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PREVENIR ES NUESTRA META

- Microplastic and nanoplastic pollution
- Combination therapies and remodeling of the left ventricle after myocardial infarction
- PVCs ablation, effective strategy for symptom relief
- Acute myocardial infarction in a young patient with HIV
- Out-of-hospital cardiac arrest, cardiopulmonary resuscitation, and gender differences
- Mexican consensus for fasting before cardiovascular interventions

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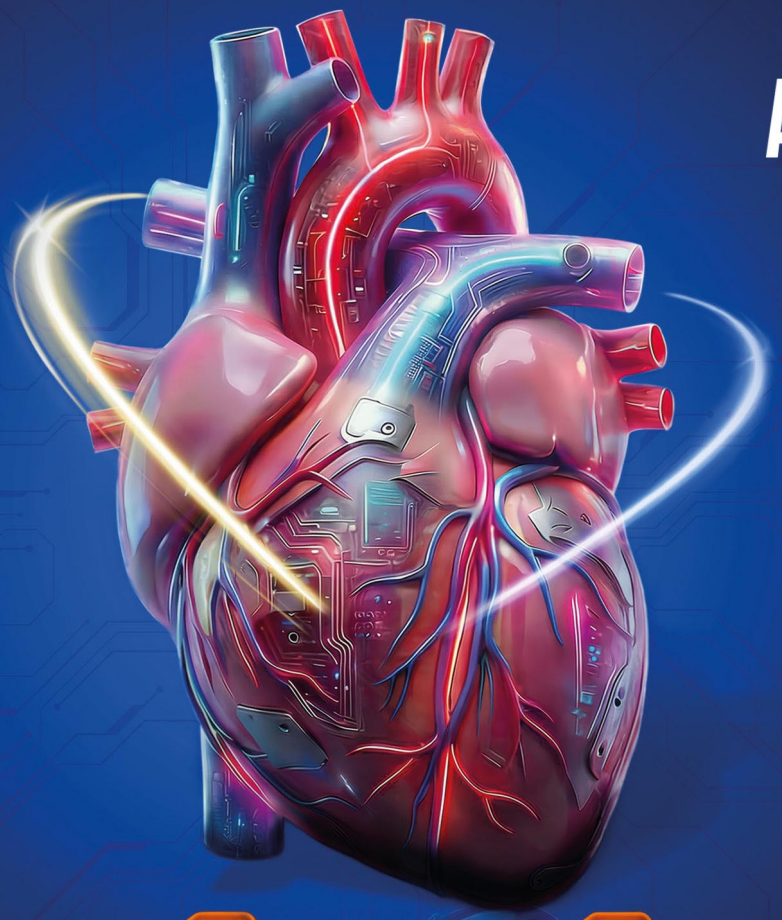

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Editorial

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Microplastic and nanoplastic pollution and cardiovascular health

Contaminación por microplásticos y nanoplásticos y la salud cardiovascular

Eduardo Meaney*

The widespread use of plastic products is a hallmark of modern times. It is estimated that millions of tons of plastic are produced on an annual basis and utilized in over 1,000 different ways. A subset of these plastics becomes integrated into our daily environment and habits, such as industrial products like tires, cosmetics, and personal care items, textiles, processed nutritional products, and contaminated fresh vegetable or animal foods, among myriad others.[1] Unfortunately, many of these organic and inorganic materials are used only once and become waste that is both biodegradation-resistant and highly contaminating. Some of these materials take centuries (literally) to degrade. The soil, the oceans, diverse waterways, the atmosphere, and beyond, outer space, have been, are, and will be flooded by these human-made catastrophic by-products that damage everything: the physics and chemistry of nature, and the organisms of all terrestrial and marine animal and plant species with whom we share the common home of the Earth, imposing serious challenges to both the planet's biosphere and human health.[2]

Microplastics, submicroplastics, and nanoparticles (MPs, SMPs and NPs, whose sizes are 1 µm-5 mm, 100 nm-1 µm, and less than 100 nm, respectively) penetrate the human body mainly through ingestion and inhalation, and less frequently by skin contact.[1-3] The leading site of invasion is the intestine, and although the route of absorption is not known with certainty, it appears to occur via macrophages and the gut lymphatic system.[4] Once inside, plastic particles penetrate the cells at a rate that depends on the size of the particle and the type of cell, through diverse entrance mechanisms. It is well known that these particles can cause strong inflammatory and nitroxidative stress responses, inducing apoptosis and autophagy in cells across different organs and systems, as well as damage to the genome and immune system.[5] There is abundant clinical evidence linking plastic small particles with diverse cardiovascular lesions and outcomes, such as arrhythmias, ventricular dysfunction, pericarditis, myocardial degeneration and fibrosis, and the development and complications of aortic, carotid, and coronary atherosclerotic lesions, among others.[5-7]

The massive *per capita* consumption of minor plastic by-products, amounting to tens of kilograms annually in industrialized nations (400 tons worldwide production[8]), must have consequences for human health that are not yet precisely identified or quantified. For example, the pandemic explosion of obesity has been parallel to the skyrocketing increase in the production and human consumption of micro, submicro, and nanoplastics, although, of course, both problems can be independent in origin, even if the one and the other are expressions of the ecocide behavior and unhealthy living habits of contemporary human beings. Some authors have found that the imbalance of the caloric intake/energy expenditure pair is not the only cause of the considerable increase in

* Editor, Cardiovascular and Metabolic Science. Professor and Researcher. Laboratorios de Cardiología y Fisiología del Ejercicio, e Investigación Cardiometabólica Integral, Sección de Estudios de Postgrado e Investigación de la Escuela Superior de Medicina. Instituto Politécnico Nacional. Mexico City, Mexico. ORCID: 0000-003-0377-4645

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body weight in the population of industrialized societies, pointing out that there must be other determinants of body weight, beyond the increase in caloric intake from the diet and the diminished energy expenditure from physical exercise.[9] The term «obesogenic»[10,11] has been recently coined to identify those substances that can increase the number and size of adipocytes, their differentiation and storage capacity, or their regulation, disrupting energy or lipid metabolism, and causing weight gain.[12] These substances (alone or mixed), called generically Endocrine-Disrupting Chemicals (EDC), can interfere with relevant aspects of hormonal and energetic metabolism.[10]

The tiny size of microplastics and nanoparticles allows not only easy penetration but also rapid diffusion throughout all organic compartments, crossing cell membrane barriers without difficulty and accumulating in lymphatic cells, the liver, the skin, and the brain, among many other systems and tissues.[12] Some plastics like polyethylene (PE), polypropylene (PP), and polystyrene (PS), in addition to plastic additives like phthalates, bisphenols, polybrominated diphenyl ethers, and organotins, among others,[13] can disrupt normal energetic physiology, eliciting strong immune, inflammatory, and nitroxidative reactions, as well as direct genome and mitochondrial damage.[13]

There are no easy, straightforward solutions to solve complex human problems. Human society must first be aware of the magnitude of the threat to act accordingly. To date, people are relatively aware of atmospheric pollution, the need to use water rationally, and the duty to manage garbage more effectively. Unfortunately, plastic pollution is less perceived. Few laypeople are fully aware of the real and potential damage caused by this particular type of pollution. A substantial proportion of physicians are either unaware of this and therefore cannot convey preventive messages to their patients. The first step, then, is to increase knowledge in this field, since the goal of prevention is achieved by following the path of understanding and recognition of the problem. Our Editorial Committee intends to invite an expert in the field to write a comprehensive review for the journal on the relationship between plastic pollution and cardiovascular and cardiometabolic diseases.

However, the final solution is rather more complex. It is not enough, in stores and supermarkets, to replace plastic bags and wrappers with other materials, such as paper (whose manufacture requires using wood, which contributes to deforestation, another very serious environmental problem). Nor is personal refusal to use single-use plastic products (diapers, straws, containers, etc.) sufficient, although it does help. Replacing all current plastic products with biodegradable alternatives is mandatory, but it is economically costly and technically complex. The industry alone will not do it. Government regulation, supported by a wide social consensus, is essential to achieving plastic conversion. Powerful economic and political forces will fight this change, as it represents a major effort and sacrifice by industry, commerce, and their allied governments. As is well known, when public health is pitted against profit, the latter usually wins.

Aside from the above, the present editorial serves as a call to action, urging us to incorporate plastic pollution into our preventive thinking. This preventative awareness is embodied in the splendid motto of our beloved association: «prevention is our goal».

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Correspondence:
Eduardo Meaney, MD, PhD
E-mail: lalitomini1@gmail.com

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ORIGINAL RESEARCH

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A comparative evaluation of sacubitril-valsartan and nebivolol-valsartan in left ventricular remodeling following chronic myocardial infarction in female Wistar rats

Evaluación comparativa de sacubitril-valsartán y nebivolol-valsartán en la remodelación ventricular izquierda tras un infarto de miocardio crónico en ratas Wistar hembras

Erika Pérez-García,* Ignacio Valencia-Hernández,‡ Diego Lezama-Martínez,§ Diana Ramírez-Hernández,¶ Germán Isauro Garrido-Fariña,‖ César Ramírez-Hernández,** Karla Reyes-Alvarado,‡‡ Isabel Hidalgo,§§ Jazmín Flores-Monroy¶¶

Keywords: cardiac remodeling, fibrosis, sacubitril-valsartan, histology, female rats.

Palabras clave: *remodelación cardiaca, fibrosis, sacubitril-valsartán, histología, ratas hembras.*

ABSTRACT

Cardiac fibrosis following a myocardial infarction (MI) leads to adverse left ventricular remodeling and heart failure, with distinct patterns observed in women. Despite having smaller infarcts and less profibrotic activity, women have a higher risk of post-MI mortality and heart failure. Since on therapies currently target fibrosis directly, studying these mechanisms is essential for developing and testing treatments, including approved heart failure drugs such as sacubitril–valsartan. This study aimed to compare and evaluate the combination of nebivolol-valsartan (NV) vs sacubitril-valsartan (SV) as a known treatment for chronic infarction in female rats; 26-weeks-old Wistar rats were used. The animals were divided into four groups (n = 6): 1) control (SHAM); 2) myocardial infarction (LADL); 3) LADL + sacubitril 30 mg/kg/day + valsartan 28 mg/kg/day (LADL + SV); 4) LADL + valsartan 30 mg/kg/day + nebivolol 5 mg/kg/day (LADL + NV). Infarct induction was performed by permanent ligation of the left anterior descending coronary artery. The treated groups received their treatments right after infarct induction for two weeks. The rats were euthanized by cervical dislocation and hearts and lungs were obtained from all groups for histology using Van Gieson and HE staining. The NV combination resulted in 50% mortality in animals, promoting pulmonary congestion and pleural effusion. Therefore, the administration of the NV combination at different times was proposed, after three and seven days post-infarction. This

RESUMEN

La fibrosis cardiaca tras un infarto de miocardio (IM) provoca una remodelación ventricular izquierda adversa e insuficiencia cardiaca, observándose patrones distintos en las mujeres. A pesar de presentar infartos de menor tamaño y una menor actividad profibrótica, las mujeres tienen un mayor riesgo de mortalidad tras un IM y de insuficiencia cardiaca. Dado que las terapias actuales se dirigen directamente a la fibrosis, el estudio de estos mecanismos es esencial para desarrollar y evaluar tratamientos, incluidos los fármacos aprobados para la insuficiencia cardiaca, como el sacubitril-valsartán. El objetivo de este estudio fue comparar y evaluar la combinación de nebivolol-valsartán (NV) frente a sacubitril-valsartán (SV) como tratamiento conocido para el infarto crónico en ratas hembras. Se utilizaron ratas Wistar de 26 semanas de edad. Los animales se dividieron en cuatro grupos (n = 6): 1) control (SHAM); 2) infarto de miocardio (LADL); 3) LADL + sacubitril 30 mg/kg/día + valsartán 28 mg/kg/día (LADL + SV); 4) LADL + valsartán 30 mg/kg/día + nebivolol 5 mg/kg/día (LADL + NV). La inducción del infarto se realizó mediante ligadura permanente de la arteria coronaria descendente anterior izquierda. Los grupos tratados recibieron sus tratamientos inmediatamente después de la inducción del infarto durante dos semanas. Las ratas fueron sacrificadas mediante dislocación cervical y se extrajeron los corazones y los pulmones de todos los grupos para su análisis histológico mediante tinción de Van Gieson y HE. La combinación de

* MS, Laboratory of Myocardial Pharmacology, Facultad de Estudios Superiores Cuautitlán (FES-C), Universidad Nacional Autónoma de Mexico (UNAM). Cuautitlán Izcalli, Estado de México, México. ORCID: 0009-0007-3578-3817
‡ PhD, College of Medicine, Instituto Politécnico Nacional. Mexico City, Mexico. ORCID: 0000-0001-7526-3524
§ PhD, Laboratory of Myocardial Pharmacology, FES-C,

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UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0000-0003-1899-3736
¶ PhD, Laboratory of Myocardial Pharmacology, FES-C, UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0000-0002-5624-1693
‖ PhD, Histology and Biology Support Laboratory. FES-C, UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0000-0003-2137-9315
** Bachelor´s degree, Laboratory of Myocardial Pharmacology, FES-C, UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0009-0004-8125-3137
‡‡ Bachelor´s degree, Laboratory of Myocardial Pharmacology, FES-C, UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0009-0006-6504-1606
§§ PhD, Immunology and Public Health Research Laboratory. FES-C, UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0000-0003-0276-9414
¶¶ PhD, Laboratory of Myocardial Pharmacology, FES-C, UNAM. Cuautitlán Izcalli, Estado de México. ORCID: 0000-0002-0431-5427

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resulted in six experimental groups. There was a reduction in the mortality rate, reduction of hypertrophy and cardiac fibrosis when the NV combination was administered seven days after ligation. In conclusion, sacubitril–valsartan appears to be a safe and effective strategy to attenuate cardiac and pulmonary fibrosis after infarction female rats, however, based on the results, early administration of nebivolol-valsartan is not recommended, as it appears to increase the risk of post-infarction complications.

NV provocó una mortalidad de 50% en los animales, lo que favoreció la congestión pulmonar y el derrame pleural. Por lo tanto, se propuso la administración de la combinación de NV en diferentes momentos, a los tres y a los siete días tras el infarto. Esto dio lugar a seis grupos experimentales. Se observó una reducción de la tasa de mortalidad, así como de la hipertrofia y la fibrosis cardiaca, cuando la combinación de NV se administró siete días después de la ligadura. En conclusión, el sacubitril-valsartán parece ser una estrategia segura y eficaz para atenuar la fibrosis cardiaca y pulmonar tras el infarto en ratas hembras, mientras que la administración temprana de nebivolol-valsartán no se recomendaría de acuerdo a los resultados, ya que aparentemente podría generar más complicaciones postinfarto.

Abbreviations:
CVDs = Cardiovascular Diseases
HF = Heart Failure
HFrEF = Heart Failure with Reduced Ejection Fraction
LADL = Left Anterior Descending Artery Ligation
MI = Myocardial Infarction
NV = Nebivolol-Valsartan
RAAS = Renin Angiotensin Aldosterone System
SNS = Sympathetic Nervous System
SV = Sacubitril-Valsartan

INTRODUCTION

Cardiovascular Diseases (CVDs) are the leading cause of morbidity and mortality in women worldwide, surpassing even the impact of other pathologies such as breast cancer.[1] Despite their high incidence, women are notably under in clinical and preclinical studies. This underrepresentation has limited the development of effective and safe therapeutic strategies specifically targeted at this population. To reduce this knowledge gap and improve the diagnosis and treatment of CVDs in women, various health campaigns have promoted the study of these diseases and their complications from a gender perspective has been promoted through various health campaigns.[2]

Cardiac fibrosis following Myocardial Infarction (MI) plays a central role in adverse left ventricular remodeling and the progression to heart failure, a major cause of morbidity and mortality worldwide.[3] Because mammalian hearts have a limited capacity to regenerate after injury, dead tissue must be replaced with collagen, which decreases the function of the repaired organ.[4] In the case of the heart, this process can be divided into three phases. The first phase involves tissue damage from ischemia. The second phase involves scarring, which takes between four and six weeks in humans and three to five days in rodents. The third phase involves the complete replacement of tissue with collagen, which takes up to eight weeks in humans and seven to nine days in a rodent.[5,6] However, evidence shows that MI characteristics, remodeling patterns, and clinical outcomes differ significantly between men and women.[7] Women are generally less likely to develop spherical left ventricular geometry and severe dysfunction. This is partly due to smaller infarct size, reduced microvascular obstruction, and attenuated activation of inflammatory and profibrotic pathways. These factors are potentially influenced by estrogen, even after menopause.[8] However, despite having a lower prevalence of obstructive coronary artery disease and Heart Failure with Reduced Ejection Fraction (HFrEF), women paradoxically have higher mortality rates after myocardial infarction, as well as higher rates of reinfarction and hospitalization for Heart Failure (HF), which are often linked to microvascular dysfunction and impaired myocardial perfusion.[9] Studying mechanisms of cardiac fibrosis and remodeling in females is crucial for identifying therapeutic strategies tailored to women's needs and improving their outcomes. Heart complications and acute HF after MI are potentially serious complications affecting the lungs and kidneys. Increased concentrations of natriuretic peptides promote pulmonary capillary

wedge pressure generating lung crackles; which can lead to congestion and edema.[10]

Currently, there are no drugs that are specifically approved for directly reversing or reducing myocardial fibrosis,[11] although some HF therapies have demonstrated indirect antifibrotic effects. In this regard, Sacubitril-Valsartan (SV), a combination of a neprilysin inhibitor (sacubitril) and an angiotensin II receptor antagonist (valsartan), has been shown to provide clinical benefits to patients with HFrEF,[12] including reduced mortality and hospitalizations. Conversely, therapeutic combinations such as Nebivolol-Valsartan (NV) have shown promising results in models of arterial hypertension in male Wistar rats, primarily due to nebivolol's vasodilatory and oxidative stress-modulating properties of nebivolol, combined with valsartan's AT1 receptor blocking effect.[13] However, most studies supporting these effects have been conducted in predominantly male cohorts or have not included sex-specific analysis, so its effectiveness and safety in women remain uncertain.[14] Furthermore, the impact of this combination on models of post-infarction myocardial injury, particularly in female participants, has not been widely explored.[15]

Against this backdrop, the present study evaluated the pharmacological combination of valsartan and nebivolol (NV) in an experimental model of chronic myocardial infarction in female Wistar rats. The aim was to determine its impact on functional and structural heart parameters, such as myocardial fibrosis, cardiac hypertrophy, and mortality rate. Furthermore, the efficacy and tolerability of this combination were compared with those of the standard SV treatment in post-ischemic conditions.

MATERIAL AND METHODS

Thirty female Wistar rats, aged 26 weeks, were used. All the animals were fed LabDiet 5001 and given access to tap water ad libitum. The rats were obtained from the Faculty of Higher Studies Cuautitlán (Facultad de Estudios Superiores Cuautitlán [FES-Cuautitlán]) animal facility. The protocol was carried out in two phases. In the first phase the animals were divided into four groups (n = 6) as follows: 1) sham control (SHAM); 2) Left Anterior Descending Artery Ligation (LADL); 3) LADL + sacubitril-valsartan; 4) LADL + nebivolol-valsartan. The combined drug doses were: sacubitril (calcium salt) + valsartan (free base): 58 mg/kg/day (30 mg of valsartan and 28 mg of sacubitril calcium salt, equivalent to 26.7 mg of sacubitril free base), nebivolol (hydrochloride) + valsartan 35 mg/kg/day (5 mg of nebivolol hydrochloride, equivalent to 4.6 mg of nebivolol free base and 30 mg of valsartan). The doses were administered orally on the day of surgery using a gastric tube, dissolved in a small volume of water. The treatment lasted two weeks. Since a high mortality index was found with NV treatment, two additional groups were included in a second phase of the study: 5) LADL + nebivolol-valsartan administered three days after LADL (LADL + NV 3D); 6) LADL + nebivolol-valsartan administered seven days after LADL (LADL + NV 7D) as shown in *Figure 1*. These timings were chosen because nebivolol, being a beta-blocker, can have a rebound effect in the first few hours after a myocardial infarction. This allowed post-infarction compensatory mechanisms to activate, thus preventing a malcompensatory effect with Nebivolol. At the end of the treatment period, the animals were euthanized by cervical dislocation and heart and lung tissue samples were obtained. In cardiac tissue, the infarct area was measured using tetrazolium blue staining. Histology was performed on left ventricle and lung tissue using hematoxylin and eosin and van Gieson staining. The care and use of the animals were conducted in strict accordance with the Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press). All procedures described herein were approved by the Internal Bioethics Committee of our institution (protocol number FES-01/16-05-2017) and complied with the Mexican Official Standard (NOM-062-ZOO-1999), which establishes the technical specifications for the production, care, and use of laboratory animals. The Ethics Committee on the Care of Experimental Animals (CICUAE-FESC by its spanish meaning) approved this protocol under registration number CICUAE-FESC C 24_08.

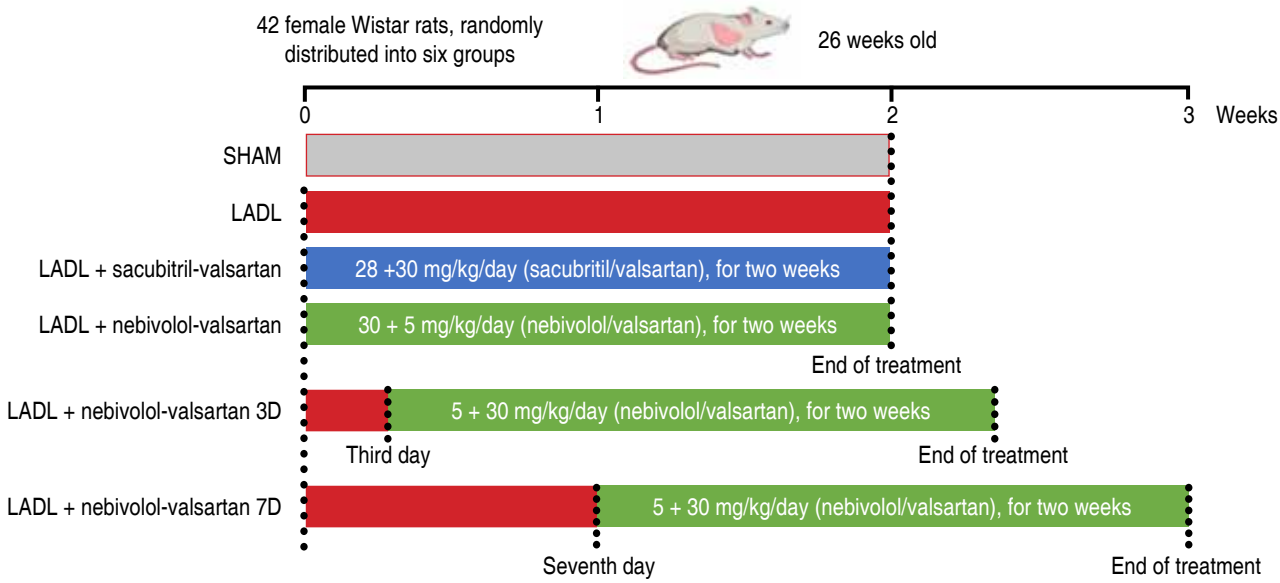

Figure 1: Experimental design.
LADL = Left Anterior Descending Artery Ligation.

Drugs. Valsartan free base, pure reagent from Sigma Aldrich®, sacubitril calcium salt, pure reagent from Sigma Aldrich®, and nebivolol hydrochloride, pure reagent from Sigma Aldrich®, were used. The drugs were dispersed in a solution of purified water containing 0.5% Poloxamer 401® for subsequent administration to the rats via gastric tube.

Left Anterior Descending Artery Ligation (LADL). The LADL surgery was performed during the estrous stage of the rats, since a previous study conducted by our team found that infarct progression is more severe at lower estrogen levels during the estrous cycle.[16] Prior to surgery, the rats were anaesthetized with an intraperitoneal injection of 20 mg/kg of ketamine + 9 mg/kg of xylazine. Once under surgical anesthesia, an incision was made through the third left intercostal space to allow exteriorization of the heart and location of the left anterior coronary artery, which was ligated with a 5-0 suture. The heart was the returned to the thoracic cavity, and the muscle and skin were sutured with 3-0 sutures. To allow for postoperative recovery, tramadol (6 mg/kg) and antibiotic cream (gentamicin) were administered. As our group has analyzed the progression of infarction according to the estrous cycle, the phases were only determined at the time of ligation surgery.

Samples for histology. To obtain cardiac and lung tissue samples, the Wistar rats were euthanized by cervical dislocation. A 100 mg portion of the left ventricle penumbra and 100 mg of the apex of the lung were removed and placed in a Petri dish containing physiological saline (0.9% NaCl), before being perfused with saline solution. The samples were then transferred to a 4% buffered formalin solution in Phosphate-Buffered Saline (PBS) at pH 7.4. The samples were stored in a refrigerator at 4 ºC for later use.

Mortality rate. To calculate the mortality rate, the number of deaths in each experimental group was quantified, and the ratio of live to dead individuals was obtained to determine the percentage.

Quantification of the infarct area. Once extracted, the heart was perfused with a physiological saline solution, wrapped in parafilm, frozen at −20 ºC for approximately one hour, and then cut into transverse slices of approximately 3 mm. These slices were placed in a 10 mL Falcon tube wrapped in aluminum foil and containing a 1% tetrazolium blue solution. The tube was then incubated at

37 ºC for 20 minutes with shaking. Finally, the stained tissue was placed between two glass slides. Photographs were captured, and the infarct area was quantified using Motic Images Plus 3.0 software.

Pulmonary and cardiac hypertrophy. This was calculated by measuring the length of each rat's tibia and weighing its heart or lung. The ratio of organ weight to tibia length was then obtained.

Histology of cardiac and lung tissue. Samples of left ventricle penumbra and lung tissue were dehydrated and embedded in paraffin. These samples were then cut into 10 µm-thick sections using a microtome. These sections were fixed on a slide. To clearly observe the collagen deposition, the van Gieson staining technique was used. The samples were be deparaffinized and hydrated by immersing the slides first in a xylene solution, then in a 1:1 mixture of ethanol and xylene, and finally in ethanol solutions, ranging from 100 to 50%. The deparaffinized samples were stained with Weigert's haematoxylin for 10 minutes. Finally, they are rinsed with distilled water and stained with Van Gieson's solution (acid fuchsin and picric acid) for three minutes. Finally, the sample is dehydrated.

Quantification of collagen in the myocardium. The percentage of collagen deposition will be measured in the left ventricular area of the samples stained with Van Gieson stain. First, a microscopic scan will be performed to identify the areas of high collagen content in the septum and the free wall of the left ventricle. These areas were then observed and images captured using AmScope software (version 4.11.20131.20220108). This procedure involves measuring three different fields for the same sample. Then, the amount of collagen present in each image will be measured using Motic Images Plus 3.0 software. Finally, the percentage of collagen deposition will be obtained by calculating the ratio of collagen-containing tissue to total tissue.

Statistical analysis. Data processing was performed using the mean ± standard error for each group (n = 6). Two-way ANOVA was used, with treatment and the gender of the Wistar rats as the two factors. Tukey's test was used as a *post hoc* test. Significant differences were considered when $p < 0.05$ and the statistical power was greater than 0.8. Mortality rates were analyzed using a contingency table and analyzed using Fisher's exact test.

RESULTS

Figure 2A shows a mortality rate of 16.6% in the untreated myocardial infarction group. In contrast, nebivolol-valsartan treatment administered right after the infarction resulted in a mortality rate of 50%. When Nebivolol-valsartan treatment was administered three days after the infarction, the mortality rate was also 16.6% notably, most of these deaths occurred during the first week of treatment. On the other hand, neither SHAM, nor sacubitril-valsartan treatment administered immediately after the infarction resulted in any deaths, nor did nebivolol-valsartan treatment administer seven days after the infarction. *Figure 2B* shows the percentage of infarct area according to the experimental group. The LADL group had an infarct area of 33%, which decreased to 22% with nebivolol-valsartan treatment administered immediately after the infarction. However, the treatments administered three and seven days after the infarction did not decrease the infarct area vs the LADL group. On the other hand, sacubitril-valsartan treatment administered immediately after the infarction decreased the infarct area by 15%, making it the most effective treatment for reducing the damaged area. *Figure 2C* shows the cardiac hypertrophy index graph, represented as a ratio of heart weight to tibial length, according to the experimental groups. There were no significant differences between groups.

Figure 3 (left), shows the graph of cardiomyocyte area according to the experimental groups. The cardiomyocyte area of the SHAM group was 129 μm^2. Following infarction, the size of the cardiomyocytes increased to 175 μm^2. The same result was observed following nebivolol-valsartan administration immediately after the infarction, with an area of 184 μm^2. This was no different to the infarcted group. Furthermore, the treatments administered three and seven days post-infarction produced similar results, with values of 192 and 175 μm^2, respectively. Sacubitril-

valsartan treatment, reversed this effect, significantly decreasing the cardiomyocyte area compared to the infarct, with a value of 148 μm^2, and showing no difference compared to the SHAM group. *Figure 3* (right) shows the morphology of the cardiomyocytes as seen with H&E staining. *Figure 3A* shows the myocytes of the SHAM group, which have a well-defined oval shape (black circles) with well-defined nuclei marked in purple (black arrows). *Figure 3B*, shows the cardiomyocytes corresponding to the infarcted group. Here, cell growth and loss of structure are notable and the cardiomyocytes have lost their characteristic oval shape (black circles). Furthermore, the nuclei appear diffuse and show loss of structure, as they appear elongated (black arrows), which could indicate cell necrosis. *Figure 3C* shows cardiomyocytes from the nebivolol-valsartan treatment group. These have a structure similar to the SHAM group, with oval/circular myocytes (black circles) and a preserved structure. However, some cells have absent nuclei and others have elongated nuclei (black arrows), which could indicate myocyte necrosis. *Figure 3D*, shows myocytes from the nebivolol-valsartan treatment group where the treatment was initiated three days after the infarction. The cells are more organized and have their characteristic oval or circular shape. The presence of nuclei in most cells, with a characteristic round shape, is also evident. *Figure 3E* shows myocytes from the nebivolol-valsartan treatment group where the treatment was initiated seven days after the infarction. The cells are very similar to those from treatment that was initiated three days after the infarction. They are organized and have their usual shape (oval/circular). Furthermore, the nuclei are circular, and are present in most cells, ruling out cell necrosis. Finally, *Figure 3F* shows the cardiomyocytes from the sacubitril-valsartan group, which were administered immediately after infarction. These cardiomyocytes are elongated and rectangular in shape (black circles) and organized, with the nuclei located in the center of most cells and retaining their usual circular shape.

Figure 4 (left) shows the collagen content graph for each experimental group. It shows that the infarction increases collagen content

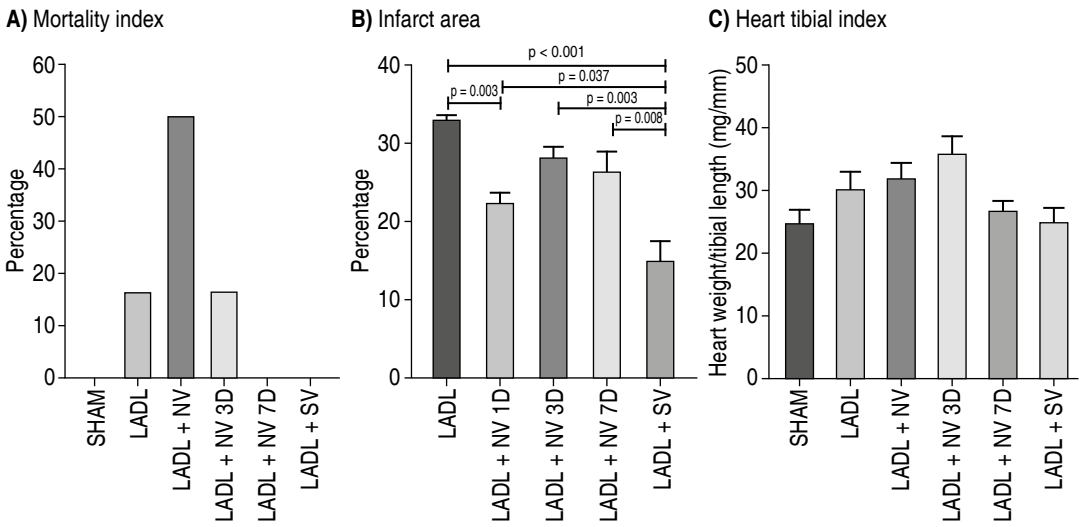

Figure 2: Physiological effects of the treatments.
A) Shows mortality rates for the different experimental groups. The results are presented as a percentage of total deaths, with n = 6 rats per experimental group. The mortality rate was analyzed using Fisher's exact test. No significant differences were found. **B)** Indicates the infarct area during the estrous stage of female Wistar rats in the different experimental groups. **C)** Points cardiac hypertrophy index, ratio of heart weight to tibial length for each experimental group. Results are presented as mean ± SE, n = 6 rats per experimental group. Analysis was performed using a one-way ANOVA, followed by a Tukey *post hoc* test. Significant differences were obtained when $p < 0.05$.

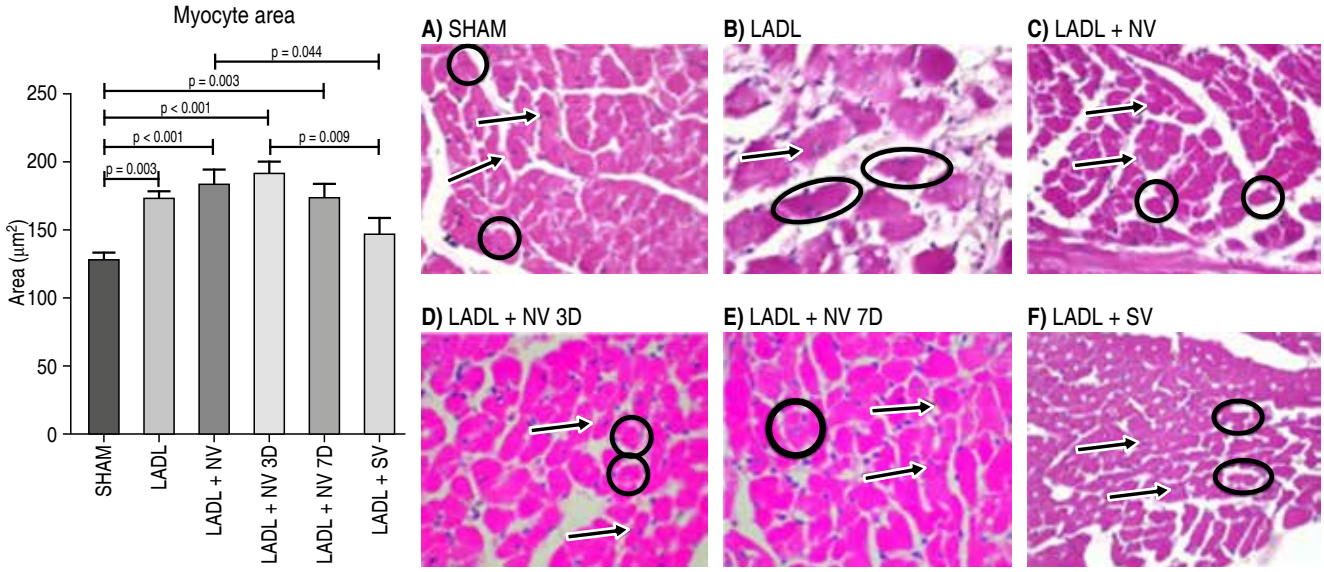

Figure 3: Cardiac tissue integrity evaluated by Hematoxylin-eosin staining.
Left shows cardiomyocyte area of female Wistar rats in the different experimental groups. Results are presented as mean ± SD, n = 6 rats per experimental group. Analysis was performed using a one-way ANOVA, followed by a Tukey post hoc test. Significant differences were obtained when $p < 0.05$. **Right** point cardiomyocytes seen with H&E staining at 40× magnification in the experimental groups: **A)** SHAM, **B)** LADL, **C)** LADL + NV, **D)** LADL + NV3D, **E)** LADL + NV7D, **F)** LADL + SV.

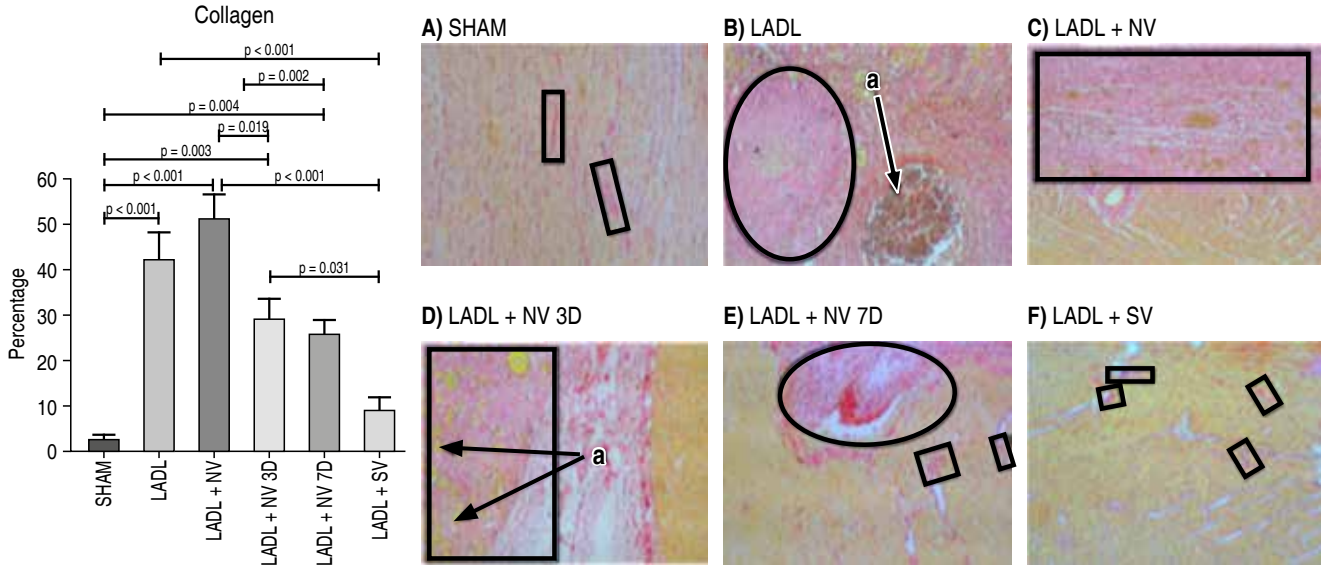

Figure 4: Collagen deposition in the heart by van Giesson staining.
Left shows Percentage of collagen in cardiac tissue of female Wistar rats from each experimental group. Results are presented as mean ± SD, n = 6 rats per experimental group. Analysis was performed using a one-way ANOVA followed by a Tukey *post hoc* test. Significant differences were obtained when $p < 0.05$. **Right** shows Collagen present in the cardiac tissue of a female Wistar rat seen with Van Gieson staining at 40× magnification in the experimental groups: **A)** SHAM, **B)** LADL, **C)** LADL + NV, **D)** LADL + NV3D, **E)** LADL + NV7D, **F)** LADL + SV.

in cardiac tissue by 40%, whereas the SHAM group has a collagen content of just 3%. The nebivolol-valsartan treatment shows a collagen content of 51%. Meanwhile, the treatments administered after three and seven days showed a decrease in collagen content of 29 and 26%, respectively. Finally, the sacubitril-valsartan treatment was observed to significantly decrease collagen content by 9%, showing no difference to the SHAM group. *Figure 4* (right) shows collagen deposition in the cardiac tissue of the experimental groups. *Figure 4A* shows the SHAM group, which exhibits small areas of interstitial collagen deposition (black rectangle), though cardiac tissue predominates. *Figure 4B* shows the infarcted group. The infarct suture is observed, and the infarcted area (black circle) surrounding it are visible, as well as a large amount of collagen, which indicates the size of the infarct. *Figure 4C* shows the nebivolol-valsartan treatment. A large area of collagen (black rectangle) is visible at the top, indicating the area affected by the infarct. *Figure 4D* shows the nebivolol-valsartan treatment administered three days after infarction. Large areas of collagen (black rectangle) deposition are still evident, although remnants of cardiac tissue are presented within the collagen (arrows labelled «a»). *Figure 4E* shows the nebivolol-valsartan treatment administered seven days after the infarction. There is a decrease in the amount of collagen in the cardiac tissue. Collagen is present in the upper portion (black circle). The rest of the tissue appears normal with slight interstitial collagen deposition (black rectangle). Finally, *Figure 4F* shows the sacubitril-valsartan treatment. Small areas of interstitial collagen deposition are observed (black rectangles), mostly in the cardiac tissue. This indicates that the treatment effectively reduces cardiac tissue death.

Figure 5 (left) shows the pulmonary hypertrophy index for each experimental group. No differences were observed between the experimental groups, indicating that neither the infarction nor the treatments administered immediately after the infarction or three or seven days afterwards modified lung size. *Figure 5* (right) shows lung tissue samples stained with haematoxylin and eosin at 40× magnification. *Figure 5A* shows lung tissue from the SHAM group and reveals a well-defined lung structure is observed, including the alveolar septum («a» arrow) and the alveolar sacs («b» arrow), both of which are a defined size. *Figure 5B* representing the infarcted group, shows a complete loss of alveolar structure, with the alveolar septum and alveolar sacs no longer distinguishable. This is indicative of lung damage. Furthermore, in the area enclosed by the black circle, shows a massive infiltration of leukocytes (black circle), indicating an inflammatory process. *Figure 5C*, representing the nebivolol-valsartan treatment, show that the alveolar structure has slightly recovered. The alveolar septum and alveolar sacs can now be distinguished. There is no leukocyte infiltration. However, the alveolar septum appears quite thick, and the alveolar sacs are very small. *Figure 5D* shows the nebivolol-valsartan treatment administered three days post-infarction, where thickening of the alveolar septum is evident. *Figure 5E*, shows nebivolol-valsartan treatment administered seven days post-infarction. Recovery of the lung structure is evident, with decreased thickness of the alveolar septum and increased in the size of the alveolar sac. Finally, *Figure 5F*, shows the sacubitril-valsartan treatment. Here, the lung structure is more defined, with a thinner alveolar septum and a larger alveolar sac and a well-defined bronchus («C» arrow).

Figure 6 (left) shows the extent of pulmonary fibrosis in each experimental group. It can be seen that treatment with nebivolol-valsartan does not reduce fibrosis caused by LADL surgery at any administration time point, but sacubitril-valsartan treatment does decrease fibrosis to baseline values. *Figure 6* (right) shows collagen deposition in the lung tissue of the experimental groups. *Figure 6A* shows collagen deposition in the SHAM group, where the lung structure remains unchanged and the alveoli are clearly visible. The thin alveolar septa and wide alveolar lumen are marked with circles. No interstitial collagen deposition is observed, with only the cellular cytoplasm (black rectangles) visible. *Figure 6B* shows the infarcted group, where loss of lung structure is evident, with disappearance of the alveolar lumen and sharp increase in the alveolar septa (black circles). An increase in interstitial collagen deposition is also evident (black rectangles). *Figure 6C*

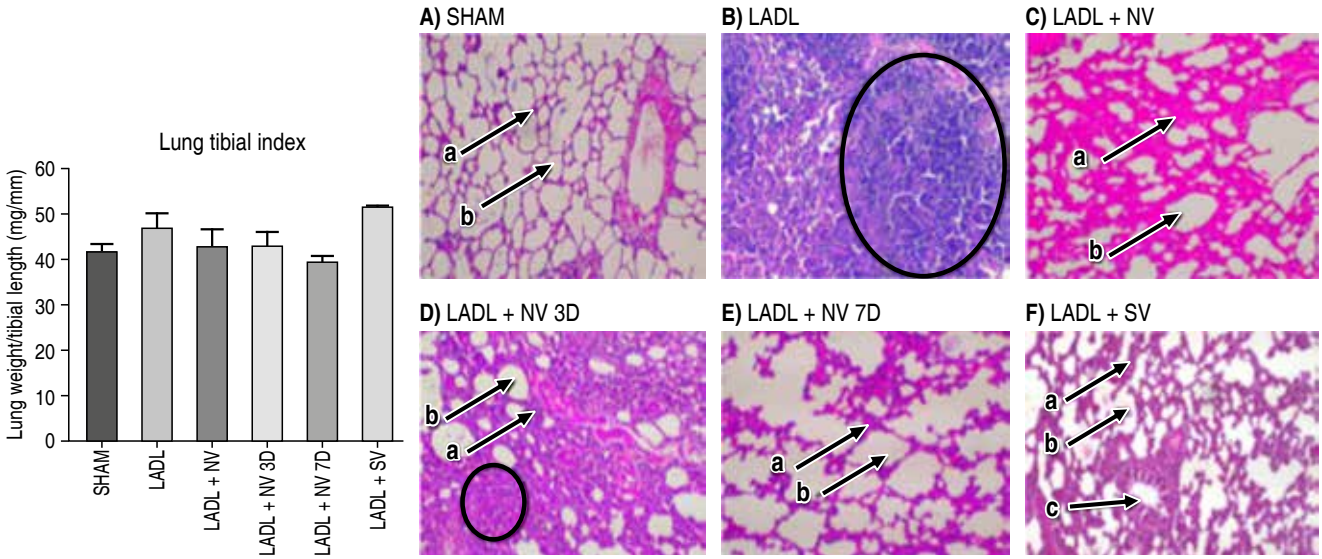

Figure 5: Lung tissue integrity evaluated by Hematoxylin-eosin staining of apex lung tissue.
Left indicate the pulmonary hypertrophy index, ratio of lung weight to tibial length for each experimental group. Results are presented as mean ± SD, n = 6 rats per experimental group. Analysis was performed using a one-way ANOVA. No significant differences were found. **Right** shows Female Wistar rat lung tissue seen with H&E staining at 10× magnification from the experimental groups: **A)** SHAM, **B)** LADL, **C)** LADL + NV, **D)** LADL + NV3D, **E)** LADL + NV7D, **F)** LADL + SV.

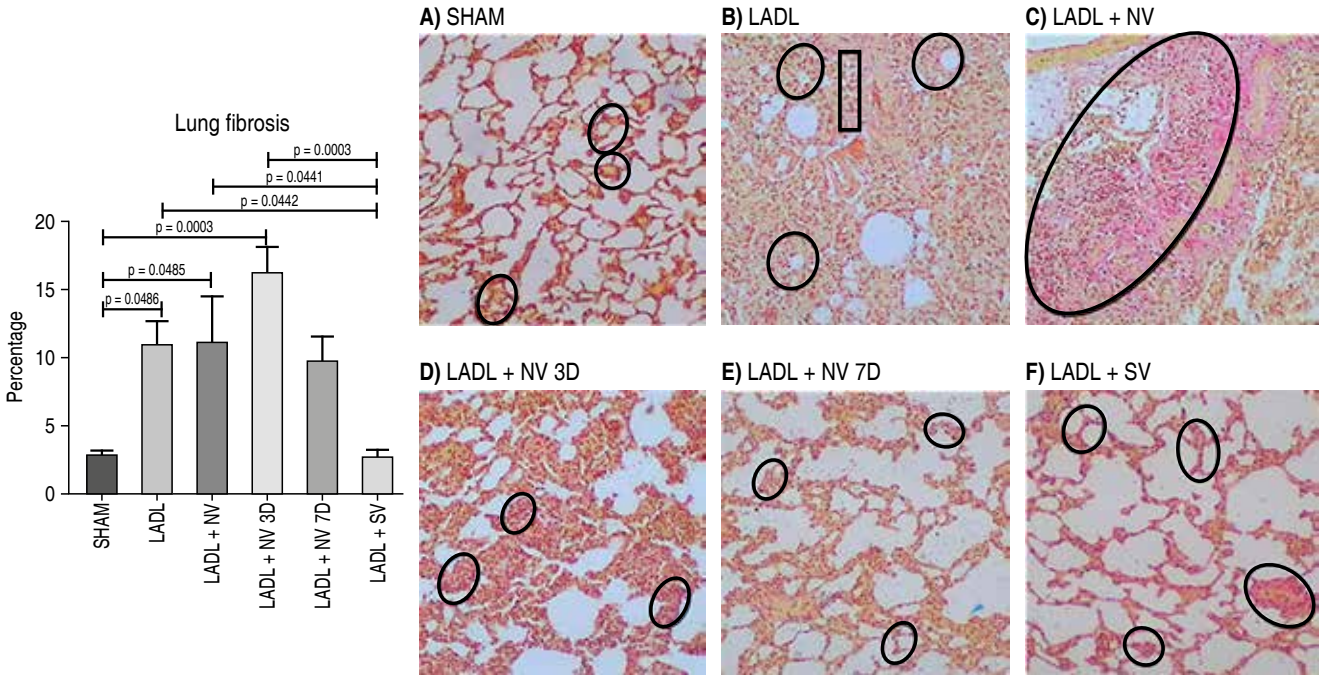

Figure 6: Collagen deposition in the lung apex by van Giesson staining.
Left indicates the collagen in lung tissue of female Wistar rats from each experimental group. The results are presented as mean ± SD, n = 6 rats per experimental group. Data were analyzed using one-way ANOVA followed by Tukey's *post hoc* test. **Right** shows collagen present in the lung tissue of a female Wistar rat seen with Van Gieson staining at 40× magnification in the experimental groups: **A)** SHAM, **B)** LADL, **C)** LADL + NV, **D)** LADL + NV3D, **E)** LADL + NV7D, **F)** LADL + SV.

shows collagen deposition in the nebivolol-valsartan treatment group. Loss of lung structure is evident here, with the alveolar septa and alveolar lumen no longer clearly visible. There is massive interstitial collagen deposition (black circle), which is even greater than that seen with the LADL. *Figure 6D* shows collagen deposition in the nebivolol-valsartan group administered three days after the infarction. Evident loose of lung structure is observed, while collagen deposition shows large areas of interstitial collagen (black circles) throughout all parts of the panel. *Figure 6E* shows collagen deposition in the nebivolol-valsartan group, which was administered seven days after the infarction. Although interstitial collagen deposition is still evident in various regions of the panel (black circles) a slight recovery of lung structure is observed. Finally, in *Figure 6F* shows that the sacubitril-valsartan group has recovered lung structure, with the alveolar septa and alveolar lumen visible. Regarding collagen deposition, the presence of interstitial fibrosis is evident (black circles), indicating that although treatment restores lung structure, it does not reduce pulmonary fibrosis.

DISCUSSION

In the present study, we evaluated the effects of two pharmacological combinations, sacubitril-valsartan (SV) and nebivolol-valsartan (NV), on cardiac and pulmonary remodeling following myocardial infarction in female Wistar rats. Our results demonstrated that these two treatments have markedly different effects on survival, myocardial structure and fibrosis. SV treatment was associated with reduced mortality, preserved cardiomyocyte morphology and reduced cardiac and pulmonary fibrosis. In contrast, early administration of NV resulted in increased mortality and more severe tissue damage. Delayed administration of NV partially improved some of these outcomes, suggesting that timing plays a critical role in the response to this therapy.

Cardiac fibrosis is the excessive deposition of extracellular matrix proteins,[5] most notably collagen. It occurs in most cardiovascular diseases, such as myocardial infarction. Initially, in this disease, fibrosis presents as a reparative process that maintains the structural integrity of the necrotic myocardium. However, as the disease progresses, it becomes a maladaptive process that increases the stiffness of cardiac tissue and puts stress on the left ventricular wall. This contributes to diastolic and systolic dysfunction, ultimately leading to heart failure,[17] which carries a poor prognosis for patients who develop it. In Wistar rats, the acute phase of infarction corresponds to the first seven days post-infarction, then the chronic phase begins, where fibroblast proliferation and collagen deposition for scar formation are observed.[18]

Animal mortality was due to lung complications and massive necrosis, as confirmed by measuring the infarct area and the staining of the lungs. In our study, we found that the infarcted group had areas of more than 30%. According to Pfeffer et al.,[19] large infarcts with areas greater than 30% increase mortality. However, the group treated with nebivolol-valsartan administered immediately after the infarction had a mortality rate of 50%. This contrasts with the results of various clinical studies, such as that of Puymirat et al.,[20] which found that administering beta-blockers such as atenolol, propranolol, and acebutolol early after the infarction improved patient survival within 30 days. It should be noted that the aforementioned clinical studies reported results based on the administration of a single drug, whereas our study involved a combination of therapy. When nebivolol-valsartan was administered for three days post-infarction, mortality was reduced, and no mortality was observed when it was administered seven days later. This suggests that at three days, the heart is still in the acute phase, and that blocking the initial compensatory systems may continue to affect cardiac function and lead to death. However, by seven days, the heart is in a chronic phase. Combined blockade of the Sympathetic Nervous System (SNS) and Renin Angiotensin Aldosterone System (RAAS) could therefore prevent or reverse the maladaptive changes caused by neurohumoral overstimulation. These results are similar to those observed by Xia et al.,[21] who administered fensartan three, 24, and 72 hours after myocardial infarction in male Wistar rats. They found that the infarct

area decreased compared to the infarcted group at three hours, 24 hours and seven days.

On the other hand, the sacubitril-valsartan treatment, did not cause mortality, and the infarcted area was very small, which is consistent with the observations of Liu et al.,[22] who administered sacubitril-valsartan to SHR rats with myocardial infarction. Similarly, Torrado et al.[23] used infarcted New Zealand white rabbits with myocardial infarction that were administered sacubitril-valsartan. In both studies, it was observed that the combined therapy decreased the infarct area compared to the infarcted group, with no deaths were reported during treatment. This can be attributed to the fact that SNS activation in the acute phase of the infarction is not blocked, and therefore, it carries out its adaptive effects of increasing blood pressure, ejection fraction, and contraction force, leading to the restoration of cardiac function.[24] Conversely, the sacubitril-valsartan combination has been shown to have an anti-inflammatory effect. Xiao et al.[25] found that administering this therapy to male C57BL/6 mice infarcted with reperfusion 30 minutes after infarction inhibited the NF-κB pathway. This could slow the initial inflammation, thereby limit myocardial necrosis and reduce the infarct area.

Collagen deposition in the left ventricle was measured to evaluate cardiac fibrosis and its progression following myocardial infarction. Treatment with nebivolol-valsartan did not reverse the effect generated by permanent ischemia. While there are no studies on the effects of this drug combination on fibrosis caused by MI, there is evidence supporting the antifibrotic effects of the drugs when used separately. Sui et al.[26] used infarcted Sprague-Dawley rats treated with valsartan and observed a decrease in collagen percentage compared to the infarcted group. Meanwhile, Zhang et al.[27] demonstrated that administering nebivolol via osmotic pumps to infarcted adult C57BL6/J mice reversed the fibrosis generated by LADL. Therefore, the results obtained with this drug combination contrast with those obtained experimentally. This finding could be explained, first, by the early onset of sympathetic blockade, which prevented the activation of the necessary compensatory mechanisms in the acute phase, such as RAAS and SNS. This exacerbated hypertrophy and, consequently, mechanical stress on the myocardium. This stress, in turn, can activate profibrotic pathways such as TGF-β/SMAD. Although nebivolol acts on β 3 receptors, promoting the production of nitric oxide (NO), with potential antioxidant and antifibrotic effects, this mechanism may not have been sufficient to counteract the intensity of the infarction and accentuated hypertrophy-induced damage. Additionally, simultaneously blocking the RAAS and the SNS could have generated a compensatory regulatory environment in which other pathways, such as the inflammatory or alternative fibroblastic pathways, took center stage. One such pathway is Endothelin-1, which is a strong fibrotic inducer.[28] Similarly, the increased necrosis observed in this group, reflected in higher mortality, could have induced a more intense inflammatory response, favoring the activation of profibrotic pathways such as NF-κB and SMAD.[11,25] Taking together, these results suggest that nebivolol-valsartan could have worsened fibrosis in this model and timeframe.

In contrast, sacubitril-valsartan treatment achieved the desired effect of reducing cardiac fibrosis. This finding is consistent with that reported by Vaskova et al.,[29] who used a chronic infarction model in Sprague-Dawley rats that were subsequently treated with sacubitril-valsartan. They observed that this treatment was effective in attenuating cardiac fibrosis and cardiac hypertrophy, suggesting a beneficial effect on post-infarction remodeling. This can be explained by the inhibition of neprilysin, which accumulates vasodilatory peptides such as bradykinin, and by blocking the AT-1 receptor. These actions both reduce the load on the ventricular wall and prevent the activation of fibrotic signaling pathways. Furthermore, other peptides such as natriuretic peptides, can inhibit tTGF-β/SMAD signaling via cGMP/PKG, as demonstrated by Burke et al.[30] Together, these findings demonstrate that sacubitril-valsartan administered immediately after myocardial infarction can effectively reverse induced cardiac fibrosis.

Finally, with regard to lung tissue histology, the LADL completely alters lung morphology and causes signific inflammation. These findings

are consistent with those of Chen et al.[31] in a pressure overload model in C57B6J mice, who demonstrated that left ventricular heart failure causes lung inflammation and thickening of the alveolar septum. These changes may have occurred due to the heart failure caused by the infarct, which decreases left ventricle end diastolic volume and generates increased pulmonary pressure, leading to fluid accumulation in the lung (increased alveolar septum thickness and leukocyte infiltration.[31] With nebivolol-valsartan treatment, however, no improvement in lung morphology was observed: the alveolar septa remained thickened, and the alveoli showed reduced lumens. However, a decrease in lung inflammation was observed. These results contrast with the beneficial effects attributed to these drugs, as demonstrated by Perros et al.[32] in a model of pulmonary hypertension model in male Wistar rats treated with monocrotaline. They found that Nebivolol improved cardiac function, lung remodeling, and inflammation. This could be explained by timing, since, when the combination was administered both immediately after the infarction and three days after LADL, the early blockade of the SNS with nebivolol could have worsened the depression of already compromised cardiac function. This would lead to a decrease in LVEDV, an increase in pulmonary pressure, and fluid accumulation in the alveoli. However, it seems that the anti-inflammatory effects of valsartan reduced the inflammation, as valsartan has been shown to modulate the MAPK and NF-kB pathways in the lung.[33] After seven days, considerable improvement in lung morphology was o, probably due to the restoration of cardiac function and the reduction in pulmonary pressure reported by Perros et al,[32] which helped reverse lung morphology.

Sacubitril-valsartan treatment showed improvements in lung morphology with thin alveolar septa and wide lumens observed. While there are currently no studies directly evaluating these effects on post-infarction lung tissue, the observed benefits could be explained by the previously described cardiovascular effects. Unlike the nebivolol-valsartan group, the sacubitril-valsartan group does not experience early sympathetic response blockades, which could allow transient cardiac function recovery and prevent LVEDV decrease and sustained pulmonary circulation pressure increase, leading to fluid accumulation in the lungs. This effect could also be potentiated by accumulated natriuretic peptides, since atrial natriuretic peptide was shown by Jin et al.[34] to decrease pulmonary pressure through its vasodilatory effect in hypoxic rats. Together with the anti-inflammatory effect of valsartan, this contributes to the reversal of the morphological and functional lung damage observed in this group.

Based on these results, we propose that the sacubitril-valsartan combination is a promising candidate for treating cardiac fibrosis in chronic myocardial infarction in females, as it was able to control the infarct area, reverse both cardiac hypertrophy and fibrosis, and restore pulmonary morphology. The alteration of this morphology contributes to the functional deterioration of the lungs. In contrast, nebivolol-valsartan, when administered immediately after the infarction, was not safe or effective in reversing fibrosis, hypertrophy, and post-myocardial infarction pulmonary damage, although improvements were seen when administered after seven days. We propose that this result is mainly due to the early blockade of the sympathetic response, the adverse effects of which have been discussed previously.

CONCLUSIONS

Our results suggest that sacubitril-valsartan represents a safer and more effective option for limiting post-infarction remodeling in females, whereas early nebivolol-valsartan administration may be detrimental.

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Correspondence:
Jazmín Flores-Monroy, PhD
E-mail: jfmqfb@cuautitlan.unam.mx

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Catheter ablation of frequent premature ventricular complexes: curative strategy for symptom relief

Ablación con catéter de complejos ventriculares prematuros frecuentes: una estrategia curativa para el alivio de los síntomas

Juan Carlos Ibarrola-Peña,*,‡,§,¶ Christian Giovanni Camacho-Mondragón,*,§,‖ Rafael García,*,** Erasmo De la Pena-Almaguer,*,§,‡‡ Mauricio Cortes-Aguirre§,§§

Keywords:
premature ventricular complexes, ventricular arrhythmias, catheter ablation, cardiomyopathies.

Palabras clave:
complejos ventriculares prematuros, arritmias ventriculares, ablación con catéter, miocardiopatías.

* Tecnológico de Monterrey. Escuela de Medicina y Ciencias de la Salud. Monterrey, Nuevo León, México.
‡ Departamento de Electrofisiología del Hospital Universitario Dr. José Eleuterio González.
§ Instituto de Cardiología y Medicina Vascular, TecSalud, Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey
ORCID:
¶ 0000-0003-4271-7512
‖ 0000-0002-6601-5251
** 0000-0001-6627-8249
‡‡ 0000-0003-3123-9594
§§ 0009-0006-3294-8252

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ABSTRACT

Introduction: premature ventricular complexes (PVCs) are linked to PVC-induced cardiomyopathy, functional deterioration, and poor quality of life (QOL). **Presentation of case:** a 54-year-old woman presented for evaluation with dyspnea and palpitations as her primary complaints. She was under follow-up for premature ventricular contractions (PVCs) and had been treated with oral antiarrhythmic therapy (bisoprolol). Despite improvement in chest pain, her response to treatment was poor. She experienced an increase in PVC frequency despite medication up-titration over a three-month follow-up period. She also reported a marked decline in functional capacity, characterized by exertional dyspnea, distress, and palpitations during moderate physical activity. Symptoms persisted at rest, with a significant negative impact on quality of life. As a result, she limited her physical activity to walking due to symptom burden and fear of palpitations. **Conclusion:** in selected cases, PVCs ablation can effectively relieve symptoms and enhance QOL.

RESUMEN

Introducción: *los complejos ventriculares prematuros (CVP) se asocian con miocardiopatía inducida por CVP, deterioro funcional y mala calidad de vida (CV).* ***Presentación del caso:*** *mujer de 54 años que acudió a valoración por disnea y palpitaciones como síntomas principales. Se encontraba en seguimiento por complejos ventriculares prematuros (CVP) y en tratamiento con terapia antiarrítmica oral (bisoprolol). A pesar de mejoría del dolor torácico, la respuesta al tratamiento fue pobre. Presentó incremento en la frecuencia de los CVP a pesar de la titulación ascendente del fármaco durante un periodo de seguimiento de tres meses. Asimismo, refirió un deterioro marcado de la capacidad funcional, caracterizado por disnea de esfuerzo, malestar y palpitaciones durante actividad física moderada. Los síntomas persistían en reposo, con un impacto negativo significativo en su calidad de vida. Como consecuencia, limitó su actividad física a caminar debido a la carga sintomática y al temor a las palpitaciones.* ***Conclusión:*** *en casos seleccionados, la ablación de los CVP puede aliviar eficazmente los síntomas y mejorar la calidad de vida.*

Abbreviations:
CMR = Cardiac Magnetic Resonance
ICE = IntraCardiac Echocardiography
LCC = Left Coronary Cusp
LVEF = Left Ventricular Ejection Fraction
LVGLS = Left Ventricular Global Longitudinal Strain
PVC = Premature Ventricular Complexes
QOL = Quality Of Life

INTRODUCTION

A high burden of premature ventricular complexes (PVCs) is associated with deterioration in ventricular function and quality of life (QOL). Current evidence demonstrates that frequent PVCs may lead to PVC-induced cardiomyopathy or aggravate pre-existing cardiomyopathy, particularly in patients with underlying structural heart disease.[1] A PVC

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burden exceeding 10% is generally considered the threshold above which the risk of developing ventricular dysfunction increases.[2] Predictors of PVC-related ventricular dysfunction include a superior PVC axis, non-sustained ventricular tachycardia, a short coupling interval, and male sex.[3] In clinical practice, differentiating PVC-induced cardiomyopathy from PVC-aggravated cardiomyopathy may be challenging, as there are often no definitive clinical or imaging markers to distinguish between the two entities. In many cases, the diagnosis is retrospective and supported by improvement in left ventricular ejection fraction (LVEF) following effective suppression of PVCs. Importantly, even in patients with previously established cardiomyopathy, catheter ablation may result in meaningful improvement in ventricular function.[4] Management strategies for PVCs depend on patient-specific factors and the anatomical location of the arrhythmogenic focus.[5] Catheter ablation may be performed using an endocardial, epicardial, or combined endo-epicardial «sandwich» approach, particularly when the focus is located in regions such as the left ventricular summit. While a PVC burden ≥ 10% supports consideration of catheter ablation, more extensive strategies, including combined approaches, are typically reserved for patients with a high PVC burden (generally ≥ 20-30%) or for those with refractory symptoms or ventricular dysfunction despite conventional endocardial ablation. The following case illustrates the diagnostic and therapeutic challenges associated with PVC-related cardiomyopathy.

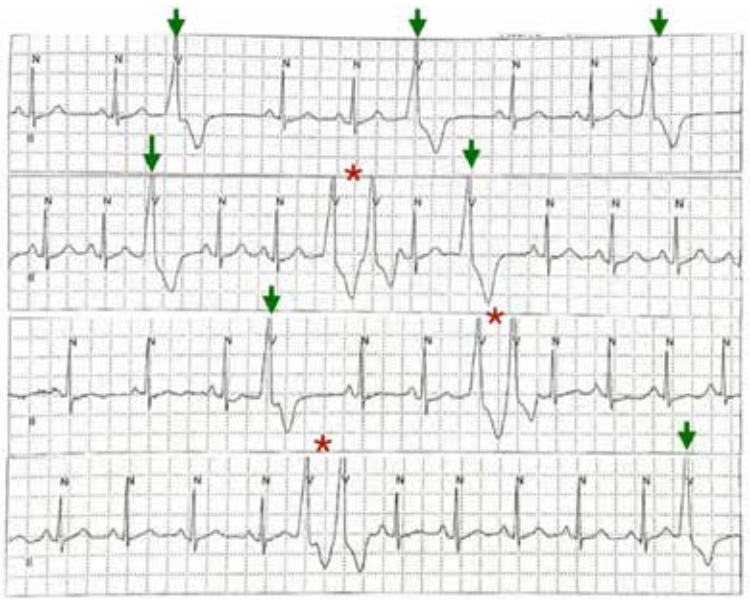

Figure 1: Ambulatory rhythm monitoring (Holter) demonstrating frequent monomorphic ventricular ectopic beats, primarily isolated (green arrow), occurring in a bigeminal pattern (red asterisks).

CASE PRESENTATION

History of presentation: a 54-year-old female presented for evaluation, reporting dyspnea and palpitations as her primary concerns. The patient was under follow-up for ventricular extrasystoles, treated with oral antiarrhythmic medication. Despite improving chest pain, the patient's response to treatment was poor. The patient had an increase in the frequency of PVCs despite the up-titration of her medication in a three-month follow-up. Furthermore, the patient had a notable decrease in functional capacity attributed to functional impairment, distress, and dyspnea during moderate exertion. The symptoms remain at rest, with an essential effect on the patient's quality of life. As a consequence, the patient was compelled to limit her physical activity to walking, considering their symptoms and palpitations fear.

Past medical history: the patient had a past medical history of myocarditis one year prior, presenting with dyspnea, chest pain, and acute heart failure with preserved ejection fraction. Cardiac magnetic resonance (CMR) at that time demonstrated an inferior and inferolateral fibrotic scar, with a left ventricular ejection fraction (LVEF) of 62% *(Figure 1)*. Following the acute event, PVCs persisted, and she remained classified as ACC/AHA stage B heart failure with NYHA functional class II symptoms. Post-myocarditis echocardiography revealed preserved biventricular systolic function, no regional wall motion abnormalities, grade I diastolic dysfunction, mild mitral regurgitation, and an LVEF within normal limits. A treadmill test was negative for ischemia and positive for arrhythmia due to frequent monomorphic PVCs. Holter monitoring demonstrated an 11% burden of monomorphic PVCs, with symptom-

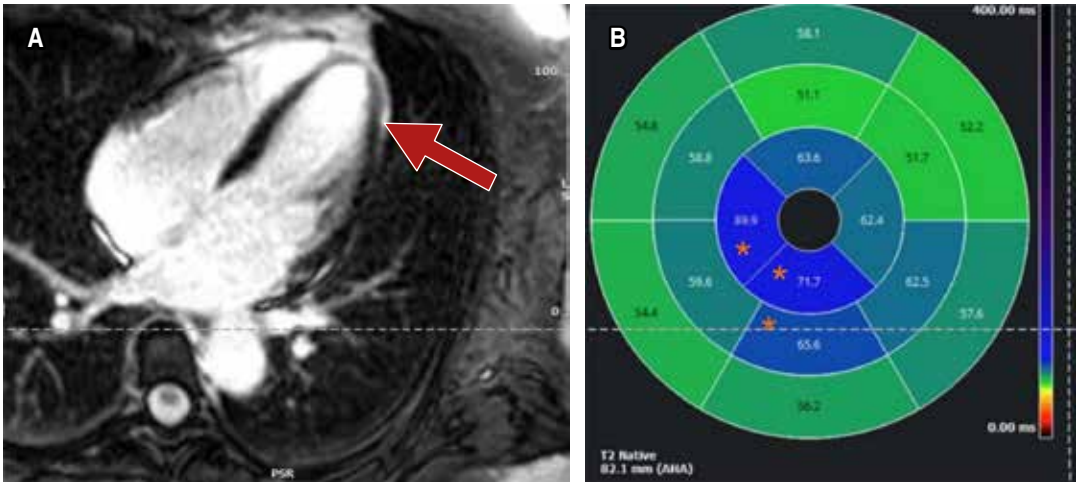

Figure 2: A) Subepicardial late gadolinium enhancement (LGE) at the inferior and inferolateral wall (red arrow). **B)** Corresponding T2 map, demonstrating increased signal intensity in the same inferolateral region (orange asterisks), suggestive of myocardial edema.

correlated episodes *(Figure 2)*. Medications prior to admission included bisoprolol; amiodarone had been previously trialed and discontinued due to lack of efficacy.

Differential diagnosis: our differential diagnosis included tachyarrhythmia, an acute electrolyte disorder, hypoxia, ischemic cardiomyopathy, deterioration in functional class, and relapse of myocarditis.

Investigation: the initial electrocardiogram demonstrated ventricular bigeminy, with PVCs exhibiting a right bundle branch block morphology *(Figure 3)*. Chest radiography was unremarkable. Transthoracic echocardiography revealed mild aortic and tricuspid regurgitation, a reduced LVEF, and mildly impaired left ventricular global longitudinal strain (LVGLS) of -13%. Despite optimized medical therapy, repeat Holter monitoring showed a 13% burden of monomorphic PVCs, frequently in bigeminy. Repeated exercise testing remained negative for ischemia but demonstrated a 50% reduction in exercise capacity, from 8:15 minutes (10.2 METs) to 4:10 minutes (7 METs), with a high PVC burden during exertion. Repeat CMR demonstrated LVEF 43%, RVEF 39%, reduced LVGLS, and persistent subepicardial late gadolinium enhancement at the inferior and inferolateral walls, consistent with prior imaging findings. Laboratory testing was unremarkable, except for an elevated BNP level. Given persistent symptoms, declining ventricular function, and a PVC burden exceeding 10%, a recognized threshold for considering catheter ablation—an electrophysiological procedure was proposed.

Management: she was admitted for an electrophysiological study and catheter ablation of PVCs. Three-dimensional electroanatomic mapping identified endocardial arrhythmogenic foci located near the left coronary cusp (LCC) at the left ventricular summit (LVS) *(Figure 3)*. The local electrograms demonstrated a complex, fractionated signal with a far-field component, and the earliest local ventricular activation was recorded 35 ms before QRS onset. Mapping and ablation were performed via a retrograde aortic approach using femoral arterial access, with femoral venous access for intracardiac echocardiography (ICE). An irrigated-tip catheter was used for radiofrequency ablation. Ablation around the LCC (120 seconds of RF delivery) resulted in a marked reduction in ectopic activity, prompting subsequent ablation at the summit, which ultimately led to complete PVC suppression

Outcome and follow-up: subsequent follow-up demonstrated enhanced functional capacity, improvement of LVEF and LVGLS, and the complete resolution of symptoms.

The subsequent HM showed a residual PVCs burden of 0%. Medical therapy was discontinued «timeline» *(Figure 4)*.

DISCUSSION

European Society of Cardiology (ESC) guidelines propose a cut-off of > 10% to define a high PVC burden, above which an association with left ventricular dysfunction and quality-of-life (QOL) impairment becomes clinically relevant.[2,6] This threshold supports consideration of catheter ablation, particularly when symptoms or ventricular dysfunction are present. However, we believe that an individualized approach is essential, integrating symptom burden, QOL impairment, and potential confounders commonly encountered in this patient population. Higher PVC burdens confer progressively greater risk. In the ABC-VT score, a PVC burden > 20% is considered an independent predictor of PVC-induced cardiomyopathy, alongside other factors such as QRS duration, epicardial origin, underlying structural heart disease, and response or intolerance to medical therapy.[7] In clinical practice, PVC burdens ≥ 20-30% are often used to justify a more aggressive rhythm-control strategy, including early referral for catheter ablation and consideration of advanced or combined endo-epicardial approaches, particularly in patients with ventricular dysfunction or refractory symptoms. Importantly, the absence of a very high PVC burden does not exclude clinically significant disease. Our patient presented with an 11% PVC burden and evidence of cardiomyopathy, with subsequent improvement in ventricular function and symptoms following ablation. This finding underscores that the > 10% threshold remains clinically meaningful and highlights the importance of a thorough diagnostic evaluation to exclude alternative causes of cardiomyopathy and to identify patients who

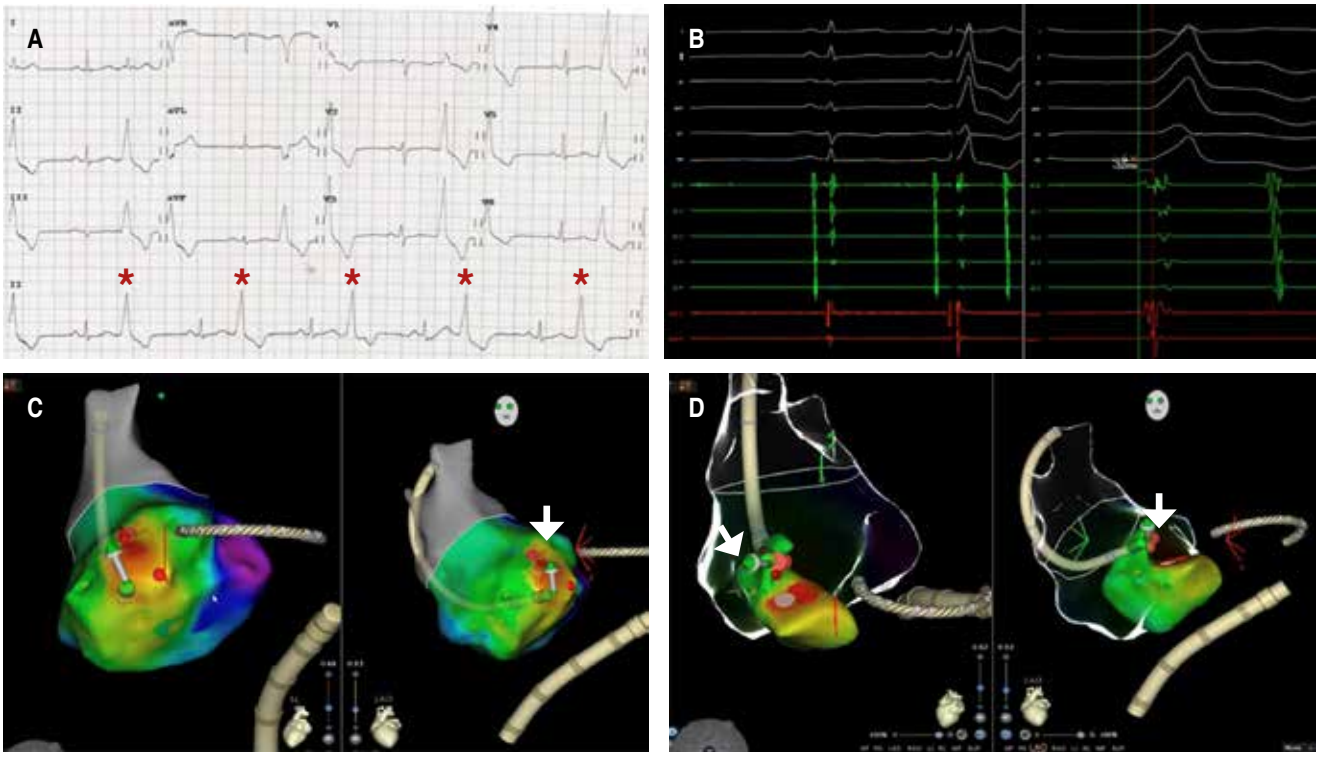

Figure 3: A) Initial electrocardiogram with ventricular bigeminy (red asterisks). **B)** Polygraph screen with PVC with a preexcitation of 35 ms (blue brackets). **C)** Initial activation map. **D)** Endomyocardial ablation for PVC around the left coronary cusp and left ventricular summit (white arrows). PVC = premature ventricular complexes.

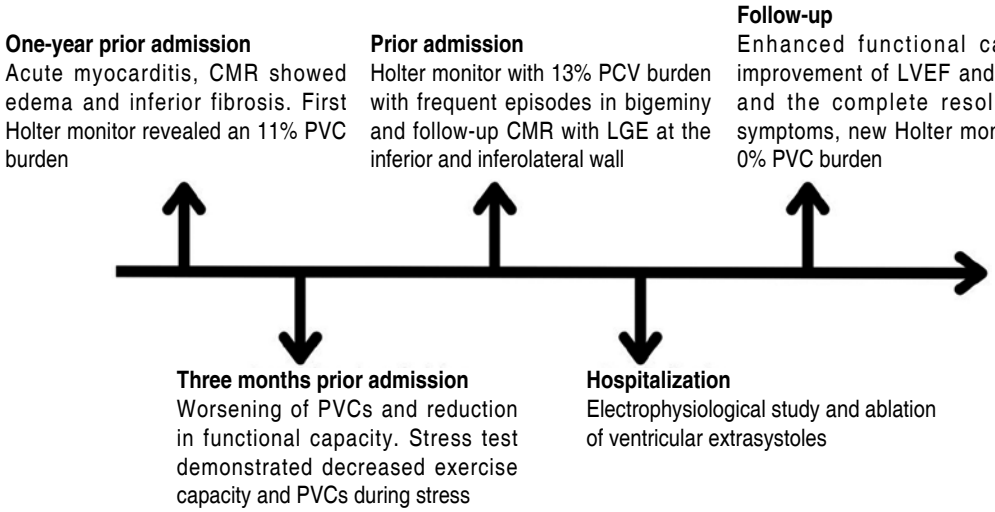

Figure 4: Timeline of events of the patient.
CMR = Cardiac magnetic resonance. LVEF = left ventricular ejection fraction. LVGLS = left ventricular global longitudinal strain. PVC = premature ventricular complexes.

may benefit from ablation even at lower burdens.[2] Although epidemiological data are limited, PVC ablation remains relatively uncommon in Latin America.[8] This low reported prevalence contrasts sharply with the high burden of cardiovascular and coronary artery disease in the region,[9] suggesting potential underdiagnosis and underutilization of catheter ablation in eligible patients.

Most idiopathic PVCs (70-80%) originate from the right or left ventricular outflow tracts. In the present case, the arrhythmogenic focus was localized to the left ventricular outflow tract at the level of the LCC, adjacent to the left ventricular summit, rather than the nonspecific term «left ventricular ostium». This anatomical region poses specific technical challenges. Pace mapping accuracy may be limited due to preferential conduction through adjacent structures, resulting in variable QRS morphologies. Additionally, some foci in this area may have an intramural or epicardial component, with close proximity to the coronary venous system or coronary arteries, mandating careful coronary assessment, particularly when coronary ostia are not clearly visualized using intracardiac echocardiography. A recent meta-analysis comparing endocardial ablation alone with combined endo-epicardial «sandwich» approaches demonstrated a significant reduction in PVC recurrence with the combined strategy, without an increase in procedural complications.[10] In our patient, an initial endomyocardial approach was selected, with a predefined plan to proceed to an endo-epicardial strategy if mapping suggested technical feasibility and incomplete suppression. This stepwise approach aimed to maximize long-term efficacy while minimizing recurrence, given the impact on left ventricular ejection fraction, QOL, and the patient's preference to avoid chronic antiarrhythmic therapy.

CONCLUSIONS

This case highlights the challenges of managing persistent PVCs in patients who, despite initial treatment efforts, exhibit significantly compromised functional capacity and quality of life. The use of advanced electrophysiological techniques, including three-dimensional electroanatomical mapping, intracardiac echocardiography, voltage mapping, epicardial approaches, and radiofrequency ablation, resulted in a substantial reduction in PVC burden and an overall improvement in the patient's quality of life. These findings underscore the effectiveness of targeted electrophysiological interventions in the management of complex ventricular arrhythmias.

Take-home messages:

1. A PVC burden exceeding 10% is associated with an increased risk of PVC-induced cardiomyopathy or worsening of pre-existing cardiomyopathy.
2. In selected patients, catheter ablation of PVCs can effectively alleviate symptoms and significantly improve quality of life.

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Correspondence:
Mauricio Cortes Aguirre, MD
E-mail: drmauriciocortes@hotmail.com

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Acute myocardial infarction in a young adult living with newly diagnosed human immunodeficiency virus

Infarto agudo de miocardio, en un adulto joven con diagnóstico reciente de infección por el virus de la inmunodeficiencia humana

Isaías G Dueñaz-Díaz,*,‡ Martha Morelos-Guzmán,*,§ Carlos A Aréan-Martínez,*,¶ Jesús E Dueñaz-Díaz,*,‖ Luis D Chora-Hernández*,**

Keywords: myocardial infarction, human immunodeficiency virus, young adult, cardiovascular diseases.

Palabras clave: *infarto del miocardio, virus de la inmunodeficiencia humana, adulto joven, enfermedades cardiovasculares.*

ABSTRACT

Human immunodeficiency virus (HIV) infection continues to be a major public health problem. However, people living with HIV are surviving to older ages and are presenting with a higher prevalence of cardiovascular disease. HIV infection itself is associated with an increased risk of atherosclerotic cardiovascular disease, most commonly manifesting as acute coronary syndrome, typically at younger ages and often in the absence of traditional cardiovascular risk factors. We present the case of a patient with ST-segment elevation acute coronary syndrome with a history of non-significant tobacco exposure (0.75 pack-years, discontinued six years prior), whose main cardiovascular risk factor was a recent diagnosis of HIV infection. Consequently, this was a treatment-naïve patient with no prior exposure to antiretroviral therapy, consistent with findings from other studies analyzing this population, which describe a low burden of comorbidities, a distinct clinical presentation of the syndrome, and a high thrombus burden at the level of the culprit plaque on coronary angiography.

RESUMEN

La infección por virus de la inmunodeficiencia humana continúa siendo un problema de salud pública. Sin embargo, los pacientes que viven con VIH están sobreviviendo a edades mayores y presentando mayor prevalencia de enfermedad cardiovascular. La misma infección por VIH se asocia con un riesgo incrementado de enfermedad cardiovascular aterosclerótica, que se manifiesta más comúnmente como un síndrome coronario agudo y usualmente a edades más tempranas y sin factores de riesgo tradicionales. Se presenta el caso de un paciente con un síndrome coronario agudo con elevación del segmento ST con antecedente de tabaquismo no significativo (0.75 paquetes-año, suspendido hace seis años), cuyo factor de riesgo principal es diagnóstico reciente de infección por VIH, siendo un paciente sin exposición previa a tratamiento antirretroviral y coincide con otros estudios donde se ha analizado esta población en donde se encuentran con escasas comorbilidades, la forma de presentación del síndrome y la alta carga de trombo a nivel de la placa en la angiografía.

* General Hospital of Morelia «Dr. Miguel Silva». Michoacán, Mexico.
‡ Internal Medicine Resident. ORCID: 0009-0000-5838-0497
§ Cardiologist, Echocardiographist, Cardiovascular Imaging Specialist. ORCID: 0009-0003-5008-4548
¶ Cardiologist, Interventional Cardiology Specialist. ORCID: 0000-0002-7102-1672
‖ Internal Medicine Resident. ORCID: 0009-0000-5646-6406

Abbreviations:
AMI = Acute Myocardial Infarction
ART = AntiRetroviral Therapy
CAD = Coronary Artery Disease
CHIP = Clonal Hematopoiesis of Indeterminate Potential
HIV = Human Immunodeficiency Virus
LVEF = Left Ventricular Ejection Fraction
PLWH = People Living With HIV

INTRODUCTION

Currently, an estimated 40.8 million people worldwide are living with the human immunodeficiency virus (HIV), with approximately 1.3 million new cases per year.[1] By 2024, 630,000 people had died from HIV-related causes; however, efforts in prevention, diagnosis, and early treatment have positively impacted life expectancy in these patients, transforming HIV infection from

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** Infectious Disease Specialist, Internal Medicine Specialist. ORCID: 0000-0002-4765-5640

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a fatal disease into a complex chronic health condition.[1] People living with HIV (PLWH) are surviving to older ages, and epidemiological studies have demonstrated that they have up to twice the likelihood of developing cardiovascular disease compared with HIV-negative individuals.[2] Coronary artery disease has been the predominant clinical manifestation of cardiovascular disease in PLWH, with a 1.5 to 2.1-fold increased risk of acute myocardial infarction compared with controls.[3] In several cohort studies, the mean age at which PLWH experienced acute myocardial infarction was 48 years, lower than that reported in the general population.[4] We present the case of a patient with acute myocardial infarction who, due to his age, is classified as a young myocardial infarction patient, whose most relevant risk factor for this event is the recent diagnosis of HIV infection.

CASE PRESENTATION

31-year-old male with a bachelor's degree in nursing, with no family history of ischemic heart disease. He had a history of smoking for five years at approximately three cigarettes per day, corresponding to a one pack-year index, discontinued six years earlier. He denied using other substances. He had no prior diagnoses of diabetes mellitus or systemic arterial hypertension.

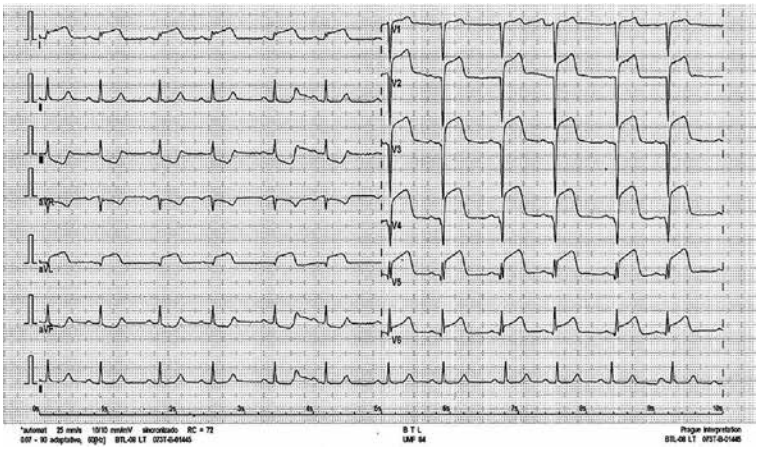

Figure 1: Initial 12-lead electrocardiogram: inversion of the T wave in leads V1 with an elevation of the ST-segment of 2 mm in leads V1-V6, DI, and aVL. aVL = augmented voltage left.

His current condition began in August 2024 with a five-hour evolution characterized by oppressive precordial chest pain, intensity 8/10 on the VAS scale, radiating to the submandibular region, accompanied by dyspnea on moderate exertion. On physical examination: heart rate 82 bpm, respiratory rate 19 breaths/minute, blood pressure 110/78 mmHg, oxygen saturation 98%. There was no respiratory distress with normal heart and respiratory sounds.

Admission laboratory studies showed leukocytes 8.5 × 10^9 /L, hemoglobin 13.7 g/dL, glucose 112 mg/dL, troponin I 14 ng/mL, glycated hemoglobin 5.2%, triglycerids 110 mg/dL, total cholesterol 106 mg/dL, HDL 20 mg, and LDL 64 mg/dL. Electrocardiogram revealed sinus rhythm, axis 48º, ST-segment elevation in leads V1-V6, DI and AVL *(Figure 1)*. Based on these findings, thrombolysis with a 35 mg tenecteplase bolus was performed, with clinical improvement and achievement of reperfusion criteria on the control ECG.

Given the patient's occupational epidemiological background, fourth-generation HIV ELISA testing was requested and resulted in a positive result. To rule out myocarditis as a differential diagnosis, cardiac magnetic resonance imaging *(Figure 2)* was performed, demonstrating subendocardial late gadolinium enhancement compatible with acute myocardial infarction of the anterior and anteroseptal walls at basal, mid, and apical levels, complicated by microvascular obstruction, with infarct size of 28% and left ventricular ejection fraction (LVEF) of 36%.

Within the following 24 hours, the patient underwent percutaneous coronary intervention *(Figure 3)*, where the left anterior descending artery demonstrated a definite thrombotic image in the mid-segment with 70% stenosis. A drug-eluting stent was implanted, achieving TIMI 3 antegrade flow. A glycoprotein IIb/IIIa inhibitor was administered and maintained for 24 hours. The patient remained asymptomatic thereafter. Additional evaluations showed viral load of 29,830 copies/mL and CD4 count of 224 cells/mm^3.Twelve weeks after the event, lupus anticoagulant was 18; anti-β2 glycoprotein I IgM and IgG were 8 SMU U/mL and 12 UGS/mL, respectively; anticardiolipin

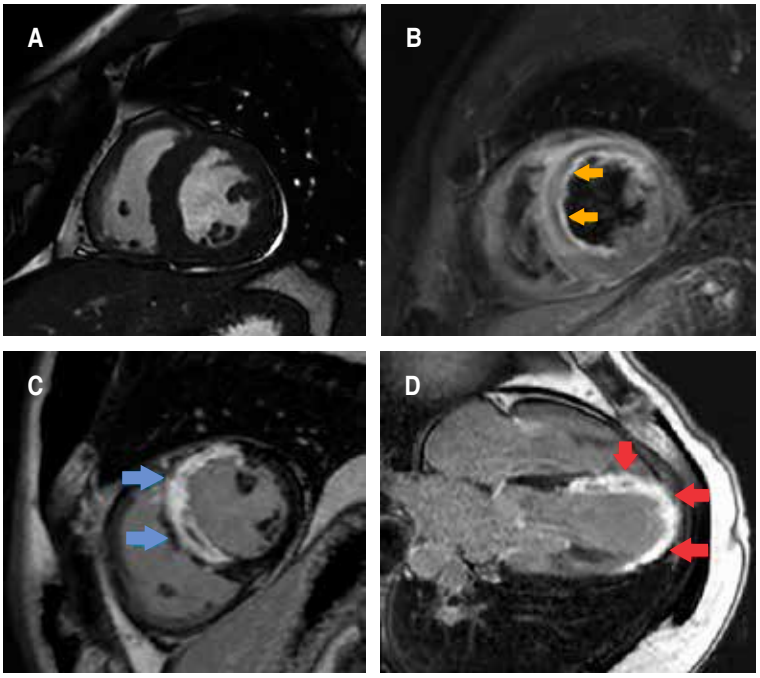

Figure 2: Cardiac magnetic resonance imaging: **A)** Short-axis cine at the mid-ventricular level (SSFP [Steady-State Free Precession]). **B)** Short-axis T2 STIR (Short Tau Inversion Recovery) showing transmural myocardial hyperintensity compatible with edema (yellow arrows). **C)** Short-axis late gadolinium enhancement (T1 GRE I-R [Inversion-Recovery Gradient Echo]) showing transmural enhancement in the anterior and anteroseptal walls (blue arrows). **D)** Four-chamber long-axis late gadolinium enhancement (T1 GRE I-R [Inversion-Recovery Gradient Echo]) involving the septal and lateral segments at the basal, mid, and apical levels (red arrows).
GRE I-R = Inversion-Recovery Gradient Echo. SSFP = Steady-State Free Precession. STIR = Short Tau Inversion Recovery.

IgM and IgG were below reference ranges, therefore negative for antiphospholipid antibody syndrome. Antiretroviral therapy with bictegravir/emtricitabine/tenofovir alafenamide was initiated, and statin therapy was changed to pitavastatin.

DISCUSSION

The association between cardiovascular disease and HIV infection has been recognized for at least two decades, including the increased risk of coronary artery disease (CAD).[5] In the Veterans Aging Cohort Study, a more than 50% higher risk of acute myocardial infarction (AMI) was identified in people living with HIV compared with healthy individuals, even after adjusting for risk factors such as smoking and substance use.[5] Although PLWH have a higher likelihood of traditional cardiovascular risk factors, the pathogenesis is complex and is potentially related to immune activation and chronic inflammation.[3] In the present case, the patient had no previously known cardiovascular risk factors, other than a history of smoking, which was considered clinically insignificant based on the consumption pattern.

Although the use of antiretroviral therapy (ART) in PLWH and its relationship with ischemic heart disease has been described since early studies involving protease inhibitors—associated with elevations in triglycerides, low-density lipoprotein, and lipoprotein(a)—the benefit and protective effect of ART clearly outweigh these risks and have significantly improved survival.[5]

Theoretically, HIV infection itself may independently predispose to premature atherosclerosis through endothelial and microvascular dysfunction, an enhanced proinflammatory and procoagulant state, and dyslipidemia.[3] In relation to this, elevated biomarker levels have been identified (C-reactive protein, interleukin-6, tumor necrosis factor-alpha), monocytic activation (CD14 and CD163), and increased coagulation activity (D-dimer).[2,5] Recent studies have explored the relationship between clonal hematopoiesis of indeterminate potential (CHIP), inflammation, and cardiovascular risk in PLWH; the prevalence of CHIP-associated somatic mutations is enriched in this population and is associated with ART, IL-6 levels, and C-reactive protein.[2] These markers could not be assessed in our patient; however, other differential diagnoses and prothrombotic states—including antiphospholipid antibody syndrome—were investigated and resulted in negative findings.

CAD in PLWH most commonly presents as acute coronary syndrome. According to several studies, the typical patient is younger than 50 years (90% of cases), male (81-97%), with an HIV diagnosis of more than eight years, on ART (53-96%), and with dyslipidemia (17-58%).[4] The most frequent presentation is ST-segment elevation myocardial infarction (29-64%).[4]

Single-vessel disease is the most common angiographic finding; however, multivessel disease is more frequently seen in HIV-negative patients.[5] There is limited information regarding CAD in ART-naïve patients. In a study by Becker et al., HIV-positive, untreated patients were found to be younger, with fewer traditional cardiovascular risk factors, less angiographic atherosclerotic burden, but greater thrombotic burden compared with controls.[6] This corresponds to our patient, who had low traditional risk, single-vessel disease, and a high thrombus burden.

The prognosis of PLWH during the acute phase of AMI does not appear to differ from that of non-infected individuals, with reported in-hospital mortality ranging from 0-8%, and without differences in acute heart failure rates.[4] Among patients undergoing percutaneous coronary intervention, rates of early and late stent thrombosis are low and comparable to controls, and stent restenosis has been reported in some studies, ranging from 9-52%.[5] At two-year follow-up, reinfarction rates were higher (9.4%), as well as the need for revascularization (20%).[4] Pharmacologic interactions between CAD therapies—including statins, antiplatelet agents—and ART must be considered.[5,7] For this reason, in conjunction with the ART initiated, statin therapy in our patient was changed to pitavastatin due to its lack of CYP3A4 metabolism.

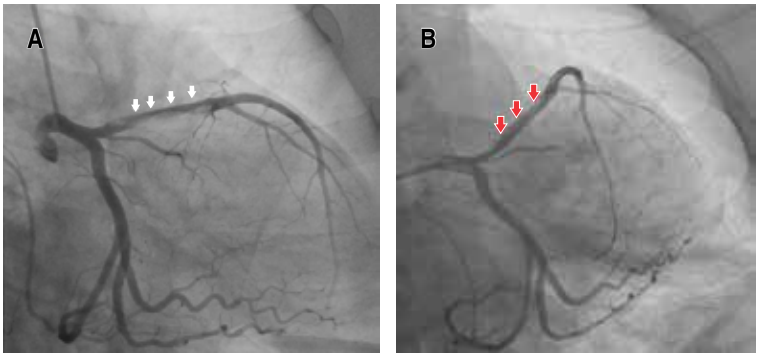

Figure 3: Coronary angiography: **A)** Right anterior oblique (RAO) projection showing a definite thrombus image in the mid-left anterior descending artery with approximately 70% stenosis (white arrows). **B)** Post-drug-eluting stent angiographic control demonstrating good angiographic outcome with TIMI 3 antegrade flow (red arrows).
RAO = right anterior oblique.

Based on the results of the REPRIEVE trial, primary prophylaxis with pitavastatin is recommended for all PLWH aged ≥ 40 years, regardless of cardiovascular risk or LDL levels.[8]

CONCLUSIONS

This case highlights the growing relevance of cardiovascular risk in PLWH as life expectancy increases. Although most reported cases involve previously diagnosed HIV patients on ART, this case involves an undiagnosed and ART-naïve patient, yet consistent with literature describing younger age, absence of traditional risk factors, reduced CD4 count, and high thrombotic burden, implicating HIV infection as a principal etiologic factor. Cardiac MRI findings suggest a poor prognosis. Primary prevention strategies such as statin therapy represent an important intervention for this population according to current evidence.

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Declaration of patient consent: protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research. Confidentiality of data. The authors declare that they have followed their center's protocols for the publication of patient data. Right to privacy and informed consent. The authors have obtained the informed consent of the patients and subjects referred to in the article. This document is in the possession of the corresponding author.

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Correspondence:
Martha Morelos Guzmán
E-mail: morelosm99@yahoo.com

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Out-of-hospital cardiac arrests and cardiopulmonary resuscitation. Is there a difference between genders?

Paro cardiaco extrahospitalario y resucitación cardiopulmonar. ¿Hay diferencia de género?

Jorge Álvarez de la Cadena-Sillas,* Enrique Asensio-La Fuente,‡ Yoloxóchitl García-Jiménez,§ Gabriela Borrayo-Sánchez,¶ Janet Mijangos-Chávez,‖ Lillian Hernández-García**

ABSTRACT

Sudden Cardiac Death (SCD) is almost twice as common in men as in women. The leading cause in both groups is Coronary Artery Disease (CAD), but most women who present with SCD have no prior history of heart disease, are asymptomatic, or have been considered low-risk subjects for SCD. Prevention of SCD in women is more difficult, although control of risk factors for CAD has been demonstrated to reduce the incidence of SCD. Women suffering from SCD are generally older, have more comorbidities, and are less likely to die in public spaces. They also receive less bystander Cardiopulmonary Resuscitation (CPR) than men. They usually present with an initial non-shockable rhythm and are less likely to survive an Out-Of-Hospital Cardiac Arrest (OHCA) and be discharged from the hospital. The present work reviews significant differences concerning risk factors, treatment, and outcomes that must prompt collective actions to reduce the mortality burden of cardiac arrest in women.

Keywords:
sudden cardiac death, women, coronary heart disease, cardio-pulmonary resuscitation, out-of-hospital cardiac arrest.

RESUMEN

La muerte súbita cardiaca (MSC) es casi el doble de frecuente en hombres que en mujeres. La principal causa en ambos grupos es la enfermedad arterial coronaria (EAC), pero la mayoría de las mujeres que presentan MSC no tienen antecedentes de cardiopatía, son asintomáticas o se han considerado sujetos de bajo riesgo de MSC. La prevención de la MSC en mujeres es más difícil, aunque se ha demostrado que el control de los factores de riesgo de la EAC reduce la incidencia de MSC. Las mujeres que sufren MSC suelen ser mayores, presentan más comorbilidades y tienen menos probabilidades de fallecer en espacios públicos. También reciben menos reanimación cardiopulmonar (RCP) por parte de testigos que los hombres. Generalmente presentan un ritmo inicial no desfibrilable y tienen menos probabilidades de sobrevivir a un paro cardiaco extrahospitalario (PCEH) y ser dadas de alta del hospital. El presente trabajo revisa las diferencias significativas en cuanto a factores de riesgo, tratamiento y resultados que deben impulsar acciones colectivas para reducir la carga de mortalidad por paro cardiaco en mujeres.

Palabras clave:
muerte súbita cardiaca, mujeres, cardiopatía coronaria, reanimación cardiopulmonar, paro cardiaco extrahospitalario.

Abbreviations:
B-CPR = Cardiopulmonary Resuscitation Bystander
CA = Cardiac Arrest
CAD = Coronary Artery Disease
CPR = Cardiopulmonary Resuscitation
ECG = electrocardiogram
EMS = Emergency Medical System
LVH = Left Ventricular Hypertrophy
OHCA = Out-Of-Hospital Cardiac Arrest
ROSC = Return of Spontaneous Circulation
SCD = Sudden Cardiac Death
VF = Ventricular Fibrillation

INTRODUCTION

Sudden Cardiac Death (SCD) is a significant health problem worldwide, with approximately 350,000 cases in the USA and 275,000 in Europe and experiencing Out-Of-Hospital Cardiac Arrest (OHCA).[1,2] and more than 120,000 in women.[1-5] Lately, the decline in SCD incidence among women has been less compared with men and could represent up to 40% of SCDs.[6]

Even though significant Coronary Artery Disease (CAD) is the leading cause of SCD in

* Cardiologist. Instituto de Corazón de Querétaro, Querétaro, Mexico. Práctica privada en San Miguel Allende, Guanajuato, Mexico. Coordinator of the Cardiac Arrest Chapter, Sudden Death, and CPR of the Asociación Nacional de Cardiólogos de México (ANCAM). ORCID: 0009-0009-5461-6154
‡ Cardiologist and electrophysiologist. Instituto de Corazón de Querétaro. Querétaro, Mexico.

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ORCID: 0000-0003-4833-2664
§ Cardiologist. Ex president of the ANCAM. ORCID: 0000-0003-4587-5698
¶ Interventional cardiologist, Unidad Médica de Alta Especialidad, Hospital de Especialidades No. 14 del Centro Médico Nacional (CMN) «Adolfo Ruíz Cortines» del Instituto Mexicano del Seguro Social (IMSS), Veracruz, Mexico. Vice president of the ANCAM. ORCID: 0000-0001-8531-9923
‖ Cardiologist. Head of the Cardiology Department, Hospital de Especialidades del Centro Médico Nacional La Raza, IMSS. Coordinator of the Heart Disease in Women Chapter, ANCAM. ORCID: 0009-0000-4182-3511
** Private practice physician. San Miguel Allende, Guanajuato, Mexico. ORCID: 0009-0001-8676-4727

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women, non-ischemic SCD in women occurs more frequently than in men. Women with SCD are less likely to have a history of CAD, structural heart condition, or left ventricular dysfunction than men. Although the prevalence of SCD in men is half to 2-3 times higher than in women, major clinical risk factors are very similar for both, but also substantial differences exist in outcomes, treatment, and predictors.[7-9]

Despite SCD incidence rates being higher for the male population, it is still a leading cause of death in both genders; SCD in women is increasing, with a different pattern. Understanding how males and females are different in the context of SCD is critical to ensure that preventive strategies are effective for both males and females in the future.

Considering that many of these elements usually depend on society and the location of the OHCA, it is understandable that there are differences, some of them significant, according to the population studied and/or in different areas of the world, in which it is presented.

We analyze gender differences across various aspects of SCD and OHCA, including epidemiology, age, clinical presentation, cause, risk factors, ECG and autopsy findings, treatment and prevention, and outcomes.

Each year, approximately 350 thousand deaths in the USA and 275 thousand in Europe are secondary to OHCA[1,2] of which 120 thousand occur in women[3-5] with an annual incidence of 30 to 97.1 per 100 100,000 inhabitants, depending on the population studied.[6] The annual survival is very low, varying between 7.6% and 12% when we talk about OHCA, compared to figures of 24.8% when the event occurs in the hospital.[7] We do not have information on SCD, OHCA, and Cardiopulmonary Resuscitation (CPR) in women in Mexico. There are only a few studies that have investigated symptoms prior to SCD in women and have found that around 50 to 70% of victims seek medical attention before the SCD event.[8-11]

Presentation of clinical aspects and coronary artery disease

It is important to mention that the spectrum of SCD in women is not so typical and out of the ordinary compared with men, with a more atypical presentation of cardiac diseases, and occurs more often without the knowledge of a previous CAD. For both men and women, the most common underlying risk factor for SCD is the presence of significant CAD. For this reason, the causes, etiology, and pathologies associated with SCD in women are more difficult to recognize, diagnose, predict, and even prevent. Data indicate that sex differences are likely to exist in coronary risk factors and the pathophysiology and clinical manifestations of CAD, despite being the main cause of death in the world; data on the cause of death among women with CAD and SCD are still limited. The rate of SCD in women has been considerably lower than in men, with an annual rate estimated to be almost half in women than in men, with the main differences in middle age around premenopausal women and early postmenopausal years.[1,12,13]

The age of presentation of an SCD event in men is generally eight years younger than in women. Differences in life expectancy between genders could explain this, as women live almost five years longer than men, and this difference in age presentation may be related to estrogen and cortisol levels. It is noteworthy that the majority of SCD events are secondary to coronary heart disease, which in turn has substantially reduced mortality by almost half during the same period.[14] Haukilahti et al., in 5,869 subjects with SCD, most patients were male (78.9%) compared to women (21.1%), $p < 0.001$. The majority of subjects with CAD and SCD were men (79.8%) compared to women (20.2%), $p = 0.005$. Women with non-ischemic etiology of SCD were more common, 28.3%, than men, 24.3% ($p = 0.005$).[15] The presence of an SCD event in women is commonly one of the first manifestations of CAD. CAD risk factors also predict SCD risk in women. Therefore, prevention of atherosclerosis, ventricular arrhythmias, and some other risk factors may reduce the incidence of SCD in women.[1]

In addition, different traditional risk factors for developing CAD and SCD in women are presented. Some other risk factors also present concerning SCD are increased sympathetic activity, heart failure with preserved left

ventricular systolic function, increased body mass index and abdominal fat, depression, and/or use of antidepressants. Prediction and prevention of SCD is an area of active investigation, but current guidelines for preventive intervention apply to a tiny portion of the population at risk.[16,17] It is also crucial to mention that it is common to present events of undetected myocardial infarction and underlying left ventricular hypertrophy detected by 12-lead rest electrocardiogram (ECG) in women. Around 30% of women with SCD have normal ECG before the event, so it is essential to understand that a normal ECG in women does not rule out an underlying risk for SCD, even in a non-ischemic SCD event. Autopsy findings indicate that women who present non-ischemic SCD have a higher prevalence of myocardial fibrosis than men. Long corrected QT interval, myocardial infarction, and congestive heart failure are independent risk factors in women with non-ischemic SCD and atrial fibrillation, diabetes, glomerular filtration rate of less than 40 mL/min/1.73 m^2, reduced LVEF, and physical inactivity are independent predictors of SCD in women with ischemic SCD.[18,19]

Women have a lower prevalence of structural heart disease, which reduces the chance of identifying predictor risk factors for SCD in these patients. The cause of SCD by gender found during an autopsy is shown in *Figure 1*. It must be taken into account that these causes may vary depending on the population and the place of the study.[15,20]

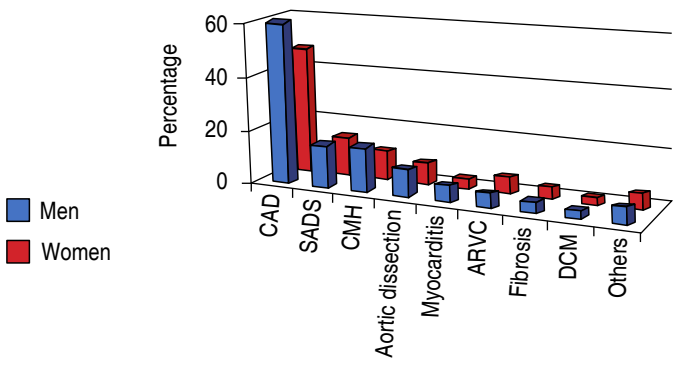

Figure 1: Causes of death in autopsy in SCD according to sex (percentage).
Modified from: Skjelbred T et al.[20]
ARVC = arrhythmogenic Right Ventricle Cardiomyopathy. CAD = Coronary Artery Disease. CMH = hypertrophic cardiomyopathy. DCM = Dilated Cardiomyopathy. SADS = Sudden Arrhythmic Death Syndrome. SCD = Sudden Cardiac Death.

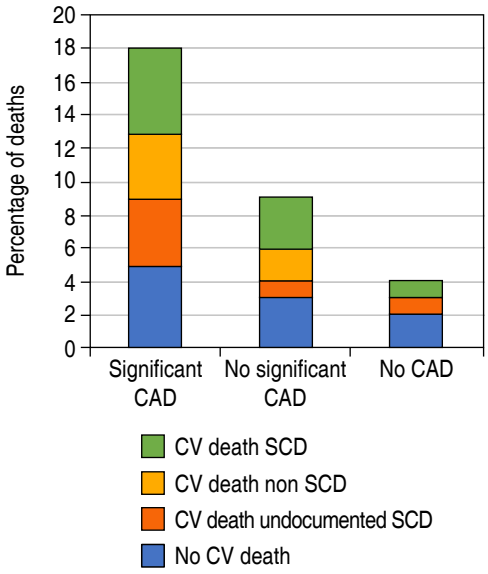

Figure 2: Mortality in women by coronary artery disease severity.
Modified from: Mehta PK, Johnson BD, Kenkre TS et al. Sudden cardiac death in women with suspected ischemic heart disease, preserved ejection fraction, and no obstructive coronary artery disease: a report from the women's ischemia syndrome evaluation study. J Am Heart Assoc. 2017; 6 (8): e005501. doi: 10.1161/JAHA.117.005501.
CAD = Coronary Artery Disease. CV = cardiovascular.

Mortality in women with SCD, according to the CAD severity, is shown in *Figure 2*. Predicted (marginal) probabilities of survival for male and female victims of OHCA versus age are shown in *Figure 3*.

Context

Approximately 83% of the OHCA are unwitnessed in women and 85% in men, with a higher incidence of ischemic SCD in men than in women. SCD occurred during exercise more often in men than in women, and even more so for those with ischemic SCD. OHCA in women occurred indoors more often than in men, 92 versus 82%, respectively, especially in women with non-ischemic SCDs, and also occurred more often between midnight and 6 am than in men, when the event happened more often during the daytime. Women with CAD and SCD also have a lower risk of lethal ventricular

arrhythmias compared to men.[21,22] Given these results, we must observe with caution in greater detail the factors that have been shown to truly affect survival during an OHCA event, such as OHCA presence by a witness, Cardiopulmonary Resuscitation Bystander (B-CPR) shockable rhythm upon arrival of the Emergency Medical System (EMS), and Return of Spontaneous Circulation (ROSC) at the site of cardiac arrest.[23] Some other demographic differences factors, like race, gender, and socioeconomic status, have also been shown to impact the survival of the OHCA.[5,24,25]

Patient sex has also been proven to influence OHCA survival, with the incidence in men threefold higher than in women.[26] The data that report worse survival in the OHCA for women most of the time are related to worse pre-hospital factors, like less B-CPR, less witnessed Cardiac Arrest (CA), less EMS CPR, and some other reports of less administration of medications (intravenous) and received fewer attempts of endotracheal intubations.[27,28]

Cultural and religious factors concerning gender, their effect on the treatment to be performed, and the sensation of feeling aggressive management of compressions in the CA, especially under certain conditions, contribute to the different results between genders. The difference in CPR between genders during OHCA is related to multiple factors, including physiological, biological, and social differences.[29-31]

The general population perceives fears about inappropriate touching, possible accusations of sexual assault, and fear of causing injury or harm as inhibiting B-CPR for women. It has been proven that education may reduce these differences during B-CPR.[32,33] Since many of these factors change based on the different societies and cultures worldwide where OHCA is produced, it is logical to observe different results.[34]

Blom MT et al. found that women with OHCA are less likely to receive B-CPR than men (69.2% vs 73.9%; $p < 0.001$). Women have lower chances than men to be resuscitated and survive OHCA.[35]

Dispatcher-assisted CPR is associated with more favorable neurological survival in men than in women and could be related to delays in initiation of chest compression CPR maneuvers, on occasions associated with the shame of uncovering a woman's breast, and being subject to possible complaints of harassment, because this generally occurs in public places, the victim will expose their chest and breast in public as well as the psychological factors of how it harms a woman, etc.[36]

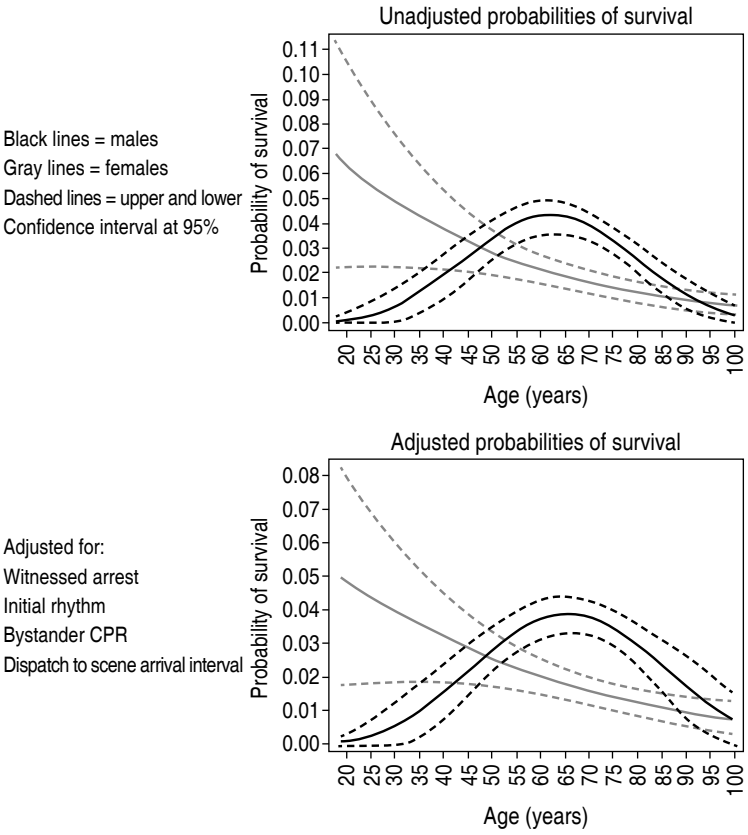

Figure 3: Predicted (marginal) probabilities of survival for male and female victims of OHCA versus age.
Modified form: Safdar B et al.[62]
CPR = Cardiopulmonary Resuscitation. OHCA = Out-of-Hospital Cardiac Arrest.

Age

Post-menopausal women, when experiencing OHCA, are, on average, eight years older than their male counterparts, a finding that is consistent in many studies. This trend could be related to differences in overall life expectancy, with females living nearly five years longer than males. It has been argued that these age differences between genders could be related

to disparities in estrogen and cortisol levels. Estrogen decreases the CA death pathway by reducing the anti-apoptotic mechanisms.[37] The drop of estrogen levels commonly seen in pre-menopause, and the loss of that positive effect on the heart-protective effect results in an increased incidence of cardiac events, including SCD.[38] Given the beneficial role of estrogen trying to reduce the death cascade in CA victims, has been proposed a role for intravenous estrogen as a stabilizing cell drug in women victims of CA.[37]

Young women

In young women less than 35 years old, males have a higher incidence of SCD than women at 1.8 versus 0.7 cases per 100,000 persons.[39]

SCD in specific groups

Pregnancy: approximately 1 in 30,000 pregnancies are complicated by maternal cardiac arrest.[40] Previous studies done in pregnant women found the causes of SCD are unexplained (54%) and cardiomyopathies (14%), including dilated, peripartum, hypertrophic, and arrhythmogenic, as the more relevant, and other causes like aortic dissection, valvular heart disease, and congenital heart disease in adults.[41] However, obesity-related cardiomyopathy has also been associated with an increased risk of SCD during pregnancy, and some autopsy findings showed that 43% of women who died from SCD were obese (43%) or overweight (16%).[42]

Eclampsia. The mortality in patients with eclampsia is secondary to cerebrovascular disease, pulmonary edema, and acute kidney injury, leading to CA. However, eclampsia has been reported as a rare entity, but it has finally been recognized as a cause of SCD.[43]

SCD in sports. In general, it has an incidence of approximately 1 in 50,000 to 80,000 young athletes,[44] and in most of the studies, males have a consistently greater risk of SCD (10 times more) compared with women.[45,46] The common cause of SCD in athletes less than five years of age is secondary to congenital heart disease, mainly hypertrophic cardiomyopathy, followed by anomalous coronary arteries. Compared with athletes over 35, most SCD events are related to CAD.[47] Racial factors may play a role in SCD in athletes, with a higher incidence in black athletes.[48] Gender differences within this subgroup have not yet been investigated. The atherosclerosis risk in community studies, including black and white athletes, found an increased risk associated with race, more pronounced in women than in men.[49]

ECG findings

The 12-lead ECG plays a vital role in risk stratification for SCD, but women are more likely to have a normal ECG than men prior to an SCD event. It is essential to remember that a normal electrocardiogram in women does not rule out an underlying risk for SCD, even in non-ischemic SCD, because almost 35% of women with SCD have normal ECGs before the SCD event.[15]

Left Ventricular Hypertrophy (LVH). The value of LVH in a 12-lead rest ECG as a marker of ischemic SCD appears greater in women than in men, with an incidence of around 22.8% in women with LVH on ECG, compared with 10.2% in men. In patients with non-ischemic SCD, LVH and repolarization abnormalities are more common in women, 10.2% of cases versus 4.6%. The Cornell index, as an ECG marker for LVH, is more frequent and has higher values in women (17.9%) than in men (10.6%).[15,19]

Silent myocardial infarction. Women with SCD have a history of the presence of silent with any abnormal Q-waves, and therefore, non-reperfused acute myocardial infarctions detected by ECG are almost twice as frequent as in men.[15]

Idiopathic monomorphic ventricular tachycardia (VT). It originates most commonly from the right ventricular outflow tract (RVOT-VT) and is more common in women.[50] Studies have found that women tend to have frequent ventricular tachycardia initiation in the premenstrual period compared with men, whereas RVOT-VT is more commonly triggered by exercise or stress.[51]

Autopsy

SCD in women is more frequently associated with non-ischemic heart disease than in

men, and primary myocardial fibrosis is more commonly found in women with SCD.[15] The cause of death in autopsy in SCD according to sex (percentage) is shown in *Figure 1*.

Arrhythmias

Ventricular Fibrillation (VF) is less common (about half) as a first rhythm in women with CA. VF and VT are more commonly the initial arrhythmia in men, and pulse less electrical activity and asystole are more common among women.[28] Women with an initial shockable rhythm are present in a smaller number of patients (mainly ventricular tachycardia) but have a better prognosis than men. However, unlike men, who show more pulseless electrical activity and ventricular fibrillation, women also present more asystole as the initial rhythm. Some of the reports that indicate a better prognosis related to initial shockable rhythms in women occur more frequently in young, NON-perimenopausal women and are therefore related to non-ischemic SCD at these ages. From this, it has been suggested that the differences observed in these initial rhythms among young women without ischemic heart disease may be related to the stage of the menstrual cycle at the time of OHCA.[52-57] This may partially explain why women have a lower survival rate, since the presence of a VF event would imply a reversible and treatable arrhythmia and potentially abort the CA event. The gender difference in the initial rhythm during OHCA is shown in *Figure 4*.

Lack of treatment

In general, women with SCD during CPR and EMS intervention receive less advanced respiratory support, intravenous adrenaline, and fewer defibrillations per encounter.[34] The CONCORDANCE acute coronary syndrome registry in Australia found that women are less likely to receive invasive management, revascularization, or preventative medication after being discharged from the hospital.[57] Women at high risk of SCD are less likely to receive implantable cardiac defibrillators.[58]

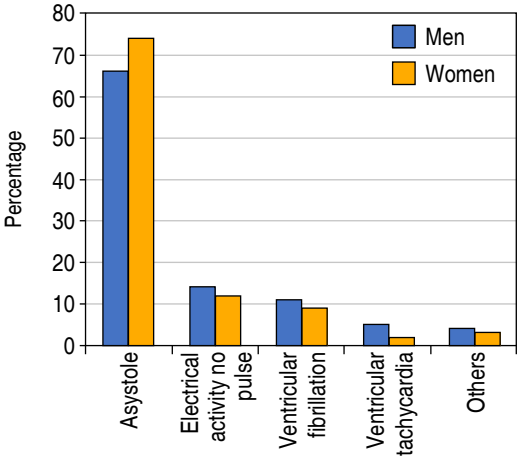

Figure 4: Differences by gender in the initial rhythm during out-of-hospital cardiac arrest.

OHCA survival and hospital discharge

It is another perspective to analyze SCD in women. Compared to men, women were less likely to receive bystander CPR (67.9% versus 72.7%), even in the subset of a witnessed CA; some studies demonstrated higher rates of ROSC during OHCA.[34] Overall survival to hospital discharge is significantly lower for resuscitated women (12.5% versus 20.1%) than men, probably related to a lower survival rate after ROSC when admitted to the hospital. This lower survival rate for women could be explained by their lower rate of having an initial shockable rhythm, a powerful survival predictor after OHCA. The in-hospital mortality of women who survive an OHCA and who are transferred to the hospital and admitted to intensive care units is higher than that of men,[59] also coupled with a worse prognosis and higher mortality at hospital discharge at 30 days after OHCA.[60] In the Opals registry, which analyzed more than 10,000 patients who presented an event of SCD and OHCA, the ratio of men to women victims of SCD was 2 to 1, with older women, having fewer initial shockable events and a smaller number of patients who received B-CPR ($p < 0.01$). *Figure 3* indicates gender differences in the initial rhythm detection during OHCA.[61] The overall survival of women with an OHCA event is lower than that of men, and this proportion decreases as age increases. Unlike men, the probability of survival varies

with age, increasing in men between 18 and 65 years of age and decreasing afterward, with a greater possibility of survival before perimenopause. Women have a lower chance of surviving an OHCA event that is directly related to age, but in young adult men who are victims of OHCA, this survival is lower when compared to men over 65 years of age; this trend is reversed. Men between 18 and 47 years have a lower probability of being discharged from the hospital after an OHCA compared to women of the same age, who have a higher percentage of survival during reproductive age. However, the survival rate to hospital discharge is generally lower in women, even when they present ROSC in an OHCA, 12.5% vs 20.1%,[19] compared to men, undoubtedly due to previously explained factors.[56]

CONCLUSIONS

Gender differences affect almost all SCD spectra, including epidemiology, age, clinical presentation, cause, risk factors, mechanisms of ECG and autopsy findings, treatment, prevention, and outcomes. In summary, although the prevalence of SCD in women is almost 30 to 50% less than in men, major clinical risk factors are present and similar for both genders; substantial differences exist in outcomes and predictors. Information must be provided to the general population and patients about the risk factors for the development of SCD, which are common in both genders, specifying, in women, those that differ and how to recognize them. It is not easy to understand why women receive fewer CPR maneuvers and treatment during CA events and post-ROSC therapies.[62] There are not enough community campaigns trying to raise awareness about the importance of CPR in the general population,[63] but also specifically in women with SCD. This could be beneficial and improve outcomes. Much is still left to be learned about gender-related differences in SCD between women and men. However, we believe that what is most important is to remove prejudices about factors that are not physiological, biological, or genetic and cannot be ethical[64] and that only respond to taboos or concepts of society concerning the difference in gender and race, regardless of the health problem, but specifically speaking of the SCD.

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Correspondence:
Jorge Álvarez de la Cadena-Sillas
E-mail: jalvarezdelacadena@gmail.com

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Consensus statement

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Mexican consensus statement on fasting before cardiovascular diagnostic and therapeutic interventions

Consenso mexicano de ayuno previo a intervenciones cardiovasculares diagnósticas y terapéuticas

Rafael Moguel-Ancheita,[1] Rafael Olvera-Ruiz,[2] María Guadalupe Jiménez-Carbajal,[3] José Juan Florencio Constancio Lozoya-Morales,[4] Nelsy González-Ramírez,[5] Giovanny Ponte-González,[6] Yoloxóchitl García,[7] Carlos Cabrera-Arroyo,[8] Gerardo Rodríguez-Diez,[9] Francisco Alejandro Félix-Téllez,[10] Mario Alberto Estrada-Jaime,[11] Carlos Ixbalamqué Rodríguez-Herrera,[12] Gabriela Atenea García-Arvizu,[13] Carlos Alfredo Narváez-Oriani,[14] Martha Sofía Nájar-Guerrero,[15] Fabiola López-Madrigal,[16] Ana Berni-Betancourt,[17] Araceli Gutiérrez-García,[18] Erick Iván Colín-Álvarez,[19] Francisco Javier Molina-Méndez,[20] María Virginia Lendewig-Barrera,[21] Fátima Miroslava Rivera-Rodríguez[22]

Keywords: preoperative fasting, sedation, general anesthesia, elective procedures, cardiac catheterization, cardiovascular catheterization.

Palabras clave: *ayuno preoperatorio, sedación, anestesia general, procedimientos electivos, cateterismo cardiaco, cateterismo cardiovascular.*

[1] MD, FSCAI. Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular (COMECITE). ORCID: 0000-0002-9846-510X
[2] MD, FSCAI. COMECITE. ORCID: 0000-0002-9028-3096
[3] MD. COMECITE. ORCID: 0000-0001-9642-4219
[4] MD, FSCAI. COMECITE. ORCID: 0000-0002-1047-3675
[5] MD. Asociación Nacional de Cardiólogos de México (ANCAM). ORCID: 0009-0006-4354-558X

ABSTRACT

Introduction: prolonged fasting before cardiac catheterization remains a routine practice in almost all institutions, despite the lack of solid evidence of its benefits. **Objectives:** to analyze and issue recommendations based on evidence and international consensus on preoperative fasting in elective cardiac catheterization procedures in adult and pediatric populations. **Material and methods:** this national consensus used the nominal group technique and Delphi methodology, with participation from organizations such as COMECITE, ANCAM, SOMEEC, and COMEXANE, and a systematic review of the literature in medical databases, including randomized controlled trials and meta-analyses. **Results:** the consensus established recommendations for adult and pediatric populations, based on current evidence. **Conclusions:** short or liberalized fasting is safe before cardiac catheterization procedures and is associated with superior patient satisfaction compared with prolonged fasting, without an increase in broncho aspiration-related complications.

RESUMEN

Introducción: *el ayuno prolongado antes de un cateterismo cardiaco sigue siendo una práctica habitual en casi todas las instituciones, a pesar de la falta de pruebas sólidas sobre sus beneficios.* ***Objetivos:*** *analizar y emitir recomendaciones basadas en la evidencia y el consenso internacional sobre el ayuno preoperatorio en procedimientos de cateterismo cardiaco electivo en poblaciones adultas y pediátricas.* ***Material y métodos:*** *este consenso nacional utilizó la técnica de grupo nominal y la metodología Delphi, con la participación de organizaciones como COMECITE, ANCAM, SOMEEC y COMEXANE, y una revisión sistemática de la literatura en bases de datos médicas, incluyendo ensayos controlados aleatorios y metaanálisis.* ***Resultados:*** *el consenso estableció recomendaciones para poblaciones adultas y pediátricas, basadas en la evidencia actual.* ***Conclusiones:*** *el ayuno corto o liberalizado es seguro antes de los procedimientos de cateterismo cardiaco y se asocia con una mayor satisfacción de los pacientes en comparación con el ayuno prolongado, sin aumento de las complicaciones relacionadas con la aspiración bronquial.*

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[6] MD. COMECITE. ORCID: 0000-0002-0276-7294
[7] MD. COMECITE. ORCID: 0000-0003-4587-5698
[8] MD. COMECITE. ORCID: 0009-0001-1180-4253
[9] MD. Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca (SOMEEC). ORCID: 0000-0001-8132-0724
[10] MD. Universidad Autónoma de Baja California. ORCID: 0000-0002-6138-3741
[11] MD. Asociación Nacional de Cardiólogos al Servicio de los Trabajadores del Estado (ANCISSSTE). ORCID: 0009-0009-9409-6018
[12] MD. Colegio Mexicano de Anestesiología (COMEXANE). ORCID: 0009-0005-7329-7946
[13] MD. ANCISSSTE. ORCID: 0009-0003-9823-7152
[14] MD. ANCISSSTE. ORCID: 0000-0002-7473-1346
[15] MD. ANCISSSTE. ORCID: 0009-0004-0643-881X
[16] MD. ANCAM. ORCID: 0009-0005-4144-784X
[17] MD. SOMEEC. ORCID: 0000-0001-9705-8142
[18] MD. COMEXANE. ORCID: 0009-0005-9254-4455
[19] MD. ANCISSSTE. ORCID: 0009-0007-8836-0850
[20] MD. SOMEEC. ORCID: 0009-0000-8274-4991
[21] Universidad Anáhuac Cancún. ORCID: 0009-0008-9922-2135
[22] Universidad Autónoma de Zacatecas. MD. ORCID: 0009-0007-1681-5596

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INTRODUCTION

Every discipline has repetitive, automatic patterns that have been learned over generations without any thorough analysis of their efficiency; medicine is no exception. Among traditions, fasting before surgery is a rather recent indication. Yet, in the 19th century, Dr. Joseph Lister, the British surgeon who introduced antiseptics in surgery and discovered catgut, gave patients a beef concentrate soup, 2-4 hours before surgery. The first report supporting preoperative fasting was published by Dr. Curtis Mendelson's paper in 1946, after finding 0.15% pulmonary gastric content in 44,016 women during obstetric anesthesia using a gas mixture of ether and oxygen.[1,2]

Decades later, the medical community and hospitals persist in strict fasting before surgery, even under conscious sedation, including catheter-based procedures, and noninvasive or minimally invasive procedures without sedation, such as the intravenous contrast computed tomography (CT) and magnetic resonance (MR).

The obligation to adhere to the fasting indication restricts patients from any meal and water for four hours or more, with the following consequences:

1. Prolonged fasting, for more than four hours, or even days, resulting in complications such as dehydration and consequent increased drug and contrast dye toxicity.
2. Deferral of scheduled procedures exposes the patient to the disease's natural history.
3. Increased procedural costs due to readmissions and hospital days.
4. Waste of the resources utilized on the deferred patients.
5. Impact on the patient's comfort and tolerance.
6. Institutional discredit.
7. Work environment deterioration.
8. Missed medication.

To illustrate the medical consequences of deferral, consider the experience of COVID-19, in which postponed cardiovascular interventions, resulted in 36% complications related to this delay.[3]

Current fasting protocols

The European Society of Anaesthesiology (ESA) and the American Society of Anesthesiologists (ASA) Guidelines[4] declared that patient safety is the primary goal of preoperative fasting; however, it must be kept to a minimum to avoid metabolic disruptions and reduce the risks associated with extended fasting.

The ESA and ASA suggested the following indications for elective procedures, including those performed under conscious sedation, local anesthesia, regional anesthesia, or a combination thereof.

Adults

Clear liquids: patients may consume water, pulp-free juices, tea, or coffee without milk up to two hours before the procedure. This technique reduces thirst, promotes hydration, and reduces the risk of aspiration.

Light diet: the treating physician determines the fasting length, recommending six hours fasting following a simple meal, such as bread, fruit, or crackers, or eight hours after consuming high-fat or high-protein meals.

Carbohydrate-rich drinks: even patients with well-controlled diabetes may consume carbohydrate-rich drinks up to two hours before surgery, to improve patient satisfaction, lessen hunger and thirst, and lower postoperative insulin resistance, without raising the risk of aspiration.

Other considerations: never cancel or postpone the procedures solely because of chewing gum, sucking on a hard candy, or smoking before the intervention, as these do not represent a clinically significant risk of aspiration.

Patients with delayed gastric emptying: follow the same recommendations outlined above.

Children

Clear liquids: permitted up to two hours before the procedure, including water, pulp-free juices, or pediatric electrolyte solutions.

Solid diet: six-hour fasting following a light meal, as in adults.

Breast milk: allowed up to four hours before the procedure, as gastric emptying is faster and safer. Other types of milk, such as formula or cow's milk, delay gastric emptying due to their higher protein and fat content, requiring a minimum six-hour fasting period.

Intravenous iodine contrast-enhanced image studies

Arbitrary tradition includes fasting in the preparation protocol for intravenous iodine contrast-enhanced imaging, despite a lack of evidence of benefit, even in the high-osmolality contrast era. Currently, in the modern era of iodine preparation, nausea and vomiting occur at non-significant, non-relevant rates of 0.013% and 0.059%, respectively. The European Society of Urogenital Radiology (ESUR) and American College of Radiology (ACR) guidelines discourage fasting before these studies.[5]

Current concepts regarding fasting

No evidence supports fasting before interventional or diagnostic cardiovascular procedures; instead, fasting is associated with increased complications and misunderstandings, particularly when medical and nursing staff interpret «nothing by mouth» literally. Prolonged fasting entails abstaining from food and water for several days. The operators and anesthesiologists believe that their patients are on a hospital fasting time routine, when in fact they are not.

Fasting is not easy; patients may eat or drink, which can lead to deferral or rescheduling of procedures by operators or other staff members. Fasting since dinner can result in up to 12 hours of fasting for the first morning procedure, and longer for subsequent procedures.[6] Deferring scheduled cardiovascular procedures negatively impacts patients' prognosis, especially those with hypertension, chronic kidney disease, and heart valve implants.[3]

Current evidence does not support the benefits of fasting, instead highlighting the harms associated with interventional cardiovascular procedures. Mishra et al., report in cardiac catheterization procedures, similar rates of primary and secondary outcomes (hypotension, aspiration pneumonitis, nausea/vomiting, hypoglycemia, patient satisfaction, and 30-day mortality).[7]

Sheila Bacus et al. report the effects of fasting in a single-center, non-emergency cardiac catheterization study of 1,030 patients; no episodes of aspiration, inadequate preprocedural hydration in patients at high risk for contrast-induced nephropathy, fasting for significantly longer periods, and fasting-related symptoms (hunger, nausea, and vomiting).[8] The TONIC trial, a single-center, prospective, blind randomized controlled trial, included 739 patients undergoing non-emergency coronary procedures, reported noninferiority of a non-fasting strategy compared to a fasting one, while improving patients' comfort.[9] Carri Woods et al. reported a single-center elective cardiac catheterization study in 197 subjects; the non-fasting group had significantly greater satisfaction without a safety risk than the fasting group.[10]

The CALORI trial, a single-center randomized trial of 198 patients undergoing cardiac catheterization, demonstrated improved patient well-being and satisfaction without compromising safety with the non-fasting strategy.[11] The multicenter randomized SCOFF trial included 716 patients; primary outcomes (aspiration pneumonia, hypotension, hyperglycemia, and hypoglycemia), and patient satisfaction scores were significantly better in the non-fasting group than the fasting group.[12] Adil Salihu et al. reported a meta-analysis of elective and nonurgent coronary angiography and found no evidence that fasting reduces adverse events, but provoked patient dissatisfaction.[13] O-K Kwon informed an open-label clinical trial of cerebral angiography in 2,554 patients; nausea and vomiting are low and not affected by diet or fasting, without pulmonary aspiration rates between groups.[14]

Many studies with thousands of patients confirmed the limited utility of fasting for the preparation for intravenous contrast-enhanced imaging, including pulmonary aspiration, nausea, vomiting, and other serious adverse events.[15-18]

Fasting in non-invasive studies

Arbitrary tradition includes fasting in the protocol for intravenous iodine contrast for enhanced imaging, despite a lack of evidence of benefit, even in the era of high-osmolarity contrast. Currently, with modern iodine preparations, nausea and vomiting occur at insignificant rates of 0.013% and 0.059%, respectively.

Nevertheless, some centers require fluid fasting prior to intravenous contrast studies to reduce the risk of aspiration pneumonia. Lee et al. published 13 studies in the medical literature on contrast-enhanced CT performed after fluid ingestion at 69 hospitals and concluded that there is little evidence that clear liquids cause aspiration pneumonia.[18] Low and iso-osmolar non-ionic contrast agents used in CT and gadolinium-based paramagnetic contrast agents used in MRI represent a lower risk of vomiting than the high-osmolarity ionic contrast agents previously used.[19] Contrary to previous beliefs, fasting before the procedure could have unpleasant effects, such as difficulties in scheduling appointments, risk of hypoglycemia in patients with diabetes mellitus, and general dissatisfaction. Hunt et al. published a study of 456,930 doses of iodinated and gadolinium contrast agents and reported adverse events (hives and nausea) in 0.11% of low-osmolar iodinated and 0.64% of gadolinium doses.[20] No gadolinium-conducted studies report the risk of aspiration pneumonia. Neeman et al. conducted a randomized controlled trial that enrolled 2,091 hospitalized patients for non-emergency contrast-enhanced CT scans. Nausea, vomiting, risk of aspiration pneumonitis, or adverse gastrointestinal symptoms did not differ statistically between the fasting and non-fasting groups.[21] Routine intravenous contrast administration does not require fasting unless sedation is required, and it follows standard anesthesia recommendations.[22]

Special considerations for pediatric patients

The topic of fasting in pediatric patients needs a separate section because they undergo these procedures, ranging from premature newborns, who apparently have slower gastric emptying than full-term infants, to adolescents with altered nutritional status and complex congenital heart disease, who have unique physiological characteristics regarding hydration and nutrition. For example, in patients with univentricular physiology, the main variables for evaluating the quality of the cavopulmonary circulation are invasive measurements of central pulmonary arterial and systemic ventricular end-diastolic pressures. These patients traditionally fast for at least eight hours, with strict control of intravenous fluids during this same period. There is some controversy about measuring these pressures on a single occasion, when patients are fasting, supine, under sedation or general anesthesia, or under conditions more representative of normal activity. However, the practical aspects of this measurement make it difficult to perform.[23]

Occult diastolic dysfunction

Peck et al. (2022), in a single-center study, measured baseline variables and repeated measurements after an intravenous bolus of crystalloid (15 mL/kg body weight) administered over less than five minutes, repeating after a five-minute stabilization period, obtaining the cardiac output by the Fick's equation, defining occult diastolic dysfunction as a systemic ventricular end-diastolic pressure of 15 mmHg or greater after crystalloid administration.[24]

Maintaining patients under near-physiological conditions as close to normal as possible, using the body's own homeostatic mechanisms and without prolonged fasting, is the best protocol for maintaining euvolemia.[25] However, it remains uncertain whether, in these patients with univentricular physiology, there are differences in baseline measurements when performed under fasting conditions, with or without intravenous fluids, and whether interventions affect dysfunction parameters. Gastric aspiration may happen in 1.3/10,000 procedures.[26]

The «no food after midnight» paradigm persists, even in pediatric patients; however, given the lack of solid scientific

evidence regarding its safety, consensus statements tend to recommend reducing preoperative fasting time.

Despite guidelines, multifactorial, generally systemic factors impede compliance with fasting hours, leading to extremely prolonged fasting times in children and to the physiological consequences of this practice, such as discomfort, irritability, fatigue, hypoglycemia, ketosis, and hypotension.[27] Alarcón-Almanza et al, published in 2024, the addition to fasting in 500 patients between 0 and 18 years old scheduled for elective procedures, demonstrated that only 40% of patients complied with the indicated fasting time, with 59.6% of children fasting for more than eight hours, of whom 18.1% were infants; 13.6% presented with hypoglycemia.[28]

Current recommendations follow the guidelines issued by the European Society of Anaesthesiology and Intensive Care, without any methodological literature on pediatric cardiovascular intervention, whose latest update in 2022 recommended maintaining a six-hour fast for solids, four hours for infant formula, three hours for breast milk, including fortified breast milk, and one hour for clear liquids.[29] The update consists of reducing the fasting time for clear liquids to one hour (level of evidence 1B/1C) and for breast milk to three hours (level of evidence 1C).[28,29]

These recommendations regarding clear liquids follow the publications of the Association of Pediatric Anesthetists of Great Britain and Ireland, the Australian and New Zealand College of Anesthetists, the European Society for Pediatric Anesthesiology, the Association of Pediatric Anesthesiologists and Resuscitators of France, and the Working Group of the Pediatric Section of the Spanish Society of Anesthesiology, Resuscitation and Pain Therapy. These societies support a three-hour fast for breast milk (whether fortified or not) and a one-hour fast for clear liquids, except in cases with risk factors for delayed gastric emptying or low cardiac output.[30]

Conversely, in 2023, the ASA published updated guidelines on preoperative fasting, replacing the 2017 guidelines. These guidelines addressed specific topics, including the administration of clear liquids containing carbohydrates with or without protein, the use of chewing gum, and the duration of pediatric fasting. This publication concludes that the evidence is insufficient to support the benefits of a one-hour clear liquid fast for patients undergoing procedures under general or regional anesthesia or sedation, and recommends a fast of approximately two hours. However, it also states that a shorter fasting duration should be at the clinician's discretion.[26]

In September 2025, the Pediatric Society of Anesthesia published the results of a survey of 430 members of the Society of Pediatric Anesthesia on the timing of clear fluid intake before procedures, supported by international anesthesia societies for a guideline reducing the clear fluid intake period to one hour in pediatric patients, consistent with the ASA updated guidelines, which maintain the recommendation of clear fluid intake for two hours before anesthesia. 73% of members adhere to the two-hour clear-fluid fasting recommendation, whereas 24% adhere to a one-hour policy. However, 71% considered the one-hour clear-fluid fasting policy adequate, and 86% stated they would shorten it to one hour if the ASA guidelines were updated.[26]

MATERIAL AND METHODS

After written invitation to the main national cardiological organizations, the Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE) collaborated with prominent members of associations and societies such as the National Association of Cardiologists of Mexico (ANCAM), the Mexican Society of Electrophysiology and Cardiac Stimulation (SOMEEC), the National Association of Cardiologists of the State Workers' Security and Social Services Institute (ISSSTE) (ANCISSSTE), and the Mexican College of Anesthesiology (COMEXANE). A consultant gastroenterologist from the *Universidad de Baja California* assessed the gastric emptying function. The consensus also included collaboration with the Social Service of the Anahuac University Campus, Cancún and the Universidad Autónoma de Zacatecas.

The consensus group elected a chair and a co-chair, then assigned specific roles to the remaining members. The authors searched medical databases, including PubMed, SciELO, Google Scholar, and Scopus, and peer-reviewed articles on fasting in preparation for cardiovascular procedures, both invasive and non-invasive, drawing on their experience.

A search was conducted across PubMed, Scopus, SciELO, and Google Scholar for publications from the last five years on fasting in pediatric patients undergoing elective diagnostic or interventional cardiac catheterization with prior sedation or general anesthesia.

The MeSH terms used were:

Preoperative fasting, cardiac catheterization, pediatric patients, children, sedation, general anesthesia, and congenital heart disease.

The consensus worked between March and September 2025.

The meetings followed a nominal group technique format, consisting of a virtual meeting in which each member presented their proposal and rationale, with no time limit.

The Delphi rounds ultimately resolved the disagreements (description of the process).[31]

Authorship

The consensus group defined the list of authors from the outset of the consensus process and revised it throughout the process. According to the International Committee of Medical Journal Editors (ICMJE).[32] All individuals who contribute and strictly meet each of the following criteria will be considered authors:

1. Make a substantial contribution to the conception or design of the work; or to the acquisition, analysis, or interpretation of data.
2. Write the work or critically revise it.
3. Approve the final version for publication.
4. Confirm the accuracy and completeness of each part of the work.

The acknowledgments section recognizes contributors who have not met all four criteria mentioned above.

RESULTS

The results from the research are described in the introduction, because it is the basic information regarding these statements.

DISCUSSION

This document highlights the opportunities to improve recommendations regarding of Randomized Clinical Trials on the duration of fasting, the study of changes in gastric emptying and gastric pH, and the utility of gastric ultrasound for estimating gastric contents, which are already established in specific situations using point-of-care gastric ultrasound (POCUS).[33] It also addresses indications for gastric ultrasound in patients with specific comorbidities, such as heart disease in children.

Likewise, this document emphasizes the importance of educating medical personnel who care for patients, the patients themselves, and their families and caregivers about preoperative fasting recommendations and guidelines. It also addresses the potential consequences of adhering to the recommended fasting times, including the risk of aspiration due to elevated gastric contents and the physiological effects of exceeding the recommended fasting period.

RECOMMENDATIONS

1. Current recommendations regarding fasting time should be the maximum permissible durations, avoiding any fasting exceeding six hours for solids and two hours for liquids.
2. Current recommendations are based on consensus.
3. Delaying a cardiovascular procedure, whether invasive or non-invasive, causes more harm than benefit to the patient and institution.
4. Cardiovascular procedures should only be delayed following multidisciplinary assessment of risks and benefits.
5. Fasting is not recommended before noninvasive imaging studies requiring intravenous contrast.
6. Deferrals due to food intake are not indicated for imaging studies with intravenous contrast.

7. All of the above apply to elective or non-immediate emergency procedures. Fasting does not apply to immediate emergency procedures.
8. Recommendations apply to coronary and structural interventions, as well as to electrophysiological procedures and implantation of pacemakers, defibrillators, and cardiac resynchronization therapy devices.
9. Each cardiovascular center may agree to perform procedures without prior fasting.

We recommend the following fasting indications, based on the revised guidelines and updates,[27,34] to improve the quality and safety of care for pediatric patients undergoing cardiac catheterization before elective anesthetic procedures:

1. Always avoid prolonged fasting (eliminate the «nothing after midnight» paradigm).
2. Clear liquids (water, pulp-free juice, tea, or coffee without milk or sugar): a two-hour fast is recommended. A one-hour fast before induction of general anesthesia, regional anesthesia, or sedation may be considered, based on clinical judgment in each case and the patient's comorbidities.
3. Breast milk: a three-hour fast is recommended for infants under six months and a four-hour fast for infants over six months.
4. Infant formula and cow's milk: a four-hour fast is recommended for infants under six months and a six-hour fast for infants over six months.
5. Solid foods and other non-clear liquids: a six-hour fast is recommended for light lunches (toast with jam or jelly; crackers; herbal teas with or without skim milk; juices with pulp).
6. Consider the hydration status of patients, paying special attention to those with complex congenital heart disease, decreased pulmonary blood flow in states of hyperviscosity, or univentricular physiology.
7. Implement strategies to promote the assessment of gastric contents using ultrasound techniques in patients for whom the time elapsed between their last meal and the start of sedation or anesthesia is uncertain, when delaying is not appropriate, or in those with comorbidities that compromise gastric emptying.
8. Implement proactive institutional strategies in which medical and paramedical staff ensure that children undergoing elective anesthetic procedures can consume clear liquids up to two hours beforehand, considering that in each case, this could be as little as one hour prior.
9. It is recommended to resume the intake of clear liquids as soon as the patient recovers from the anesthetic procedure or sedation, on demand, according to the patient's tolerance, provided there are no contraindications.

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Correspondence:
Rafael Moguel-Ancheita
E-mail: cathboss@gmail.com

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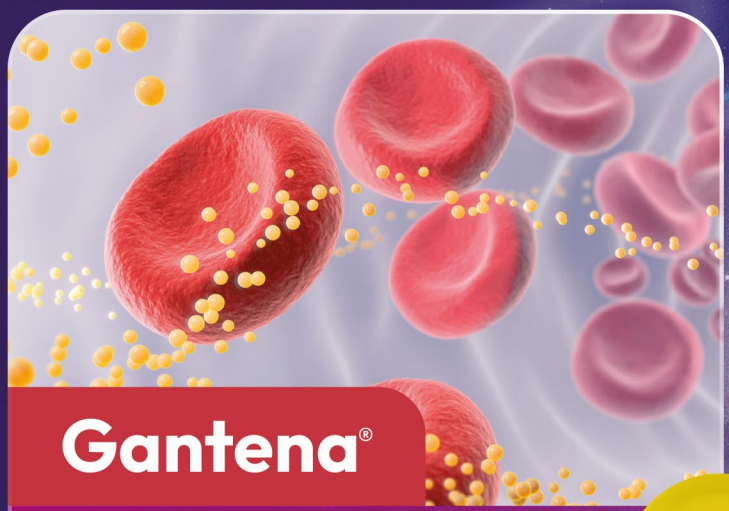

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