessment of myocardial ischemia and not be limited only to the absence of necrosis on CMR imaging with gadolinium-based contrast agent or resting myocardial perfusion scan.

We cannot claim an improvement in ventricular function after revascularization without first understanding the pathophysiology of ventricular dysfunction.

Conflicts of interest

None declared.

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

Table 1. Proposal for a simplified nomenclature for viability.

	Significant necrosis	Coronary artery disease	Hibernation or significant ischemia	Improves with revascularization
Clinically significant viability	NO	YES	YES	YES
Non-viable alive myocardium	NO	NO	NO	NO
Non-viable necrotic myocardium	YES	YES	NO	NO

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Shaggy Aorta: Ideal Substrate for Disaster

Aorta Shaggy: sustrato ideal para la fatalidad

KEVIN VELARDE-ACOSTA[1], JOSH YEFRY MOSCOSO RAMÍREZ[1], PAOL JHULLIAN ROJAS[1,2], LUCY SUSANIBAR[1], ANGELA CACHICATARI[3], ROBERTO BALTODANO-ARELLANO[4]

INTRODUCTION

The aorta, the largest artery in the body, serves as an elastic conduit essential for transmitting pressure throughout the arterial bed. This blood vessel, as well as those of medium and small caliber, is susceptible to the development of atherosclerosis due to a combination of acquired, hereditary, sex- and age-related factors. In addition to mechanically obstructing blood flow, the atheromatous plaque poses risks of rupture leading to obstructive or embolic vascular thrombosis. Shaggy aorta (SA) represents an extreme manifestation of aortic atherosclerosis, characterized by extensive and severe atheromatous disease featuring scattered ulcers, soft, loosely held debris, weakened medial arterial layer and tendency towards thrombus formation. (1) While the precise etiology behind the heightened vulnerability of the aorta remains elusive, it is believed to involve complex interactions between hydrodynamic patterns affecting the aorta and genetic predispositions to atherogenesis. (2) The clinical importance of this pathology relies on the various syndromes that can develop from its etiopathogenesis, which generate great morbidity and mortality in affected individuals, and its utility as a risk factor of operative mortality. Furthermore, the advancement of diagnostic tools underscores the importance of multimodality of images in achieving timely and accurate diagnoses, thereby facilitating appropriate decision regarding patient management. Within this context, we present three clinical cases exemplifying the nature of this disease and the spectrum of different syndromes associated with SA. We also highlight the various imaging tools that allowed us to make the diagnosis and its management.

CLINICAL CASES

Case 1: An 80-year-old female patient was admitted to the emergency room due to 3 days of oppressive, severe, self-limited retrosternal chest pain, associated with palpitations and neurovegetative symptoms, after moderate physical exertion. Medical history included hypertension and dyslipidemia.

On physical examination, the patient was tachycardic with all other vital signs preserved. Cardiac auscultation revealed rhythmic heart sounds of good intensity without murmurs or aggregate sounds. Additionally, no jugular ingurgitation or hepatojugular reflux was found. The electrocardiogram showed sinus rhythm with ST-segment elevation >1 mm and biphasic T waves in leads V1-V4. Laboratory tests revealed troponin I elevation (3.113 ng/mL, normal value <0.028 ng/mL). The patient was admitted with a diagnosis of 3-day evolving anterior Q infarction. During her hospitalization the patient developed chest pain recurrence associated with T-wave inversion in precordial leads V1-V6 and new troponin mobilization; therefore, invasive angiography was performed. During the attempt to cannulate the left coronary artery, with a JL 3. 5 5F catheter, contrast retention was detected in the ascending aorta. CT angiogram showed double lumen at the ascending aorta with presence of dissection flap at the sinotubular junction (without compromising the ostia of the coronary arteries) with ascending trajectory to the proximal aortic arch (Figure 1), and extending through the brachiocephalic trunk to the proximal segment of the subclavian artery (at the level of the humeral head). Diffuse atheromatosis was also observed at the aortic arch with an image suggestive of intraluminal thrombus. A diagnosis of SA, Stanford "A" aortic dissection, brachiocephalic trunk and right subclavian artery dissection was made. Emergency surgical treatment was indicated but unfortunately the patient died during the intervention. Histopathological study of the affected ascending aorta was performed (Figure 2), showing circumferential atheromatosis and the entrance flap of the aortic dissection.

Rev Argent Cardiol 2025;93:70-76. https://doi.org/10.7775.rac.v93.i1.20587

Correspondence: Kevin Velarde-Acosta. Email: kevin_velarde.93@hotmail.com

[1] Clinical Cardiology Department; Hospital Guillermo Almenara Irigoyen – EsSalud, Lima, Perú
[2] Interventional Cardiology Department; Hospital Guillermo Almenara Irigoyen - EsSalud, Lima, Peru; Clinical Cardiology Department; Hospital Guillermo Almenara Irigoyen – EsSalud, Lima, Perú
[3] Cardiac imaging area of Cardiology Department, Hospital Guillermo Almenara Irigoyen – EsSalud, Lima, Perú
[4] School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru; Cardiac imaging area of Cardiology Department, Hospital Guillermo Almenara Irigoyen – EsSalud, Lima, Perú

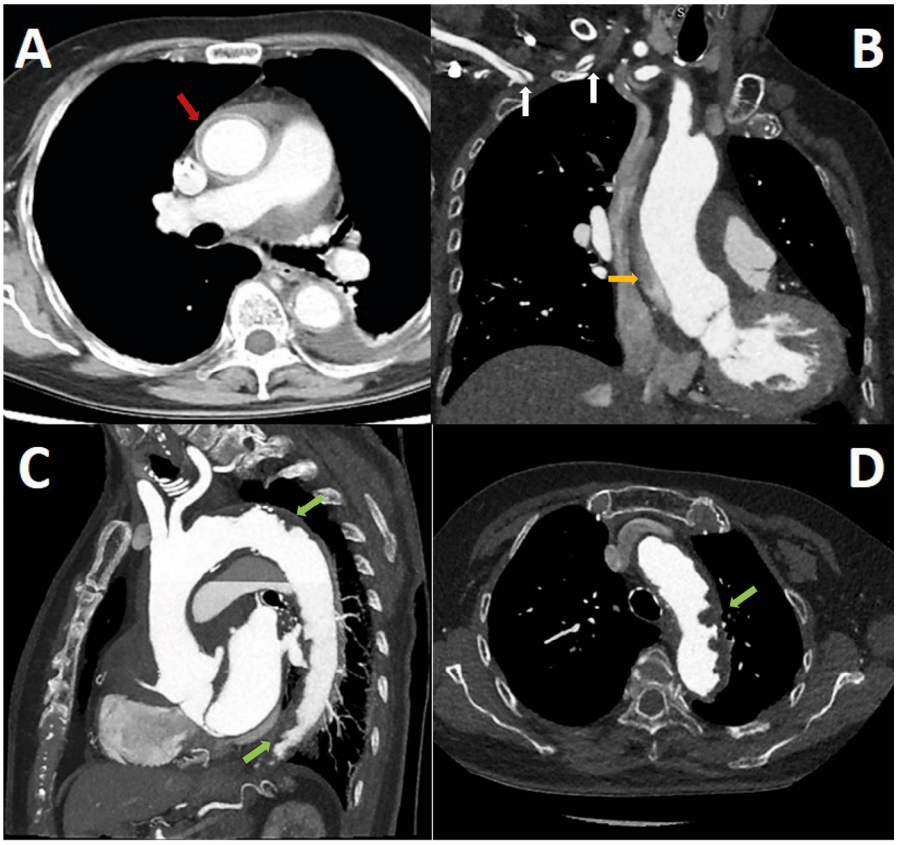


Fig. 1. CT angiogram. **A**, **B**. Dissection flap is seen at the sinotubular junction (red arrow), with ascending trajectory to the proximal aortic arch (orange arrow) and extending through the brachiocephalic trunk to the proximal segment of the right subclavian artery (white arrows). **C**, **D**. Complicated plaques in the aortic arch and descending aorta (green arrows). Diffuse atheromatosis is observed at the aortic arch with an image suggestive of intraluminal thrombus.

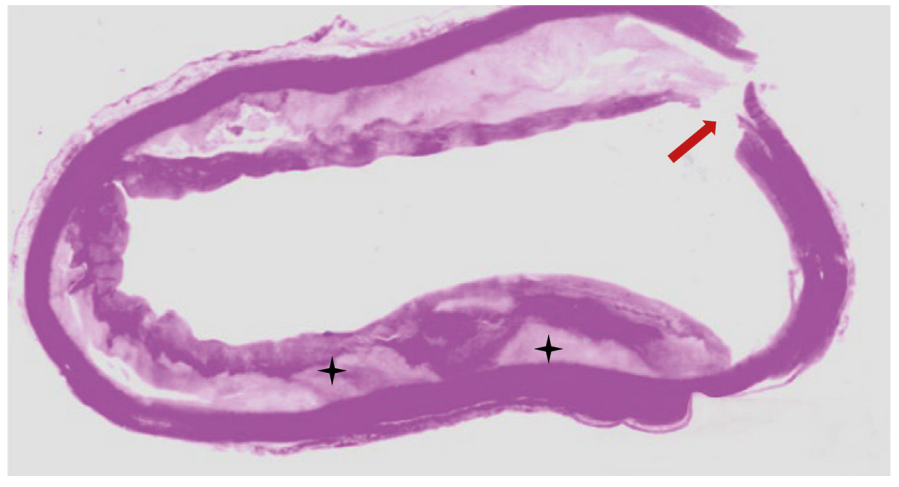


Fig. 2. Microscopic view of atheromatous ascending aorta. The patient underwent emergency Bentall de Bono surgery for acute aortic dissection Stanford A; however, she died during the intervention. Circumferential atheromatous plaque in ascending aorta with cholesterol deposits in the subintimal layer (black asterisks). The aortic dissection entry flap can be seen (reddish arrow).

Case 2: A 76-year-old man with a history of arterial hypertension, cigarette smoking, atrial flutter, abdominal aortic aneurysm corrected by bilateral aortofemoral bypass, referred intermittent claudication of the lower limbs, predominantly on the left, when walking less than 100 meters (stage IV according to the Fontaine classification). He was admitted on an outpatient basis for peripheral revascularization.

On physical examination he had preserved vital signs, and thinned, cold, pale lower extremities with trophic changes. On cardiac auscultation heart sounds were arrhythmic, of good intensity, associated with a III/VI holosystolic murmur located in mitral focus, radiating to the axilla. On vascular examination both femoral pulses were preserved; however, popliteal, posterior tibial and pedal arterial pulses were absent bilaterally. The rest of the physical examination was unremarkable. The electrocardiogram showed atrial flutter rhythm, complete left bundle branch block and ventricular premature complexes. The presurgical evaluation was complemented with transesophageal echocardiography (TEE) due to poor acoustic window

in the transthoracic approach. The relevant findings were biventricular systolic dysfunction with left ventricular ejection fraction (LVEF) 38%, and right ventricular fractional area change (FAC) 29% due to diffuse global hypokinesia; dilatation of both atria: left atrial volume index (LAVI) 54 ml/m2 and right atrial (RA) area 20 cm2; and severe mitral insufficiency: effective regurgitant orifice area (EROA) 0.4 cm2, regurgitant volume (RV) 65 ml and regurgitant fraction (RF) 68%. Likewise, evaluation of the aorta showed multiple complex atheromatous plaques distributed circumferentially and extending from the aortic arch to the descending aorta (Figure 3). Computed tomography aortic angiogram showed multiple ulcerated atheroma plaques arranged in tandem along the entire course of the aortic arch and descending aorta, associated with low-attenuation images suggestive of thrombi (Figure 4). The common iliac arteries presented multiple internal and external calcified plaques that conditioned severe stenosis predominantly on the left and permeable aortofemoral bypass.

Because of these findings, coronary revascularization and mitral valve replacement with subsequent peripheral revascularization was decided. However, the patient did not tolerate the cardiac surgery and died during the procedure.

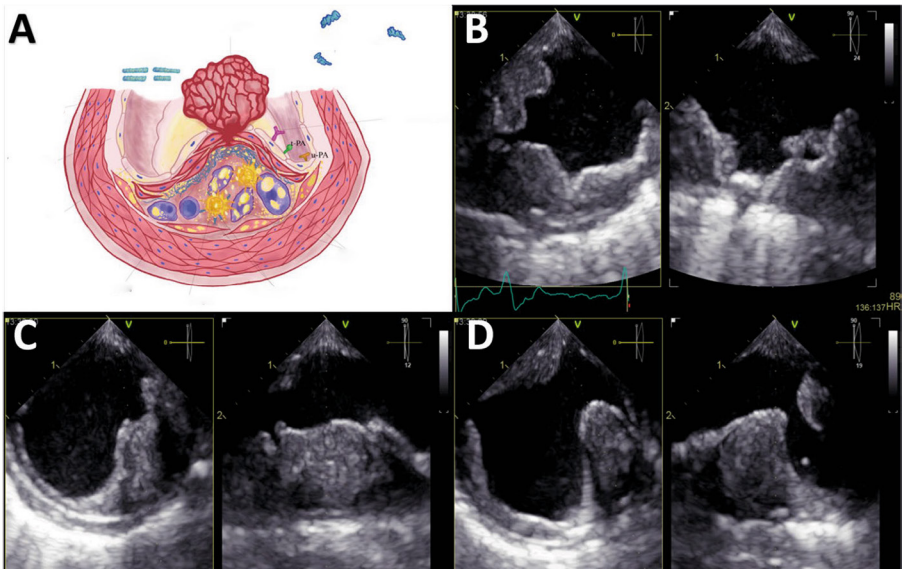
Case 3: An 84-year-old male patient was admitted at the emergency room with acute diarrhea associated with severe diffuse abdominal pain. Medical history included hypertension, diabetes mellitus, chronic kidney disease and senile dementia.

Physical examination revealed tachycardia, pale, earthy skin, sweating and capillary refill time >2 sec. Cardiac sounds were rhythmic and tachycardic; no murmurs were identified. On pulmonary auscultation, the vesicular murmur was preserved in both lung fields. Laboratory tests showed severe anemia (Hb: 6.9 mg/dL), leukocytosis with left shift, elevated azotemia (creatinine 3.11 mg/dL, urea 134 mg/dL) and hyperlactacidemia. A thoracoabdominal computed tomography (CT) angiography was requested, revealing a SA with severe parietal calcification associated with an abdominal aortic aneurysm of up to 85 mm, with presence of mural thrombosis (Figure 5). Mesenteric ischemia was suspected, with embolic source coming from complex atheromatous aortic plaques or abdominal aortic aneurysm. The patient was admitted to the operating room for an exploratory laparotomy. However, he died during the operative procedure.

DISCUSSION

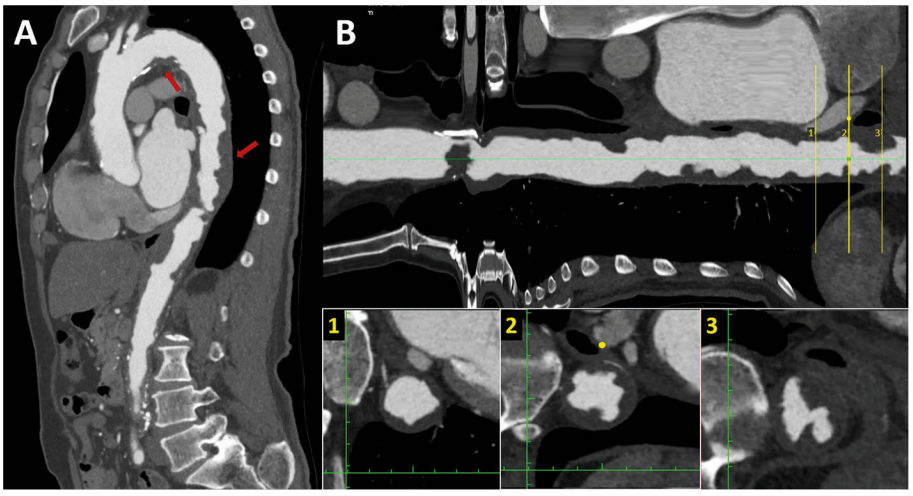
Definition

A uniform definition of SA has not been clearly established due to the different diagnostic methods used. However, some definitions have been postulated. SA is a descriptive term that has been used for atherosclerotic aortic segments, which show localized or diffuse irregularity and typical obstructive and spiculated images that are visualized with different diagnostic tools. The shagginess is imparted by complications in



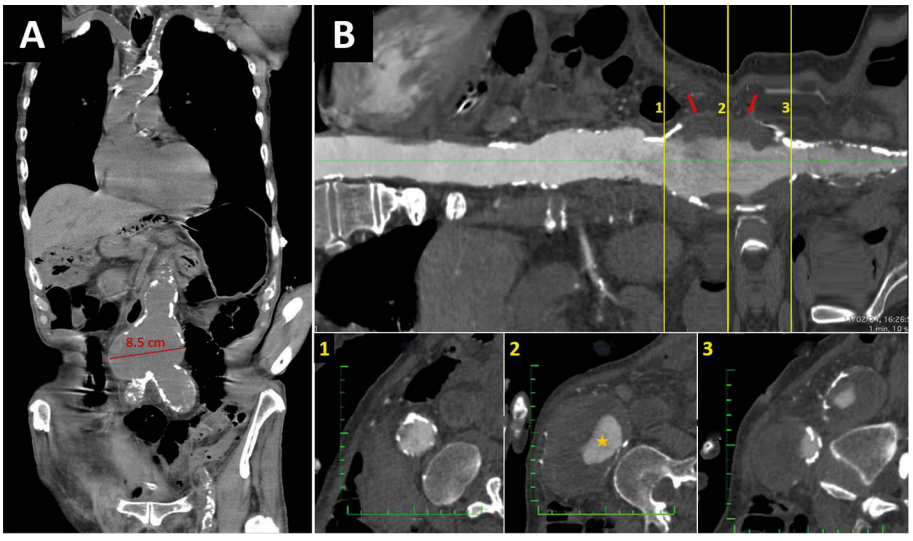
EC: endothelial cell; PAI-1: type 1 plasminogen activator inhibitor; TEE: transesophageal echocardiography; t-PA: tissue-type plasminogen activator; u-PA: urokinase-type plasminogen activator.

Fig. 3. A. After rupture of the fibrous cap, coagulation molecules from the bloodstream come into contact with foam cells, tissue factor, and microparticles derived from apoptotic atheroma cells, triggering thrombus formation in the ruptured plaque. The thrombotic equilibrium will determine whether plaque rupture will culminate in the formation of a persistent, distant-migrating thrombus or in its dissolution. **B**. TEE - Proximal third of the descending aorta. Orthogonal images showing extensive mural thrombotic formation of irregular border that occupies up to one third of the arterial lumen, with small movable elements on its surface in the long axis. **C**. TEE - Middle third of the descending aorta. Orthogonal images showing crescent-shaped thrombus in the short-axis view. **D**. TEE - Distal third of the descending aorta. Orthogonal images of wedge-shaped thrombus. Secondary thrombotic elements in opposite position to the initial one.



AL: anterior and left; CT: computed tomography; HU: Hounsfield units;; LPI: left posterior and inferior; PR: posterior and right; RAS: right anterior and superior.

Fig. 4. A. CT angiogram - Sagittal section of the aorta. Multiple atheromatous plaques, in tandem, along the entire course of the aortic arch and thoracoabdominal aorta (red arrows), predominantly in the supradiaphragmatic portion. **B**. Longitudinal reconstruction of the aorta. The cross section shows plaques with low attenuation coefficient (35 HU), irregular borders (lower central box), ulcerated and associated with images suggestive of thrombus (lower right box).



AR: anterior and right; CT: computed tomography; LA: left and anterior; PI: posterior and inferior; RP: right and posterior.

Fig. 5. A. Non-contrast thoracoabdominal CT - Coronal section. Severe calcification of the aorta is observed, predominantly in the aortic arch and abdominal aorta. Also, there is an aneurysmal dilatation of the infrarenal aorta with a maximum diameter of up to 8.5 cm. **B**. Longitudinal reconstruction of the aorta. The transverse sections at the level of the abdominal aortic aneurysm demonstrate the calcification of the abdominal aneurysm wall along with the presence of extensive mural thrombus (red arrows) and a reduced luminal diameter (orange star).

the form of multifocal ulcerations, calcification, and/or overlying thrombi. (3) Another definition used for the SA is the appearance of a hemp-like fluff on the inner surface of the aorta due to severe diffuse atherosclerotic lesions in the aorta. Clinically, it is often referred to an imaging finding of contrast-enhanced CT or echography. (1)

Epidemiology and pathophysiology

The prevalence and incidence of SA in the general population is unknown. However, there are some reports on the prevalence and incidence of SA in certain risk groups. Thus, in one study it was found that 48/447 patients (11%) having elective aortic abdominal aneurysm repair had SA. Also, the incidence of major complications and mortality was 4.1 times higher in patients with SA than in patients without severe atherosclerotic aorta. (4) In another study, it was reported that the prevalence of SA in patients undergoing total aortic arch replacement was 19 %. (5) Likewise, it has been seen that most of the patients with SA are elderly, predominantly males with comorbid conditions like hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary and peripheral artery disease, and stroke. (3)

Severe atherosclerotic degeneration of the aorta is a multifactorial process in which various modifiable and of the organism itself (non-modifiable) risk factors intervene. The initial event that gives rise to ath-

eroma formation is unknown; however, the "response to injury" hypothesis considers atherosclerosis as a chronic response of inflammation and scarring in the arterial wall after endothelial injury with subsequent evolution of the atheroma due to the interaction of modified lipoproteins, the immune system and the smooth muscle cells of the arterial wall. (6)

After accumulation of lipoprotein particles in the subintimal space and their binding to proteoglycans, these particles are affected by oxidative stress (oxidation and glycation). These modified lipoproteins induce the synthesis of cytokines that promote chemotaxis of inflammatory cells (monocytes, T lymphocytes), phagocytizing this material. These macrophages (foam cells) are a source of new mediators that favor the migration of smooth muscle cells toward the intima, which are responsible for the elaboration of the extracellular matrix that accumulates within the atherosclerotic plaque (allowing its growth). (2)

The spatial heterogeneity of atherosclerotic lesions in patients with SA has been difficult to explain. It is believed that this is not only the result of a response to the different hydrodynamic patterns that affect the aorta (normal pulsatile lamellar flow generates greater shear force that is associated with lower atherogenicity), but also of a genetic predisposition specific to the individual. Thus, those with higher expression of genes encoding for the enzymes superoxide dismutase, nitric oxide synthase and Kruppel-type factor 2 are less predisposed to severe atherosclerotic degeneration, by reducing the formation of oxygen free radicals, inhibiting proinflammatory nuclear factor-kappa B (NF-kB) and favoring vasodilatation. (2)

Diagnostic implications

The clinical importance of this pathology lies in the various syndromes that can develop from its etiopathogenesis, which generate great morbidity and mortality in affected individuals. The presence of severe atherosclerotic degeneration in the aorta will be associated with an increased risk of developing aortic aneurysms, aortic dissection, thromboembolism or peripheral atheromatous embolization (to the digestive system, renal, spinal cord or peripheral limbs manifested as SA syndrome), ischemic stroke and penetrating atherosclerotic ulcer (CENTRAL ILLUSTRATION). (7) Similarly, SA is an independent and significant risk factor for operative mortality.

The predisposition for the development of aneurysms and aortic dissection has a multifactorial basis involving chronic inflammation and ischemia of the aortic wall, which generates remodeling and increased susceptibility. The presence of severe atherosclerosis is associated with increased local expression of proteinases that contribute to tissue destruction, cell necrosis and apoptosis. (8,9) On the other hand, the blood supply of the aorta is provided by simple diffusion (2/3 internal) and through the vasa vasorum (1/3 external), except for the infrarenal aorta, which lacks an independent vascular supply; (10) therefore, the presence of atheromas favors ischemia of the media with subsequent apoptosis of smooth muscle cells and weakening of the wall. (11) This phenomenon, together with a simultaneous stressful stimulus, which exceeds the strength of the aortic wall, increases susceptibility to the development of aneurysms and/or aortic dissection.

Another of the syndromes associated with SA is embolism, central or peripheral, of thrombi or cholesterol crystals. Plaque stability will be the result of the balance between mechanical resistance and the forces that affect the coating. Thus, unstable plaques will be characterized by the presence of a thin fibrous plaque, with few smooth muscle cells, covering a large lipid core with abundant foam cells and tissue factor. (12) Fracture of the sheath will expose the atheroma tissue factor to blood clotting proteins, thus initiating the coagulation cascade and the formation of fibrin-rich thrombi (Figure 4), which embolize to the brain or peripheral organs. Likewise, the exposure of cholesterol crystals, contained within the lipid core, can be embolized to the peripheral organs or extremities giving rise to a SA syndrome (diffuse atheromatous embolization). (13)

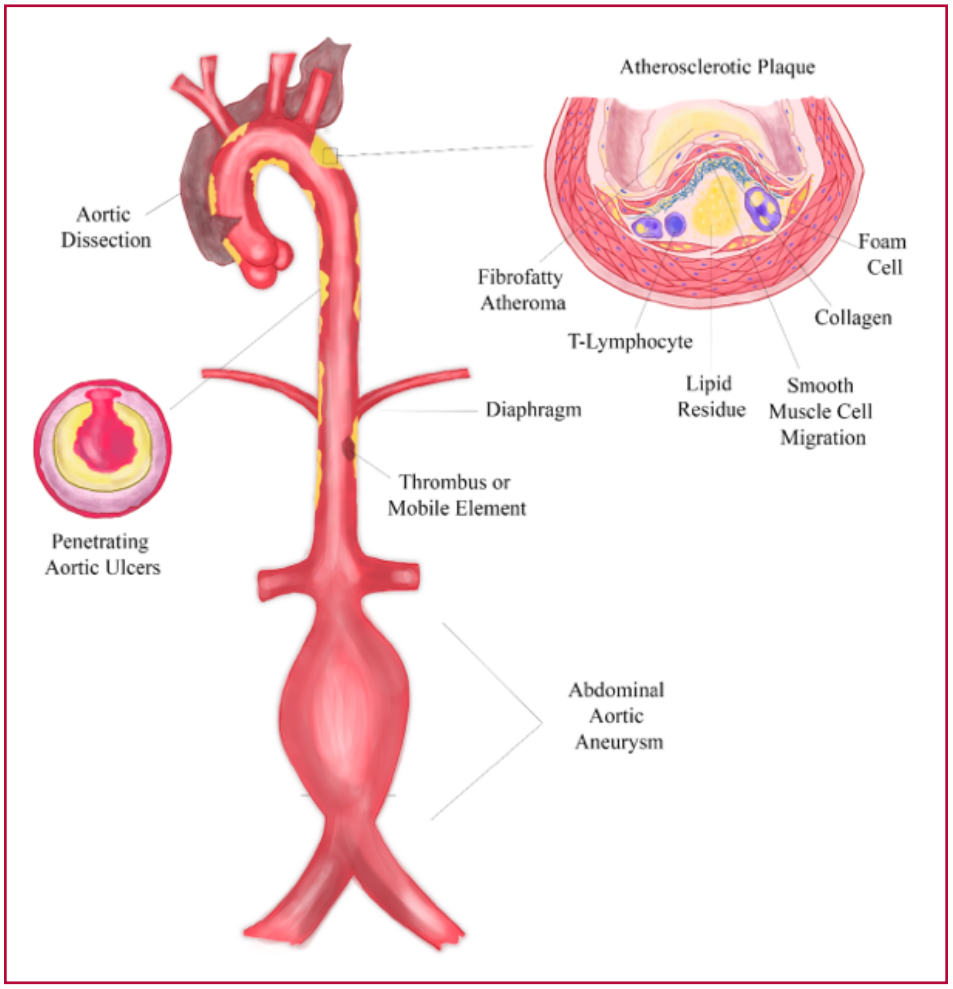
Penetrating atherosclerotic ulcers (PAU) are caused by ulceration of the atherosclerotic plaque with extension into the media producing a mushroom-shaped excrescence. They occur as unifocal or multifocal lesions in diffusely atherosclerotic aortas, particularly in the mid-portion and distal third of the descending aorta. Its timely diagnosis is essential as large PAU (>20 mm), with a depth greater than 10 mm, are responsible for 2-7% of cases of acute aortic syndrome. (3,14)

Diagnosis and multimodality

When evaluating aortic pathology, the method of choice will depend on the diagnostic suspicion, the patient's comorbidities and the availability of the method. These include transthoracic echocardiography (TTE), TEE, CT and magnetic resonance imaging (MRI). Generally, more than one diagnostic tool will be used, emphasizing the importance of multimodality for proper diagnosis, and its choice will depend on the individualization of each case.

TTE allows visualization of the aortic root, sinotubular junction (STJ), ascending aorta (AAo), distal portion of the aortic arch and proximal portion of the descending aorta (DAo). However, it is limited by the acoustic window of each patient. On the other hand, TEE allows visualization, with higher spatial resolution, of the AAo, the arch and the thoracic DAo, with the exception of a "blind spot" located at the junction of the AAo and the aortic arch. (15) The higher spatial resolution is due to the proximity of the esophageal transducer to the aorta and the higher wave frequency. For this reason, TEE is the imaging modality of choice to diagnose plaques in the thoracic aorta and to specify its morpho-structural characteristics. (15) Thus, the aortic plaque is defined as an irregular thickening of at least 2 mm with increased echogenicity with respect to the adjacent intimal surface. A complex aortic plaque, defined by a thickness ≥4 mm, ulcerated or with associated mobile component, is associated with increased risk of cardiovascular and cerebrovascular events and mortality. (16)

CT makes it possible to visualize the aorta in its entirety, detect calcified plaques, tortuosity, aneurysm and evaluate adjacent organs. The visualization of the lumen requires the use of contrast media, which



Central illustration. Shaggy aorta is characterized by severe atherosclerotic degeneration, resulting from a multifactorial pathophysiological process (with chronic inflammation, ischemia, aortic wall shear stress, and individual genetic susceptibility being fundamental to parietal remodeling and increased vulnerability). The clinical importance of this disease lies in the different clinical conditions to which it predisposes (aortic dissection, penetrating aortic ulcer, aneurysmal dilatation and systemic embolization) and in its role as an independent and significant risk factor for operative mortality.

can accurately define the aortic wall, perform precise measurements, identify and characterize aortic plaques, as well as their complications (endoluminal thrombi and the different forms of acute aortic syndrome). (16) Therefore, when acute aortic syndrome is suspected, it is considered the first diagnostic study, as long as it is contrasted and triggered. Its main limitations lie in the use of radiation and iodinated contrast.

MRI perfectly characterizes the composition of the aortic plaque (fibrous cap and lipid core) and identifies thrombi attached to the plaque. (17) Its diagnostic capability is superior to TEE, particularly in the AAo and aortic arch; nonetheless, TEE has a better image quality regarding the DAo. (18) In addition, it allows assessment of cardiac and valvular function, information that is of interest in aortic pathology. Despite these advantages, its high cost, limited availability, longer acquisition time and occasional use of contrast, make it an ineligible method for diagnosis and follow-up.

Management

Although there is no clear indication for endovascular aortic treatment of the abdominal or thoracic aorta in patients with SA, we know that these patients are at increased risk for embolization and development of acute and chronic aortic complications. Evidence suggests that ''prophylactic'' endarterectomy of a severely atherosclerotic aorta for protruding atheroma as an adjunct to a cardiac procedure is not recommended because of the high incidence of intraoperative stroke. (19) Nevertheless, patients with recurrent peripheral or visceral embolization and presence of SA with favorable anatomical features for endovascular reperfusion may undergo such treatment (Recommendation Class IIb, Level of Evidence C). (20) On the other hand, the management of complications associated with SA are beyond the scope of this review.

CONCLUSIONS

SA refers to severe atherosclerotic degeneration of the aortic surface, which is extremely friable and predisposes to various complications such as aneurysms, acute aortic syndromes, and peripheral embolization. The incidence and prevalence of SA in the world population is unknown but is estimated at 10-20%. The fundamental bases for the development of SA and its complications are chronic inflammation, ischemia, aortic wall shear stress and individual genetic susceptibility. On the other hand, multimodality imaging is essential for the timely and correct identification and characterization of aortic atherosclerotic plaques, es-

pecially complex ones, which are typical of SA. Each of these diagnostic tools has certain characteristics that favor or limit their usefulness. Finally, there is no consensus regarding the interventional or surgical management of SA, but its finding constitutes an important risk factor for operative and long-term mortality

Conflicts of interest

None declared (See authors' conflicts of interest forms on the website).

Financing

None.

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SCIENTIFIC LETTER

Bivalvular Tricuspid and Aortic Bacterial Endocarditis Associated with Multiple Septic Complications in an Immunocompromised Patient A Case Report

Endocarditis bacteriana bivalvular tricuspídea y aórtica asociada a múltiples complicaciones sépticas en paciente inmunocomprometido. A propósito de un caso

HERNÁN L. PEREYRO[1], LAURA M. MILAR[2], DANIELA F. CALDERÓN[2], TOMÁS M. VANEGAS RODRÍGUEZ[2], PAUL VARGAS MIELES[2], ADRIÁN J. LESCANO[2,3, MTSAC]

Infective endocarditis (IE) is predominantly an infection of the valvular endocardium, produced by endothelial damage due to microorganisms implanted via a hematogenous route, generating vegetations. (1) Despite improved understanding of its pathophysiology, more precise diagnostic methods and more effective antibiotics, it is associated with high morbidity and mortality, and even more than 50% of patients suffer some complication during its evolution. (2)

The EIRA-3 study carried out in Argentina showed an overall in-hospital mortality of 25.5% and established age over 65 years, history of kidney failure, mitral valve disease and the presence of heart failure as predictors of mortality. The most frequently isolated pathogens were Gram-positive cocci: *Staphylococcus spp* (46.3%), *Streptococcus spp* (28.2%) and *Enterococcus spp* (12.8%). The main in-hospital complications observed were persistent fever after initiation of antibiotic therapy, new kidney failure, peripheral embolisms and new heart failure. (3)

The aim of this communication is to present a clinical case with extensive structural cardiac involvement and multiple distant septic embolization. The clinical presentation, initial management, treatment of extracardiac complications and final surgical resolution will be analyzed.

We present the case of a 61-year-old male patient, smoker, with a history of human immunodeficiency virus (HIV) infection since 2000, on antiretroviral treatment with lamivudine and dolutegravir, right kidney atrophy with subsequent chronic kidney disease secondary to left obstructive uropathy (requiring renal replacement therapy from January 2022 to March 2023), non-insulin-requiring type 2 diabetes, and hospitalization for one month in February 2023 for bacteremia with rescue of multi sensitive Enterococcus faecium that responded to treatment with vancomycin.

He consulted on this occasion for disabling low back pain of 3-month evolution, and a magnetic resonance imaging (MRI) study showed discopathy at the L5-S1 level, indicating surgical resolution. Among the pre-surgical complementary examinations, a transthoracic echocardiogram revealed an image suggestive of tricuspid valve vegetation associated with moderate regurgitation (Figure 1), requiring hospitalization for study and treatment.

Upon interrogation, the patient reported febrile episodes associated with non-productive cough, asthenia and weight loss of 10 kilograms in the past two months. On physical examination he was lucid, with mucocutaneous pallor, without signs of neurological focus, with clinical signs of heart failure, good ventilatory mechanics with cavitary murmur in the right lower lung field, isolated underlying fine crackling rales, attenuated first heart sound and normal second heart sound, systolic murmur of 3/6 intensity in aortic focus and diastolic murmur of 2/6 intensity in tricuspid focus, symmetrical extremities without edema and peripheral pulsus *magnus et celer*.

The admission electrocardiogram presented sinus rhythm, heart rate of 75 bpm and complete right bundle branch block. Laboratory analysis showed: hematocrit 26.9%, hemoglobin 8.90 g/dL, leukocyte count 14 910/mm3 (75% neutrophils), urea 116 mg/dL and creatinine 2.71 mg/dL. Chest X-ray revealed two cavi-

Rev Argent Cardiol 2025;93:77-80. https://doi.org/10.7775/rac.v93.i1.20861

Correspondence: Hernán L. Pereyro: 11-6938-9453. Danel 1438, Department 8, Autonomous City of Buenos Aires, Argentina (C1242ADB). E-mail: hernanpereyro@hotmail.com

[1] Hospital Español, Autonomous City of Buenos Aires, Argentina
[2] Centro Gallego, Autonomous City of Buenos Aires, Argentina
[3] Sanatorio de la Trinidad, Quilmes, Province of Buenos Aires, Argentina

tated images with hydro-aerial level in the right lower pulmonary lobe (Figure 2), with free costophrenic sinuses and no other pathological findings. In the simple chest and abdomen tomography, the presence of pulmonary abscesses and a hypodense image in the spleen were reported. A transesophageal echocardiogram exhibited severe aortic regurgitation and moderate tricuspid regurgitation, with vegetations in these valves and in the Chiari network (Figure 3). Blood culture samples were taken and vancomycin-resistant *Enterococcus faecium* (VRE)was found, so major (blood cultures and positive image) and minor (fever,

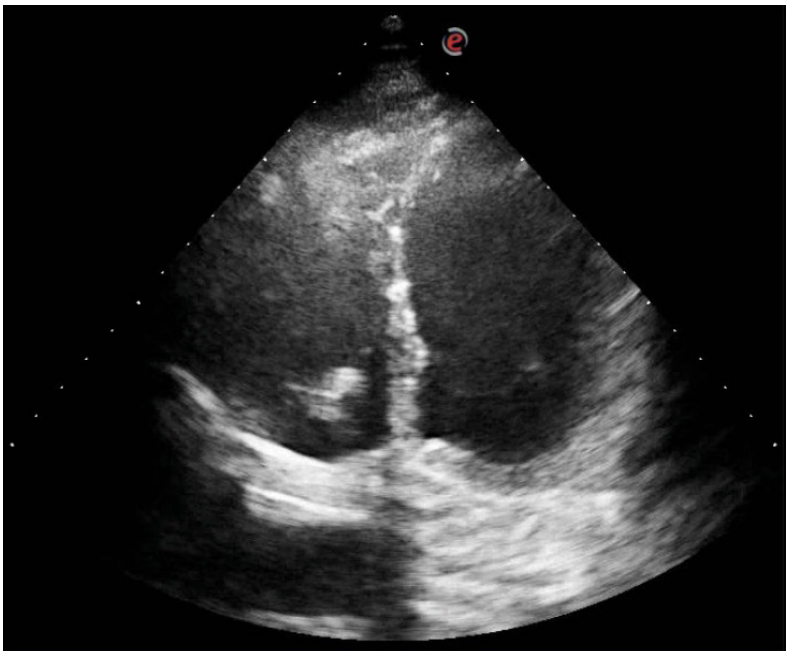

Fig. 1. Transthoracic echocardiogram in 4-chamber apical view. The right ventricle shows image compatible with tricuspid valve vegetation

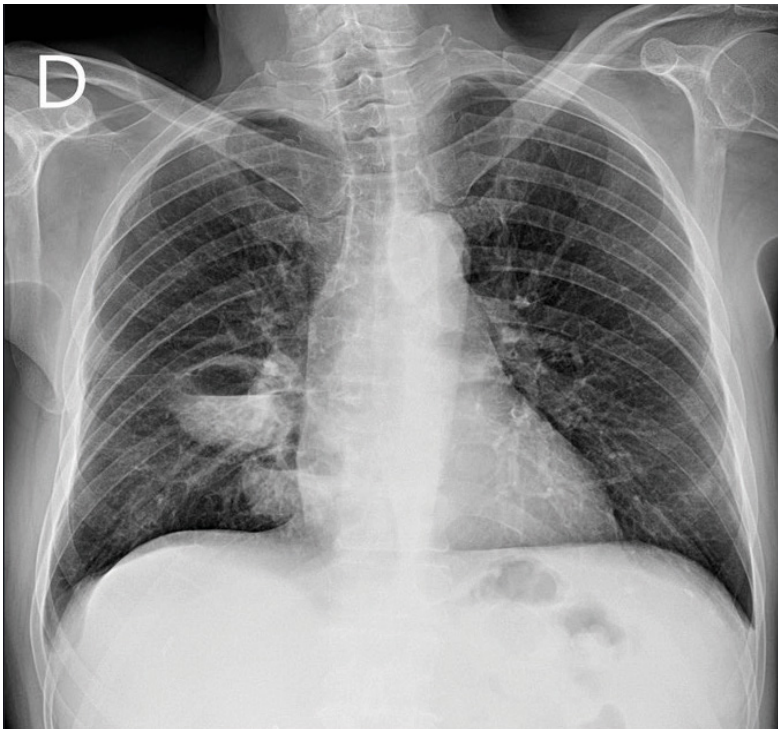

Fig. 2. Simple postero-anterior chest X-ray showing two cavitated lesions with hydro-aerial level.

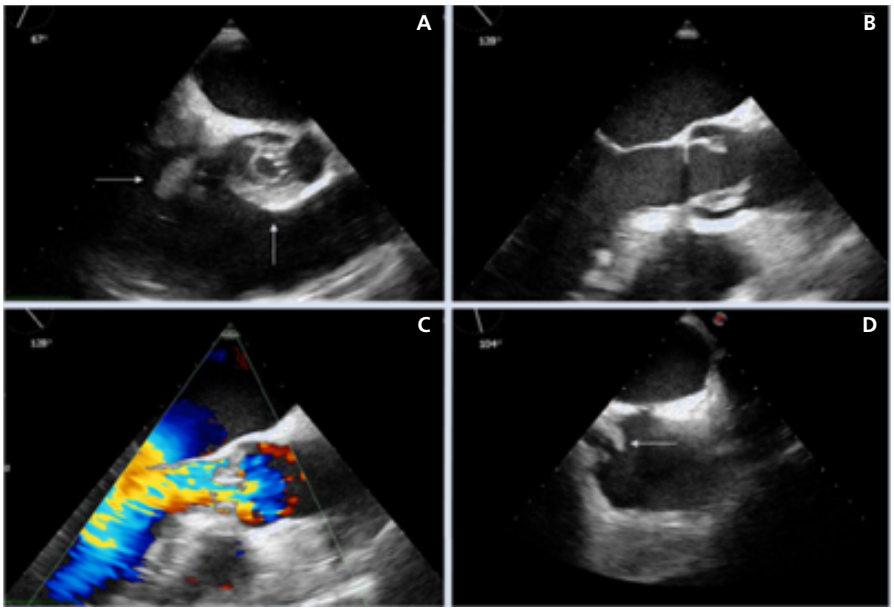

Fig. 3. Transesophageal echocardiogram. **Image A** shows an axial view at the basal level of the great vessels, with aortic valve compromise (vertical arrow) that prevents its correct closure, and the ventricular projection of a vegetation of the tricuspid septal leaflet (horizontal arrow). **Image B** shows a longitudinal view of the left ventricular outflow tract, with two vegetations in the aortic valve. **Image C** shows the color Doppler of the previous image, in which an aortic regurgitant flow in diastole can be observed. **Image D** shows a slightly rotated bicaval view in which a vegetation (horizontal arrow) can be seen over the mouth of the inferior vena cava, compatible with vegetation of the Chiari network

peripheral embolic phenomena) criteria of the modified Duke diagnosis for IE were easily met. (4) Therefore, a targeted antibiotic regimen with linezolid was started.

With respect to the pulmonary and splenic abscesses, the Percutaneous Surgery Service performed their drainage guided by tomography and fluoroscopy respectively, rescuing the same bacteria.

In conjunction with the Division of Infectious Diseases, a new MRI of the spine with gadolinium was performed due to suspicion of spondylodiscitis. Signal increase was observed in the prevertebral plane with fine laminar collections, which are initial signs of inflammatory changes compatible with incipient spondylodiscitis. As it was not a drainable collection, medical treatment was decided. Dentistry performed exodontia of tooth 4.5 due to the presence of penetrating caries.

The patient evolved with signs of heart failure for which he received intravenous treatment with loop diuretics. With negative water balance the clinical response was favorable. The patient evolved without leukocytosis or fever and with negative control blood cultures one week after starting antibiotic therapy.

As relevant intercurrences, after 15 days of treatment he presented thrombocytopenia that was interpreted as secondary to medullary toxicity of linezolid, so antibiotic therapy was rotated to daptomycin and minocycline. Once the infectious foci were controlled, coronary angiography was performed and no angiographically significant lesions were observed. Two hours after the procedure, the patient presented a febrile and clinical record compatible with acute cerebellar syndrome, which was interpreted as septic embolization associated with the procedure. Maintaining the antibiotic regimen, the symptoms subsided spontaneously after 48 hours. Hemodialysis was restarted due to an increase in nitrogen products. After multidisciplinary evaluation, surgery was decided. (4)

On the 53rd day of hospitalization, the Cardiovascular Surgery team performed aortic valve replacement with biological prosthesis number 23, subaortic repair and vegetectomy of the anterior leaflet of the tricuspid valve. There were no relevant postoperative intercurrences.

Methicillin-sensitive *Staphylococcus aureus* was recovered from the tricuspid valve, so antibiotic therapy was continued for two weeks after surgery, with negative control blood cultures, and control echocardiogram with no evidence of vegetations. It was decided to discharge him and he is currently under outpatient follow-up, with good therapeutic adherence and no new complications.

Patients diagnosed with HIV who present IE have a higher percentage of comorbidities and complications. (5) It is of utmost importance for these patients to have a close multidisciplinary approach and follow-up to help make quick and effective medical-surgical decisions, especially during the first days of hospitalization, which conditions the prognosis. Surgical resolution in this case is indicated once the non-valvular infectious foci are controlled, except in the case of hemodynamic complications, according to the guidelines.

Ethical considerations

Not applicable

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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SCIENTIFIC LETTER

Ergospirometry in Patients with Precapillary Pulmonary Hypertension: Evaluation of the Predictive Value of Echocardiographic Variables

Ergoespirometría en pacientes con hipertensión pulmonar precapilar: evaluación del valor predictivo de variables ecocardiográficas

NICOLÁS M. D'AMELIO[1], PAULA J. KAPLAN[1], MANUEL LAGO[1], GERMÁN J. SOUTO[1], MIGUEL AMOR[1, MTSAC], MARTÍN BRUZZESE[1]

Ergospirometry or cardiopulmonary exercise test (CPET) in patients with pulmonary artery hypertension (PAH) and non-surgical chronic thromboembolic pulmonary hypertension (CTEPH) allows obtaining predictor variables, such as peak oxygen uptake (peak VO_2) and ventilation (VE)/carbon dioxide production (VCO_2) ratio, and is suggested by the Guidelines on Pulmonary Hypertension for risk stratification, as is the tricuspid annulus plane systolic excursion distance (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio measured by transthoracic echocardiography (TTE). (1) The predictive association between the TAPSE/sPAP ratio and the above mentioned CPET variables is not defined in this population.

The primary objective of this study was to evaluate echocardiographic parameters of right ventricular (RV) function as predictors of exercise capacity in patients with PAH and non-surgical CTEPH. Secondary objectives were to determine the association between VE/VCO_2 and echocardiographic variables such as TAPSE, sPAP, right ventricle (RV) fractional area change (FAC) and right atrial area.

It was an observational, cross-sectional, pathophysiological and prospective study.

We recruited 7 patients aged between 18 and 65 years, of whom 5 were diagnosed with idiopathic PAH, 1 with PH associated with connective tissue disease, and 1 with non-surgical CTEPH. All were followed up as part of the Pulmonary Hypertension Program at Hospital Ramos Mejía. The diagnosis of PH was confirmed by right heart catheterization according to the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines on Pulmonary Hypertension. (1)

Patients were required to be on stable drug therapy for at least the last 4 weeks prior to study entry. This was defined as no new PH-specific therapy or no change in the dose of the current specific therapy.

The CPETs and TTEs were performed no more than 15 days apart and by the same operator in each study. Patients were at low risk according to REVEAL 2.0. The CPETs were performed with portable equipment, on a treadmill, using a COSMED model K5 gas analyzer and a modified Bruce protocol with procedures in accordance with the current guideline recommendations. (1) The following variables were considered: peak VO_2, VCO_2, minute ventilation (VE) and heart rate. The echocardiograms were performed using a General Electric VV7 equipment. All measurements of cardiac structure and function were performed according to the current guidelines. (2)

Statistical analysis was performed using Student's test and Wilcoxon rank-sum test for paired data and a p-value < 0.05 was considered significant.

Five of the seven patients were female. The median age (interquartile range, IQR) was 48 (29-53) years. Two patients received treprostinil, macitentan and sildenafil, two received sildenafil, ambrisentan and selexipag, two received tadalafil and ambrisentan and one received sildenafil and ambrisentan. Table 1 shows the hemodynamic values of the population.

Among different echocardiographic variables, a statistically significant association was found in linear regression between the TAPSE/sPAP variable and peak VO_2 with a β coefficient = 27.5 ($p=0.003$) (Figure 1). No significant association was found among other CPET parameters with predictive value in PAH, such as the VE/VCO_2 ratio, and other echocardiographic variables.

Remodeling of the arterioles, inherent to precapillary pulmonary hypertension, causes a progressive increase in physiological dead space, that is, an increase

Rev Argent Cardiol 2025;93:81-83. https://doi.org/10.7775/rac.v93.i1.20853

Correspondence: Nicolas D'Amelio . E-mail: nicolasdamelio@hotmail.com

[1] Pulmonary Hypertension Program
Cardiology Department and Pneumotisiology Unit of the Hospital Gral. de Agudos J. M. Ramos Mejía

Table 1. General characteristics

Characteristic	Median (IQR)
mPAP (mmHg)	59 (34-70)
CO (L/min)	4.75 (4.3-5)
CI (L/min/m^2)	2.83 (2.6-2,9)
ISV (mL/m^2)	34.5 (27.5-41)
PA SaO_2 (%)	68 (63-73)
PVR (WU)	11 (7.8-12,3)
peak VO_2 (mL/kg/min)	17.1 (15.7-21)
peak VE/VCO_2	34.1 (28.4-43.2)
Right atrium (cm^2)	20 (18-23)
TAPSE (mm)	18 (17-19)
sPAP (mmHg)	40 (35-69)
TAPSE/sPAP	0.45 (0.26-0.49)
FAC (%)	35 (24-48)

CI, cardiac index; CO: cardiac output; IQR, interquartile range; FAC: right ventricular fractional area change; ISV: indexed left ventricular systolic volume; mPAP: mean pulmonary artery pressure; MV: minute volume; PA SaO_2: pulmonary artery O_2 saturation; PVR: pulmonary vascular resistance; sPAP: systolic pulmonary artery pressure; TAPSE, tricuspid annulus plane systolic excursion; VE/VCO_2: minute ventilation/CO_2 production ratio at peak exercise; WU: Wood unit; peak VO_2: peak oxygen uptake;

in the number of alveoli that are healthy and well-ventilated but poorly perfused at rest. As the disease progresses and remodeling continues, the number of perfused alveoli decreases, as does their recruitment during exercise. This ventilation/perfusion mismatch causes progressive ventilatory inefficiency that is responsible for the exertional dyspnea in these patients: they need to increase ventilation to take in O_2 and eliminate CO_2. The pathophysiology of patients with PAH that becomes evident during CPET has been described in numerous studies. (3)

As pulmonary vascular disease progresses, adaptive and maladaptive right ventricle remodeling occurs, conditioning the right ventricular-pulmonary artery coupling (RV-PA). (4,5)

The TAPSE/sPAP ratio is a noninvasive measurement that correlates with invasive measurement of RV-PA coupling. This association has prognostic implications in patients with precapillary PH. Ghio et al. examined the RV-PA coupling, assessed as TAPSE/sPAP, during a dobutamine stress test in patients with precapillary PH. (6) Considering the inclusion of the TAPSE/sPAP parameter in the Guidelines on Pulmonary Hypertension and the demonstration of its predictor value in patients with PH as well as the already

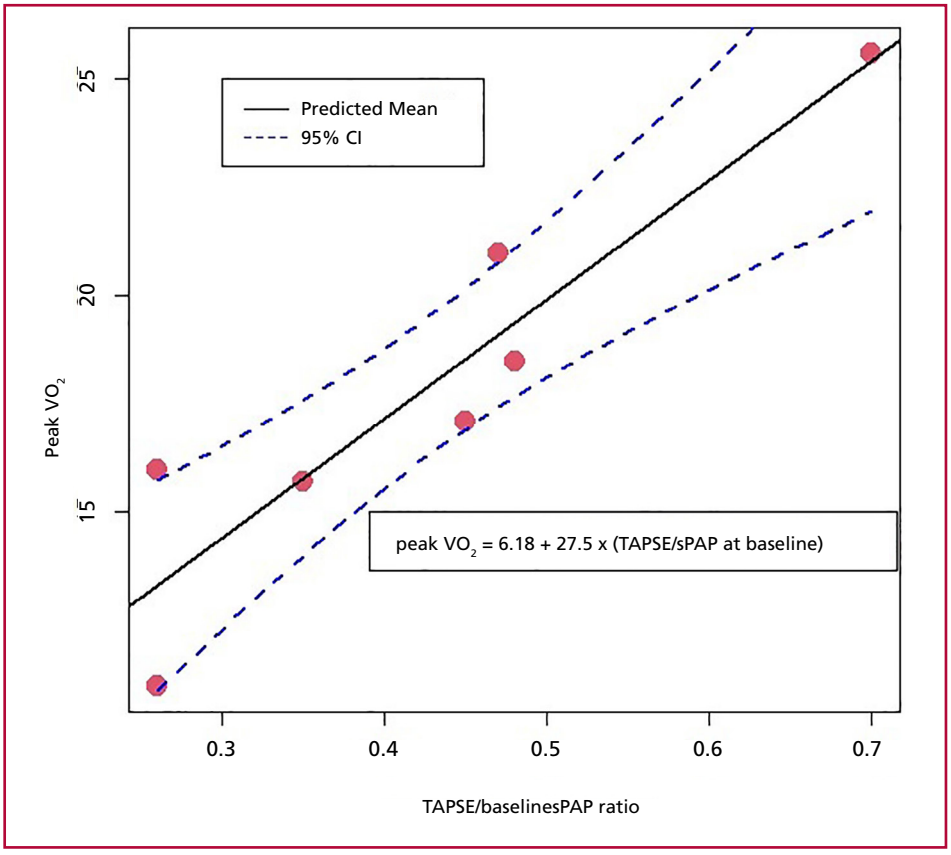

Fig. 1. Association between peak VO_2 and TAPSE/sPAP ratio.

95% CI: 95% confidence interval; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; peak VO2: peak oxygen consumption.

established usefulness of the CPET for risk stratification, diagnosis and follow-up of these patients, the main finding of our study is the solid association between baseline TAPSE/sPAP variable with peak VO2 in only 7 patients.

At the time of writing, no further evidence on the association between TAPSE/sPAP variable and peak VO_2 has been found. The predictive information of an easily obtained parameter such as the TAPSE/sPAP ratio is very useful in view of the accessibility and lower cost of echocardiography compared to ergospirometry, especially in contexts such as the treatment of this hemodynamic condition in low and middle-income regions. In our opinion, this result allows the development of a hypothesis that will encourage the performance of a study involving a larger number of patients.

Ethical considerations
Not applicable

Conflicts of interest
None declared.

(See conflicts of interest forms on the website).

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The Importance of Knowing Specific Populations and their Cardiovascular Reality

La importancia de conocer poblaciones específicas y su realidad Cardiovascular

ROCÍO VILLA FERNÁNDEZ[1], MARIO PRINCIPATO[2, MTSAC]

In the extensive surface of the Argentine Republic, with a great diversity of geographic areas, customs, access to food and health, there are logically disparate characteristics in different regions, and even within them.

The evaluation of cardiovascular variables in native communities of the Calchaquí Valleys through the SONQO-CALCHAQUÍ III program, as well as the previous versions of 2018 and 2022, allow us to know the reality of populations far from urban areas that are underrepresented in the RENATA 2 study or in the IV National Survey of Risk Factors. (1) This third edition highlights the fact that the community of Colalao del Valle has a better cardiovascular health status, probably due to a better educational level, greater treatment of patients with hypertension and diabetes and a higher percentage of inhabitants with normal neck circumference, whereas the inhabitants of Fuerte Quemado have better sleep quality and higher self-esteem. (1)

M. Bassett et al. studied a similar population in 2008, and observed that, with a low socioeconomic and educational level, and a low average energy intake, they showed a high prevalence of overweight, obesity and an elevated risk of cardiovascular disease according to central adiposity values. This could be due to the introduction of new high-energy foods and a more sedentary lifestyle or to the possibility that the biological characteristics of these individuals make them more predisposed to a rapid increase in adiposity. (2)

P. Durán describes the epidemiological transition process as one with changes in the morbidity patterns of populations, with prevalence of chronic noncommunicable diseases, in which the changes are not only demographic, but also of lifestyle and dietary habits. (3)

A westernization of diet habits is observed in Latin America. In a short period of time, there has been a general increase in energy intake, particularly from refined sugars and saturated fats, and a decrease in fiber intake. (4)

Consequently, a greater survey of the area could be carried out, given that the sample of this work represents 4.4% of the population according to the National Census of 2022. After analyzing the results, interventions in (health promotion, education) could be proposed together with the communal delegates, encouraging healthy eating habits and prescribing physical activity, and subsequently evaluating the results of these interventions.

The effort of the working group was very useful, as it allowed us to learn valuable local information. It would be very interesting to have other teams committed as this one, in order to learn about the realities of other non-urban regions of the country and Latin America, and to act accordingly.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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Correspondence: Rocío Villa Fernández, General Urquiza 609, City of Buenos Aires. E-mail: rociovillafernandez@gmail.com

[1] Staff physician, Cardiology Division, HGA Ramos Mejía, Autonomous City of Buenos Aires

[2] Chief of Hospitalization, Cardiology Division, HGA Ramos Mejía, Autonomous City of Buenos Aires

AUTHORS' REPLY

The SONQO-CALCHAQUÍ working group is grateful for the comments of Dr. Rocío Villa Fernández regarding our published studies. We highlight her ability to synthesize the main points of our study in a few lines.

The various editions of the SONQO-CALCHAQUÍ Program involve the voluntary and disinterested work of many people from different regions of our country, and being able to see our efforts reflected in your comment reinforces that we are on the right path. We are trying to reach mountain populations with cardiovascular health, with difficult access to health care due to their geographic condition. Your opinion is valuable. We share the view that native populations are underrepresented in other studies due to the difficulty of access and that each community has its own cardiovascular characteristics, customs, habits and beliefs (which should be taken into account when carrying out prevention campaigns). In addition, we share your interest in evaluating more deeply the changes that are occurring in the diet of these populations. We also believe that climate and altitude could be factors to be taken into account when assessing these populations.

As Dr. Rocio Villa Fernandez points out, it is very important that these studies are replicated in other communities in Argentina and Latin America, that has always been our dream. We are currently planning the V Edition of the Program, which this year will be carried out at a great height.

Ricardo Sebastián Galdeano
Sonqo Calchaquí Program Director

Myocardial Work in Stress Echocardiography with Dipyridamole

Trabajo miocárdico en ecocardiograma estrés con dipiridamol

MILAGROS SEIJO BEHETY

Stress echocardiography (SE) is a widely used technique in our setting, due to its availability and prognostic value in different cardiac pathologies, especially in coronary artery disease. The use of pharmacological stress with dipyridamole may sometimes be slightly limited owing to the lack of access, patients with contraindications, or simply lack of confidence or knowledge of the professional requesting it. The evidence of studies that directly compare the sensitivity and specificity of SE with dobutamine or dipyridamole is wide and diverse, several studies agree that dobutamine has a slight superior sensitivity, which could determine its more frequent use on a daily basis, while other studies claim that both have similar sensitivity and specificity. (1,2) Cardiology guidelines do not prioritize one drug over the other, although dobutamine is usually mentioned more frequently as an example in different works.

The article "Behavior of myocardial work as a marker of ischemia in stress echocardiography with dipyridamole" by Saad et al. opens the possibility of extending the echocardiographic search to less usual determinations such as myocardial work and its derivatives, to increase the sensitivity and specificity of those individuals with ischemia. (3) It also reinforces the points in favor of ES with dipyridamole, such as the determination of coronary flow reserve of the left anterior descending coronary artery, and global longitudinal strain (GLS).

Global longitudinal strain determination for behavioral assessment or complementary evaluation of different pathologies, (from valvulopathies and coronary artery disease to cardiotoxicity, etc.) is requested by many cardiologists as additional data. The inclusion of blood pressure measurement allows us to indirectly calculate myocardial workload in a non-invasive manner.

Non-invasive evaluation of myocardial work by echocardiography has an attractive pathophysiological basis, which has been demonstrated in several studies in recent years. (4, 5)

The evidence of myocardial work analysis in studies with dobutamine is scarce and so far, without promising results. This opens the opportunity for the use of pharmacological stress with dipyridamole, which allows to increase the specificity of the measurement

Rev Argent Cardiol 2025;93:85-86. https://doi.org/10.7775/rac.v93.i1.20868

Correspondence: Milagros Seijo Behety, Estoril 450, Santiago, Chile. E-mail: miliseijo@gmail.com

Medical Echocardiographer, Clínica Las Condes, Santiago, Chile

and to unmask those patients with ischemia,owing to the demonstration of wasted work and the decrease of efficient work in this condition.

Although the data obtained in this study is encouraging, as pointed out by its authors, their limitations, (retrospective study, number of patients, lack of anatomical follow-up, etc.) are still clear. This should encourage us to further explore this area, thus reinforcing the importance of keeping up to date and adding, to the conventional analysis of motility and ejection fraction, myocardial work as an advanced and noninvasive tool for the evaluation of left ventricular function, in order to offer more accurate and appropriate diagnoses for our patients.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

First of all, we would like to thank Dr. Milagros Seijo Behety for her interest and comments on our work. Stress echocardiography (SE) has many advantages over other imaging techniques, mainly related to its low cost, the absence of radiation and low environmental contamination. (1) However, SE with dipyridamole is sometimes inadequately used due to unfamiliarity with the method and/or lack of drug availability. The main clinical practice guidelines propose the use of quantitative tools to analyze the results, not only in relation to myocardial motility, but also in the measurement of contractile and coronary reserve, among other parameters. (1, 2) In this sense, longitudinal strain and myocardial work, which takes into account loading conditions, can help to improve the sensitivity and specificity of the study to detect myocardial disease, since SE with dipyridamole allows obtaining good quality images, that are ideal for the use of this tool. However, as Dr. Seijo mentions in her letter, larger studies are needed to confirm these findings.

Ariel K. Saad MTSAC

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Dr. Hernán Claudio Doval at the GESICA Foundation

Dr. Hernán Claudio Doval en la Fundación GESICA

For those of us who shared intimate moments with Hernán at the GESICA Foundation, his departure is an irreplaceable loss that touches us deeply. We went through many challenges and projects together, with some successes and also frustrations, a framework of camaraderie and professional respect that forged a strong friendship over the years

Thirty-six years have passed since the first meetings in the basement of the Hospital Italiano where we sought to carry out a large-scale national multicenter clinical trial to demonstrate the benefits of the systematic use of amiodarone in patients with chronic heart failure, giving rise to the GESICA (*Grupo de Estudio de la Insuficiencia Cardiaca en Argentina*) study. From the beginning, Hernán stood out as a great host and then as the natural leader of this project, sharing with us his conviction that it was possible to conduct independent clinical research in our country.

The study was initiated in March 1988 and its results were presented as a late-breaking clinical trial at the American Heart Association Scientific Sessions in November 1993 and were published in the Lancet in 1994. It was the most cited Argentine article in the medical literature until well into the 2000s, and other observations from the study generated several national and international publications. As a result of this research Hernán was invited to give one of the keynote lectures at the American Heart Association Scientific Sessions in 1997.

In 1998, the GESICA Foundation was created to support the management of its own research projects. In the same year, a National Registry of Heart Failure was initiated, involving over 50 centers across the nation and a systematic program of titration with beta-blockers was implemented. Based on this registry, the DIAL study was carried out, a multicenter clinical trial that showed the efficacy of a telephone intervention performed by trained nurses to improve the outcome of heart failure. Its results were presented as a late-breaking clinical trial at the American Heart Association meeting in 2003 and published in the British Medical Journal in 2005, triggering a new cycle of international presentations and publications.

Without interruption, we continued with a collaborative project with the prestigious GISSI group to carry out the FORWARD study which evaluated the efficacy of Omega-3 to prevent recurrent atrial fibrillation which was presented at the American Heart Association Congress in 2013 and published in the Journal of the American College of Cardiology that same year

In recent years, the GESICA Foundation, chaired by Hernán Doval, has served as a platform and support for young professionals, enabling numerous clinical research projects to be carried out in the country. In line with his social commitment, Hernán focused on long-cherished project, to train health agents capable of assessing risk factors in poor neighborhoods.

Those of us who had the privilege of working with Hernán recognized his extraordinary intelligence, in a personality that overflowed with humility. His encyclopedic knowledge, and his ability to recall and relate scientific information were unique. He used to say that his wisdom was not great, it was just years of accumulated experience and a good memory.

The long hours of work we spent together on research projects were always interspersed with discussions (and sometimes passionate debates) of complex clinical cases, national and international politics, history, literature, art or philosophy. While steadfast in

Rev Argent Cardiol 2025;93:87-88. https://doi.org/10.7775/rac.v93.i1.20866

his convictions, he was always open to constructive dialogue and debate of ideas.

Hernán Doval was much more than a doctor; he was a man of principles, of strong values, of an unwavering vocation, and above all a human being deeply committed to the welfare of society. His passion for medicine was not only professional; it was deeply rooted in his ideology, which defined his career and his life. Hernán's clear medical vocation, together with his strong humanistic values, led him from thought to action in the field of social medicine. His scientific thought, however complex, consistently, always concluded with a humanitarian and social perspective. Hernán was not only a reference in medicine; he was also a **teacher** in the deepest sense of the word. His lessons were not only about cardiology, but also about the art of being a physician, ethics, responsibility and commitment to others; he trained countless generations of physicians and students who saw him as an example to follow. The fact that, although he was one of the most outstanding cardiologists of his generation, he never received a formal diploma is a paradox that underscores his authenticity.

Not only his colleagues and students recognized his career. He was named Distinguished Citizen of the city of Buenos Aires, as a tribute to his professional and human legacy. A man who dedicated his life to the well-being of others, who made social medicine and cardiology a passion he shared with everyone around him.

In an age of overwhelming technology, Hernán never succumbed to the dictatorship of the cell phone or the Google resource. Although we knew he was always at the hospital, it was not easy to find him. He was given the well-deserved nickname "Professor Herman" when we arrived at the Berlin airport and found a person waiting for him with a sign bearing that inscription. Today, his departure leaves a deep void, but his legacy remains intact, and his influence will continue to guide new generations of doctors, scientists and people committed to a better world.

Dear "**Professor Herman**", as we affectionately called you, your spirit, your vision and your love for science and social medicine will live on in those of us who knew and appreciated you.

Hugo Grancelli[MTSAC], **Daniel Nul**[MTSAC]
Sergio Varini[MTSAC]
GESICA Foundation

Dr. Hernán Claudio Doval (1941-2024)

If I die today...

Since the beginning of my life as a physician, I spent my time with Hernán Doval.

While it would be great to list all the positions he has held, his achievements in care, research, teaching and medical innovation to describe him, it would be insufficient.

I cannot imagine seeing his face in a photograph in front of a wall covered with diplomas, degrees, and certificates. It was not his style.

Unfortunately, we all have an inexorable destiny, which, as the popular saying states, is the only sure thing in life.

While I was trying to write these lines, a question came to my mind: if I die today..., how would I like to be remembered by my colleagues?

Surely, I hope no one will have doubts about my honesty in my medical performance, and as Maimonides' prayer says, no one will think I was guided by thirst for profit or ambition for renown.

I want to be remembered as a trainer of young cardiologists, and I hope that in time they will recognize me as their teacher in the profession.

I hope they have perceived that I was tenacious and sometimes even stubborn when I defended an idea, and that I was called upon to make the final decision to solve a complex case.

I want to be remembered as a person capable of going against the tide and of moving away from the flock to opt for a different, original opinion.

A prudent person to analyze so much novel information ignoring the trends and pressures we face.

A person who always keeps the enthusiasm alive when young doctors bring new ideas and support them in their projects.

I want to be remembered as a man who encourages the concept that doubt is the cornerstone, not only in philosophy, but also in medicine, and that raising doubt and exploring it should be our daily challenge.

I hope my colleagues will remember the frequent comments on history, politics or literature, which, beyond the practical aspect that allows us to get closer to the patients, enrich us, move us away from a merely technical role and bring us closer to being a more complete person.

That social issues and medicine as a tool for equity

should be a point of interest in decisions.

How would I like to be remembered by patients?

I want to be remembered as someone who listens to them, generates trust, knows their interests and will undoubtedly try to solve their problems.

These paragraphs are far from referring to me personally, because I do not meet all these conditions, but they are truly my wishes and my goals, which in part, I must admit, were an attempt to be like Hernán, because we always want to be like our mentors.

The doctor we are saying farewell to has fulfilled all the requirements I have mentioned, and I believe that those who have known him will share this opinion. I have no doubt that this list, although succinct, defines his figure.

Fundamentally, we will remember him as a Master of Medicine and one of the founders of what I consider the school of cardiology at Hospital Italiano de Buenos Aires.

César Belziti[MTSAC,]

The SAC is a Unique Institution

La SAC es una institución única

The Argentine Society of Cardiology (SAC) is a unique institution, a beacon that guides many other societies in our country. Its prestige is due to the hierarchy of its members, its evolution, its leadership and the actions carried out during 90 years, which have made it a reference also in Latin America. To say 90 years is not a mistake, we believe that, since the Journal of the Society was launched, we have been exercising our mission and vision. That is why one of our fundamental objectives is to continue working so that the Journal can be selected for indexing in Medline and thus honor the history of the SAC.

This leadership was reflected during the crisis in the healthcare system in 2023 and 2024, when the SAC led the charge in raising awareness of the serious problem the system was facing and the impact it was having on our patients and our community. We worked together with the Argentine Federation of Cardiology (FAC), the College of Cardiovascular Surgeons (CACI) and other cardiology-related societies to highlight the need to raise awareness among all stakeholders in the healthcare system about the importance of refocusing the system on the two main actors: the patient and the medical human resource.

WHY DOES A SCIENTIFIC SOCIETY BRING US TOGETHER AND EXCITE US? WHY DO WE COME TO THE SAC?

Scientific societies have been defined, in simple terms, as working groups composed of people with common interests. History demonstrates the expansive effect that collaboration has on scientific discussion. A notable example is the Pythagorean Society, founded in southern Italy around 530 B.C., where the foundations of mathematics were laid. In this society, all goods were communal, and its members were expected to devote themselves fully to the study of numbers, acting with simplicity and ethics towards their colleagues and fellow man.

Whatever happened to physics if Isaac Newton had not been able to discuss his ideas with Robert Hooke at the Royal Society? This interaction was fundamental to the creation of his masterpiece, "The Mathematical Principles of Natural Philosophy," which dominated much of the sciences. The society's motto, "*Nullius in verba*," embodies the idea that knowledge should be based on evidence and reason, not authority or tradition. This principle has been crucial to the development of critical thinking and scientific research throughout history.

In our country, the first scientific society was founded by Domingo Faustino Sarmiento in 1872. Our three Nobel Prize winners in the hard sciences were among its members: Bernardo Houssay, Federico Leloir and César Milstein. Our SAC was founded by prominent members of public hospitals in Buenos Aires, Córdoba and Rosario, as well as directors of institutes of physiology, such as Braun Menéndez in Buenos Aires and Oscar Orías in Córdoba. Since its inception, the SAC has been driven by the purpose of advancing science.

These people, brought together by their common interest in cardiology, created a powerhouse of knowledge through the SAC journal 90 years ago. So perhaps the answer to why we go to SAC is that it is the most important place for scientific and human growth where one can be, with the patient being the primary beneficiary of this entity.

However, the reality we face today is very different from that of Braun Menéndez, Battro and others. At the 2024 SAC Congress, the round table on "Cardiology in Peril", organized with all the cardiology societies, revealed a unanimous diagnosis by the main stakeholders in the national healthcare system: we are going through the deepest crisis of the system. This crisis is multifactorial and includes financing problems in an impoverished country, management of resources, difficulties of public and private institutions to be sustainable, emigration of highly trained human resources and inequalities in spending and quality.

To top it all off, we are facing a new generation of young people for whom traditional teaching methods and deadlines have been replaced. The University of Buenos Aires has reduced the length of the career by one year, along with a change in traditional pedagogical strategies. This was explained at the table "Car-

Rev Argent Cardiol 2025;93:90-92. https://doi.org/10.7775/rac.v93.i1.20867

diology in Peril", but what is even more worrying is the lack of interest in the medical residency program as a form of postgraduate training. A recent survey by *Cardiología Unida* revealed that 15% of cardiology residency positions remained unfilled, and a concerning 35% of residents dropped out of residency program for various reasons. The migration of trained physicians abroad has led to the dismantling of entire services, while costs have increased exponentially due to the emergence of new technologies. The irruption of artificial intelligence poses a significant challenge to the future role of the physician and the organization of cardiology services. Undoubtedly, this is a very complex scenario and perhaps one of the most challenging in recent decades.

WHAT CAN WE DO AT THE SAC IN THIS NEW CONTEXT?

During a three-day retreat with the most prominent members of the boards of directors who will be working in the next three years, we reflected on our strengths, threats, weaknesses, and opportunities. We also examined the career path of a SAC member since choosing medicine and this specialty.

It was essential to understand the journey of a physician in his or her professional growth and how we all arrived at this meeting. There, we identified the factors that significantly influenced our professional development. The initial question was: Why did we want to become physicians? The dedication to service and the desire to help others were the fundamental driving forces in choosing this wonderful profession, and we defined it as the first factor in the beginning for most of us: the dedication to service, something that is built together with our human convictions from our roots.

The second factor is the influence of mentors in our journey, whether in the university or in medical institutions with faculty members. In these spaces, many of us found those teachers who marked our path. I had the honor of being a fellow at the Basic Research Institute of the Favaloro Foundation during my fourth year of medical school. There I met Dr. Ricardo Pichel, physicist and physician, who left an indelible mark on my training, as well as Dr. Edmundo Cabrera Fischer, Dr. Juan Barra, Dr. Alberto Crottogini, Dr. Ricardo Armentano and Dr. Peter Wilshow. "Why" rather than "what for" in medical sciences was the basis for learning and research for an entire generation that was there.

The third factor, for all of us, is our possibility of entering a medical residency program in an institution that organizes learning by competencies. I had the experience of being part of the first class of the recently inaugurated residency program of the Favaloro Foundation, located in the building on Belgrano Avenue. I had the privilege of experiencing the beginning of this avant-garde project, formed by professionals from top level public and private hospitals. The merger between the excellent departments of cardiovascular surgery of *Sanatorio Güemes* and of clinical cardiology of *Hospital de Clínicas* and *Hospital Fernández* generated in its members a powerhouse of teaching and research, with the greatest benefits for patients and cardiologists trained in that model. It was also demonstrated that public and private medicine can be strengthened.

In the SAC we are aware that without public and private medical institutions that consider teaching and research as part of their project, medicine is condemned to mediocrity, and the patient is the main loser. Our Society has been a leader in the accreditation of residency programs and in its prestigious biannual course for residents at the SAC Central Headquarters and the triannual course in Córdoba, led by the local District. We are committed to continue promoting and improving this training system, convinced of its effectiveness and benefits. We have agreed on an irrevocable position on how training should be for the present and future generations, adapting it to the realities and technological advances, but always in the field of residency programs with serious and audited programs.

The fourth factor was the emergence of the SAC in our training, generally from the second year of residency, through the presentation of papers, monographs or the bi- or tri-annual courses for residents. Then, the participation in different areas of the SAC shaped us and allowed us to interact with other colleagues in knowledge and experiences.

We believe that we must continue to work on the basis of the factors mentioned -dedication to service, mentors, residency programs in institutions with serious programs and scientific societies- and adapt them to the new reality. The empowerment of patients and human resources in health (doctors, nurses and technicians) is the only way to reverse the situation in the healthcare system.

Based on this diagnosis and analysis, we have begun work on a strategic plan, which is an agreement that defines the long-term direction and priorities of our organization for the next three years, redefining our mission and vision.

We are committed to promoting excellence in cardiovascular health through the comprehensive and continuous development of healthcare teams and the defense of professional practice, guided by humanistic values, ethical principles and a commitment to quality and equity in access to patient care.

We have an obligation to continue generating and disseminating scientific knowledge through research, education and training, and to promote value-based medicine that optimizes health outcomes and resource efficiency.

Respecting the history and the great achievements of our society and full of prudence, understood by Aristotle as good judgment, the art of measure and the opportunity to act, we have decided to rethink, based on the already existing structures, three pillars for all the actions of our society.

First, an Area that deals with the members of the SAC, which we will call "SAC Members"; a Teaching Area, defined as the Continuing Education Institute; and the already known Research Area. On these three pillars, the SAC areas of Councils, Districts, Heart and Women, and SAC Young Community will act transversally. Our goal is to synchronize all actions with a strategic objective defined by the boards of directors for the next three years.

The SAC Members Area will focus on understanding the path walked by the members and developing strategies for guidance, training and support according to their professional progression, from medical residency, post-residency and the rest of the career path. We must identify our leaders and train them.

The Teaching Area will be responsible for the creation of the Continuing Education Institute, in which Héctor Deschle has been working on together with Amanda Galli, Sandra Swieszkowski, María Pagés, among others, where the teaching activity of the SAC, on-site and virtual courses for residents, will have a defined objective in the professional model that we need in this scenario, not only in the scientific but also in the ethical and moral bases of this profession.

In the Research Area, we want to add new registries and measurements of interventions to the excellent work already done, professionalizing them and working on the quality of the data from monitoring and representative samples of the heterogeneous reality of health in our country. This is one of the objectives we are working on to be able to collaborate with the authorities on real data.

The SAC areas will act transversally on these pillars. Regarding the Inland Districts, we believe that we must segment our actions according to the realities of the provinces. We have decided to empower Córdoba to coordinate the entire North, according to the needs of each region. The Province of Buenos Aires, both in the outskirts and in the cities, will have its own strategy adapted to its needs, as will each province and region of the country. The Districts, together with the Councils, must work in synchrony and involve members throughout the country.

Another change we have decided to implement is the empowerment of intermediate structures in the management of SAC, such as the coordination of Areas and Councils, to make their own decisions according to the objectives set by the Board of Directors.

We want to work with greater synchronization and interaction of all areas of SAC, based on the three pillars already explained.

The doors of SAC are open to all who wish to collaborate on its mission and vision. As Henry David Thoreau said: "Though I do not believe a plant will spring up where no seed has been, I have great faith in a seed. Convince me that you have a seed there, and I am prepared to expect wonders."

Pablo Stutzbach MTSAC
President of the Argentine Society of Cardiology