ISSN en trámite

Cardiovascular and Metabolic Science

Continuation of the Revista Mexicana de Cardiología

2021

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VOLUME 32, NUMBER 3
JULY-SEPTEMBER 2021

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Editorial coordination: Dr. José Rosales Jiménez and Marco Antonio Espinoza Lorenzana. Editorial design: Diego Lozano Saavedra.
Art, design, typesetting, pre-press and printing by **Graphimedic, SA de CV.** Tel: 55-8589-8527 to 32. E-mail: emyc@medigraphic.com. ***Printed in Mexico.***

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 32 No. 3
July-September 2021

CONTENTS / CONTENIDO

Cardiovascular and Metabolic Science www.ancam.org.mx

Editorial

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101303

First study the science, then practice the art: Leonardo da Vinci

Primero estudia la ciencia, luego practica el arte: Leonardo da Vinci

José Luis Moragrega-Adame*

Modern medicine gravitates around the scientific achievements that have changed a basically intuitive practice, to one that more and more resembles an applied science. But it is known –or rather should be widely known– that unlike mathematics, medicine is not a pure science. Two plus two will always be four, but chest pain plus diabetes will not always be myocardial infarction. The elements that make the difference are the influence of probability and complexity. The results obtained from a variety of tools may be different in different moments and settings, and we have to consider the different levels of evidence. The interpretation of an EKG could be different for two observers and even for the same observer in different moments. It has been rightly mentioned that scientific truths are not true for all times, and today's truth may be tomorrow's folly.[1] A publication in Mayo Clinical Proceedings shows that in ten years' time, almost half of the concepts that were the state of the art, are no longer valid.[2] The half-life of truth in medicine is short, and around half of what is true today will be proven to be incorrect in the next five years; unfortunately, we do not know the half that is going to be wrong.[3]

Applied science is the utilization of scientific tools and concepts to solve specific classes of practical problems. Moreover, amid all this, the idea of the practice of clinical medicine as an art persists. The humanistic approach stresses that, first and foremost, every person is a human being, and I must emphasize here, it is not just a case or a number. Health care workers not only care for their patients but care about them. Pérez Tamayo[4] prefers the term «humanitarian» instead of humanistic medicine when the term is related to patient care because humanism is defined as cultivating culture.

The aim to receive a humanitarian medicine lies at the center of patients hopes and has been performed by part of the medical community worldwide. But in some places and moments through history, many social and economic factors have driven the practice out of its traditional objectives. At the same time, although it is widely recognized that medicine is part art and part science, the debate continues over the status of both aspects.

The art of tending to the sick is as old as humanity itself. Over its long history, physicians have cared for and comforted their patients, and they are supposed to understand them as a person, different to every other one. All sickness events wil also be unique, and as scientific knowledge is far from perfect, uncertainty is an inseparable part of medical practice. We will see in this review that humanitarianism, art, and science entwine in a profound and sometimes surprising way.

Humanitarianism aims to provide essential relief to those destabilized by crises. This includes the aid to those suffering the consequences of war, natural disasters, or forced displacement, but we will treat here the concept of helping for the consequences of the disease.[5]

«Humanitarian medicine» has been defined by Masellis[6] in the following paragraph:

* Private practice of medicine. Clinical cardiology, biostatistics and epidemiology. Irapuato, Gto. Mexico.

How to cite: Moragrega-Adame JL. First study the science, then practice the art: Leonardo da Vinci. Cardiovasc Metab Sci. 2021; 32 (3): 114-116. https://dx.doi.org/10.35366/101303

While all medical intervention to reduce a person's sickness and suffering is in essence humanitarian, humanitarian medicine goes beyond the usual therapeutic act and promotes, provides, teaches, supports, and delivers people's health as a human right, in conformity with the ethics of Hippocratic teaching, the principles of the World Health Organization, the Charter of the United Nations, the Universal Declaration of Human Rights, the Red Cross Conventions and other covenants and practices that ensure the most humane and best possible level of care, without any discrimination or consideration of material gain.

Humanism in healthcare is characterized by a respectful and compassionate relationship between physicians and all other members of the healthcare team and their patients. It reflects attitudes and behaviors that are sensitive to the values and the cultural and ethnic backgrounds of others. The humanitarian aspect of medicine is related to the traditional form of charity, originally practiced based on religious principles and later becoming a need of the community to support its own members.

In early times, medicine was an art, along with poetry and painting; today, we try to make it a science besides mathematics, astronomy, and physics; but happens that with the progress of science and its applications, there is a rapid decline in the human elements of health care providers which dilutes the age-old doctor-patient relationship.

Rene Dubos[6] mentioned that ancient medicine was the mother of science and played a large role in the integration of early culture. The worst man of science is the one who is not at the same time an artist, and the worst artist, the one who is not a scientist. Panda[7] prefers to say that medicine is an «art based on science» and concludes that a physician must be an artist armed with basic scientific knowledge in medicine for successful practice.

In Cecil's Textbook, medicine is described as «a profession that incorporates science and scientific methods with the art of being a physician». Some state that as physicians undertake various kinds of activities that, although they are not indeed scientific, are essential to the practice of medicine. These activities constructed with evidence-based medicine, collectively constitute the art of medicine. The art of caring and comfort, guided by millennia of common sense as well as an approach to medical ethics, remains the cornerstone of medicine. Without these humanistic qualities, the application of modern science of «medicine» is suboptimal, useless, and even detrimental.

The scientific basis of medicine is in constant evolution. The need of mingling all these different aspects of individuality and evidence requires the implementation of the art of medicine.

On many occasions, physicians are criticized for their insensitive behavior and for ignoring the emotional distress and strain affecting a sick individual. The health care provider needs to be essentially a good human being. As Saunders said,[8] *The practice of clinical medicine with its daily judgments is both science and art. In the practice of clinical medicine, the art is not merely part of the 'medical humanities' but is integrated to medicine as an applied science*.

So, medicine is both art and science. Both are interdependent and inseparable, just like two sides of a coin. And now here follows the comparison of the two aspects that have been related to the art in medicine. Some have stated that the importance of the art of medicine is because we have to deal with a human being, their body, mind and soul. To be a good medical practitioner, one must become a good artist with sufficient scientific knowledge. The technology covered with a layer of art can bring relief to the sick. For me, this is the humanitarian aspect of the profession. The other approach to which I adhere to define the art reminds us that the practice of modern medicine is the application of science, the ideal of which is to obtain a neutral truth. The reality can be different, and the practice varies widely. The evidence from randomized controlled trials or observational methods cannot dictate obligatory actions in any particular circumstances. Their conclusions are applied by value judgments, which must be specified to every individual case. Herein lays the art which is integral to the practice of medicine as an applied science.

Finally, to enjoy the practice of our profession, we can follow the saying of Albert

Einstein: *The most beautiful thing we can experience is the mysterious. It is the source of all true art and all science*.

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Cardiovascular and Metabolic Science www.ancam.org.mx

Original Research

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101304

Sex-related differences of the aortic root in a middle-aged Mexican population: insights of a structural and functional assessment by cardiac computed tomography

Diferencias de la raíz aórtica, relacionadas con el sexo, en una población mexicana de mediana edad: hallazgos de una evaluación estructural y funcional mediante tomografía computarizada cardiaca

Diego Xavier Chango-Azanza,* Mónica Chapa-Ibargüengoitia,*
Zuilma Vásquez-Ortiz,‡ Sandra Rosales-Uvera*

Keywords:
Aortic root, sex-related differences, cardiac computed tomography.

Palabras clave:
Raíz aórtica, diferencias relacionadas al sexo, tomografía computarizada cardiaca.

ABSTRACT

Introduction: Specific aortic root (AR) features appear to have clinical and prognostic implications, and sex-related differences have been described previously. However, there is a lack of data on the Mexican population. **Objectives:** To describe the sex-related variances regarding the AR qualities in a structural and functional analysis. **Material and methods:** We analyzed information of cardiac computed tomography (CCT) of the AR in 71 Mexican patients having a three-leaflet aortic valve and without stenosis or history of aortic aneurysm. We divided the sample to describe the sex-specific disparities; it had 53.5% (n = 38) women and 46.5% men (n = 33). The median age was 56 years (interquartile range IQR: 49-64), with a similar prevalence of hypertension, diabetes, smoking, and dyslipidemia. Weight, height, and body surface area (BSA) stood significantly lower in females, without distinctions in body mass index (BMI). There were no relevant differences regarding systolic and diastolic aortic annulus (AA), eccentricity, and diastolic aortic angulation. Nevertheless, systolic aortic angulation was higher in ladies, and systolic annulus dimensions were significantly greater in men. The initial AR sizes were more prominent in men, but when indexed to BSA, they proved larger in women. A small AA was found in 71% of females and 18.1% in men, and a small AR was pointedly higher in men than women (30.3% versus 2.6%, p = 0.001). **Conclusions:** Individual characteristics such as weight, height, and BSA had consequences in comparing aortic magnitudes. Sex-related

RESUMEN

Introducción: *Los rasgos específicos de la raíz aórtica parecen tener algunas implicaciones clínicas y pronósticas, y las diferencias relacionadas con el sexo se han descrito previamente. Sin embargo, faltan datos sobre la población mexicana.* ***Objetivos:*** *Describir las discrepancias relacionadas con el sexo con respecto a las características de la raíz aórtica en un análisis estructural y funcional.* ***Material y métodos:*** *Se analizaron los datos de hallazgos de la tomografía computarizada cardiaca de la raíz aórtica en 71 pacientes mexicanos con válvula aórtica de trivalva, sin estenosis valvular ni antecedentes de aneurisma de la aorta. Se dividió la población para describir las desviaciones específicas por sexo; mujeres 53.5% (n = 38) y hombres 46.5% (n = 33). La mediana de edad fue de 56 años (IQR: 49-64) con una prevalencia similar de hipertensión, diabetes, tabaquismo y dislipidemia. El peso, altura y área de superficie corporal (ASC) fueron significativamente más bajos en las féminas, sin divergencias en el índice de masa corporal. No hubo disparidades notorias con respecto a la excentricidad del anillo aórtico durante la sístole y la diástole y la angulación de la aorta durante la diástole. No obstante, la angulación aórtica durante la sístole fue mayor en mujeres y las dimensiones del anillo aórtico en sístole resultaron ostensiblemente más altas en varones. Las magnitudes de la raíz aórtica se revelaron superiores en los hombres, pero cuando se indexaron a ASC fueron más elevadas en las señoras. Se encontró un anillo aórtico pequeño en 71% de las féminas y 18.1% de los varo-*

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Received:
02/01/2021
Accepted:
16/07/2021

How to cite: Chango-Azanza DX, Chapa-Ibargüengoitia M, Vásquez-Ortiz Z, Rosales-Uvera S. Sex-related differences of the aortic root in a middle-aged Mexican population: insights of a structural and functional assessment by cardiac computed tomography. Cardiovasc Metab Sci. 2021; 32 (3): 117-127. https://dx.doi.org/10.35366/101304

disparities in these parameters, such as low physical stature in Mexican females, could explain the greater prevalence of small AA, especially when indexing dimensions to bodily height and the aortic features at different levels. The clinical implications of such findings remain unclear.

nes, y una raíz aórtica pequeña fue significativamente mayor en los señores en comparación con las señoras (30.3% versus 2.6%, p = 0.001). ***Conclusiones:*** *Características individuales como el peso, estatura y ASC tienen consecuencias al comparar las dimensiones aórticas. Las diferencias de estos parámetros entre sexos, como la baja estatura corporal en las mujeres mexicanas, podrían explicar la alta prevalencia de un anillo aórtico pequeño, especialmente cuando la medida se indexa por altura del cuerpo y las otras particularidades de la aorta a diferentes niveles. Las implicaciones clínicas de estos hallazgos permanecen inciertas.*

INTRODUCTION

Currently, as medical specialties advance, personalized medicine is emerging. Some patient characteristics have been considered relevant in this discipline, including age, sex, and comorbidities. In addition to the lack of data on age, thoracic aortic diameter values have been determined regardless of sex. As a result, one-size-fits-all cut-off quantities are used. At the same time, the Framingham Heart Study has indicated that age and sex matter for vascular sizes, such as thoracic aortic caliber. Vascular area differences in women seem to have clinical and prognostic implications. Therefore, a need for sex-specific cut-off numbers in this setting could be evaluated and be variable in dissimilar female populations.[1] Aortic dimensions are variably dependent on age, gender, and body size.[2,3] However, reported ranges of average extents are limited by reduced sample sizes, diverse measurement sites, and heterogeneous cohorts.[4,5] Transthoracic echocardiography is the first-line modality to evaluate the aortic root morphology and proportions because it is widely available, safe, and cost-effective.[6,7] Nevertheless, this measurement can differ from the maximum aortic dimensions,[8] since it may be significantly underestimated because echocardiography is traditionally assessed based on the measurements performed in only one plane. The evaluation of the maximum size of the AR should be done on the cross-section of the aorta, preferably using a 3D multiplanar reconstruction mode in CCT or magnetic resonance imaging.[9] Specifically, there is a lack of records on AR anatomic and functional qualities in Mexican people. We aimed to describe the sex-related divergences by CCT analysis from an integrated structural and functional viewpoint.

MATERIAL AND METHODS

The study sample comprised 71 patients referred for CCT coronary angiography at the National Institute of Clinical Derivation. In all of them, the aortic root was analyzed retrospectively on the acquired CCT scan to determine differences in structural and functional parameters of the AR. They all had tricuspid aortic valves without significant stenosis and no history of aortic aneurysm or dilatation. The total sample was divided into two groups: men (n = 33) and women (n = 38) to detect sex-related disparities. The clinical data of patients were recorded previous to the imaging acquisition.

Cardiac computed tomography

The CCT examinations were performed using a 64-slice multi-detector CT scanner (IQon Spectral; Phillips, Netherlands). For the CCT coronary angiogram, collimation of 64 × 0.5 mm and a rotation time of 400 ms were used. A multisegment reconstruction algorithm was employed, resulting in a temporal resolution of 330 ms. The tube current was 300 mA at 120 kV. Nonionic contrast material, from 80 to 110 mL, was administered in the antecubital vein, at a rate of 5.0 mL/s, depending on the total scan time. Automated peak enhancement detection in the ascending aorta was used for the timing of the scan. After the threshold level of +110 Hounsfield units was reached, data acquisition

was automatically initiated. Such process was performed during an inspiratory breath-hold of approximately 8 to 10 s. ECG was recorded simultaneously to allow retrospective gating of the figures. The dataset of the contrast-enhanced scan was reconstructed at 30-40% and 75-80% of the RR interval for the systolic and diastolic phases, respectively. All images were rebuilt with a slice thickness of 0.6 mm and a reconstruction interval of 0.3 mm. Then, axial datasets were transferred to a remote workstation for post-processing and subsequent image examination. Additionally, we used the free ProSize^{AV} plugin in Horos version V3.3.6 for estimating aortic annulus area, eccentricity, and aortic angulation in the course of systole and diastole.

Functional analysis of the aortic root

The functional assessment of the AR during systole and diastole included measuring the AA dimensions in an anteroposterior orientation, area, eccentricity, and aortic angulation. Caution was taken to correctly orient both views by reviewing the reconstructed double oblique transverse view at the level of that aortic ring. Aortic angulation was defined as the angle between the horizontal plane and the plane of the aortic collar. Examples of the coronal, single oblique sagittal, and double oblique transversal views are shown in *Figure 1*.

Anatomical analysis of the aortic root dimensions

Standard orthogonal axial and sagittal views were used for initial orientation on the AR sizes at different levels: sinuses of Valsalva, sinotubular junction, and ascending aortic portion. Because the AR is oriented obliquely to the standard axial view, a coronal and a single oblique sagittal view through the aortic valve were reconstructed. These steps allowed

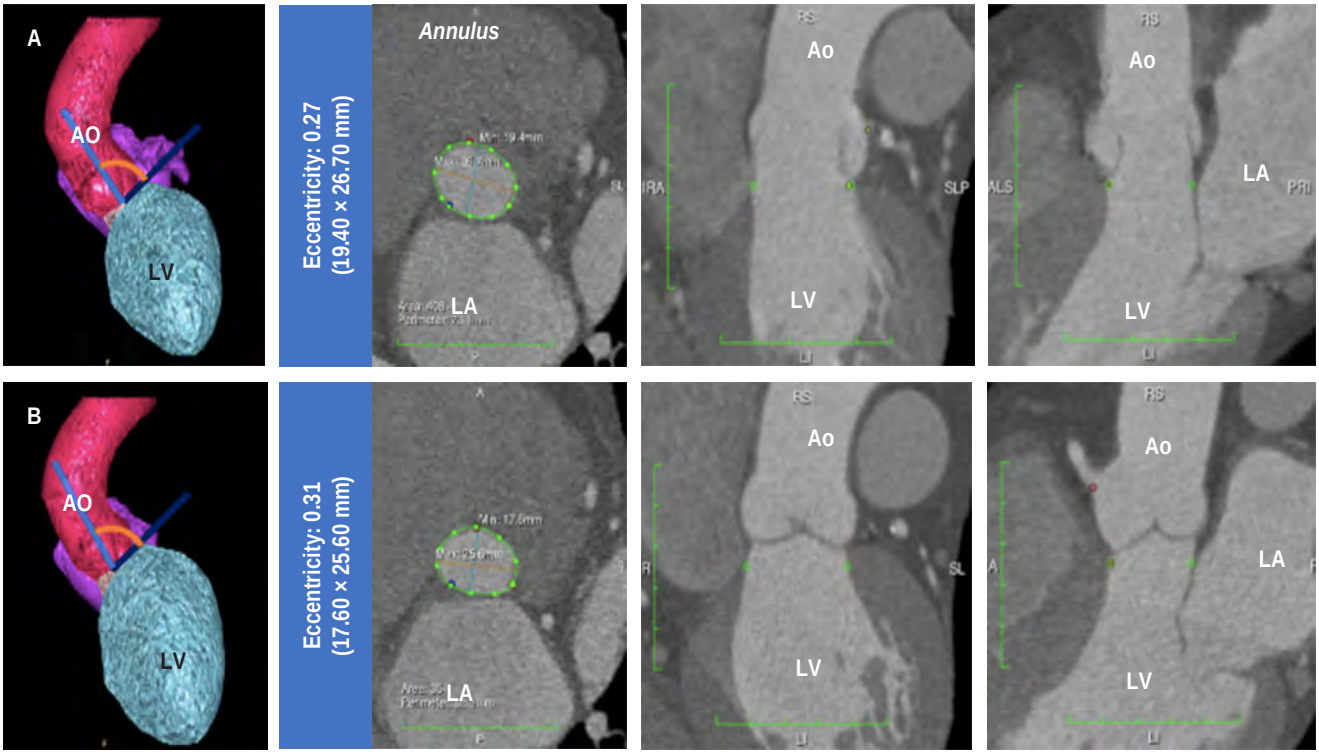

Figure 1: Cardiac computed tomography (CCT) analysis of the functional assessment of features of the aortic root during systole **(A)** and diastole **(B)**. Left upper and bottom: aortic angulation, middle-upper, and bottom: aortic annulus dimensions, eccentricity, and area; right upper and bottom: coronal and sagittal views of the AR. Ao = aorta; LV = left ventricle; LA = left atrium.

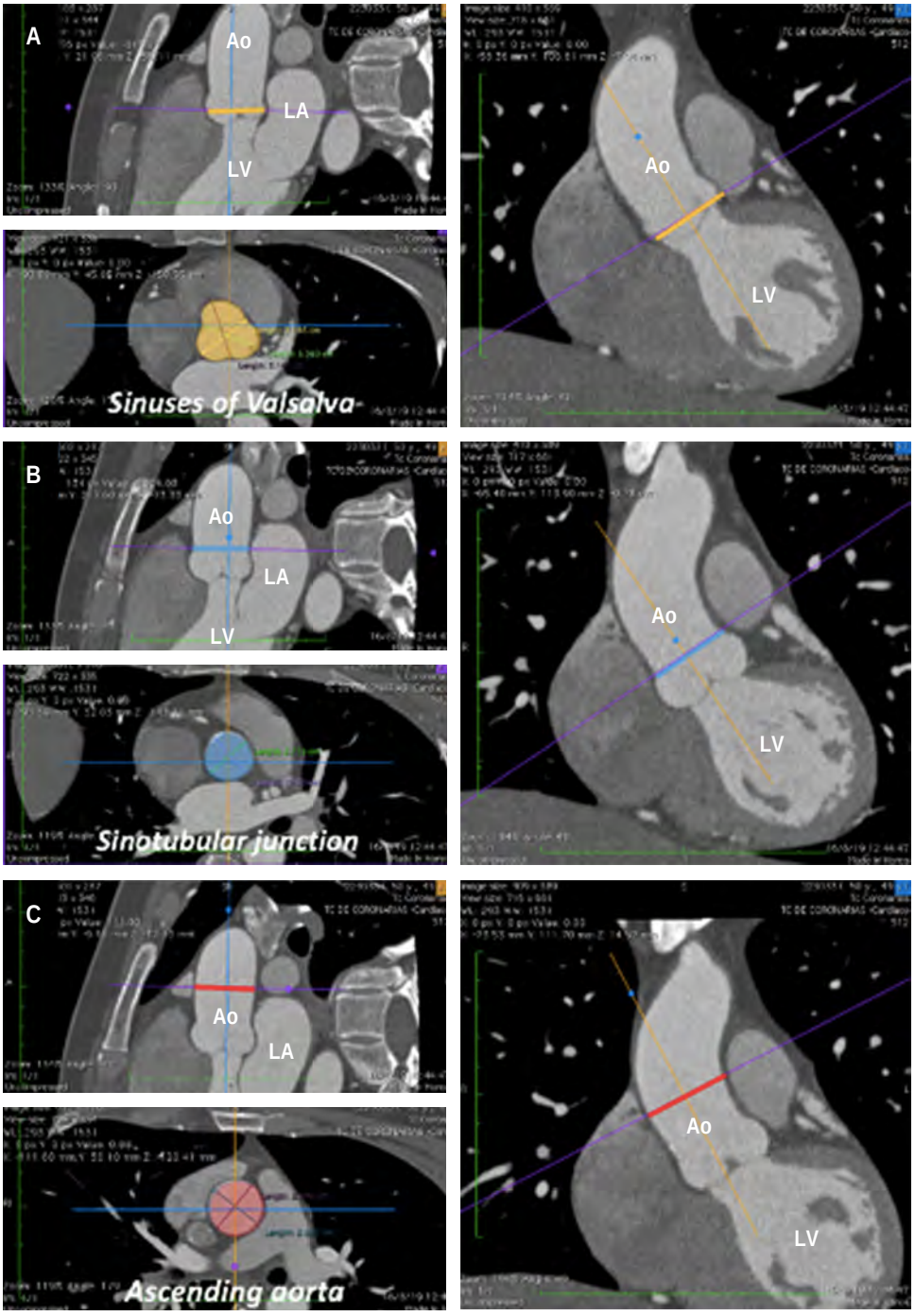

Figure 2:

Cardiac computed tomography (CCT) analysis of the anatomical assessment of features of the aortic root at different levels during diastole**: A)** At the level of the sinuses of Valsalva, sinus to commissure dimension. **B)** At the level of the sinotubular junction and **C)** at the level of the proximal ascending aorta. Ao = aorta; LV = left ventricle; LA = left atrium.

an accurate orientation of both views by reviewing the reconstructed double oblique transverse thus:

A. Diastolic phase 75-80% for calculating maximal dimensions at three distinct levels: 1. At the sinuses of Valsalva, performing a sinus to commissure measurement, 2. At the sinotubular juncture, and 3. At the proximal aortic ascending portion to 40 mm from the AA. All measurements became indexed for BSA for comparative scrutiny. A specific cut-

off indexed body stature dimension of < 15 mm/m in men and < 14 mm/m in women was used to define small AR at the level of the sinotubular aortic junction accordingly using previous information available to avoid the overestimation of adjustment in obese subjects,[10,11] and

B. Systolic phase 30% for the measurement of the AA. A specific cut-off dimension of *Figure 2*.

Statistical analysis

All analyses were performed using SPSS v26.0 (SPSS Inc., IBM, Chicago, IL). The normality of data distribution was assessed using the Shapiro-Wilk test. If normally distributed, continuous variables were expressed as mean and standard deviation (SD) and as the median and interquartile range (IQR) if non-normally distributed. Continuous variables were analyzed using the Student t-test or the Mann-Whitney U test depending on the normality of the distribution. Categoric variables were expressed as percentages. The distribution of these variables was compared using the χ^2 test. All tests were two-sided, and a p-value of < 0.05 was considered indicative of a statistically relevant difference.

RESULTS

Seventy-one patients, comprising 38 women (53.5%) and 33 men (46.5%), were studied. The median age was 56 years (IQR 49-64). 46.4% had hypertension, 19.7% diabetes, 8.4% smoking, and 23.9% dyslipidemia. There were no statistically meaningful differences between both groups. The female population had significantly lower weight, height, and BSA when likened to men, and both clusters had similar BMI. The baseline characteristics of the sample are listed in *Table 1*.

Functional analysis of the aortic root

In all patients, adequate CCT images for evaluating the aortic root dynamics during systole and diastole were available. Indexed to BSA aortic systolic annulus area was higher in systole 2.36 ± 0.38 cm^2/m^2 compared to diastole 2.16 ± 0.36 cm^2/m^2 in the total population. Sex-related dissimilarities were found in such indexed expanse, showing greater quantities in males contrasted to females over the course of both systole and diastole (2.56 ± 0.39 versus 2.18 ± 0.20 cm^2/m^2, p < 0.001 and 2.33 ± 0.38 against 2.02 ± 0.28 cm^2/m^2, p < 0.001; respectively).

Aortic annulus eccentricity due to the elliptical shape of the structure was higher in diastole, having a mean value of 0.24 ± 0.05 when matched systole with a median number of 0.19 (IQR: 0.15-0.22); there were no statistically noteworthy differences in both sets. Aortic angulation was not significantly

Table 1: Baseline characteristics of the total population.

Baseline characteristics	Total N = 71	Male N = 33 (46.5%)	Female N = 38 (53.5%)	p
Age, years (IQR)	56 (49-64)	53 (46-63.50)	58.50 (52-66.20)	0.051
Hypertension (%)	46.40	48.40	44.70	0.752
Diabetes (%)	19.70	24.20	15.70	0.372
Smoking (%)	8.40	12.10	5.20	0.300
Dyslipidemia (%)	23.90	21.20	26.30	0.610
Weight (kg)*	72.90 ± 16	80.10 ± 18	66.60 ± 11.20	< 0.001
Height (m)*	1.61 ± 0.10	1.69 ± 0.07	1.55 ± 0.07	< 0.001
BMI (kg/m^2)*	27.70 ± 50	27.90 ± 5.90	27.60 ± 4.20	0.770
BSA (m^2)*	1.76 ± 0.21	1.89 ± 0.21	1.65 ± 0.13	< 0.001

BMI = body mass index; BSA = body surface area; IQR = interquartile range. * Mean ± standard deviation.

Table 2: Functional aortic root features in total population.

Aortic root functional features	Total N = 71	Male N = 33 (46.5%)	Female N = 38 (53.5%)	p
Indexed systolic annulus area (cm^2/m^2)*	2.36 ± 0.38	2.56 ± 0.39	2.18 ± 0.28	< 0.001
Indexed diastolic annulus area (cm^2/m^2)*	2.16 ± 0.36	2.33 ± 0.38	2.02 ± 0.28	< 0.001
Systolic eccentricity (IQR)	0.19 (0.15-0.22)	0.19 (0.14-0.22)	0.19 (0.16-0.23)	0.632
Diastolic eccentricity*	0.24 ± 0.05	0.24 ± 0.05	0.24 ± 0.05	0.900
Aortic systolic angulation (degrees)*	47.20 ± 8.30	44.10 ± 7.40	49.80 ± 8.20	0.004
Aortic diastolic angulation, degrees (IQR)	45.50 (41-51.10)	44.20 (39.30-49.40)	47.70 (43.40-51.80)	0.075

IQR = interquartile range. * Mean ± standard deviation.

different in diastole in both groupings. Men's median angulation was 44.2º (IQR: 39.3-49.4), whereas women revealed a median angulation of 47.7º (IQR: 43.4-51.8), p = 0.075. However, there was a statistically meaningful difference through systole showing greater angulation in females contrasted to males (44.1 ± 7.4 against 49.8 ± 8.2º, p = 0.004) *(Table 2)*.

Anatomical analysis of the aortic root dimensions

Data on the AR dimensions were available in all patients. The dimension of the systolic AA in an anteroposterior orientation, as usually measured by a two-dimensional method, had a mean value of 20.6 ± 2.4 mm. There was a statistically significant difference in both groups. It reached a higher number in men than in women (22.18 ± 2.20 versus 19.3 ± 1.7 mm, p < 0.001). We found a mean figure of 4.17 ± 0.89 cm^2 when estimating systolic annular area and statistically relevant differences in both clusters, displaying a greater quantity in males than in females (4.83 ± 0.76 against 3.60 ± 0.52 cm^2, p < 0.001). These alterations persisted even after adjusting the value to BSA (2.56 ± 0.39 versus 2.18 ± 0.28 cm^2/m^2, p < 0.001).

We defined a small AA as having an anteroposterior dimension < 23 mm. The women group had a statistically significant higher prevalence of a small AA with 100% (38/38 patients) contrasted with 60% of men (20/33 of them), p < 0.001. Otherwise, defining a small AA as a zone < 4 cm^2, the female population also had statistically meaningfully more prevalence of a small AA, reaching 71% (27/38 patients) compared with 18.1% of males (6/33 of them), p < 0.001.

At the level of the sinuses of Valsalva, maximal sizes measured in diastole (sinus to commissure dimension) became notably greater in males when likened to ladies. Right coronary sinus to commissure (30.1 ± 2.6 against 27.2 ± 2.5 mm, p < 0.001), left coronary sinus to commissure (30.7 ± 2.1 versus 27.5 ± 2.7 mm, p < 0.001) and non-coronary sinus to commissure (31.2 ± 2.4 against 27.9 ± 2.2 mm, p < 0.001). These differences did not persist after fine-tuning by BSA. They had a higher value in women than in males but without statistically significant distinctions. Indexed right coronary sinus to commissure was (16.08 ± 2 versus 16.50 ± 1.60 mm/m^2, p = 0.27), then indexed left coronary sinus to commissure (16.4 ± 1.7 against 16.7 ± 1.5 mm/m^2, p = 0.32) and, finally, indexed non-coronary sinus to commissure, men median number 16.7 mm/m^2 (IQR: 14.8-18) contrasted with female median figure 16.9 mm/m^2 (IQR: 15.9-18.1), p = 0.496.

At the level of the sinotubular juncture, maximal dimension in males was significantly greater than in females (26.4 ± 2.6 against 25.1 ± 2 mm, p = 0.017) but after adjusting by BSA was higher in women against men (men 14.1 ± 1.8 mm/m^2 versus women 15.2 ± 1.3 mm/m^2, p = 0.004).

A small AR, defined as a dimension adjusted by body height at the level of sinotubular junction < 15 mm/m in males and < 14 mm/m in females, statistically was appreciably less prevalent in females than in males in this investigation (30.3% in men against 2.6% in women; p = 0.001).

Lastly, the proximal ascending aorta; its maximal dimension had no statistically noteworthy difference in both groups. The median value in males of 28.6 mm (IQR: 25.5-30.8), and females, a median figure of 28.2 mm (IQR: 25.7-29.8), p = 0.81. After correcting by BSA was statistically higher in women having a median rate of 16.5 mm/m^2 (IQR: 15.4-18.5) versus men with a median number of 15.2 mm/m^2 (IQR: 13.2-17.2), p = 0.002 *(Table 3)*.

DISCUSSION

The primary purpose of the present study was to evaluate sex-related distinctions in structural and functional assessment of the aortic root by CCT findings in Mexican patients. This study is the first to describe those features in such a population, to the best of our knowledge. Our records were similar to others confirming that the normal aortic annulus is oval and more circular with less eccentricity and more prominent in systole than diastole.[12-14] The AA was analogous in both sexes. The impact of the appropriate measurement of the systolic AA due to its elliptical shape by a three-dimensional modality as CCT is critical in the setting of aortic stenosis. It aids in the calculation of the left ventricular stroke volume

Table 3: Anatomical aortic root features in total population.

Aortic root (AR) anatomic features	Total N = 71	Male N = 33 (46.5%)	Female N = 38 (53.5%)	p
Systolic aortic annulus (AP diameter)*	20.60 ± 2.40	22.18 ± 2.20	19.30 ± 1.70	< 0.001
Small aortic annulus (AP diameter < 23 mm) (%)	58/71 (81.60)	20/33 (60.00)	38/38 (100)	< 0.001
Systolic aortic annulus (area cm^2)*	4.17 ± 0.89	4.83 ± 0.76	3.60 ± 0.52	< 0.001
Small aortic annulus (area < 4 cm^2) (%)	33/71 (46.40)	6/33 (18.10)	27/38 (71.00)	< 0.001
Systolic aortic annulus area Indexed BSA (cm^2/m^2)*	2.36 ± 0.38	2.56 ± 0.39	2.18 ± 0.28	< 0.001
Ao sinus to commissure diameter (RCS) (mm)*	28.50 ± 2.90	30.10 ± 2.60	27.20 ± 2.50	< 0.001
Ao sinus to commissure diameter (LCS) (mm)*	29 ± 2.90	30.70 ± 2.10	27.50 ± 2.70	< 0.001
Ao sinus to commissure diameter (NCS) (mm)*	29.40 ± 2.80	31.20 ± 2.40	27.90 ± 2.20	< 0.001
Ao sinus to commissure diameter (RCS) indexed BSA (mm/m^2)*	16.30 ± 1.80	16.08 ± 2	16.50 ± 1.60	0.270
Ao sinus to commissure diameter (LCS) indexed BSA (mm/m^2)*	16.60 ± 1.60	16.40 ± 1.70	16.70 ± 1.50	0.320
Ao sinus to commissure diameter (NCS) indexed BSA (mm/m^2) (IQR)	16.90 (15.80-18)	16.70 (14.80-18)	16.90 (15.90-18.10)	0.496
Ao sinotubular junction maximum diameter (mm)*	25.70 ± 2.40	26.40 ± 2.60	25.10 ± 2	0.017
Ao sinotubular junction maximum diameter indexed BSA (mm/m^2)*	14.70 ± 1.70	14.10 ± 1.80	15.20 ± 1.30	0.004
% Small AR Indexed body height (men < 15 mm/m, women < 14 mm/m) (%)	11/71 (15.40)	10/33 (30.30)	1/38 (2.60)	0.001
Aortic tubular maximum diameter (mm) (IQR)	28.30 (25.70-30)	28.60 (25.50-30.80)	28.20 (25.70-29.80)	0.810
Aortic tubular maximum diameter indexed BSA (mm/m^2) (IQR)	15.80 (14.60-18)	15.20 (13.20-17.20)	16.50 (15.40-18.50)	0.002

IQR = interquartile range. * Mean ± standard deviation.

and the aortic valve area since there was a 29% underestimation of said parameters when calculated by a two-dimensional method. Consequently, as many as 25% of patients with severe aortic stenosis are reclassified as having only moderate stenosis when inputting the correct aortic left ventricular outflow tract extent into the continuity equation.[15]

Additionally, knowing the normal range for the systolic AA dimension has direct clinical applications. Using the typical values for AA size should facilitate diagnosing a fixed component of obstruction based on increased aortic gradients of unclear origin.[14] These expected ranges are variably dependent on age, gender, and physical size. There is a lack of data due to its heterogeneity in different populations depending on race and demographic locations. Our study found that women had shorter systolic AA size, measured as anteroposterior orientation, and a shorter systolic area. This list of differences persists even after the adjustment to BSA. To date, no clear consensus has been established regarding the cut-off number for defining a small AA, which results in multiple definitions used in various studies for the same concept.[16] A small AA is most frequently described as an annulus in the surgical series that would not accommodate a prosthesis extension of > 21 mm.[15,17,18] Due to the lack of statistics regarding typical values of AA in our sample, we chose an AA diameter ≤ 23 mm, described by echocardiography.

The systolic aortic angulation was significantly higher in females, demonstrating a more horizontal aortic orientation in those patients compared with men. Therefore, at similar BMI, a probable explanation of these findings can be related to specific somatotypes in Mexican women with a low body height which determines a different position of the heart and aorta in the thorax.

The degree of angulation between the aorta and the heart can have some procedural implications in aortic transcatheter valve replacement. The accurate positioning is more demanding, particularly in horizontal AR with a vertical aortic annulus.[19,20] There are no precise data regarding the feasibility of this procedure in different aortic angulations in men and women in Mexico. Still, the increased horizontal aortic angulation in them may result in the worst procedural success rate.

When evaluating sex-related differences between AR maximal magnitudes, our records are consistent with other studies,[21] showing significantly lower values in females contrasted to males in diverse AR levels. Interestingly, these change after adjusting to BSA with bigger numbers in females compared with males. The Mexican women's BSA can have some consequences in this finding, and lower BSA can lead to higher indexed dimensions. Therefore, the indexed measurement in this population can have a different cut-off, but such features need to be consistently demonstrated.

Having a diminished aortic root has important clinical and prognostic implications. It was demonstrated that a small AR in itself is associated with increased cardiovascular morbidity and mortality during the progression of moderate asymptomatic aortic stenosis.[22] A small AR is a frequent finding in aortic stenosis patients, reported in the range of 17-33%.[23-25] Inconsistent definitions have been used, reflecting that no precise definition of a small AR is given in current guidelines.[5,26,27]

The indexation of the aortic diameter to body size is recommended.[28-30] The inner AR caliber is recommended by the American College of Cardiology/American Heart Association guidelines for the diagnosis and management of people with thoracic aortic disease.[5] It is also routinely used in other imaging modalities such as magnetic resonance[31] and computed tomography.[32] Because the aortic sinotubular junction is well defined in most aortic stenosis patients, we chose the inner aortic sinotubular juncture caliber based upon recently published average values to identify a small AR.[29] To avoid the overestimation of adjustment in obese subjects, we chose to index aortic diameter for physical stature.[10,11]

When analyzing the prevalence of small AR defined as a maximal caliber at the sinotubular coupling indexed to bodily height < 15 mm/m in males and < 14 mm/m in women, we found a significantly lesser prevalence of small AR in females compared to males (30.3% in males and 2.6% in females; p = 0.001) and a higher indexed BSA maximal dimension at this level in ladies.

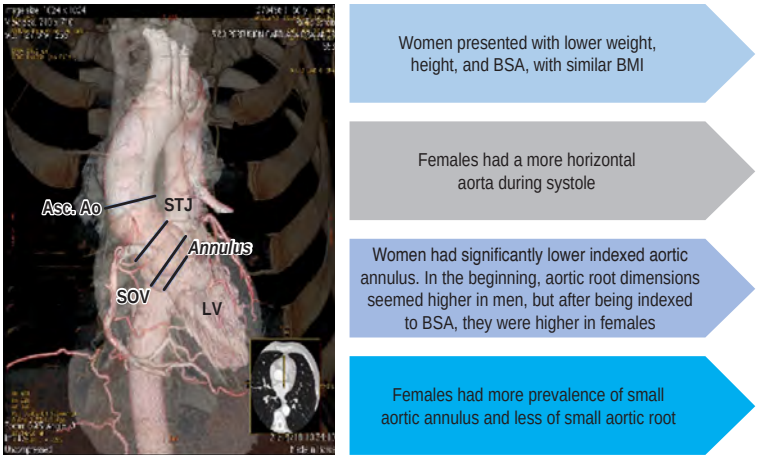

Figure 3: Sex-related differences of the aortic root features in a structural and functional cardiac computed tomography (CCT) analysis.
BSA = body surface area; body mass index = BMI; LV = left ventricle; SOV = sinuses of Valsalva; STJ = sinotubular junction; Asc. Ao = ascending aorta.

A possible explanation could be lower tallness in Mexican women with a mean figure of 1.55 ± 0.07 meters; this contrasted with other populations, when indexing AR dimension for body height and compared to men with a mean value of 1.69 ± 0.07 meters, who presented a more similar bodily stature to previously reported studies with similar BSA in a population of Asian patients.[33] Moreover, individuals with small AR dimensions also had a remarkably smaller annulus diameter (mean, 21.3 mm) than those with a standard AR.[22] Asian populations have a significantly smaller AA caliber than their European counterparts (20.40 ± 1.46 mm against 22.00 ± 1.84 mm, $p < 0.01$).[33] Our women sample ended having a high prevalence of small AA (100% patients with anteroposterior dimension) *(Figure 3)*.

Limitations

Our study had several limitations. It was a retrospective study with a limited number of middle-aged people of a single-center population. We did not have typical values described in our sample regarding aortic root in healthy people to compare our data. The definitions of a small aortic annulus and a small AR depend on several factors as clinical demographics, sex, age, and comorbidities. The cardiac imaging modality used affects the definitions as well. The majority of studies defining these features used information of echocardiographic evaluation, and there is a lack of statistics by CCT. We did not have figures of aortic gradients to evaluate the functional effects of having a small annulus or AR dimensions. More extensive studies of measuring aortic magnitudes by different cardiac imaging techniques are necessary to increase such findings. A more in-depth explanation about somatotype Mexican measures such as BMI, BSA, and especially body height, to confirm a low stature compared to other populations is needed to determine these specific findings' clinical and prognostic implications in women patients contrasted with men.

CONCLUSIONS

Aortic dimensions are measured in specific levels to define standard cut-offs in particular populations. When comparing sex-related findings in our sample by CCT analysis, we found differences in females related to the imaging technique used and specific anthropometric characteristics. BMI was similar in both sexes, but Mexican women appear to have somatotype characteristics with low stature, explaining a different orientation of the aorta in the thorax and distinct cut-off values at different levels. A high prevalence of small aortic root dimensions, indexed to height, was found in this setting, but these discoveries and specific clinical and prognostic implications need to be consistently studied.

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Funding or support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors declare no conflict of interest.

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Cardiovascular and Metabolic Science www.ancam.org.mx

Clinical Case

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101305

Coronary rotational aterectomy in an injury with unexpanded stent restenosis

Aterectomía rotacional coronaria en una lesión con reestenosis de stent subexpandido

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Keywords:
Rotational atherectomy, percutaneous coronary intervention, calcified coronary lesion, unexpanded coronary stent.

Palabras clave:
Aterectomía rotacional, intervención coronaria percutánea, lesión coronaria calcificada, stent coronario no expandido.

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Received:
30/11/2020
Accepted:
07/05/2021

ABSTRACT

High calcium content lesions are probably the most challenging and more likely to negatively impact both acute and long-term results in a percutaneous coronary intervention. The rotational atherectomy technique has shown to be safe and effective in treatment when labeled as a removal technique of the subsets of calcified coronary lesions. Several studies show an increase in the procedure's success with a relatively low rate of complications of dissection or perforation. However, there is a margin of error in which we found ourselves with cases where atypical situations occurred that carry a risk of dissection, perforation, and slow/no reflux, among other complications. Therefore, this work shows a patient with complications after undergoing rotational atherectomy, the corrective procedure for eliminating the presented problem, and displays a precedent on the procedure in case of complications with rotational atherectomy.

RESUMEN

Las lesiones con alto contenido de calcio, son probablemente las más desafiantes y tienen más probabilidades de impactar negativamente tanto en los resultados agudos como a largo plazo en la intervención coronaria percutánea. La técnica aterectomía rotacional se muestra segura y efectiva en el tratamiento donde se ha etiquetado como una técnica de eliminación de subconjuntos de lesiones coronarias calcificadas. Diversos estudios muestran un éxito del procedimiento fue muy alto con una tasa relativamente baja de complicaciones de disección o perforación. La información apunta a ser un método efectivo, sin embargo, hay un margen de error por lo cual nos vemos con la particularidad de encontrarnos con casos donde se presentan situaciones atípicas que conllevan un riesgo de disección, perforación y reflujo lento/nulo entre otras complicaciones. Por tal razón, el presente trabajo muestra el caso de un paciente con complicaciones tras ser sometido a una aterectomía rotacional, mostrando el procedimiento correctivo para la eliminación de la problemática presente, mostrando un precedente sobre el método de actuar en caso de complicaciones de la aterectomía rotacional.

INTRODUCTION

High calcium content lesions (HCCL), specifically the coronary artery calcification (CAC), are defined as the angiographic presence of radiodensities within the vascular wall at the site of the stenosis; these types of lesions are probably the most challenging and are more likely to negatively impact both acute and long-term outcomes in the percutaneous coronary intervention (PCI), considered a predictor of poor prognosis in patients undergoing PCI,[1-3] associated with immediate complications plus late failure due to sub-expansion and poor stent placement.[4] However the development of technologically more advanced devices and methods, such as support catheters, cutting balloons, high pressure and low-

How to cite: Flores-Galaviz AAO, Salinas-Aragón MÁ, Rodríguez-Barriga EA, Calero-Barba AP, Vasconcelos-Ulloa JJ. Coronary rotational aterectomy in an injury with unexpanded stent restenosis. Cardiovasc Metab Sci. 2021; 32 (3): 128-131. https://dx.doi.org/10.35366/101305

profile balloons, orbital, laser atherectomy, or lithoplasty, rotational atherectomy (RA), these methods continue to be the most widely used techniques worldwide to modify plaque calcifications.[2]

The RA technique, introduced in 1990, is safe and effective in treatment where it has been labeled as a technique for removing subsets of calcified coronary lesions. Its primary mechanism of action involves a high-speed rotational plate ablation (140,000-160,000 revolutions per minute, rpm) and grinding by the diamond-coated abrasive bur.[5,6]

RA is considered the standard technique for preparing highly calcified lesions before stent implantation, mainly when the lesions cannot be passed through with a balloon device. The success of the procedure was remarkably high (99.1%), with a relatively low rate of complications from dissection (7%), perforation (1%), or slow/no flow (1.1%). On the other hand, there is the J-PCI study, which included 13,355 RA cases, also reported low rates of death in the hospital (0.6%), tamponade (0.64%), and the need for emergency surgery (0.18%).[3]

The information points to RA as an effective method. However, there is a margin of error in which we found ourselves with cases where atypical situations occurred that carry a risk of dissection, perforation, and slow/no reflux, among other complications.[3]

Therefore, the present work shows the case of a patient with complications after undergoing RA, and showcases the corrective procedure to eliminate the presented problem, displaying a precedent on the method of acting in case of complications of RA.

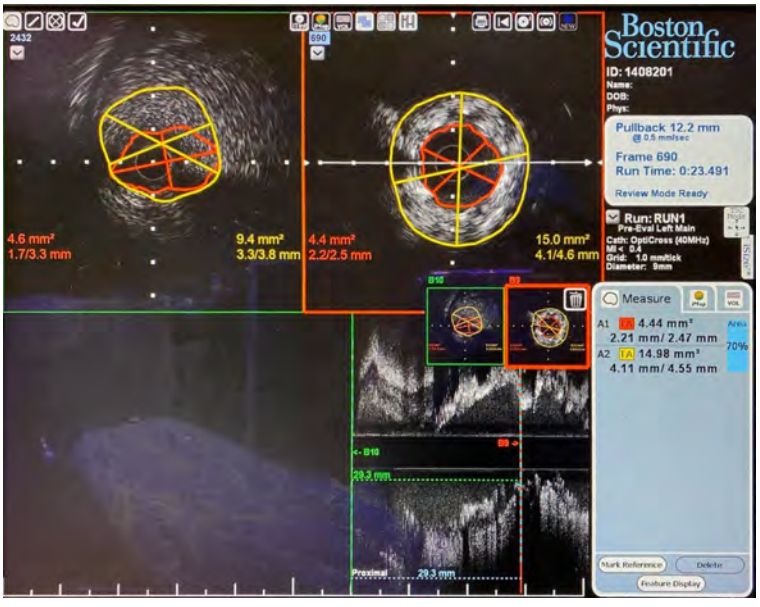

Figure 1: Left anterior descending artery (LAD) distal segment 70% in-stent restenosis.

CASE PRESENTATION

The patient is a 79-year-old male with a history of systemic arterial hypertension, type 2 diabetes mellitus, ischemic heart disease with angioplasty and stent (PTCA) in the medial and distal segment of the diagonal branch of the left anterior descending artery (LAD) on 2016; placement of a double chamber pacemaker on May 2019, and a previous cardiac catheterization on May 2019 where two stents were placed in the right coronary artery and the diagonal branch of the LAD, and cardiac catheterization on August 2019 where the LAD artery with severe calcification is shown. Presence of two overlapping stents involving the proximal and middle segment with sub expansion in a residual lesion with maximum stenosis of 70% as seen in *Figure 1*, a distal segment of a vessel smaller than 2 mm with total chronic occlusion which receives RENTROP I homocoronary collateral circulation, and in the second diagonal branch with a diffuse disease with maximum stenosis of 50%. TIMI 3 distal flow.

The patient reported: fatigue, dizziness, and stabbing pain in the precordial region with three months of evolution, for which he was scheduled for rotational atherectomy with the ROTABLATOR and ROTAWire system on August 2019. The procedure initialized by advancing the angioplasty guide to the LAD, in-stent restenosis of 70% was detected in the distal segment *(Figure 1)*, from the LAD artery CHOICE PT guide filament to the distal segment of the second diagonal branch, then the THREADER microcatheter went over the guide and exchanged for ROTAWIRE 0.009″ Floppy 6 Fr. Subsequently, a 1.5 mm drill was used, and three steps of 20 seconds were performed. In the last step, the ROTAWIRE 0.009″ Floppy 6 Fr drill was caught in the

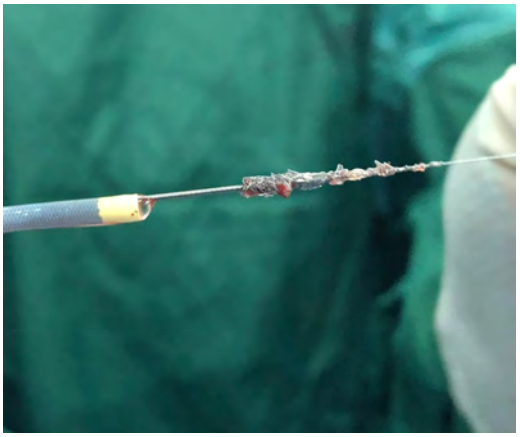

Figure 2: Released bur system with remains of the stent.

proximal segment of the stent, without loss of distal flow and finally, it was released with traction, observing image radiopaque behind the bur, so it was decided to remove the entire system bloc, *Figure 2* shows the released system with remains of the stent behind the bur. It was cannulated again with a MACH I VL 3.5, 7 Fr guide catheter, a BALANCE MIDDLEWEIGHT UNIVERSAL II 0.014" 150 cm intermediate angioplasty guide was used, and an intravascular ultrasound (IVUS) OptiCross 3.0 Fr probe was also used, observing a lesion distal to the stent and corroborating the sub-expansion of the previous stents. Predilated with an NC EMERGE 2.0 × 15 mm balloon at 20 atm and a subsequent NC EMERGE 3.5 × 12 mm balloon up to 22 atm. A GUIDEZILLA II 6 Fr guide extender was used, to improve support, it was moved towards the lesion of the second diagonal branch directed to the middle and distal LAD artery, the PROMUS PREMIER 2.25 × 28 mm stent was delivered, everolimus releasing, overlapping the previous to nominal 11 atm and the proximal part is post-dilated to 22 atm. Then the second PROMUS PREMIER 3 × 24 mm eluting everolimus proximal spliced before delivery and at 20 atm was implemented. It was optimized with the same NC EMERGE 3.15 × 12 mm balloon at 24 atm. Finally, the IVUS OPTICROSS 3 Fr probe was mobilized. Adequate expansion and apposition of the stents and adequate minimum luminal area were observed without a dissection image or thrombus. Final flow TIMI 3, TMP 3.

DISCUSSION

The incidence of coronary calcifications increases with age and with the presence of chronic degenerative diseases like diabetes mellitus, hypertension, dyslipidemia, and renal disease.[7] In this case, we are dealing with an elderly patient with coronary artery disease in the LAD. Stent implantation was decided with unexpected angiographic results, with a 70% residual lesion and inadequate expansion of the stent due to a calcified lesion later visualized by intravascular ultrasound.

During ablation, the operator should be aware of any possible warning signs, which can be: visual (lack of smooth advancement under fluoroscopy), acoustic (changes in tone with variation in resistance encountered by the abrasive bur), or tactile (resistance on the feed knob or excessive driveshaft vibration). If entrapment occurs, timely action is required to eliminate trapped abrasive burs,[8] it should be noted that the use of rotational atherectomy as a therapeutic measure for calcific atheromatosis has been highly effective, reporting a success rate greater than 90%. Furthermore, it has complication in less than 5% of cases; Complications have been reported during RA such as excessive stent damage, distal embolization of metallic particles, excessive heat generation, and trapping of the abrasive bur in the stent;[9] although various eventualities can occur during RA, the entrapment of the abrasive bur has been reported in 0.5 to 1% of these rare complications.[7] One way to solve this complication is to move the patient to an emergent surgical procedure, being the most reliable option to eliminate the trapped abrasive bur. However, surgical removal is invasive, time-consuming, and requires preparation and organization before the procedure, especially for unstable hemodynamic cases. Before sending the patient to surgery, several non-surgical techniques can be tried to retrieve the stuck abrasive bur. Careful and conservative techniques, including diligent stress relief before RA, are critical elements of prevention. In the event of entrapment, the single best technique to remove the abutter is to pull on the ROTAWire, taking advantage of the 0.014-inch spring tip of the wire.[10] To prevent thrombosis,

sufficient heparinization, and glycoproteins IIb/IIIa is recommended prior to these attempts. An intracoronary injection of nitroglycerin and/or verapamil is also suggested to relieve spasm and facilitate antegrade coronary flow.[11] It has been observed that the simplest method to perform is to remove the entire rotating system manually. Extreme force on the shaft and abrasive bur can cause shaft fracture;[11] In this case, the abrasive bur was extracted from the lesion by removing the RA system bloc and exchanging the angioplasty guides for stent repositioning, thus obtaining a successful result.

CONCLUSIONS

Calcified atherosclerosis is a disease of high relevance in the current society; therefore, methods have been developed to combat it. One of the most used options is RA, a highly effective method; however, there exists a complication rate that indicates the need to have protocols to follow according to the eventualities that present themselves along with the procedure, the case presented shows a successful entrapment of the abrasive bur, which marks a precedent on the procedure's methodology.

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Funding/support: No financial support was received for this study.

Conflict of interest: The authors declare no conflict of interest.

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Cardiovascular and Metabolic Science www.ancam.org.mx

Clinical Case

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101306

Spontaneous left main coronary artery dissection as a cause of myocardial infarction in a young man

Disección espontánea de la arteria coronaria principal izquierda que causa infarto de miocardio en un hombre joven

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Keywords:
SCAD, PCI, CABG, Takayasu, sudden cardiac death.

Palabras clave:
DEAC, ICP, CABG, Takayasu, muerte cardiaca súbita.

ABSTRACT

In the last decade, spontaneous coronary artery dissection has been recognized as a common cause of acute myocardial infarction and cardiac death. There is a combination of several predisposing factors that can influence and increase susceptibility to develop this pathology. We present the clinical case of a young patient of Chinese origin, who developed spontaneous coronary artery dissection of rare location and angiographic findings of the ascending aorta, which are considered to have been involved in its evolution. Treatment of the patient was timely and successful with percutaneous coronary intervention; however, he developed severe complications within the following 24 hours with hemodynamic and electrical instability that led to a fatal outcome.

RESUMEN

En la última década, la disección espontánea de la arteria coronaria ha sido reconocida como una causa común de infarto agudo de miocardio y muerte cardiaca. Existe una combinación de varios factores predisponentes que pueden influir y aumentar la susceptibilidad a desarrollar esta patología. Presentamos el caso clínico de una paciente joven de origen chino, que desarrolló una disección coronaria espontánea de rara localización y hallazgos angiográficos de la aorta ascendente, que se consideran implicados en su evolución. El tratamiento del paciente fue oportuno y exitoso con una intervención coronaria percutánea; sin embargo, desarrolló complicaciones severas en las siguientes 24 horas con inestabilidad hemodinámica y eléctrica que llevaron a un desenlace fatal.

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INTRODUCTION

Historically, spontaneous coronary artery dissection (SCAD) was considered a rare cause of acute coronary syndrome (ACS) and sudden cardiac death, with an incidence of 0.1% to 4%.[1-4] However, in the last decade, this entity has lost the designation of «rare» condition, being recognized as a cause of myocardial infarction and cardiac death, especially in young women.[5,6] Myocardial infarction as a result of SCAD has been documented in adolescence up to the ninth decade of life and, although its physiopathology is still a subject of controversy, there is a combination of predisposing factors that can influence and increase the susceptibility to develop this pathology, including sex, hormonal fluctuations, collagen diseases and physical or emotional precipitants.[6,7] Women account for more than 90% of SCAD cases, so sex hormones have been implicated in its development.[4,5,7,8] However, there are reports of cases in women with SCAD, without hormonal influences.[3,9] Other conditions such as basal artery disease are frequent, with fibromuscular dysplasia being the associated pathology in > 70%; and other connective tissue diseases such as Marfan, Loeys-Dietz, and Ehlers-Danlos in a smaller proportion, of 5%.[7,10]

SCAD is an acute coronary event that is presented by the development of a

How to cite: Sonqui SJP, Hernández MMA, Sánchez HO, Soto VM, Orozco CJ, Morales BNE. Spontaneous left main coronary artery dissection as a cause of myocardial infarction in a young man. Cardiovasc Metab Sci. 2021; 32 (3): 132-137. https://dx.doi.org/10.35366/101306

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Received: 18/12/2020
Accepted: 04/05/2021

hematoma within the medial tunic, producing a separation of the arterial intima and the consequent compression of the true lumen.[7] This process can be carried out by two different mechanisms: 1) spontaneous disruption of the intima, creating an entry point for the accumulation of an intramural hematoma in the false lumen, leading to the separation of the arterial wall, and 2) hemorrhage from the vasa vasorum into the arterial wall, resulting in an intramural hematoma, with expansion and increased pressure in the false lumen and external pressure in the true coronary lumen.[5,11]

Coronary angiography represents the main diagnostic method for SCAD, with the indication to resort to intracoronary imaging methods only in cases where there is doubt about the diagnosis or where percutaneous coronary intervention (PCI) is required[6,7] PCI has 57% of successful procedures,[6,12] being associated with high rates of complications. Typically, conservative therapy is the most accepted because of its high rate of complete resolution over time[2,6] with values of up to 86% spontaneous healing in control angiography.[13]

CASE REPORT

28 year old male patient, of Chinese descent, cook, active smoker from 20 to 28 years old, five cigarettes a day with a tobacco index of two, with no other cardiovascular risk factors, refers not to consume medicines, drug addiction not reported as cocaine or intravenous drugs, no blood or urinary toxicological tests were performed. He has a family history of a mother who died at age 50 from heart disease and a sister with a current diagnosis of heart disease (both with unspecified heart disease). He started the symptoms suddenly while working, presenting dyspnea and thoracic pain of oppressive characteristics, 10/10 intensity, diaphoresis than lasted for more than an hour. He had no previous history of angina. He arrives at the emergency department where

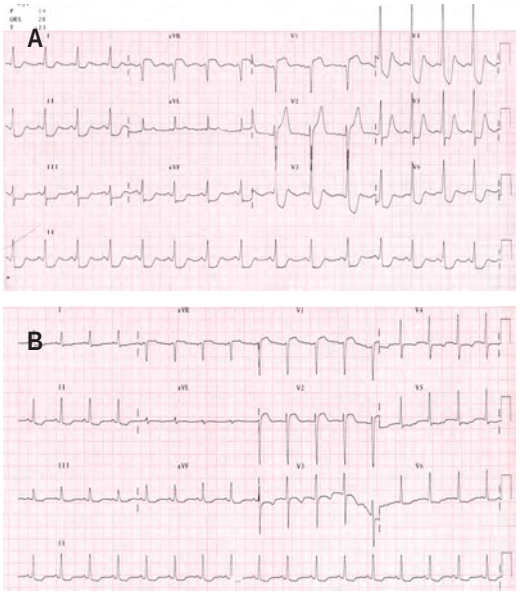

Figure 1: A) Initial 12-lead electrocardiogram. **B)** Control electrocardiogram, post percutaneous coronary intervention (PCI).

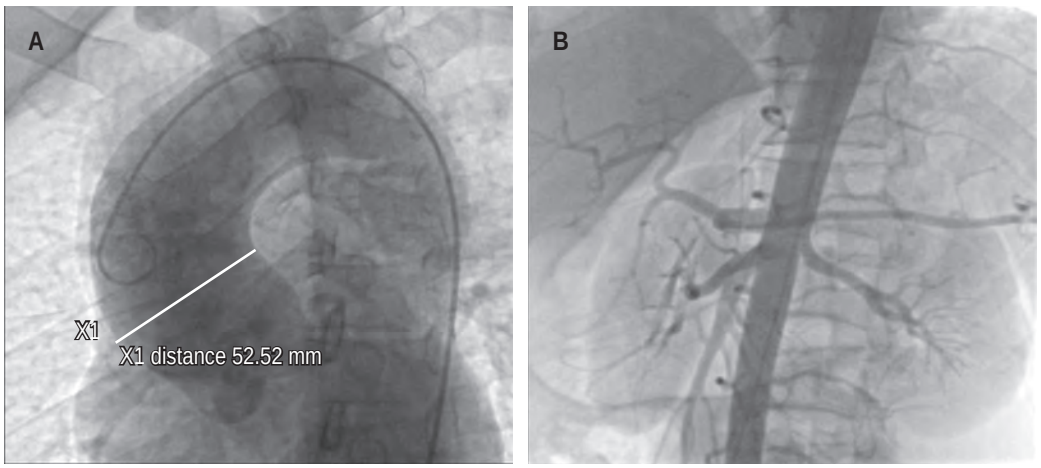

Figure 2:

A) Aortic root dilation. **B)** Descending aorta at renal artery level.

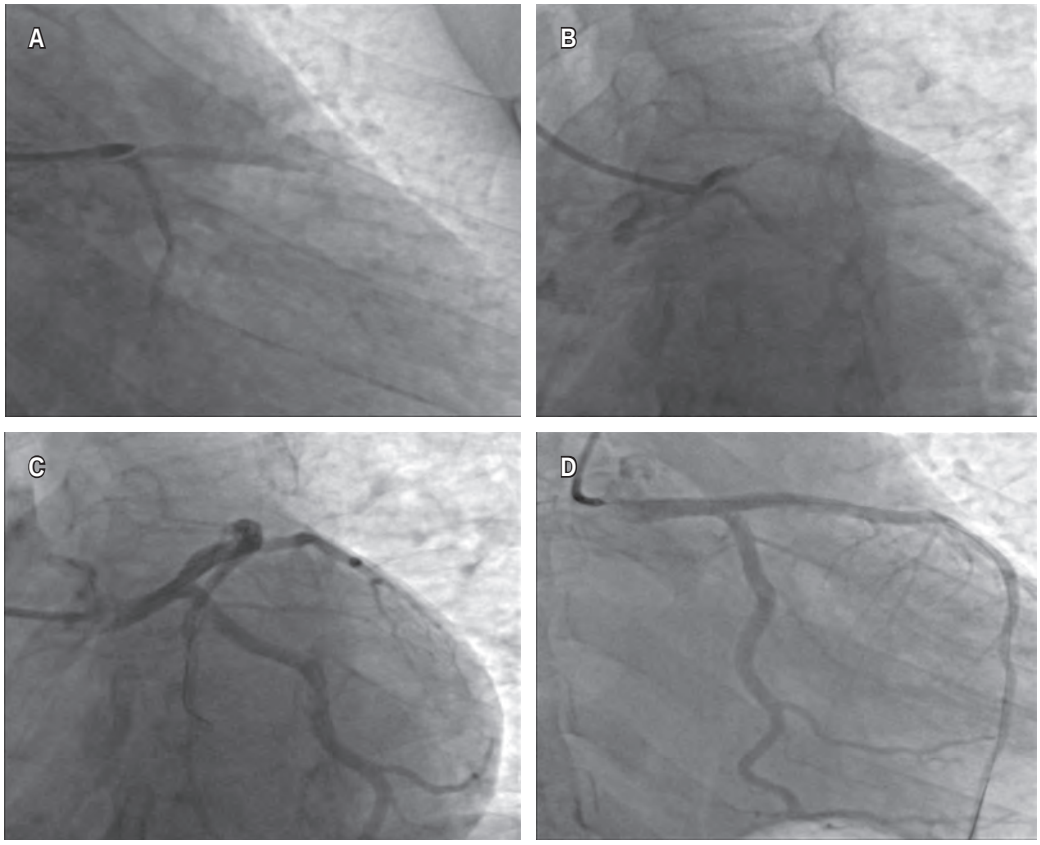

Figure 3:

Coronary angiography: **A)** selective cannulation of left main coronary artery (LMCA), **B)** subselective cannulation with image of LMCA dissection, **C)** after crossing guide to left anterior descending (LAD) and **D)** angiographic result after direct stent implantation to LMCA.

is observed, diaphoresis, facies of distress, and hemodynamic instability (BP 80/50 mmHg, HR 112 bpm, RR 15 bpm and SaO_2 90% ambient air). On physical examination there was no murmurs were found, and no third or fourth sounds, were noticed. No other signs of heart failure were detected. It is worth mentioning that in the context of emergency care for acute coronary ischemic syndrome, physical examination revealed only a fair complexion and short stature (158 cm) for his age and gender. No long arms, legs, fingers and toes, flexible joints or very elastic skin were documented, which would point to a group of hereditary connective tissue disorders associated with Marfan or Ehlers-Danlos syndrome.

The initial electrocardiogram showed sinus rhythm with ST segment elevation of 2 mm in aVR and V1, and ST segment depression in DII, DII aVF, and V3 to V6 *(Figure 1)*. A clear evidence of elevated cardiac enzymatic markers was documented, with troponin T levels > 30 ng/mL. Coronary angiography was performed, finding significant dilatation of the ascending aorta *(Figure 2)*. The urgency of the case, the evidence of SCAD and the patient's clinical condition prevented the implementation of intracoronary imaging. Antegrade flow TIMI 2 towards circumflex and anterior descending was shown *(Figure 3)*. It was decided to implant a direct drug-eluting stent 4.5 × 24 mm, obtaining a TIMI 3 antegrade flow and pain reduction. In stable condition was admitted to the intensive care unit. However, during his 24-hour surveillance he presented acute heart failure data and tissue hypoperfusion: dyspnea, tachycardia, pulmonary congestion, and SaO_2 80%, requiring mechanical ventilation, and the use of inotropes and vasopressors. The control electrocardiogram *(Figure 1)* showed bursts of sustained ventricular tachycardia treated with amiodarone infusion. Transthoracic echocardiogram documented systolic dysfunction with left ventricular

ejection percentage of 40%, severe anterior hypokinesia, and no evidence of mechanical complications. Hours later (24 hours after the coronary intervention), he presented sustained ventricular tachycardia and later asystole without response to cardiopulmonary resuscitation maneuvers, which could suggest a total occlusion of the anterior descending artery, related to a possible propagation of a intramural hematoma distal to the lesion. Unfortunately, the autopsy was not carried out due to the refusal of the relatives.

DISCUSSION

SCAD is an increasingly recognized cause of acute coronary syndromes and cardiovascular death. In recent years, the impact of an early invasive approach with coronary angiography on patients with ACS, and the more recent adoption and accessibility of intracoronary imaging methods as a diagnostic tool such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT),[11] has led physicians to pay more attention to reassessing this entity in greater depth.[5,12]

Although the mechanism by which the dissection develops is known, different clinical characteristics and predisposing factors influence its process. These factors, the clinical presentation and natural history of the disease, are documented mainly in women, since more than 90% prevail in them, while cases of SCAD in men have been little described in the literature.[8,13,14] The risk factors most frequently associated in men (in addition to those already commonly described in both sexes) are isometric stress, active smoking and drug use,[3,14] however, these are a minority. SCAD is associated with predisposing arteries, with connective tissue diseases, autoimmune or inflammatory diseases.[11] Fibromuscular dysplasia shows the highest correlation with SCAD, > 70%.[5,6,9] Any artery can be affected in SCAD, however, it has been found that the anterior descending artery is the most affected (middle to distal) and its branches, producing 45 to 60% of the cases; followed by the circumflex artery and its branches with 15 to 45%; and a lower incidence, when dealing with the left coronary trunk, 0-4%.[5,7,12]

Spontaneous dissection of the left main coronary artery is extremely rare and, regarding the present clinical case, a strong association is suggested with the angiographic finding of dilatation and aneurysmal disease of the ascending aorta. There are various anomalies whose main pathophysiological finding is mainly limited to disproportionate aortic dilation, within which systemic inflammatory diseases such as Takayasu disease can be included, which although it is rare, with a reported incidence of 2-3/1,000,000 per year,[15,16] being most common in young adults between the second and third decade of life, especially Asian women.[2,3] This motivated us to consider the patient's family history.

Table 1: Comparison of outcomes following SCAD from 5 published series.

Study lead author	Death (in hospital)	Death post discharge (median follow-up in months)	Recurrent AMI post discharge (median follow-up in months)	Recurrent de novo SCAD (median follow-up in months)
Tweet	1/189	3/189 (27)	37/189 (27)	29/189 (27)
Lettieri	3/134	4/127 (22)	2/127 (22)	6/127 (22)
Rogowski	1/64	0/64 (54)	3/64 (54)	3/64 (54)
Nakashima	0/63	1/63 (34)	18/63 (34)	7/63* (34)
Saw	0/327	4/327 (37)	55/327 (37)	34/327 (37)

AMI = acute myocardial infarction; SCAD = spontaneous coronary artery dissection.
Source: Adlam D et al.[6]
* Recurrent events in this series reported as events beyond 30-days after index SCAD event.

Table 2: In-hospital and 30-days cardiovascular events in 750 patients.

	n (%)
Overall in-hospital MAE	66 (8.8)
	95% CI 6.9-11.1
Death	1 (0.1)
Recurrent MI	30 (4.0)
Extension of SCAD segment	15 (50.0)
Iatrogenic dissection	9 (30.0)
Other	6 (20.0)
Severe ventricular arrhythmia	29 (3.9)
Requiring ICD	6 (0.8)
Haemodynamic instability	15 (2.0)

MAE = major adverse events; MI = myocardial infarction; SCAD = spontaneous coronary artery dissection; ICD = implantable cardioverter defibrillator. Source: Saw J et al.[3]

One of the main genetic contribution to the disease pathogenesis is supported mainly by its association with the HLA (Human Leukocyte Antigen) complex, which associations are varied according to the patient ethnic background. The strongest association has been established with HLA-B52 in Japanese population, as well as associations with HLA-B5 described in patients with Asian and Mexican Mestizo background and certain polymorphisms HLA-B in Chinese population. Although the mechanism described by which distal ischemia usually develops in Takayasu disease is due to occlusion and stenosis of the vessels, a mechanism of dissection of the main branches; such as the left coronary artery in the present case, is not ruled out due to the weakening and destruction of its muscular and elastic layers.[10,14,15]

Cystic media degeneration is a histopathological finding characterized by an accumulation of basophilic ground substance in the media, degenerative disruptions of collagen, elastin and smooth muscles may result in weakening of the arterial wall.[17] This phenomenon might be the underlying cause of left main coronary artery dissections due to its uncommon location; even though it can be found in many other pathologies, it is mainly associated with connective tissue disorders such as Marfan syndrome.[18] However, no phenotypic features of Marfan syndrome were observed in the patient, thus an association cannot be made.

The decision to revascularize the patient though PCI was based upon the compromised anatomy, clinical presentation; left main involvement and hemodynamic instability.[7,11,19] There were many modulating factors and triggers that, in the context of a previously vulnerable myocardium, could have generated a rapidly growing hematoma that expanded and dissected all the way to de anterior descendant artery which is, in fact, one of the most frequently reported complications of PCI in patients with SCAD[8] *(Tables 1 y 2)*,[3,6] leading to distal occlusion, ischemia and electrical instability that finally led to a fatal outcome. This rapid sequence of events limited the definitive diagnosis of his underlying pathology that led to SCAD, and protocolize and stratify his treatment.

CONCLUSIONS

Spontaneous dissection of the left main coronary artery is an uncommon condition, often with fatal outcomes. Although there are case reports in the literature, no precise associations have been described with diseases or structural alterations of the ascending aorta, which are suspected to have been involved in this patient, whose acute clinical condition allowed timely percutaneous coronary intervention, with a successful angiographic result. Post-procedure complications prevented identification of the cause of cardiac arrest by invasive and non-invasive tests, making it impossible to perform a new diagnostic-therapeutic coronary angiography. For future cases, the use of intracoronary images will be necessary to measure the size of the stent according to the longitudinal extension of the false lumen, to minimize complications such as the spread of the intramural hematoma. As well as the intracoronary images after the intervention, to evaluate the adequate stent expansion. Finally, the result urges us to include for early scrutiny, the scarcely documented modalities associated with this entity, to generate awareness and suspicion of a preventive nature in the treating physician when faced with probable cases of SCAD and not to wait for its result as a finding in a necropsy.

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Funding/support: No financial support was received for this study.

Conflict of interest: The authors declares to have no conflict of interest.

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Cardiovascular and Metabolic Science www.ancam.org.mx

Clinical Case

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101307

Hypertrophic obstructive cardiomyopathy in an octogenarian patient

Miocardiopatía hipertrófica obstructiva en una paciente octogenaria

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Keywords:
Hypertrophic cardiomyopathy, HCM, elderly, alcohol septal ablation.

Palabras clave:
Miocardiopatía hipertrófica, MCH, adulto mayor, ablación septal con alcohol.

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Received:
06/02/2021
Accepted:
07/05/2021

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most common inhered cardiac disease. Although clinical manifestations have been most commonly reported between the third and fifth decades of life, significant clinical symptoms can appear beyond the seventh decade of life, but this is less well appreciated. We present an 80-year-old female referred to our tertiary care center with the diagnosis of non-ST-elevation myocardial infarction. The invasive coronary angiography showed epicardial arteries with no significant lesions and the presence of left ventricular outflow tract obstruction, identified through the Brockenbrough-Braunwald-Morrow sign. In the past, HCM had been reserved as a relevant clinical entity in the young population because of its higher risk of sudden cardiac death, but its clinical behavior covers a broad spectrum of manifestations; currently, HCM is becoming more frequent to be diagnosed at advanced ages due to advances and accessibility of imaging modalities. Despite alcohol septal ablation and surgical myomectomy are the main therapeutic options for obstructive HCM, management of elderly HCM patients is still discussed. A multidisciplinary team must individually evaluate the case based on the clinical presentation, comorbidities, anatomical characteristics, and the hospital's expertise to decide the best therapeutic approach.

RESUMEN

La miocardiopatía hipertrófica (MCH) es la enfermedad cardiaca hereditaria más común. Aunque las manifestaciones clínicas se han descrito con mayor frecuencia entre la tercera y la quinta décadas de la vida, pueden aparecer síntomas clínicos significativos más allá de la séptima, aunque esto es menos reconocido. Presentamos a una mujer de 80 años de edad enviada a nuestro centro de tercer nivel de atención con el diagnóstico de síndrome coronario agudo sin elevación del ST. La angiografía coronaria invasiva mostró arterias epicárdicas sin lesiones significativas y la presencia de obstrucción del tracto de salida del ventrículo izquierdo, identificada mediante el signo de Brockenbrough-Braunwald-Morrow. En el pasado, la MCH se había reservado como una entidad clínica relevante en la población joven por su mayor riesgo de muerte súbita cardiaca, pero su comportamiento clínico abarca un amplio espectro de manifestaciones; actualmente, es cada vez más frecuente el diagnóstico de MCH en edades avanzadas debido a los avances y a la accesibilidad de las modalidades de imagen cardiovascular. A pesar de que la ablación septal con alcohol y la miomectomía quirúrgica son las principales opciones terapéuticas para la MCH obstructiva, el manejo de los pacientes ancianos con MCH sigue siendo discutido. Un equipo multidisciplinar debe evaluar individualmente el caso en función de la presentación clínica, las comorbilidades, las características anatómicas y la experiencia de cada hospital.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inhered cardiac disease. Echocardiography-based epidemiologic studies have shown a prevalence of 1:500 in the general population, but HCM is often underrecognized, especially in women.[1] Maron et al. estimated that only 10% of cases are clinically identified (6% symptomatic and 4% asymptomatic), while the other 90% are unidentified.[2]

Although this disease occurs worldwide, its phenotypic expression and genetic substrate do not fluctuate significantly between populations.

How to cite: Urzúa-González AR, Nieto-Saucedo JR, Muñiz-Castillo F, Rivera-Chávez MJ, Preciado-Anaya A. Hypertrophic obstructive cardiomyopathy in an octogenarian patient. Cardiovasc Metab Sci. 2021; 32 (3): 138-143. https://dx.doi.org/10.35366/101307

HCM is inhered by an autosomal dominant pattern or caused by de novo mutations in 11 or more of the cardiac sarcomere protein genes, with more than 2,000 mutations identified to date. However, the genotype-phenotype correlation has shown variable expressivity and age-related penetrance.[1,3,4] It has also been proposed that genetic modifying factors can compensate or aggravate a causal mutation.[5]

The most common clinical findings in HCM are chest pain, palpitations, congestive heart failure, and sudden cardiac death (SCD).

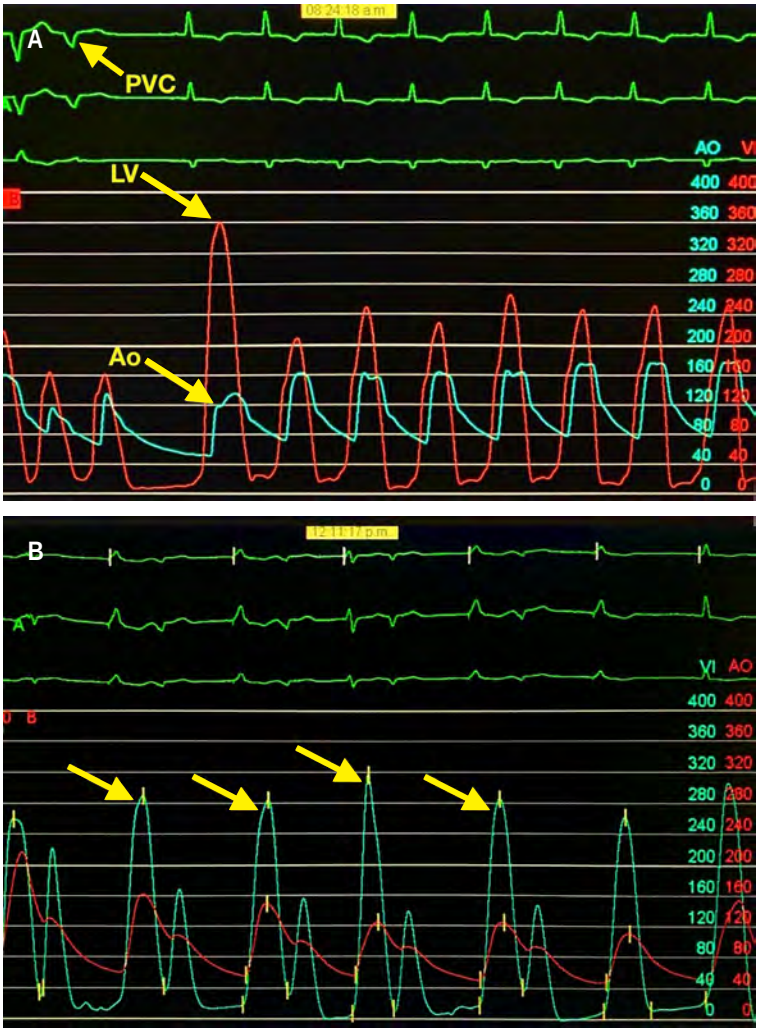

Figure 1: A) Post-extrasystolic boosting effect, also known as the Brockenbrough-Braunwald-Morrow sign. Note the presence of a gradient of 240 mmHg between the left ventricular (LV) and aortic pressures (Ao) after the premature ventricular contraction (PVC). **B)** Transaortic gradient observed in each pacemaker stimulation (arrows).

Although clinical manifestations have been most commonly reported between the third and fifth decades of life, significant clinical symptoms in some individuals can appear beyond the seventh decade of life, but this is less well appreciated.[6-8]

Elderly patients with HCM are more likely to present with congestive heart failure symptoms that are often attributed to more common clinical entities, such as myocardial ischemia, hypertensive heart disease, and aortic stenosis.[6] We present a case of late-onset hypertrophic cardiomyopathy referred to our tertiary care center.

CASE PRESENTATION

An 80-year-old female was sent from a regional hospital's emergency room to our tertiary referral center with the diagnosis of non-ST-elevation myocardial infarction (NSTEMI). Her past medical history showed insulin-dependent diabetes mellitus and essential hypertension since 30 years ago; currently, under pharmacological control with telmisartan/hydrochlorothiazide (40/12.5 mg), she had no dyslipidemia or smoking history. Her gynecologic history showed G8 P8 and menopause at the age of 50. She had also been studied for a rheumatic valvular disease 15 years ago and had a coronary angiography ten years ago with no significant coronary artery disease. Besides that, she described a persistent atypical chest pain, for which an echocardiogram and a magnetic resonance were performed ten years ago, showing asymmetric septal hypertrophy. However, the intervention was not carried out, attending multiple dyspnea episodes, dizziness, lipothymia, and hypertensive urgencies since then. Nevertheless, she denied a family history of sudden death or cardiomyopathies.

Her current condition began three days before hospital admission with disorientation, dizziness, a blood pressure of 165/70 mmHg, and hyperglycemia, for which she was hospitalized in a regional care center with the diagnosis of NSTEMI. After she was sent to our center, an electrocardiogram was taken, showing a sinus rhythm, incomplete left bundle branch block, inverted T-waves in V4-V6, and no ST-segment elevation. On physical examination, she was

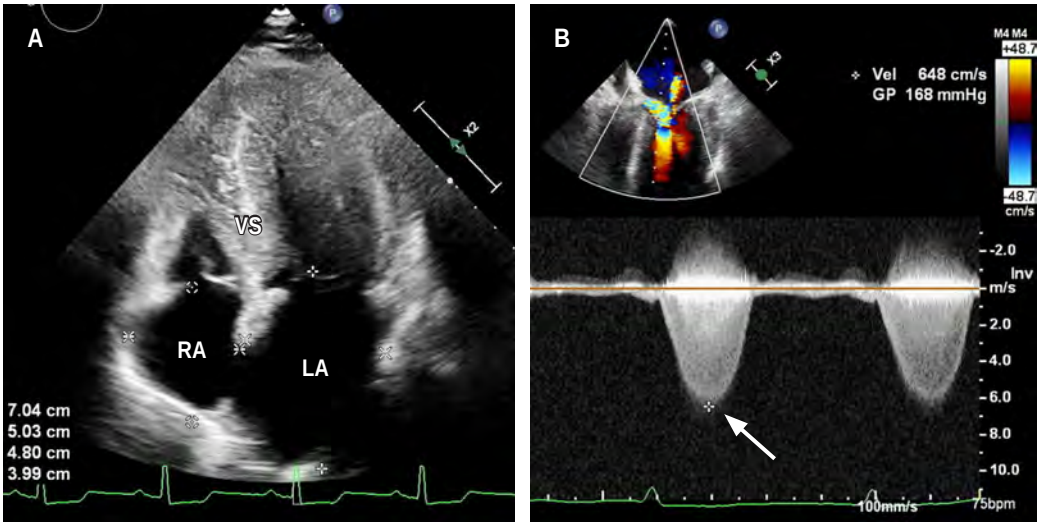

Figure 2:

A) Two-dimensional echocardiogram image. Four-chamber view showing asymmetric septal hypertrophy and biauricular dilatation. **B)** Transesophagic echocardiogram showing an intraventricular gradient pressure at the rest of 168 mmHg (white arrow). VS = ventricular septum; LA = left atrium; RA = right atrium.

aware, oriented, with obesity (BMI of 31.6) and a positive Frank's sign. To auscultation, an expulsive aortic murmur (III/VI) and a mitral regurgitation murmur (III/VI) were evident. She denied chest pain and dizziness.

Cardiac troponin I (cTpI), creatinine phosphokinase (CPK), and B-type natriuretic peptide (BNP) were ordered. Her levels were: cTpI 1.39 ng/mL, CPK 27 IU/L, and BNP 1200 pg/mL.

A new invasive coronary angiography showed epicardial arteries with no significant lesions (TIMI 3 flow grade). The left basal catheterization showed an aortic pressure of 160/65 mmHg, left ventricular pressure of 280/20 mmHg, and a resting gradient of 120 mmHg. A post-extrasystolic gradient of 240 mmHg was identified *(Figures 1A and 1B)*, described as the Brockenbrough-Braunwald-Morrow sign, demonstrating the presence of left ventricular outflow tract (LVOT) obstruction.[9]

A transthoracic (TTE) and a transesophageal echocardiogram (TEE) were requested to determine the gradient site and assess the possibility of alcohol septal ablation. The TTE showed a predominantly anterior septal hypertrophy, with a maximum thickness of 27 mm; significant left atrial dilation, with an increased volume of 56 ml *(Figure 2A)*; mitral valve sclerosis with calcification spots and mild-moderate mitral regurgitation. The TEE showed generalized low-grade hypokinesia, left ventricular ejection fraction (LVEF) of 64%, and an intraventricular gradient at rest greater than 168 mmHg, with an anterior systolic movement of the anterior mitral leaflet *(Figure 2B)*.

Due to the LVOT obstruction, the persistent symptoms, and the comorbidities previously mentioned, together, the hemodynamic, echocardiography, and cardiology teams decided to schedule the alcohol septal ablation. Through a trans-jugular approach, a temporary pacemaker was placed in the right ventricle. A guide was advanced through the left coronary artery to the first septal artery using a bilateral radial approach *(Figure 3A)*, where an OTW balloon catheter was dilated (2.0 × 1.5 mm) until the complete occlusion was verified. With echocardiographic support, the right anatomical site was also confirmed. Initially, 7 ml of 70% ethanol was slowly injected, but only a partial occlusion was observed *(Figure 3B)*; thus, an additional 3 mL injection was added, observing a complete embolization *(Figure 3C)*. No complications in the anterior descending coronary artery or electrical abnormalities were detected, but it was decided to leave the pacemaker implanted on ventricular demand pacing. The post-extrasystolic intraventricular gradient was measured again, and a minimum residual gradient was recorded (aortic pressure of 160/55 mmHg, left ventricular pressure of 190/40 mmHg, and a peak gradient of 30 mmHg), while the resting gradient was absent *(Figure 4)*. No periprocedural complications were presented.

She was admitted to the coronary intensive care unit for close monitoring of possible complications. She remained asymptomatic on physical examination, and her mesotelesystolic aortic murmur decreased in intensity (I/VI). A new echocardiogram was performed, showing an LVOT mean gradient of 57 mmHg and akinesia of the basal anteroseptal wall. After 72 hours, she was discharged from the hospital without any cardiovascular or metabolic complications.

DISCUSSION

HCM is defined as a nondilated left ventricular hypertrophy (LVH), identified through echocardiography or magnetic resonance imaging, which occurs in the absence of another cardiac, metabolic, or systemic disease. The typical pattern of HCM is the asymmetric septal hypertrophy, but other forms can occur.[1,10] HCM is predominantly an obstructive heart disease,[11] usually produced by mitral-valve systolic anterior motion and septal contact due to flow drag, showing mitral regurgitation.[1]

Previously, HCM had been reserved as a relevant clinical entity in the young population because of its strong association with a higher risk of SCD in adolescents and young adults due to coronary microvascular dysfunction and ischemia.[1] Now, it is well known that the clinical course of HCM covers a broad spectrum of manifestations, where many patients will remain asymptomatic with an average life expectancy, but others will progress along with the disease's natural history and its complications.[8,12,13]

Although SCD is one of the most feared complications, HCM patients who survive beyond the age of 60, paradoxically, seem to be protected against SCD (similar rates compared with the general population).[1,6] These patients can have more than one conventional clinical marker associated with increased risk for premature SCD, but they do not have the same prognostic significance. Therefore, the recommendation for primary prevention with implantable defibrillators may be unnecessary in patients who have survived for many decades.[8] Other relevant features in elderly HCM patients are the risk of atrial fibrillation and consequent embolic stroke.[7]

According to various genetic-based studies, mutations in the cardiac myosin-binding protein C (*MYBPC3*) gene are the most common cause of delayed hypertrophy expression (late-onset HCM).[7] It has a more benign prognosis than mutations in other sarcomeric protein genes, such as the β-myosin heavy chain (*MYH7*) and troponin T (*TNNT2*).[4,5] Family screening must be performed with a phenotypic or genotypic strategy, depending on the genetic

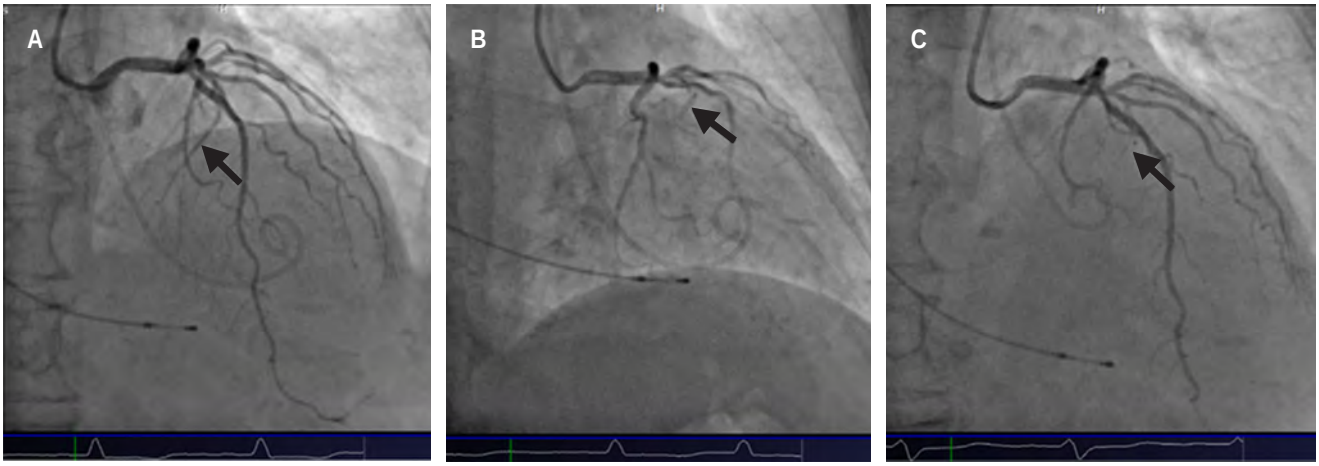

Figure 3: A) Coronary angiography, where the first septal artery is observed as a branch of the anterior descending coronary artery (Arrow). **B)** The first septal artery is occluded with a balloon, and the alcohol is injected. **C)** The absence of blood flow on the first septal artery is observed after the alcohol septal ablation.

Figure 4: The absence of a significant transaortic gradient was observed after alcohol septal ablation.

test availability, although the yield of genetic testing is lower for elderly patients without a family history of HCM.[14]

Imaging findings variate from young patients to elderly ones. Wall thickness is more significant in the young population than elderly patients with less severe hypertrophy, related to a better prognosis. Older patients also have shown less diffuse myocardial involvement, often confined to the ventricular septum. Key features that distinguish HCM from hypertensive heart disease are the asymmetric distribution of the hypertrophy and left ventricular outflow tract (LVOT) obstruction.[6,15]

Management options in symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) are β-blockers, non-dihydropyridine calcium channel blockers, and disopyramide, alone or in combination. Hypertension is frequent as a comorbid condition in these types of patients, and many antihypertensive drugs are relatively contraindicated in HOCM because of the risk of decreased cardiac output, such as diuretics and vasodilators.[16]

In addition to medical therapy, HOCM patients can be approached by surgical myectomy or alcohol septal ablation to reduce the LVOT gradient. Alcohol septal ablation has gained popularity since it uses a transcoronary administration of ethanol via a percutaneous approach to induce a localized infarction of the basal septum, where the anterior mitral valve leaflet is located.[17] The American College of Cardiology Foundation/American Heart Association guidelines on HCM state that alcohol septal ablation should be reserved for elderly patients and patients with severe comorbidities.[17] A recent meta-analysis showed that alcohol septal ablation is associated with lower periprocedural complications but higher re-interventions and pacemaker implantation rates due to atrioventricular block.[18] The 5- and 10-year survival rates following alcohol septal ablation in patients older than 55 years are 93% and 82%, respectively, and the risk of adverse arrhythmic events is low (1.4% per year), comparable to age-matched non-obstructive HCM patients.[19]

The life expectancy of late-onset HCM patients beyond the seventh decade of life is likely to be more influenced by their comorbidities than HCM itself. In a study with 428 patients between the ages of 60 to 91 years at study entry, survival at 5 and 10 years (accounting for all-cause mortality) was 77% and 54%, respectively. Mortality events related to HCM were 0.64% per year due to atrial fibrillation-related embolic stroke, arrhythmic sudden death events, progressive heart failure, postoperative complications, and heart transplantation for end-stage disease.[20]

For the reasons mentioned above, the management of elderly HCM patients must be individually evaluated by a multidisciplinary team, taking into account the clinical presentation, comorbidities, mitral valve anatomy, coronary anatomy, septal thickness, and the hospital's expertise for each procedure.[19]

CONCLUSIONS

Late-onset HCM usually comprises a more benign spectrum of the disease, but severe cases may occur. Despite being uncommon in the elderly, it should be included in the differential diagnosis of congestive heart failure and myocardial ischemia. A multidisciplinary team must individually assess the clinical characteristics to decide the best therapeutic approach for the patient.

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Funding/support: No financial support was received for this study.

Conflict of interest: The authors declare no conflict of interest.

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Cardiovascular and Metabolic Science www.ancam.org.mx

Review

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101308

Up to date concepts in valvular heart disease

Actualización de conceptos en cirugía de reemplazo valvular

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Keywords:
Valve replacement, valvular heart disease, valvular grafts, allografts.

Palabras clave:
Reemplazo valvular, valvulopatías, injertos valvulares, aloinjertos.

ABSTRACT

The prevalence of valvular heart diseases (VHD) has evolved over time. While industrialized countries have reduced the rheumatic fever-related VHD, developing countries still have a substantial number of cases due to this reason. Nevertheless, rheumatic fever is still the main cause of VHD around the world. Regardless of rheumatic or degenerative etiology, it is essential to highlight that left-sided valves still represent the surgery's main indication for valve replacement. The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) joined forces to write the VHD Guidelines for the first time in 2012 and updated them in 2017. From our perspective, guidelines are useful in guiding the decision-making of health professionals in daily practice. However, patient's options must be individualized and taken carefully by caregiver and physician according to the specific case. Currently, in VHD management, the medical option is still an indication in specific cases, percutaneous procedures and its indications have dramatically increased, and the surgical approach of repair versus replace is dependent upon a variety of factors. We focus this review on the indications of valve replacement and the grafts available when the surgery is indicated.

RESUMEN

La prevalencia de las enfermedades valvulares del corazón (EVC) ha evolucionado con el tiempo. Mientras que los países industrializados han reducido las valvulopatías relacionadas con la fiebre reumática, los países en desarrollo todavía tienen un número sustancial de casos debido a esta razón. Sin embargo, la fiebre reumática sigue siendo la principal causa de EVC en todo el mundo. Independientemente de la etiología reumática o degenerativa, es fundamental destacar que las válvulas izquierdas siguen representando la principales involucradas al momento de indicar una cirugía para el reemplazo valvular. La Sociedad Europea de Cardiología (SEC) y la Asociación Europea de Cirugía Cardio-Torácica (AECCT) unieron sus fuerzas para redactar las guías de EVC por primera vez en 2012 y las actualizaron en 2017. Desde nuestra perspectiva, las guías clínicas representan un sistema que facilita la toma de decisiones de los profesionales de la salud en la práctica diaria, pero cada indicación, decisión clínica y opciones que se ofrecen a los pacientes deben ser individualizadas y tomadas por el cuidador y médico, según el caso específico. Actualmente, en el manejo de la EVC, la opción médica sigue siendo una indicación en casos específicos, los procedimientos percutáneos y sus indicaciones han aumentado dramáticamente, y el abordaje quirúrgico de reparación versus reemplazo depende de una variedad de factores. Centramos esta revisión en las indicaciones de sustitución valvular y los injertos disponibles cuando la cirugía está indicada.

INTRODUCTION

The prevalence of valvular heart diseases (VHD) has evolved over time. Currently, there has been a significant decrease in industrialized countries thanks to better management of rheumatic fever. However, developing countries still have a substantial number of cases due to this reason.[1]

Nevertheless, industrialized countries have increased their life expectancy. In consequence, this implicitly brings an increased rate of degenerative valve disease (DVD). Even though the VHD or DVD are not considered a public health problem, a significant number of patients require an answer to their problem in an ever-changing field of cardiac surgery.[2]

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Received:
13/01/2021
Accepted:
23/04/2021

How to cite: Guevara-Noriega KA, Castro-Ríos JG, Rivera-Aguasvivas L, Villamizar M. Up to date concepts in valvular heart disease. Cardiovasc Metab Sci. 2021; 32 (3): 144-148. https://dx.doi.org/10.35366/101308

It is essential to highlight that left-sided valves still represent the surgery's main indication for valve replacement, being the aortic valve the most common, followed by the mitral valve. Currently, at the moment of offering a solution to the patient, either open or percutaneous procedures are available, and specific indication has been established for each one.[3]

In this field, cardiologists and surgeons had joined forces to write the valvular heart disease guidelines for the first time in 2012 when the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) published an unavoidable document to read when we are talking about VHD in Europe.[2]

In 2017, ESC/EACTS updated the guidelines due to new evidence on percutaneous interventional techniques and risk stratification concerning the timing of intervention in VHD. Simultaneously, the American College of Cardiology/American Heart Association (ACC/AHA) also published guidelines for VHD. Many differences between the two major society guidelines have been described and, even a small number of the guideline recommendations seem contradictory. Author of reviews about these differences considers more randomized trials are required to clarify recommendations.[4,5]

From our perspective, guidelines and their recommendations in any specialty are just guides to facilitate decision-making of health professionals in their daily practice. However, every indication, clinical decision and options offered to the patients must be individualized and taken by caregiver and physician according to the specific case.

Particularly in valve heart disease management, the medical option is still an indication in specific cases, percutaneous procedures have dramatically increased in number and indications, and the surgical approach of repair versus replace is dependent upon a variety of factors, including surgical experience, valve morphology, surgical risk, mechanism of the affectation, anticoagulation planning, and patient age.

We focus this review on the indications of surgeries and the grafts available when performing the surgery.

SUMMARIZING SURGICAL INDICATIONS

Aortic stenosis (AS) is the most common valvular disorder in Europe, and the 2017 ESC/EACTS guidelines consider balloon aortic valvotomy, transcatheter aortic valve implantation (TAVI), or surgical aortic valve replacement (SAVR) as suitable options in patients requiring intervention.[2,6]

For establishing indications, symptomatic versus asymptomatic patients must be differentiated. Indications could be summarized as follow:

- Intervention is indicated in symptomatic patients with severe, high-gradient aortic stenosis (mean gradient ≥ 40 mmHg or peak velocity ≥ 4.0 m/s). It is also indicated if severe low-flow, low-gradient (< 40 mmHg) aortic stenosis with reduced ejection fraction and evidence of flow (contractile) reserve excluding pseudo-severe aortic stenosis.
- Patients with low-flow, low-gradient (< 40 mmHg) and aortic stenosis should undergo surgery if they have normal ejection fraction after careful confirmation or if they have a reduced ejection fraction without flow (contractile) reserve, particularly when CT calcium scoring confirms severe aortic stenosis.
- Symptomatic severe AS demands intervention in nearly all clinical circumstances. However, quality of living, benefits for the patient, comorbidities or surgical risk must be analyzed before indicating the surgery.
- Asymptomatic patients have indications only if severe aortic stenosis and systolic LV dysfunction (LVEF) not due to another cause, an abnormal exercise test showing symptoms on exercise related to aortic stenosis or an abnormal exercise test showing a decrease in blood pressure below baseline.
- In Asymptomatic patients should indicate a surgery if they have low surgical risk and very severe aortic stenosis defined by a Vmax > 5.5 m/s, or severe valve calcification and a rate of Vmax progression ≥ 0.3 m/s/year or markedly elevated BNP levels

confirmed by repeated measurements without other explanations or in cases of severe pulmonary hypertension without other explanation.[2]

Specific details about open surgery or percutaneous, or concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery procedure is beyond this review, and we strongly recommend reviewing the 2017 ESC/EACTS guidelines.[2]

Regarding aortic regurgitation, every symptomatic patient or anyone with acute aortic regurgitation requires surgical intervention, and the latter often demands emergent surgical intervention. Asymptomatic patients have an indication of surgery if resting left ventricular ejection fraction (LVEF) < 50%. Also, should be considered the surgery for asymptomatic patients with resting ejection fraction > 50% with severe LV dilatation: LVEDD > 70 mm or LVESD > 50 mm (or LVESD >25 mm/m^2 BSA in patients with small body size). Surgery is indicated in patients undergoing CABG or surgery of the ascending aorta or another valve.[2,6]

Mitral regurgitation (MR) remains the second most common indication for valve surgery in Europe. Patients with acute severe mitral regurgitation must be provided for urgent surgical intervention, according to the 2017 ECS/EACTS guidelines. In contrast, for deciding about surgery in chronic MR, symptomatic and asymptomatic patients must be differentiated.[2,6]

The surgery is indicated for symptomatic patients with MR if LVEF > 30%. For asymptomatic patients, surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥ 45 mm and/or LVEF 60%) and atrial fibrillation secondary to mitral regurgitation, as well as, patients with pulmonary hypertension. Indication of surgery should be considered in asymptomatic patients with preserved LVEF (> 60%) and LVESD 40-44 mm when a durable repair is likely, surgical risk is low, the repair is performed in a heart valve center, and presence of flail leaflet or significant Left Atrium (LA) dilatation in sinus rhythm.[2,6]

The guidelines exposed recommendation IIa and IIb for specific techniques, valve repair, valve replacement or percutaneous procedures. However, these details go beyond our scope, and we strongly recommend to review the ECS/EACTS guidelines for this information.

The scenario is different for patients with Mitral stenosis because surgery has been displaced by percutaneous mitral commissurotomy (PMC). Currently, only symptomatic patients who are not suitable for PMC or asymptomatic patients with unfavorable anatomic and clinical characteristics undergo surgery. For all the other patients with moderate or severe mitral stenosis requiring intervention, PMC is the mainstay.[2,6]

Regarding right-sided valves, the 2017 ES/EACTS guidelines recommend surgery for symptomatic patients with severe tricuspid stenosis. Surgery is also indicated for patients with severe tricuspid stenosis who are undergoing left-sided valve surgery. In cases of tricuspid regurgitation (TR), indications of surgery have been established for symptomatic patients but also should be considered in asymptomatic patients when progressive right ventricle (RV) dilatation or decline of RV function is observed as well as, patients with severe primary tricuspid regurgitation undergoing left-sided valve surgery. Mildly symptomatic (or asymptomatic) patients with progressive RV dysfunction and severe primary tricuspid regurgitation.[2,6]

GRAFTS FOR VALVE REPLACEMENT

Once the indication of valve replacement has been established according to the guidelines or because individualization of the case lead to think this is the best option, surgeons will have a wide range of options to choose. However, this selection seems to be related to geographical areas, personal experiences, research conducted in specific locations, regional/national guidelines and/or an attempt to adjust the grafts to the patient.

Guidelines limit the choice between a mechanical and a biological valve. This selection is made based on the risk of anticoagulation-related bleeding and thromboembolism with a mechanical valve versus the risk of structural valve deterioration with a bioprosthesis. Although the patient's life expectancy and

lifestyle are considered for this selection, the guideline does not go beyond to thought the emerging alternatives.

Allografts are one of these alternatives to grafts. At the moment, cryopreserved human heart valve allografts still represent almost perfect substitutes for heart valves. In fact, valve allografts have wide acceptance, and they have been in several indications. However, the most common procedure where the valve allografts are used is the Ross procedure. This technique dates back to 1967, when Donald Ross transferred the patient's pulmonary valve into the aortic root. An allograft replaces the pulmonary valve. Since the 60s, excellent long-term results and the possibility of combination with other techniques have encouraged to continue this technique.[7]

However, the Ross procedure is a complex operation; careful patient selection and experienced surgeons are mandatory requirements to achieve satisfactory results.[7]

In Europe, several groups have worked with allografts, and new variants have been proposed with the aims of creating a graft with improved durability compared to routinely used valve substitutes. The most significant and more exciting proposal involving allografts and tissue-engineered aortic valve (TEV) came in 2013 from the Department of Cardiothoracic, Transplant and Vascular Surgery at the Hannover Medical School. This project has evolved and currently is called ARISE. Now, it is a European Commission-funded project, led by the Hannover Medical School, nine hospitals, six tissue banks and an innovative biotechnology company providing the decellularization service that came together for the world-wide first prospective study on cell-free allografts for aortic valve replacement.[8,9]

After extensive preclinical work and their first publication in 2013 performed in sheep, the group leader, Haverich et al., have used decellularized allogenic heart valve matrices for aortic valve replacements (AVR) based on compassionate use in 34 patients with tentative assessment showing favorable initial clinical results. However, transferring this regenerative approach to routine clinical application necessitates controlled prospective clinical trials lacking to date.[8]

Simultaneously, tissue-engineering heart valve (TEHV) has emerged as an interesting alternative to find a solution for the increasing demand for cardiac valves. TEHV has centered on its research lines in creating an ideal scaffold to be seeded by cells, which are expected to proliferate to resemble a natural human heart valve. Scaffolds materials can be classified into natural and synthetic. Natural scaffolds are decellularized xenografts purified from animal valves, and the synthetics as they are called come mainly from polycarbonate urethane and polyether urethane. To avoid an immune reaction, cells to seed in the scaffold must come from an autologous source.[10]

A combination of the natural and synthetic scaffold has also been developed. Decellularized bovine pericardium extracellular matrix modified with synthetic polymers by coating the structure with a layer of polycaprolactone-chitosan (PCL-CH) nanofibers have been previously described as an attractive hybrid scaffold with superior mechanical properties and promising results.[11]

Tissue-engineered heart valves are an increasing alternative with the hope of eventually to develop an ideal and clinically suitable cardiac valve replacement to cover the growing demand. Currently, TEHV is considered the only technology is working on the potential creation of tissues analogous to a native human heart valve, with longer sustainability and fewer side effects.[10]

Other exciting alternatives to valve replacement are the xenografts. In this regard, an endovascular alternative worth to be highlighted. The melody transcatheter valve (Medtronic, Minneapolis, MN, USA) is a heart valve from a cow's vein attached to a wireframe that has demonstrated to be safe and effective in pediatric patients with excellent short- and mid-term follow-up hemodynamic results. However, their approved indications are limited to treat bioprosthetic valves dysfunction, mainly in pulmonary position.[12]

The melody transcatheter valve (Medtronic, Minneapolis, MN) has emerged in the era of percutaneous cardiac valves. Another percutaneous alternative is SAPIEN S3 from Edward Lifesciences (Edwards, Irvine, CA, USA). However, transcatheter valve replacement is

not the scope of this review, and we will not go deep into this alternative.

Among the xenografts, also highlight The Edwards Inspiris Resilia® valve (Edwards Lifesciences, Irvine, CA, USA), which is bovine pericardial tissue transformed by a preservation technique which was primarily designed as the aortic valve, but because of availability of small size have been tested in children. Currently, The Edwards Inspiris Resilia® valve (Edwards Lifesciences, Irvine, CA, USA) has been accepted to be potentially used in mitral position in children. However, there are not robust clinical trials, and more studies are required.[13]

Regarding synthetic valve replacement, the classical concept is that by implanting a mechanical valve, the patient will require permanent anticoagulation. However, Lapeyre et al. have performed a preclinical assessment of a trileaflet mechanical valve. They have tried to develop a mechanical valve that will not require permanent anticoagulation.[14,15]

Finally, it is essential to highlight that the decellularization technique and valves fully built with polyurethane are being developed. However, until having enough trials and studies, these options are also too young to extract conclusions.

ACKNOWLEDGMENTS

The workgroup gratefully acknowledges to the support given by the Cardiovascular Surgery Department at Jackson Memorial Hospital.

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Funding/support: No financial support was received for this study.

Conflict of interest: Authors state there is no conflict of interest.

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CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

REVIEW

Vol. 32 No. 3
July-September 2021

doi: 10.35366/101309

The role of vitamin D and cardiovascular risk in COVID-19 patients

El papel de la vitamina D y el riesgo cardiovascular en pacientes con COVID-19

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Keywords:
Vitamin D deficiency, vitamin D and COVID-19, cardiovascular disease.

Palabras clave:
Deficiencia de vitamina D, vitamina D y COVID-19, enfermedad cardiovascular.

ABSTRACT

Vitamin D deficiency has long been associated with the incidence of cardiovascular disease. It also thought to play a role in the severity of COVID-19 patients. A serum concentration of 25(OH) D < 50 nmol/L (vitamin D deficiency) is found in patient with severe COVID-19 manifestation requiring intensive care. These patients are thought to stem from an uncontrolled complex immune response. The role of vitamin D in the COVID-19 infection reaction is by supporting antimicrobial peptides response in the respiratory epithelium and reducing inflammatory reactions to SARS-CoV-2 infection. Therefore, it can reduce the severity of COVID-19 infection. Vitamin D has also involved in several cardiovascular diseases that could increase the severity of COVID-19 infection; i.e., hypertension, lipid metabolism, atherosclerosis, and heart failure. Vitamin D affects endothelial cell function, thus regulating vasodilatation of dependent endothelial cells. It can prevent atherosclerosis and vascular calcification, which COVID-19 patients are at an increased risk. It also reduces pro-inflammatory cytokines, which has an anti-remodelling effect to reducing the fatality risk of obesity and heart failure among COVID-19 patients. Understanding the importance of avoiding vitamin D deficiency, the fulfilment of daily intake should be taken into account. The recommended daily dose of vitamin D is 200 IU per day for those aged < 50 years, 400 IU per day for those aged 50-70 years and 600 IU for individuals aged > 70 years. It is estimated that for every 100 IU of vitamin D, the 25(OH)D level increases by 2.5 nmol/L.

RESUMEN

La deficiencia de vitamina D se ha asociado durante mucho tiempo con la incidencia de enfermedades cardiovasculares. También se cree que juega un papel en la gravedad de los pacientes con COVID-19. Se encuentra una concentración sérica de 25(OH)D < 50 nmol/L (deficiencia de vitamina D) en pacientes con manifestaciones graves de COVID-19 que requieren cuidados intensivos. Se cree que estos pacientes provienen de una respuesta inmune compleja no controlada. El papel de la vitamina D en la reacción de infección por COVID-19 es el apoyo a la respuesta de los péptidos antimicrobianos en el epitelio respiratorio y la reducción de las reacciones inflamatorias a la infección por SARS-CoV-2. Por lo tanto, puede reducir la gravedad de la infección por COVID-19. La vitamina D también se ha involucrado en varias enfermedades cardiovasculares que podrían aumentar la gravedad de la infección por COVID-19; es decir, hipertensión, metabolismo de lípidos, aterosclerosis e insuficiencia cardiaca. La vitamina D afecta la función de las células endoteliales, regulando así la vasodilatación de las células endoteliales dependientes. Puede prevenir la aterosclerosis y la calcificación vascular, a lo que los pacientes con COVID-19 tienen un mayor riesgo. También reduce las citocinas proinflamatorias, que tiene un efecto anti-remodelador para reducir el riesgo de muerte por obesidad e insuficiencia cardiaca entre los pacientes con COVID-19. Entendiendo la importancia de evitar la deficiencia de vitamina D, se debe tener en cuenta el cumplimiento de la ingesta diaria. La dosis diaria recomendada de vitamina D es de 200 UI al día para los menores de 50 años, 400 UI al día para los de 50 a 70 años y 600 UI para los mayores de 70 años. Se estima que por cada 100 UI de vitamina D, el nivel de 25(OH)D aumenta en 2.5 nmol/L

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Received:
07/02/2021
Accepted:
23/03/2021

INTRODUCTION

Cardiovascular disease is the most common cause of death and morbidity in many countries. Evidence suggests a possible link between vitamin D deficiency and cardiovascular disease (CVD), including hypertension, coronary heart disease (CAD), heart failure (HF), peripheral vascular disease (PAD), diabetes mellitus (DM), and

How to cite: Purnama DI, Kusuma WLF, Purnama DK, I, A. The role of vitamin D and cardiovascular risk in COVID-19 patients. Cardiovasc Metab Sci. 2021; 32 (3): 149-156. https://dx.doi.org/10.35366/101309

metabolic syndrome.[1,2] Vitamin D deficiency is associated with the prevalence and incidence of cardiovascular disease.[3] Vitamin D acts as a bone bioregulator and mineral metabolism in the cardiovascular system. Vitamin D supplementation is beneficial for calcium-phosphorus metabolism and affects myocardial contractility.

Vitamin D deficiency causes secondary hyperparathyroidism. Both primary and secondary hyperparathyroidism is associated with cardiovascular disorders. Secondary hyperparathyroidism further leads to increased insulin resistance and pancreatic β cell dysfunction, a predisposing factor for metabolic syndrome and DM. Secondary hyperparathyroidism also activates the renin-angiotensin-aldosterone system (RAAS), increases blood pressure (BP), and causes left ventricular (LV) hypertrophy, which in turn causes apoptosis and fibrosis of the heart cells. Systemic and vascular inflammation, as well as an increased risk of atherogenesis, may also occur.[4,5]

Coronavirus disease 2019 (COVID-19) is an infectious disease of the respiratory system caused by the coronavirus SARS-CoV-2. Although the primary clinical symptoms are respiratory-related, many studies show a high prevalence of cardiovascular comorbidities in COVID-19 patients.[6] Vitamin D is thought to play a role in the severity of COVID-19 patients. Studies show that vitamin D deficiency (serum concentration 25(OH) D.[7] In this literature review, the discussion focuses on recent evidence, potential mechanisms, and the possible role of cardiovascular vitamin D supplementation, especially in COVID-19 patients.

VITAMIN D METABOLISM

Vitamin D is one of the four fat-soluble vitamins required by the body. Vitamin D is a potent steroid vitamin made in the body from cholesterol through a process triggered by ultraviolet light (UVB) or sunlight. Whether made in the body or obtained from food, Vitamin D is the result of hydroxylation in the liver to the dominant form in the circulation, calcidiol or 25(OH)D. Calcidiol is then converted by rehydroxylation in the kidneys and tissues to calcitriol or 1,25-dihydroxyvitamin D ($12.5(OH)_2D$). Calcitriol, with a half-life of 15 hours, is the main active form of vitamin D.

Vitamin D deficiency (serum 25(OH)D 2D), binds to the vitamin D receptor (VDR). VDR is particularly prevalent in endothelium, vascular smooth muscle, enterocytes, and osteoblasts.[8,9] In the cardiovascular system, VDR is found in the myocardium and endothelial cells.[10] *In vitro*, vitamin D inhibits the proliferation and hypertrophy of cardiomyocytes.[11]

VITAMIN D PATHOPHYSIOLOGY AND CARDIOVASCULAR DISEASE IN COVID-19

The pathophysiology underlying the clinical manifestations of COVID-19 infection is thought to stem from an uncontrolled complex immune response. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE 2) receptor, which is expressed in the lungs, intestinal system, kidneys, and blood vessels. When SARS-CoV-2 binds to the ACE 2 receptor, there is a downregulation of ACE 2 activity and expression resulting in a disruption of the balance between ACE/ACE 2, which causes increased activity of angiotensin II (Ang II) and increased production of pro-inflammatory cytokines.[12]

Cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL) 1β, IL-8, and IL-12 play important roles in the disease pathogenic cascade. The most important mediator of this cytokine storm is IL-6. IL-6 can be produced by immune system cells (B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells), stromal cells, and many non-lymphocyte cells, including fibroblasts and endothelial cells. IL-1β and TNF-α are key activators for IL-6 secretion.[7]

The role of vitamin D in the COVID-19 infection reaction is to support the production of antimicrobial peptides in the respiratory epithelium so that viral infections and the development of signs and symptoms of COVID-19 are lighter. In addition, vitamin D can also help reduce inflammatory reactions to SARS-CoV-2 infection. Changes in the regulation of the response to these inflammatory reactions, particularly RAAS, are characteristic of COVID-19, and excessive activation levels

are associated with a poor prognosis. Previous research identified an association between higher ACE 2 levels and increased COVID-19 morbidity outcomes.[13]

Several studies have demonstrated increased plasma renin activity, Ang II concentrations, and higher RAAS activity due to low vitamin D status. The same is true for renin activity which decreases with increasing vitamin D levels. There is an inverse relationship between circulating 25(OH)D and renin. Vitamin D is a negative regulator of renin expression and reduces renin expression by repressing the renin gene promoter's transcription activity. $1,25(OH)_2D$ induced repression of renin gene expression is independent of Ang II feedback regulation. A permanent increase in renin levels with an increase in angiotensin I (Ang I) formation, indicating that in vitamin D deficiency, renin expression and secretion are increased in the early stages. This will increase fluid and salt intake and cause an increasing in BP. *Figure 1* provides a brief overview of vitamin D's impact on RAAS in COVID-19.[14]

Patients with chronic disease have a higher risk of death from respiratory infections. On the other hand, vitamin D deficiency is associated with an increased risk of various diseases, including CVD. Since preliminary studies on the relationship between hypovitaminosis D and COVID-19, vitamin D has been recognized as a potentially useful therapy for SARS-CoV-2 infection based on its anti-inflammatory and antithrombotic properties.[15] Vitamin D, as an anti-inflammatory, can modulate nitric oxide (NO) production and inhibit endothelial protein expression for leukocyte adhesion. Meanwhile, as an antithrombotic, vitamin D plays a role in the downregulation of pro-thrombotic plasminogen activator inhibitor-1 (PAI-1) and thrombospondin-1 mRNA expression, as well as plays a role in the upregulation of thrombomodulin.[15]

Vitamin D and hypertension in COVID-19

The renin-angiotensin-aldosterone system plays a crucial role in the pathogenesis of

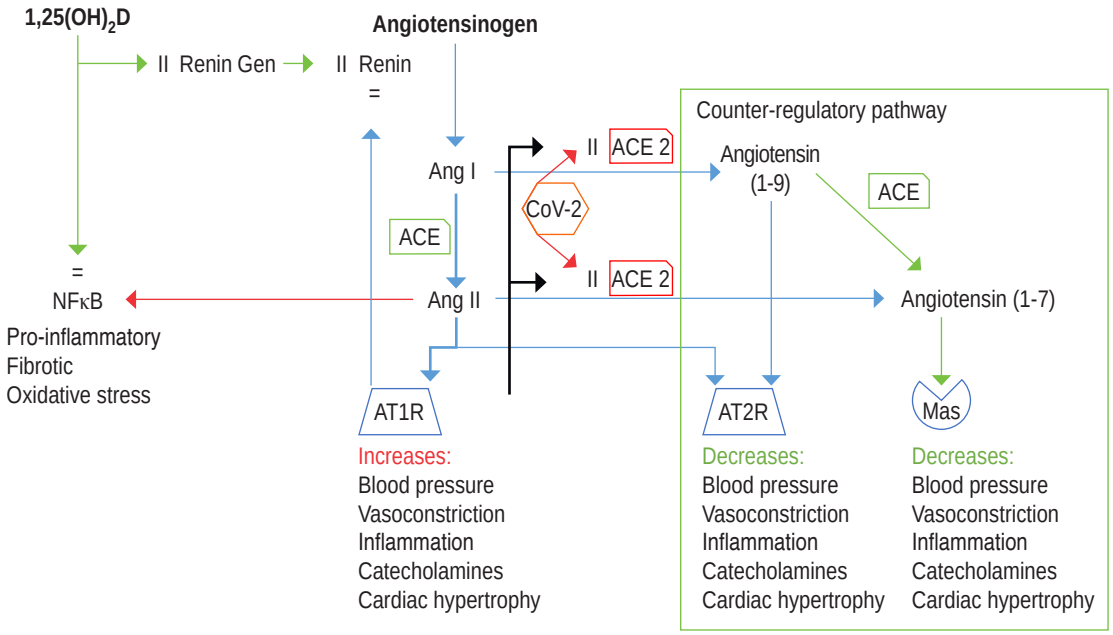

Figure 1: An imbalance system of RAAS regulation will increase Ang II formation, renin synthesis, and inflammatory response. This is important in low vitamin D levels because vitamin D ($1,25(OH)_2D$) can combat this imbalance through a negative expression of the renin gene resulting in lower renin synthesis, independent of Ang II. If this counter-regulation is disrupted by ACE 2 dysfunction due to SARS-CoV-2 infection, the classic pathway becomes uncontrolled and increases the pro-inflammatory reaction and BP contributing to cardiovascular problems and acute respiratory distress syndrome (ARDS).[14]

the cardiovascular disease. Vitamin D plays RAAS regulation, and vitamin D deficiency predisposes to RAAS upregulation and smooth muscle cell hypertrophy and LV. Left ventricular hypertrophy is a known risk factor or marker for CVD. $1,25(OH)_2D$ inhibits RAAS and can reduce BP. One study showed that UVB radiation from sunbathing three times a week for three months caused an almost 200% increase in 25(OH)D levels and a 6 mmHg decrease in BP in both systolic and diastolic BP. Vitamin D also affects endothelial cell function, regulating vasodilation of dependent endothelial cells.[9,16,17] The risk factors for clinical severity of COVID-19 patients predicted based on C-reactive protein (CRP) levels with low vitamin D levels (75 nmol).[14]

Vitamin D and lipid/obesity metabolism in COVID-19

The enzyme, 3-hydro-3-methylglutaryl coenzyme A (HMG-CoA) reductase, plays a key role in regulating cholesterol synthesis. Defay et al. found that the hydroxylation of vitamin D inhibited HMG-CoA reductase activity in lymphocyte stimulation with phytohemagglutinin. Experimental studies on multiple cells have shown that therapy with cholecalciferol (vitamin D3) and its metabolites, 25(OH)D, $1,25(OH)_2D$, and 24,25-dihydroxycholecalciferol inhibits cholesterol synthesis due to inhibition of HMG-CoA reductase activity. Vitamin D deficiency can result in an abnormal lipid profile with increased peripheral insulin resistance and contributes to metabolic syndrome. Serum levels of $1,25(OH)_2D$ were inversely correlated with very-low-density lipoprotein (VLDL) and triglycerides. Studies show that statin therapy can increase vitamin D levels, which is a nonlipid pleiotropic effect of statins.

Obesity is a risk factor for the clinical severity of COVID-19 infection. In a cohort study of 383 COVID-19 patients, patients with a BMI > 28 kg/m^2 had a 142% risk of developing clinically severe pneumonia than patients with a normal BMI.[14] In the adipose tissue biopsy of obese patients, there is an increase in the number of macrophages contributing to the increase in cytokines such as IL-6, TNF-α, and IL-1β. This increase in inflammation is associated with increased mortality.[18] Vitamin D is active in adipocyte cells and interacts with membrane phosphatase receptors and coregulatory nuclear proteins, participating in gene expression and cell signaling. Based on *in vivo* studies, vitamin D reduced levels of pro-inflammatory cytokines and chemokines in lipopolysaccharide-injected mice and obesity model mice. Vitamin D's anti-inflammatory effect is mediated by inhibition of the NFκB and MAPK signaling pathways and decreased expression of the toll-like receptor (TLR).[19]

Vitamin D and coronary artery disease in COVID-19

Vitamin D can be linked to CAD through its effects on BP, glycemic and parathyroid (PTH) control. In COVID-19 infection, elevated PTH levels increase intensive care risk compared to patients with normal PTH levels. Disruption of the PTH-vitamin D axis during the healing phase was also associated with a longer length of stay.[20] Low 25(OH)D and elevated PTH levels increase the risk of inflammation, indicated by elevated levels of CRP and IL-10. Administration of $1,25(OH)_2D$ in vitamin D deficiency has been shown to reduce inflammatory biomarkers such as CRP and IL-10 in COVID-19 patients.[17,21] Vitamin D also has an effect on endothelial function and decreases vascular calcification. Vitamin D can prevent atherosclerosis and vascular calcification, directly affecting vascular smooth muscle cells (VSMCs). A multicentre study evaluating hospitalized patients with acute coronary syndrome (ACS) found that about 96% of patients had abnormal 25(OH)D levels.

The lowest level of 25(OH)D was around 17.8 ng/mL in the general population. This epidemiological study indicated that poor vitamin D status was associated with poor cardiovascular outcome.[1,22] CAD is a prevalent condition in COVID-19 patients, ranging from 2.5-10% of cases with a mortality probability up to three times that of COVID-19 patients without clinical CAD.[23] In another study, COVID-19 patients experiencing mortality had clinical CAD (82% vs 55%, $p = 0.02$) as well as low levels of 25(OH)D (15.2 vs 18.9 ng/mL, $p = 0.02$).[24]

Vitamin D and heart failure

Much evidence supports that calcitriol deficiency contributes to the severity of chronic heart failure (CHF).[25,26] Some of the potential mechanisms that explain vitamin D's direct protective effect on heart failure include effects on myocardial contractile function, regulation of natriuretic hormone secretion, effects on extracellular matrix remodelling, reduction of LV hypertrophy, and regulation of inflammatory cytokines. Indirectly, vitamin D can also affect heart function by altering PTH and serum calcium levels.[26] In uremic cardiomyopathy patients undergoing dialysis, treatment with 1-α hydroxyl cholecalciferol 1 μg/day for six weeks resulted in decreased plasma parathyroid concentrations and increased shortening of fractional fibers on M-mode echocardiography.[1]

The causes of heart failure are not fully understood. In recent years, CHF's pathophysiological concept has changed from an isolated hemodynamic view to a more complex one; involving neurohormonal overactivation and increased concentrations of pro-inflammatory cytokines, such as TNF-α and IL-6. In particular, TNF- α may contribute to the pathogenesis and progression of CHF. Therefore, measures to mitigate the adverse effects of TNF-α on CHF progression may be a promising therapeutic approach.[27]

Regarding COVID-19 infection, a study of 452 COVID-19 patients in Wuhan showed that patients with clinical severity had elevated levels of TNF-α.[28] Increased cytokine TNF-α can cause septic shock and multi-organ failure, lead to myocardial damage and circulatory failure.[29]

SOURCES OF VITAMIN D AND NORMAL SERUM LEVELS

The synthesis of vitamin D3 in the skin from sun exposure is the primary source (80-90%) of human vitamin D under natural conditions. Total-body sun exposure to at least 1 erythemal dose when wearing a swimsuit is equivalent to 250-500 g (10,000-20,000 IU) of vitamin D per day. Serum 25(OH)D is the major metabolite of circulating vitamin D and reflects vitamin D input from the synthesis in the skin and dietary intake. Serum levels of $1,25(OH)_2D$ may be normal or even elevated in patients with vitamin D deficiency.

Vitamin D derived from the daily diet is small compared to the build-up in the skin but can be an essential vitamin D source in supplement form. Fish oil derived from salmon, mackerel, herring, and sardines is a rich source of vitamin D. Fortified milk and juices contain 100 IU of vitamin D per 8-oz. Daily dietary sources typically provide 2.5 g (100 IU) of vitamin D per day, and fortified foods can provide up to 5-10 g (200 to 400 IU) of vitamin D daily.[30]

Hernandez et al. showed that vitamin D deficiency was found in 82.2% of COVID-19 cases and 47.2% in the control population ($p < 0.0001$). The serum 25(OH)D levels in COVID-19 patients were significantly lower than in the control population (13.8 ± 7.2 ng/mL vs 20.9 ± 7.4 ng/mL, $p < 0.0001$).[22] The most useful serum 25(OH)D level is at 30 ng/mL or 75 nmol/L. In COVID-19 patients, the goal of vitamin D therapy is to normalize vitamin D levels. Patients with vitamin D levels below 50 nmol/L should be treated until they reach a vitamin D level of at least 75 nmol/L.[14] Vitamin D intoxication is indicated when the level of 25(OH)D > 375 nmol/L.[31]

Serum vitamin D levels may also be involved in determining the prognosis of COVID-19. Vitamin D deficiency has been shown to contribute to acute respiratory distress syndrome and the increased case mortality rates with age and populations with comorbid conditions such as hypertension and CVD, which have also been reported as low prognostic factors for COVID-19.[12,22]

DAILY INTAKE RECOMMENDATIONS, TOXICITY, AND VITAMIN D TESTING IN COVID-19

In the United States, the recommended daily dose of vitamin D is 200 IU per day for those aged 70 years. It is estimated that for every 100 IU of vitamin D, the 25(OH)D level increases by 2.5 nmol/L.[32]

Research by Ohaegbulam et al. on COVID-19 patients with vitamin D deficiency showed that patients with high doses of vitamin D supplementation (50,000 IU) showed shorter treatment times and duration of oxygen use

than patients with standard-dose vitamin D supplementation (1,000 IU).[33] This clinical evidence is also supported by decreased levels of CRP and lactate dehydrogenase (LDH). The protective effect of vitamin D supplementation was more significant in patients with serum 25(OH)D 25 nmol/L.[34] Another study showed high doses of vitamin D (250,000-500,000 IU) were safe for use in critically ill patients on ventilator support and was associated with a reduced duration of treatment.[35] The study by Liu et al., provided vitamin D supplementation at a higher dose of 300,000 IU single dose by the oral or intramuscular route, taking into account the safety level of vitamin D supplementation and the rare toxicity.[36] Whereas in the ongoing COVIT Trial study, COVID-19 patients were divided into two study groups, a group that took vitamin D at a single dose of 50,000 IU orally and the next group was given vitamin D with the highest dose of 400,000 IU orally a single dose.[37]

Vitamin D intoxication is very rare but can be caused by excessive consumption or too high a dose. Doses > 50,000 IU per day raise 25(OH)D levels to more than 375 nmol/L and are associated with hypercalcemia and hyperphosphatemia. A dose of 10,000 IU of vitamin D3 per day for up to five months usually does not cause toxicity. A case report showed that vitamin D 150,000 IU per day for 28 years and serum concentrations up to 1.126 nmol/L did not result in significant hypercalcemia side effects.[1,38] Vitamin D hypervitaminosis has been reported when supplementing with vitamin D at a dose of 500,000 IU with the effect of increasing the risk of falls and fractures in older women.[39] There are no studies related to hypervitaminosis of vitamin D in COVID-19 patients.

VITAMIN D AND MORTALITY IN COVID-19

Numerous studies and meta-analysis studies suggest that vitamin D deficiency negatively affects survival, whereas supplementation decreases overall mortality. Regular intake of vitamin D supplements has been associated with reduced mortality. The relationship between baseline vitamin D status, vitamin D supplement dose and total mortality remains to be investigated. Apart from CVD, vitamin D deficiency is associated with an increased risk of total mortality. Most studies on this topic have noted increased mortality in patients with low 25(OH)D concentrations. A meta-analysis in 6,853 patients showed increased PTH secretion, activation of RAAS, and decreased death risk. These findings are in line with the results of the RCT meta-analysis, in this Autier and Gandini report that vitamin D supplementation was associated with a significant reduction of 7% in total mortality.[40]

Another meta-analysis study showed that vitamin D deficiency has a significant correlation with the outcome and prognosis of COVID-19 patients.[41] A study in India by Sasikala et al., showed a positive correlation between vitamin D deficiency and mortality in COVID-19 patients.[13] Whereas in another study that measured the fatality rate of COVID-19 patients with and without vitamin D deficiency, it was found that patients with vitamin D deficiency had a fatality rate of 21% compared to patients without vitamin D deficiency of 3.1%.[7]

Studies related to the outcome of vitamin D supplementation in COVID-19 patients with vitamin D deficiency have not been widely studied. Studies related to respiratory tract infections showed a 64% reduction in the risk of developing respiratory tract infections after vitamin D supplementation (95% CI 0.49-0.84; p = 0.0014).[12] One study on COVID-19 patients with a small sample size showed that giving high doses of vitamin D (50,000 IU) for five days had an effect on reducing the duration of treatment and oxygen supplementation; compared to patients receiving vitamin D therapy in standard doses (1,000 IU), where patients with high doses of vitamin D were able to achieve concentrations of ≥ 75 nmol/L while patients with standard doses were unable to achieve minimum levels of vitamin D concentrations.[33]

SUMMARY

Vitamin D has various essential functions among RAAS regulation, as anti-inflammatory by reducing the production I of pro-inflammatory cytokines including L^{-6} and TNF-α, as

antithrombotic, plays a role in lipid metabolism through inhibition of the enzyme HMG-CoA reductase, plays a role in heart function through PTH regulation, and calcium. Vitamin D deficiency is associated with cardiovascular events as well as an increased fatality rate in COVID-19 patients. Giving high doses of vitamin D is relatively safe, with case reports of hypervitaminosis are infrequent.

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Funding/support: The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest: The authors declare that there is no conflict of interest.

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Hidroclorotiazida ..... 12.5 mg o 25 mg

Excipiente cbp. ..... 1 tableta

4. Indicaciones terapéuticas: ROFUCAL® es un diurético de la familia de las tiazidas que está indicado en: Hipertensión arterial. Como monoterapia o combinado, para incrementar el efecto de otros antihipertensivos cuando se trata de formas más severas de hipertensión. En Edema, cuando está asociado a insuficiencia cardiaca congestiva, cirrosis hepática y en terapia con corticoesteroides y estrógenos. ROFUCAL® es útil también en el tratamiento de edemas relacionados con disfunción renal, como el síndrome nefrótico, la glomerulonefritis y la insuficiencia renal crónica. **5. Contraindicaciones:** el uso de ROFUCAL® está contraindicado en pacientes con anuria e hipersensibles al principio activo o componentes de la formulación, así como a otros fármacos derivados de las sulfonamidas. **6. Precauciones generales:** en pacientes que reciben tratamiento con dosis mayores de tiazidas, se pueden presentar casos de hiperuricemia o franca gota. Una diabetes latente puede hacerse manifiesta con el tratamiento a base de tiazidas. Los diuréticos pueden en dosis mayores precipitar una azoemia en pacientes con insuficiencia renal. **7. Restricciones de uso durante el embarazo y la lactancia:** no se recomienda su uso en embarazadas sanas o con edema pues se expone a la madre y al feto a un riesgo innecesario. Los diuréticos no previenen el desarrollo de toxemias del embarazo y no hay evidencia concluyente de que sean útiles en su tratamiento. Las tiazidas cruzan la barrera placentaria y aparecen en la sangre del cordón umbilical existiendo un riesgo de ictericia neonatal, trombocitopenia y otros posibles efectos adversos. **8. Reacciones secundarias y adversas:** Sistema gastrointestinal: Anorexia, irritación gástrica, náuseas, vómito, diarrea y muy ocasionalmente pancreatitis y sialoadenitis. Sistema Nervioso Central: Mareos, vértigo, parestesias y cefaleas. Hematológicos: Leucopenia, neutropenia/agranulocitosis, trombocitopenia, anemia aplásica y anemia hemolítica. Cardiovasculares: Hipotensión ortostática, vasculitis. Hipersensibilidad: Púrpura, fotosensibilidad, erupción cutánea, urticaria, fiebre y reacciones anafilácticas. Renales y urinarias: Disfunción renal y nefritis intersticial. Otros: Hiperglucemia, glucosuria, hiperuricemia, espasmo muscular, debilidad, inquietud, visión borrosa transitoria, calambres. **9. Interacciones medicamentosas y de otro género:** cuando se administran en forma conjunta otros fármacos puede ocurrir interacción con diuréticos tiazídicos como ROFUCAL®. **Alcohol, barbitúricos o narcóticos:** Puede haber aumento de la presión ortostática. **Aminas presoras:** Puede disminuir la respuesta a las aminas presoras, pero no lo suficiente como para no utilizarlas. **Anfotericina B, corticoesteroides o corticotropina:** Pueden intensificar el desequilibrio hidroelectrolítico, hipocalemia especialmente. **Anticoagulantes orales:** Pueden disminuir los efectos anticoagulantes. **Agentes antiinflamatorios no esteroideos:** Éstos pueden disminuir el efecto diurético. **Colestiramina y colestipol:** Retardan la absorción de ROFUCAL®. **Glucósidos digitálicos:** La hipopotasemia o la hipomagnesemia inducida por tiazidas favorece la aparición de arritmias cardiacas inducidas por digital. **Hipoglucemiantes orales e insulina:** Puede requerirse ajuste de la dosis de antidiabéticos. **Litio:** Los diuréticos disminuyen la depuración renal de litio y aumentan el riesgo de toxicidad. **Medicamentos para la gota:** La hidroclorotiazida puede aumentar el nivel de ácido úrico sérico. **Otros antihipertensivos:** Efecto aditivo o potencializante de sus efectos. **Sales de calcio:** Los diuréticos tiazídicos pueden incrementar los niveles séricos de calcio debido a la reducción de la excreción. **Probenecid o sulfinpirazona:** Se recomienda aumentar su dosis ya que la hidroclorotiazida puede tener efectos hiperuricémicos. **Relajantes no despolarizantes del músculo esquelético (ej. tubocurarina):** la hidroclorotiazida puede potenciar el efecto. **Ciclofosfamida, metotrexato:** Las tiazidas pueden reducir la excreción renal de los fármacos citotóxicos y potenciar su efecto mielosupresor. **10. Precauciones en relación con efectos de carcinogénesis, mutagénesis, teratogénesis y sobre la fertilidad:** estudios conducidos en animales no reportaron efectos carcinogénicos, mutagénicos así como tampoco alteraciones sobre la fertilidad a dosis terapéuticas. **11. Dosis y vía de administración:** ROFUCAL® se administra por vía oral. La dosis aplicada debe ser individual y acorde a la respuesta del paciente. ESQUEMA POSOLÓGICO DE ROFUCAL®. **Pacientes adultos con hipertensión arterial:** Inicio: 25 mg/día dosis única o repartida en varias tomas.*Ajustar la dosis según las cifras de tensión arterial. Máx: 50 mg diarios. **Pacientes adultos con edema:** 25 a 100 mg/día en una o dos tomas. Máx: 100 mg diarios.**

Premenstrual: 25-50 mg. Una o dos veces al día hasta el inicio de la menstruación.

*Algunos pacientes responden con una dosis inicial de 12.5 mg/día sola o combinada con otros antihipertensivos.

**Algunos pacientes responden al tratamiento intermitente (en días alternos o de tres a cinco días/semana).

Pacientes pediátricos con hipertensión arterial: Dosis pediátrica usual: 2.5 mg/kg/día en dos tomas. Lactantes <6 meses: hasta 3.5 mg/kg/día en dos tomas. Niños hasta 2 años: 12.5-37.5 mg/día en dos tomas. Niños 2-12 años: 37.5-100 mg/día en dos tomas. Muy pocos pacientes requieren de dosis altas sostenidas. **12. Manifestaciones y manejo de la sobredosificación o ingesta accidental:** además de la diuresis esperada, la sobredosis de ROFUCAL® puede producir grados variables de letargia, la cual puede progresar al coma en pocas horas con mínima depresión de las funciones respiratorias y cardiovasculares y sin evidencia de cambios en los electrolitos séricos o deshidratación. Además del lavado gástrico y del tratamiento de apoyo para el estupor o coma, puede ser necesario tratamiento de los efectos gastrointestinales. No se ha establecido claramente el grado en que la hidroclorotiazida es eliminada por hemodiálisis. Se debe mantener la hidratación y el equilibrio hidroelectrolítico, la respiración, las funciones cardiovascular y renal. **13. Presentaciones:** Caja de cartón con 15, 30 o 60 tabletas de 12.5 mg en envase de burbuja. Caja de cartón con 20 o 30 tabletas de 25 mg en envase de burbuja. **14. Leyendas de protección:** su venta requiere receta médica. No se deje al alcance de los niños. No se use durante el embarazo ni en mujeres en periodo de lactancia. Literatura exclusiva para médicos. Reporte las sospechas de reacción adversas al correo: farmacovigilancia@cofepris.gob.mx Para mayor información del producto o para reportar eventos adversos comuníquese al teléfono en la ciudad de México 4040-7671 0 LADA nacional sin costo al 01800-200-0170 o correo electrónico: farmacovigilancia@probiomed.com.mx **15. Nombre y domicilio del laboratorio:** PROBIOMED S.A. DE C.V. Yácatas No 307, Colonia Narvarte, Delegación Benito Juárez 03020 México, D.F. **16. Número de registro del medicamento ante la secretaría:** Reg. No. 74276 SSA IV.

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Flujo continuo

En el **manejo y prevención** de eventos **aterotrombóticos**

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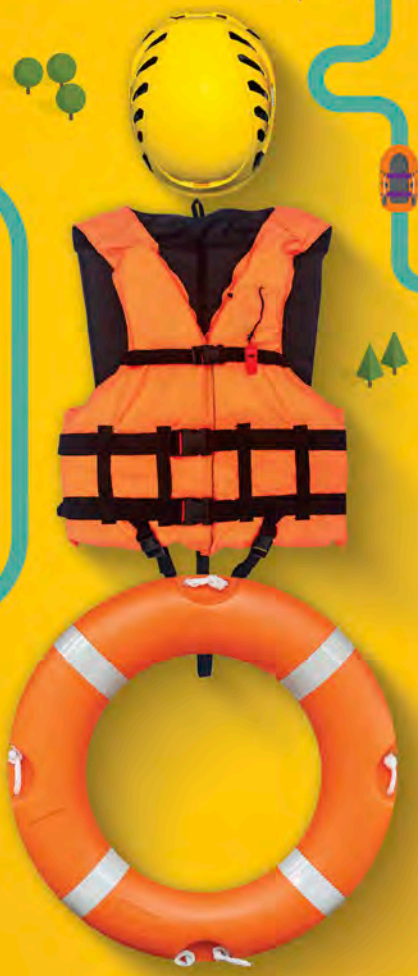

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ALTIA

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Controla eficazmente

los niveles de colesterol en sangre

Las enfermedades cardiovasculares siguen siendo la **primera causa de muerte en el mundo** y el factor común son los niveles elevados del colesterol LDL.

- Coronariopatía
- Angor pectoris
- Infarto al miocardio
- Accidente vascular cerebral

Consulte la IPP

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OK EN HIPERTENSIÓN

Porque la **hipertensión** es un problema de salud global que daña órganos blanco y que tiene como consecuencia:

- Insuficiencia cardiaca
- Daño renal
- Retinopatía
- Demencia vascular

OKSEN Es la cápsula de contenido líquido que da el **OK en hipertensión**

+ Telmisartán Hidroclorotiazida

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IPAL

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Aligere la vida de su paciente.

En monoterapia o en combinación,

Rofucal®

Hidroclorotiazida

Cuida tu corazón.

Es el diurético de primera línea
y **piedra angular** del tratamiento antihipertensivo.[1]

Los **diuréticos tiazídicos** han demostrado que en **monoterapia** o **combinación**, **reducen** el **riesgo** de **cardiopatía**, enfermedad **vascular cerebral** e **infarto** de **miocardio**.[1]

Es **ideal** para usarse en **terapia combinada**, ya que tiene efecto **aditivo** o **potencializador** con otros antihipertensivos.[2,3]

Indicado en el **tratamiento** del **edema** asociado a **insuficiencia cardíaca congestiva** y/o **cirrosis hepática**.[2]

Dosis recomendadas:[2]

HTA*: 25 mg/día dosis única o repartida en varias tomas. **Dosis máxima:** 50 mg diarios.

Edema: 25 a 100 mg/día en una o dos tomas. **Dosis máxima:** 100 mg diarios.

***HTA:** Hipertensión Arterial.

Referencias: 1. Bell K, *et al.* Hypertension: the silent killer: Updated JNC-8 Guideline Recommendations (2015). Alabama Pharmacy Association; 1:1-8. **2.** Información para prescribir amplia. Rofucal®. **3.** Uchiwa, H., Kai, H., Iwamoto, Y., Anegawa, T., Kajimoto, H., ... Fukuda, K. (2017). Losartan/hydrochlorothiazide combination is safe and effective for morning hypertension in Very-Elderly patients. Clinical and Experimental Hypertension, 40(3), 267–273.

Reporte las sospechas de reacciones adversas al correo: farmacovigilancia@cofepris.gob.mx y a farmacovigilancia@probiomed.com.mx y al teléfono 55-4040-7671 desde la CDMX o al 800-200-0170 del interior de la República Mexicana.

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Metformina:
Hipoglucemiante

Biguanida, fármaco de **1° línea**: Manejo de la **diabetes tipo 2**

Resveratrol:
Antioxidante

Polifenol extraído de la cáscara de la uva

Sus efectos principales son:

- **Disminución** de la producción hepática de glucosa
- **Aumento** del uso de glucosa periférica por los músculos

Mediante la activación de SIRT1:

- **Evita la apoptosis** de células beta
- **Mejora la sensibilidad** a la insulina

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