Molecular Autopsy in a Girl with Sudden Cardiac Death. Practical Approach to Surviving Family Members

A 7-year-old girl collapsed while running across the beach. Her mother performed basic cardiopulmonary resuscitation; then she was transferred to a hospital, where, according to the medical report, she was admitted lifeless.

One month later, the parents, a young non-consanguineous couple who also had a healthy 8-month-old son, consulted Cardiogenomics and Cardiac Genomic Clinic of the Pediatric Electrophysiology and Arrhythmia Care Unit of *Hospital Italiano de Buenos Aires*, Argentina.

The girl had been born full-term without complications, and had no history of hospitalizations, surgeries, serious illnesses, or chronic medical conditions. She was not taken any medications. One year before the episode, she had undergone preparticipation physical evaluation which included cardiovascular examination and an electrocardiogram that resulted normal.

In young (< 35 years) and apparently healthy subjects with sudden, unexpected cardiac death, the autopsy reveals that cardiovascular diseases are the most common causes (70-80%). Of these, the most significant are hypertrophic cardiomyopathy (36%), anomalous origin of the coronary arteries (17%), myocarditis (6%) and arrhythmogenic right ventricular cardiomyopathy (4%). Up to 30% of autopsies are considered "negative" when the heart is structurally and histopathologically normal, there are no other extracardiac causes of death, and the toxicological examination is negative; these cases are referred to as "sudden arrhythmic death syndrome". (1)

As death occurred in the thoroughfare, a forensic autopsy was performed, with negative results. Tissue samples were preserved embedded in paraffin, and a peripheral venous blood sample was stored in an EDTA tube at refrigerated temperatures, but not frozen.

After cardiac genetic counseling, the parents agreed to give their written consent to retrieve the blood sample for a postmortem genetic testing (GT), or molecular autopsy.

A comprehensive cardiomyopathy and arrhythmia genetic testing panel was ordered. (Figure 1)

Postmortem GT was performed using next generation sequencing (NGS). A likely pathogenic variant in CALM1 (calmodulin) gene was identified and confirmed by Sanger sequencing, and three variants of uncertain significance were identified in three different genes: EYA4 (eyes absent 4, transcriptional coactivator and phosphatase 4), MYH11(myosin heavy chain 11 smooth muscle) and MYPN (myopalladin) (Figure 2).

Fig. 1. Detail of the panel of genes tested by NFG

Fig. 2. Results of postmortem genetic testing (molecular autopsy)

Our team of cardiovascular genomics defined the likely pathogenic variant in CALM1 as the only one relevant and related with the sudden arrhythmic death of the girl due to a **variant in CALM1, heterozygous mutation c.293A>G (p.N98S) in exon 5**.

The CALM1 gene is located in the long arm of chromosome 14q32.11. Two other homologous genes (CALM2 and CALM3) are present in the human genome and seem to have a similar function.

This gene encodes a protein called calmodulin, one of the main sensors of intracellular calcium concentrations, which interacts with many enzymes, ion channels and other proteins modulating their function, known as "calmodulation". One of its most important interactions is to regulate the function of some cardiac ion channels, including voltage-gated calcium channel that gives rise to L-type calcium currents (CaV1.2; CACNA1C), the cardiac sodium channel (NaV1.5; SCN5A) and the cardiac isoform 2 of the ryanodine receptor (RyR2).

In the sample analyzed, we found a change in the DNA sequence of the CALM1 gene in exon 5 where adenine nucleotide is substituted by guanine nucleotide at the position corresponding to nucleotide 293 (c.293A>G). This variation in the DNA sequence implies a change in the protein synthesized, in which the amino acid asparagine (P) is substituted by the

amino acid serine (S) at codon 98 of the CALM1 protein (p.N98S).

This type of genetic change is called a "missense" or "missense change", which means that a single nucleotide of DNA is changed, resulting in a single replacement of one amino acid in a protein with a different amino acid.

The position of the amino acid asparagine at codon 98 in the calmodulin protein is highly preserved in humans and related vertebrate species, i.e., asparagine is always found at this position in calmodulin protein reflecting evolutionary conservation.

Moreover, calmodulin has a completely conserved amino acid sequence across all vertebrates. Given this degree of conservation, it was long thought that mutations in CALM1 were incompatible with life. (2)

There are moderate physicochemical differences between the amino acids asparagine and serine.

This variant is not present in ethnically similar control population databases (1000 genomes with no reported frequency).

The same variant was found in a patient with catecholaminergic polymorphic ventricular tachycardia (CPVT). (3)

The analysis of the internal structure of CALM1 protein and experimental functional studies have demonstrated that this missense variant would attenuate calcium binding to CALM1 protein. (4)

Of the 14 computational algorithms developed to predict the effect of this genetic change on the structure and function of the protein, 10 predicted the pathogenicity of this variant and 4 predicted the variant was benign (Source: VarSome).

The patient was a heterozygous carrier of this variant, which means that the genetic change was present in only one of the maternal or paternal chromosomes, while the other had a normal copy of the CALM1 gene.

We recommended GT to find the presence or absence of the pathogenic variant in CALM1 in the girl's parents (family cascade screening) to evaluate the family risk. None of them carried this genetic change.

Current guidelines recommend postmortem GT, the "molecular autopsy", in young decedents of sudden cardiac death with a negative autopsy when arrhythmias are suspected. (5) Despite the recommendations and evidence, postmortem GT is still not routinely required.

CALM1 mutations have been associated with CPVT inherited in an autosomal dominant manner and long QT syndrome. (6)

From our personal experience and literature data, we know that more than 50% of CALM1 mutations that cause CPVT are "de novo" (not inherited from the parents).

During the genetic counseling consultation after GT, we informed the family that the risk of a similar episode for them and their youngest child, and the risk of recurrence in future pregnancies is the same as that of the general population (almost zero).

Six years later, the family is doing very well, and they have another daughter who has normal cardiovascular examination, electrocardiogram and echocardiogram.

Molecular autopsy is a powerful tool to make a genetic diagnosis when traditional autopsy is inconclusive. The proper preservation of a venous blood sample in EDTA during the autopsy allowed the identification of the genetic cause, not only providing the family with an answer that helped them understand what had happened to their daughter, but also helped us as a medical team to perform an optimal genetic assessment of the risk of familial recurrence through family cascade screening of the surviving family members.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

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REFERENCES

1. Castiglione V, Modena M, Aimo A, Chiti E, Botto N, Vittorini, S, et al. Molecular Autopsy of Sudden Cardiac Death in the Genomics Era. Diagnostics 2021;11:1378. https://doi.org/10.3390/diagnostics11081378.
2. Jensen HH, Brohus M, Nyegaard M, Overgaard MT. Human Calmodulin Mutations, Front. Mol. Neurosci 2018;11:396. https://doi.org/10.3389/fnmol.2018.00396
3. Nyegaard M, Overgaard MT, Søndergaard MT, Vranas M, Behr ER, Hildebrandt LL, et al. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. Am J Hum Genet. 2012;91:703-12. https://doi.org/10.1016/j.ajhg.2012.08.015.
4. Yu CC, Ko JS, Ai T, Tsai WC, Chen Z, Rubart M, et al. Arrhythmogenic calmodulin mutations impede activation of small-conductance calcium-activated potassium current. Heart Rhythm. 2016;13:1716-23. https://doi.org/10.1016/j.hrthm.2016.05.009.
5. Wilde AM, Semsarian C, Marquez MF, Sepehri Shamloo A, Ackerman MJ, Ashley EA, et al. European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. POSITION PAPER. Europace 2022;24:1307-67. https://doi.org/10.1093/europace/euac030
6. Prakash O, Held M, McCormick LF, Gupta N, Lian LY, Antonyuk S, et al. CPVT-associated calmodulin variants N53I and A102V dysregulate calcium signalling via different mechanisms. Biochim. Biophys. Acta. 2015;1850:2168-76

3D Transesophageal Echocardiography for Surgical Repair of the Aortic Valve in a Patient with Libman-Sacks Endocarditis and Antiphospholipid Syndrome

Libman-Sacks endocarditis (LSE), known as nonbacterial thrombotic endocarditis, is rare and may be associated with other entities such as antiphospholipid antibody syndrome, systemic lupus erythematosus, and malignant tumors. (1) It is characterized by sterile vegetations on the heart valves; in some cases, embolic events may occur. (2)

Both transthoracic (TTE) and transesophageal (TEE) echocardiographies are essential in the preoperative, intraoperative and early and late postoperative periods of valve surgery, due to their excellent temporal and spatial resolution for the anatomical and functional study of the valves. (3) Resolutions can be represented in a one- or two-dimensional form —and more recently— in a three-dimensional (3D) form. Advantages of 3D echocardiography compared to other methods include improved anatomical visualization and complex relationships with cardiac structures, calculation of volumes or mass, ventricular and atrial function, and valve dysfunction. (3)

We report a case to highlight the importance of echocardiography —in this case, three-dimensional echocardiography— in the intraoperative period as a complementary method for a more guided and effective surgical treatment. This is a 26-year-old male patient admitted to the emergency room of our hospital for progressive dyspnea of recent onset (2 months), gradually worsening to dyspnea at rest. Physical examination revealed tachypnea (20 rpm) and hypoxemia, with SpO2 88% in room air, heart rate of 80 bpm and blood pressure 110/84 mmHg, with regular heart rhythm and no evidence of cardiac murmurs.

The patient had a history of antiphospholipid syndrome (APS), with deep vein thrombosis (DVT) in the lower limbs and chronic pulmonary thromboembolism (CPTE), with evidence of pulmonary hypertension. Therefore, hospitalization was decided to perform surgical pulmonary thromboendarterectomy. As part of the preoperative evaluation, a 2D TTE was performed, which showed normal cardiac chamber dimensions and left ventricular systolic function, but with mild right ventricular dysfunction. The aortic valve (AoV) was thickened, with no other valve disorders, and the pulmonary artery (PA) systolic pressure by Doppler was 29 mmHg. A lung ventilation-perfusion scan showed heterogeneous radiopharmaceutical distribution, with areas of hypoperfusion of the anterior and posterior segments of the right upper lobe, with high chances of CPTE. Submaximal cardiopulmonary exercise test revealed decreased aerobic capacity and VO2 max, increased VE/VCO2 ratio, and decreased PETCO2, suggesting involvement of the pulmonary function. On right heart catheterization, mean PA pressure was 50 mmHg and pulmonary vascular resistance was 480 dynes-sec-cm^{-5}. Left catheterization

showed no evidence of obstructive coronary lesions. Chest CT angiography with PET protocol showed partial lack of filling in the left lower lobar branch, extending to subsegments of the left lung, consistent with CPET. Pulmonary thromboendarterectomy was proposed and accepted by the patient.

Intraoperative 3D TEE showed thickened AoV, with multiple 15 x 6 mm homogeneous, hypoechogenic, mobile images with irregular borders in the ventricular and aortic projection, suggestive of vegetations on the cusps, causing reduction in the coaptation surface area (Figures 1, 2, 3). Moreover, maximum transvalvular jet velocity was 3.3 m/s, mean transvalvular gradient was 21 mmHg, and valve area by continuity equation and planimetry was 1.3 cm², with minimal valve regurgitation. However, due to evident morphological alterations of the AoV and risk of embolic phenomena, AoV replacement with a mechanical prosthesis No. 23 was performed. Both procedures were uneventful. Macroscopic analysis of the AoV revealed opacification of the semilunar valves with a large amount of bonded dark-red amorphous material of irregular shape (Figure 4). Pathological examination showed a large fibrin thrombus with areas of white and red blood cells, consistent with non-infective thrombotic endocarditis; semilunar valves showed thickening of fibrous connective tissue (Figures 5 & 6). Twenty-one days after the procedures, due to good progression, improved dyspnea and no need for supplemental oxygen, oral anticoagulation was maintained and the patient was discharged. At 6-month follow-up, the patient remained clinically stable, with unusual dyspnea on exertion and no further embolic events.

Echocardiography plays a key role in the diagnosis and prognosis of valvular heart disease. (4) 2D
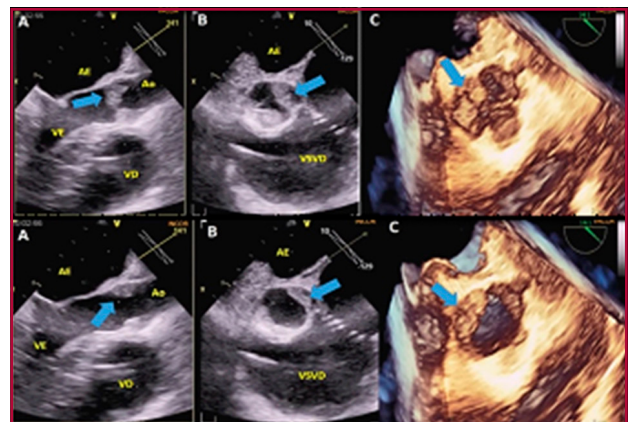
Fig. 1. Above. 2D & 3D transesophageal echocardiography (TEE) in diastole. (A) Orthogonal plane, mid esophagus, longitudinal axis 141°, aortic valve thickening (*arrow*). (B) Transverse axis 60°, right ventricular inflow and outflow tract with valve thickening (*arrow*). (C) Real-time three-dimensional image, surgical view with morphological alterations of the aortic valve (*arrow*). **Below.** 2D & 3D TEE in systole. A, B and C with similar findings.
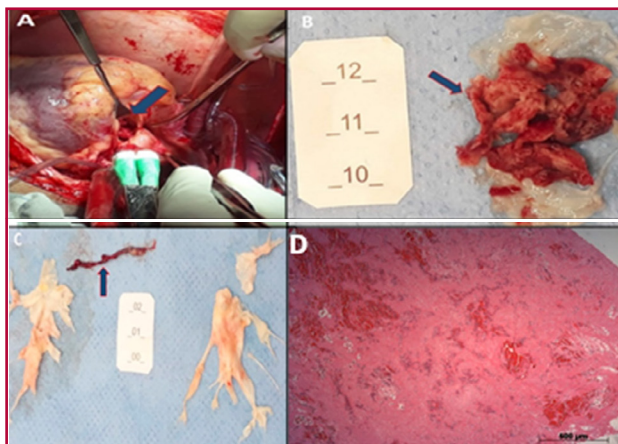
Fig. 1. Macroscopic image. (**A**) Intraoperative image of aortic valve replacement (*arrow*). (**B**) Large amount of dark red, irregular, amorphous material attached to the semilunar valves. (**C**) Thrombus after pulmonary artery thromboendarterectomy. (**D**) Histological examination of the dark red amorphous material attached to the valve: fibrin thrombus with hemorrhagic areas. Hematoxylin-eosin staining

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REFERENCES
1. Saric M, Armour AC, Arnaout MS, Chaudhry FA, Grimm RA, Kronzon I, et al. Guidelines for the Use of Echocardiography in the Evaluation of a Cardiac Source of Embolism. J Am Soc Echocardiogr 2016;29:1-42. https://doi.org/10.1016/j.echo.2015.09.011
2. Roldan CA, Sibbitt WL Jr, Qualls CR, Jung RE, Greene ER, Gasparovic CM, et al. Libman-Sacks endocarditis and embolic cerebrovascular disease. JACC Cardiovasc Imaging 2013;6:973-83. https://doi.org/10.1016/j.jcmg.2013.04.012
3. Zuily S, Regnault V, Selton-Suty C, Eschwège V, Bruntz JF, Bode-Dotto E, et al. Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. Circulation 2011;124:215-24. https://doi.org/10.1161/CIRCULATIONAHA.111.028522
4. Roldan CA, Qualls CR, Sopko KS, Sibbitt WL Jr. Transthoracic versus transesophageal echocardiography for detection of Libman-Sacks endocarditis: a randomized controlled study. J Rheumatol 2008;35:224-9.
5. Roldan CA, Tolstrup K, Macias L, Qualls CR, Maynard D, Charlton G, Sibbitt WL Jr. Libman-Sacks Endocarditis: Detection, Characterization, and Clinical Correlates by Three-Dimensional Transesophageal Echocardiography. J Am Soc Echocardiogr 2015;28:770-9. https://doi.org/10.1016/j.echo.2015.02.011
6. Moyssakis I, Tektonidou MG, Vasilliou VA, Samarkos M, Votteas V, Moutsopoulos HM. Libman-Sacks endocarditis in systemic lupus erythematosus: prevalence, associations, and evolution. Am J Med 2007;120:636-42. https://doi.org/10.1016/j.amjmed.2007.01.024

TTE is the initial test for functional and morphological evaluation of valvular heart disease. However, in patients with inadequate acoustic window —as in the present case—, this method has major limitations; therefore, TEE is an excellent complement, accurately distinguishing anatomical and functional details of the valves, with sensitivity and specificity > 90% for the detection of masses such as vegetations. (4, 5) In clinical practice, real-time 3D TEE has additional and complementary value compared to 2D TEE, providing high spatial resolution, multi-angle observation, and good reproducibility. Therefore, it is a relevant, complementary, increasingly used method for the differential diagnosis of intracardiac masses. APS commonly occurs in young and middle-aged individuals, predominantly in female patients; thromboembolic phenomena may occur in 20% of cases, being DVT one of the most common. It can also be related to ischemic stroke, myocardial infarction and valvular heart diseases that may require valve replacement. (5, 6)

In the case described, AoV lesion was not suspected with 2D TTE; it was only diagnosed by intraoperative 3D TEE. Thus, AoV replacement was performed in addition to PA thromboendarterectomy, due to the presence of vegetations (non-infective endocarditis), and a history of APS and thromboembolic events. Thus, 3D echocardiography has been a key tool in this case.

Conflicts of interest
None declared.
(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations
Not applicable.

Effusive-Constrictive Pericarditis and Pericardial Decompression Syndrome: A Multiple-Image Approach

Effusive-constrictive pericarditis (ECP) is a disease involving significant pericardial effusion and heart constriction. Pericardial decompression syndrome is defined as hemodynamic deterioration following pericardial drainage. Both diseases are uncommon in the population and result in high morbidity and mortality rates. Therefore, it is important to understand said conditions, suspect of them and treat them.

Our aim is to present the clinical case of a male patient aged 36, sedentary and former smoker, who visited the emergency department because of functional class II-III dyspnea associated with lower limb edema after a month. The physical examination showed signs of heart failure: tachycardia (120 bpm), blood pres-

sure 140/80 mmHg, hypophonetic heart sounds, jugular venous distension 3/3, lower limb edema, left base hypoventilation, 98% O2 saturation on room air, and abdominal distension.

Lab tests did not show any relevant findings (hematocrit 45%, creatinine 1.2 mg/dL; urea 25 mg/dL; platelets 240 000/mm^3, leukocytes 9 100/mm^3). The ECG showed sinus tachycardia with low-voltage QRS, and the chest x-ray, increased cardiothoracic ratio with water-bottle silhouette. (Figure 1 A).

A bedside Doppler echocardiography was performed. It evidenced severe circumferential pericardial effusion, with a maximum separation of the pericardial layers of 7.5 mm, preserved left ventricular function, collapse of the right chambers, and dilated caudal vena cava (Figure 1 B). These findings led to an emergency pericardial drainage, and 2.2 L of yellow-citrine fluid was collected.

Pericardial fluid culture was positive for Escherichia coli, therefore, targeted antibiotic treatment was administered. Later, this finding was interpreted as contaminant. In addition, to assess the etiology of effusion, blood samples were collected for tumor markers, antibody profile, serology (HIV, hepatitis, CMV, VDRL, Chagas disease), and inflammatory factors, all of which were negative.

Following the pericardiocentesis, the patient presented oligoanuria, somnolence, hypotension, and distal coldness. This led to a new echocardiography that showed biventricular dysfunction and severe right chamber dilatation. Intravenous inotropic support was administered, and the patient had an adequate response.

Once the patient was stable, a chest CT was performed. It excluded pericardial calcification and showed mild to moderate pericardial effusion associated with passive atelectasis of the left lung parenchyma. The evaluation ended with a cardiac magnetic resonance (CMR). The CMR showed preserved left ventricular ejection fraction, volume and wall thickness, impaired right ventricular ejection fraction and right ventricular dilatation, biatrial dilatation, moderate pericardial effusion, and systolic flattening of the interventricular septum. Late gadolinium enhancement was observed in the pericardium (Figure 2, A, B, and C). These findings were consistent with effusive-constrictive pericarditis.

Right heart catheterization was performed. It showed equalization of end-diastolic pressures in right and left chambers, and the left ventricular diastolic pressure curve showed the typical square root morphology. The patient improved hemodynamically. Inotropic support was discontinued after 48-72 hours, and hemodynamic decompression syndrome was diagnosed. The patient was discharged with scheduled follow-up.

The patient had a new intercurrent condition with signs of fluid overload and recurrent severe pericardial effusion associated with pericardial adhesions. Effusive-constrictive pericarditis of probable idiopathic
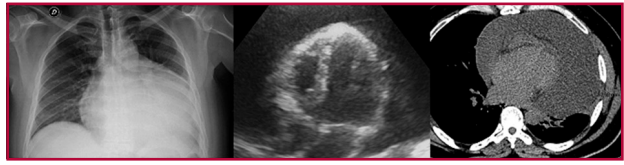

Fig. 1. A: Chest x-ray: increased cardiothoracic ratio (water-bottle silhouette). **B**: Doppler echocardiography: severe pericardial effusion and collapse of the right chambers. **C**: Chest CT: moderate pericardial effusion
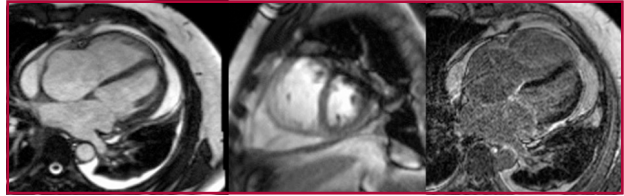

Fig. 2. Cardiac magnetic resonance. **A**: Mild to moderate pericardial effusion. **B**: Septal motion towards the ventricle upon forced inhalation. **C**: Late gadolinium enhancement in the pericardium.

origin was diagnosed. A total pericardiectomy was performed, and a pericardial tissue sample was collected for biopsy. Gross findings were brownish tissue with bright off-white smooth surfaces and firm-elastic consistency, while microscopic findings were fibrous pericardium with congestive vessels, chronic inflammatory infiltrates with perivascular predominance and no atypical cells. The surgical procedure was well tolerated and uncomplicated.

ECP etiology is unclear; 30-40% of the cases are idiopathic or viral. Additional etiologies include pericarditis due to radiation therapy or neoplasm, chemotherapy, tuberculosis, trauma, postoperative and end-stage kidney disease, among others.

ECP is a rare form of pericardial syndrome involving cardiac constriction in the presence of significant pericardial effusion, mainly at expense of the visceral pericardium. As a result, the pericardiocentesis may lead to temporary improvement, with recurrent effusion and clinical features, making pericardiectomy necessary. As regards pericardiocentesis, draining large amounts of pericardial fluid in a short time may lead to severe dilatation of the right chambers because of hemodynamic deterioration and decompression. Therefore, progressive gradual drainage is advised.

A multiple-image approach of these pericardial diseases allows us not only to determine hemodynamic involvement, but also to identify its etiology, take actions, and improve the patient's treatment, which is particularly important due to the torpid progress of this disease.

Conflicts of interest
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Ethical considerations
Not applicable.

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REFERENCES
1. Área de Normas y Consensos. Consenso de enfermedades del pericardio. Sociedad Argentina de Cardiología. Rev Argent Cardiol 2017;85(7).
2. Hancock EW. A clearer view of effusive-constrictive pericarditis. N Engl J Med 2004;350:435-7. https://doi.org/10.1056/NEJMp038199
3. Sagristá-Sauleda J, Almenar L, Ferrer JA, Bardají A, Bosch X, Guindo J, et al. Guías de práctica clínica de la Sociedad Española de Cardiología en patología pericárdica. Rev Esp Cardiol 2000;53:394-412. https://doi.org/10.1016/S0300-8932(00)75105-0
4. Yacoub M, Quintanilla Rodriguez BS; Mahajan K. Constrictive-Effusive Pericarditis. 2022 Jan. NCBI. NIH. https://www.ncbi.nlm.nih.gov/books/NBK519579/
5. Sagristá-Sauleda J, Angel J, Sánchez A, Permanyer-Miralda G, Soler-Soler J. Effusive–Constrictive Pericarditis. N Engl J Med 2004;350:469-75. https://doi.org/10.1056/NEJMoa035630
6. Sagristá-Sauleda J. Diagnóstico y guía terapéutica del paciente con taponamiento cardíaco o constricción pericárdica. Rev Esp Cardiol 2003;56:195-205. https://doi.org/10.1016/S0300-8932(03)76845-6

2D and 3D Echocardiographic Assessment of a Coronary Artery with a Retroaortic Course

The most common anomalous origin and course of the coronary arteries is the emergence of the circumflex coronary artery (Cx) from the right or noncoronary sinus of Valsalva with a retroaortic course (estimated prevalence of about 0.39%). In most cases it is an isolated anomaly, and its association with other birth defects is very rare. (1)

In the echocardiography, retroaortic course a coronary artery (RCCA) is shown as an anechoic image with double echogenic wall between the aorta and the atria. It should be visualized in more than one plane to rule out artifice. (2)

RCCA is usually an incidental echocardiographic finding, and the Cx is the most commonly artery involved, followed by the right or the left coronary artery; therefore, it is essential to analyze the origin and course of all vessels.

The anomalous origin and retroaortic course of the Cx artery is considered a benign anomaly. This has been called into question by the reports of some cases of myocardial infarction or cardiac arrest in middle-aged subjects with no coronary risk factors or atheromatous plaques. (3)

As regards imaging techniques, 2D echocardiography (2D TTE) is key as the initial diagnostic tool, mainly in young patients with a good acoustic window. Recently, the usefulness of 3D transthoracic echocar-diography (3D TTE) to evaluate the origin and course of the coronary arteries has been published. 3D TTE is a fast, non-invasive procedure, without radiation exposure for patients. Coronary CT angiography is considered the method of choice to confirm the diagnosis, and evaluate high-risk anatomical features and the presence of associated plaques. (4, 5)

As for drug stress tests, high-load echocardiographic stress test is indicated particularly in asymptomatic individuals who practice high-intensity physical activity, or in coronary anomalies with high-risk anatomical features (slit-like origin, angle of origin < 45°, intramural course or associated atherosclerotic disease). Drug stress tests show lower sensitivity than in obstructive coronary artery disease, therefore, a negative test does not rule out an ischemic event in cases with high-risk anatomical features. (6)

We report the case of a 69-year-old female patient with controlled Grade-I hypertension who performed aerobic mild to moderate physical activity three times a week with adequate tolerance.

Physical examination and ECG were normal. 2D TTE apical views showed an image consistent with RCCA. Low velocity systo-diastolic flow was detected in the left parasternal short axis color, close to the commissure between the right and noncoronary sinus (Figure 1A, spectral signal could not be obtained).

The assessment was completed with 3D transthoracic echocardiography (3D TTE). The aortic root volume was measured (Figure 1B), and the normal origin of the right (Figure 1C, white arrow) and left (Figure 1B, D, yellow arrow) coronary arteries from their respective sinuses of Valsalva were visualized in the multiplanar reconstruction analysis. With these
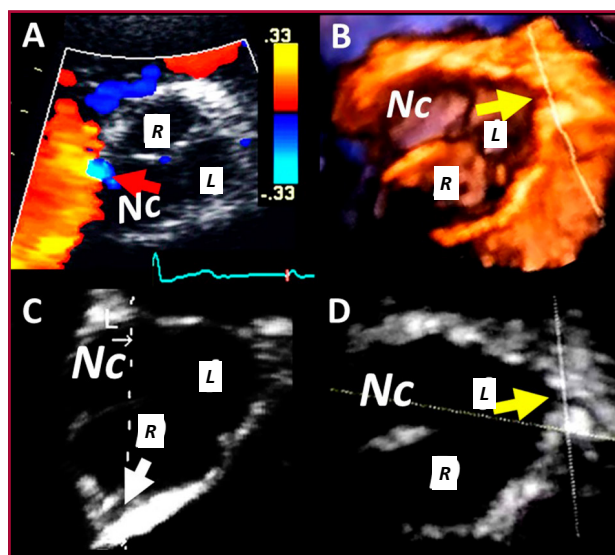

Fig. 1. Left parasternal short axis view. Color 2D TTE showing diastolic flow at hour 9. Rest of the 3D TTE views showing the origin of the left (*yellow arrow*) and right (*white arrow*) coronary arteries from their respective sinuses.
R: right; L: Left; Nc: non-coronary.

data, we can conclude that the artery with retroaortic course is the Cx artery.

A complete volume was acquired with the apical 4-chamber view. In the post-processing analysis, the course of the vessel was followed (Figure 2, upper panel), and several planes confirmed that it was a coronary artery and not an artifact (Figure 2, lower panel).
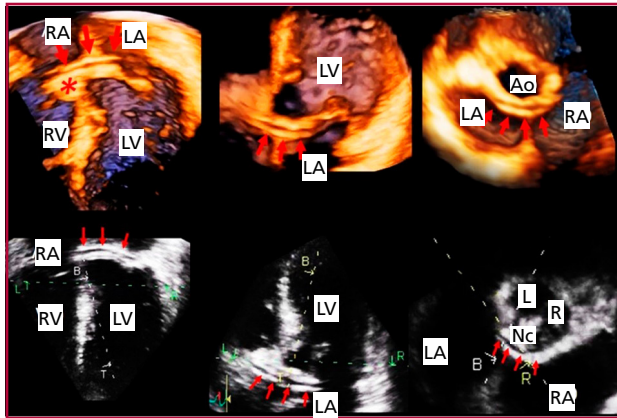

Fig. 1. Upper panel, complete volume obtained with 3D TTE showing the retroaortic course of the vessel surrounding the noncoronary sinus of Valsalva (*asterisk*), and passing between the aorta and the atria. Lower panel, vessel tracking from multiplanar reconstruction views. LA: left atrium; LV: left ventricle RA: right atrium; RV: right ventricle; Ao: aorta; R: right; L: Left; Nc: non-coronary

Echocardiographic stress test was enough, and showed no evidence of ischemia (92% of the theoretical maximum heart rate).

Given that this patient practices recreational exercise, we believe that the studies performed are enough to continue with her regular physical activity.

In our case, 3D TTE provided additional information to 2D TTE (it was possible to identify the origin of all the arteries, confirm the retroaortic course of the vessel in planes not accessible by 2D imaging, evaluate the relationship between the vessel and the surrounding structures, etc.).

We believe that 3D TTE could be initially used as an adjunct diagnostic tool to 2D TTE, and later evaluate anatomy and risk stratification with coronary CT angiography.

Conflicts of interest
None declared.
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Ethical considerations
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REFERENCES
1. Mancinelli A, Golino M, Miglierina E, My I, Crippa M, De Ponti R. Three Echocardiographic Signs to Identify Anomalous Origin of the Circumflex Coronary Artery from the Right Sinus of Valsalva. CASE: Cardiovascular Imaging Case Reports October 2020;4:324-7. https://doi.org/10.1016/j.case.2020.07.008
2. Gupta SK, Gupta A, Ramakrishnan S, Kothari SS. False positive retroaortic left circumflex coronary artery in a patient with atrial septal defect. Echocardiography. 2017;34:799-801. 1. https://doi.org/10.1111/echo.13510.
3. Carrión Ríos E, Valencia Serrano F, Sánchez Espino A, Fajardo Molina R. REC Imagen en cardiología. Imagen multimodal y origen anómalo de arteria circunfleja. Cardio Clinics. 2021;56:311-2. https://doi.org/10.1016/j.rccl.2021.02.004
4. Del Torto A, Baggiano A, Guglielmo M, Muscogiuri G, Ponton G. Anomalous origin of the left circumflex artery from the right coronary sinus with retroaortic course: A potential malign variant. Journal of Cardiovascular Computed Tomography. https://doi.org/10.1016/j.jcct.2019.01.021
5. Sánchez ME, Garcia-Zamora S, Ratto R, Makhoul S, Veloso S. Precompetitive evaluation of the coronary arteries with 3D transthoracic echocardiography Acta Cardiol 2022:1-3. https://doi.org/10.1080/00015385.2022.2131997.
6. Gentile F, Castiglione V, De Caterina R. Coronary Artery Anomalies. Circulation. 2021;144:983-96. https://doi.org/10.1161/circulationaha.121.055347.

The Most Feared Consequence of Exercise-Stress Echocardiography. A Case Report

We report the case of a 66-year old male patient, with a history of ischemic heart disease and four coronary stents. His risk factors included difficult-to-manage systemic hypertension, dyslipidemia, diabetes and obesity, treated with valsartan, atenolol, metformin, simvastatin and aspirin. The patient was asymptomatic at rest, but reported fatigue and mild precordial pain when walking, so an ambulatory treadmill stress echocardiography was performed at our center.

Baseline ECG showed sinus bradycardia, preserved axis and normal atrioventricular and intraventricular conduction. Asymmetric, flat-negative T-waves from V4 to V6, DI and aVL were the relevant findings. Echocardiography at rest revealed concentric left ventricular remodeling, with preserved global and regional systolic function, left ventricular ejection fraction (LVEF) 60% and mild diastolic dysfunction. Moderate left atrial enlargement was observed. No valve diseases or other significant functional or structural alterations were detected. It is important to mention that, at the time of the test, the patient presented with high blood pressure (160/90 mmHg), despite having taken his medication. However, since the patient was asymptomatic, it was decided to continue with the test.

The Bruce stress protocol was implemented. During the first minute of the second stage of the test, when the patient had reached 68% of the heart rate expected for his age, leads V3 to V6 showed 1-mm hor-

izontal ST-segment depression. Although the patient had shown adequate hemodynamic response without arrhythmias, and only reported muscle fatigue, it was decided to stop the treadmill. A few seconds later, the patient reported dyspnea, and appeared anxious and uneasy. At that point, the monitor showed ECG recording of wide QRS rhythm and sudden onset, which was interpreted as ventricular tachycardia, progressing to torsade de pointes and ventricular fibrillation (VF) in a few seconds (Figure 1), with loss of consciousness and fall.

The resuscitation protocol was activated, first with chest compressions, followed by electric shock of 360 joules, reverting VF to sinus rhythm with recovery of consciousness. Echocardiography scanning in supine position soon after the shock showed hypokinesis of the anterior septum, anterior wall and apex, suggest-
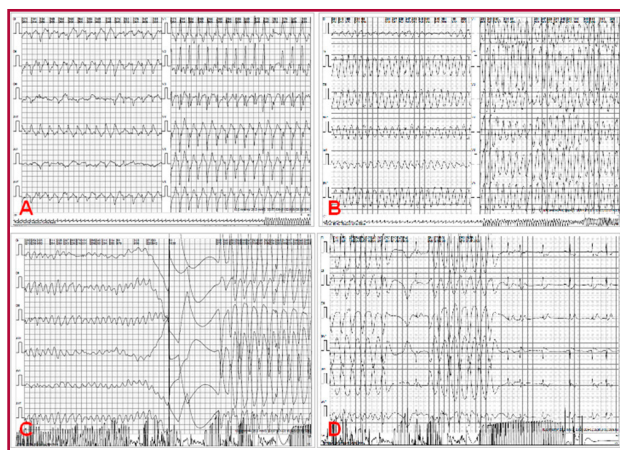

Fig. 1. Electrocardiographic sequence of the event. **A**: Wide QRS tachycardia (167 bpm), with morphology of right bundle branch, superior axis and signs of ventricular origin (AV dissociation and fusion beat). **B**: Progression to polymorphic ventricular tachycardia (torsade de pointes type). **C**: Defibrillator discharge. **D**: Conversion to sinus rhythm.
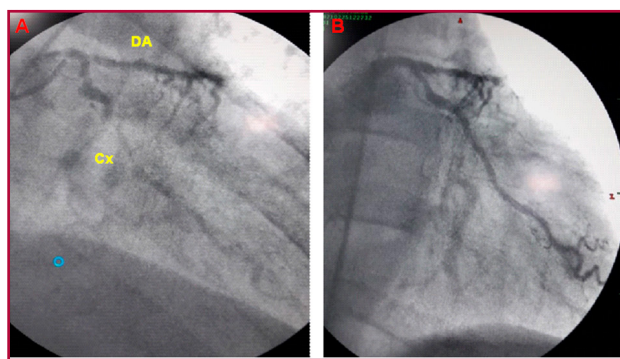

Fig. 2. Coronary angiography: **A**: Contrast injection in the left coronary artery trunk, showing occlusion of the left anterior descending artery and significant lesions in the circumflex artery. **B**: Contrast injection after angioplasty with stents in the circumflex artery and flow restoration.

ing compromised perfusion in the territory of the left coronary artery.

Due to the ambulatory nature of our center, the patient was referred to a tertiary care center, where he was admitted to the Coronary Care Unit; coronary angiography revealed occlusion of the left anterior descending artery (Figure 2), with collateral circulation from the right coronary artery, and significant circumflex artery stenosis. Coronary angioplasty with the placement of two stents was performed. Upon leaving the catheterization laboratory, the patient was stable and without complications, and was discharged a few days later. Due to a history of malignant arrhythmia, his medical team decided to place an automatic implantable cardioverter-defibrillator.

The acceptable safety of an exercise stress test on a treadmill or bicycle ergometer has already been demonstrated. However, some reports show an incidence of complications, acute myocardial infarction and sudden death in around 1 per 2000 to 2500 tests. (1, 2) Our case is an example that life-threatening complications —despite their low frequency— should still be considered during testing, particularly in patients with coronary artery disease, since physical activity can trigger coronary spasm or increase the imbalance between oxygen supply and demand, turning ischemic myocardial areas into arrhythmogenic substrate for tachycardia and ventricular fibrillation.

It should be pointed out that the cardiac arrest experienced by our patient occurred during the first seconds of recovery, which is consistent with a retrospective review of 10 751 symptom-limited stress tests, where 5 cardiac arrests were observed during the first 4 minutes of the recovery stage, surviving all 5 patients due to prompt application of a defibrillatory shock. (3)

Clinical presentation of ventricular arrhythmia secondary to acute ischemia is variable; palpitations, dyspnea or chest pain are reported. The stability or tolerance of VT is related to the rate of tachycardia, presence of retrograde conduction, ventricular function, and the integrity of peripheral compensatory mechanisms. Furthermore, there is a group of patients with hemodynamically unstable ventricular tachycardia or ventricular fibrillation resulting in syncope or sudden death, similar to our case. (4)

Analyzing the characteristics and electrocardiographic sequence of the event, we can point out that it began with a wide QRS tachycardia and criteria suggestive of ventricular origin, inferolateral region —correlated with findings in the coronary angiography, where significant lesions in the circumflex artery were detected. The arrhythmia progressed to nonsustained polymorphic ventricular tachycardia (torsade de pointes type), causing ventricular fibrillation (Figure 1). This pattern is common in cases of ischemic etiology, as opposed to other causes that manifest with monomorphic ventricular tachycardia. (5)

In conclusion, it is essential that the staff conduct-

ing this type of testing be trained to recognize the criteria for stopping the test or stress echocardiography and the application of emergency protocols, including cardiopulmonary resuscitation maneuvers and management of defibrillators, in order to mitigate and solve complications.

Conflicts of interest
None declared.

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

Ethical considerations
Not applicable.

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REFERENCES
1. Kharabsheh S, Al-Sugair A, Al-Buraiki J, Farhan J. Overview of Exercise stress testing. Ann Saudi Med 2006;26:1-6. https://doi.org/10.5144/0256-4947.2006.1
2. Gibbons LW, Mitchell TL, Gonzalez V. The safety of exercise testing. Prim Care 1994;21:611-29.
3. Cobb LA, Weaver D. Exercise: A Risk for Sudden Death in Patients With Coronary Heart Disease. J Am Coll Cardiol 1986;7:215-9:215-9. https://doi.org/10.1016/s0735-1097(86)80284-4
4. European Heart Rhythm Association; Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006;48:e247-346. https://doi.org/10.1016/j.jacc.2006.07.010.
5. Benito B, Mack J. Ventricular Tachycardia in Coronary Artery Disease. Rev Esp Cardiol 2012;65:939–95. https://doi.org/10.1016/j.recesp.2012.03.027