The mitral annulus disjunction as a risk marker in mitral valve prolapse

Disyunción del anillo mitral como marcador de riesgo en prolapso de válvula mitral

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Abstract

Disjunction of the mitral valve annulus is a structural abnormality consisting of an atrial displacement of the articulation point of the mitral valve, leading to an altered spatial relationship between the valve and the adjacent posterior ventricular wall. Studies have shown the relationship between mitral annular disjunction, ventricular arrhythmias, and myocardial fibrous degeneration, which increases the risk of sudden death, especially among young women. The case of a 30-year-old woman with no relevant pathological history with frequent palpitations is presented, in whom an increase in ventricular automatism with a progressive increase in the arrhythmic load of up to 20% with a weight of pharmacological management is documented. In a cardiac magnetic resonance, a 15 mm displacement towards the atrium of the mitral leaflets compatible with mitral annular disjunction and late enhancement foci of mesocardial, non-coronary distribution were observed. Given the findings and the persistence of symptoms, an electrophysiological study, 3D mapping, and ablation were performed. Two hyperechoic regions were seen on intracardiac ultrasound, one in the length of the anterior papillary muscle and the other in the mesocardium of the base of the posterior papillary muscle. Both foci related to the morphological sites of interest in which radiofrequency energy was applied. During the procedure presented an episode of ventricular fibrillation. A malignant ventricular extrasystole was considered and therefore a cardio defibrillator was implanted for the secondary prevention of sudden death. The literature was reviewed and the specific pathophysiological relationships between mitral annular disjunction, premature ventricular complexes, and risk of sudden death were analyzed. The role of electrophysiological study and ablation in symptomatic patients refractory to pharmacological treatment is described.

Key words: Catheter ablation. Ventricular fibrillation. Sudden death. Ventricular tachycardia. Mitral valve.

Resumen

La disyunción del anillo valvular mitral es una anomalía estructural que consiste en un desplazamiento auricular del punto de articulación de la válvula mitral, lo que lleva a una relación espacial alterada entre la válvula y la pared ventricular posterior adyacente. Los estudios han demostrado una relación entre la disyunción del anillo mitral, las arritmias ventriculares y la degeneración fibrosa miocárdica, lo que incrementa el riesgo de muerte súbita, en especial en mujeres jóvenes. Se presenta el caso de una mujer de 30 años, sin antecedentes relevantes, con palpitaciones frecuentes,

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en quien se documentó un aumento del automatismo ventricular con incremento progresivo de la carga arrítmica hasta el 20% a pesar del manejo farmacológico. En la resonancia cardíaca se apreció un desplazamiento de 15 mm hacia la aurícula de las valvas de la mitral compatible con disyunción del anillo mitral, además de focos de realce tardío de distribución mesocárdica, no coronariana. Ante los hallazgos y la persistencia de los síntomas, se llevó a estudio electrofisiológico, mapeo 3D y ablación. En la ecografía intracardiaca se apreciaron dos regiones hiperecoicas, en la longitud del músculo papilar anterior y en el mesocardio de la base del músculo papilar posterior; ambos focos relacionados con los sitios morfológicos de interés, en los cuales se aplicó energía de radiofrecuencia. Durante el procedimiento presentó un episodio de fibrilación ventricular que se consideró una extrasistolia ventricular maligna, por lo que se implantó un cardiodesfibrilador para prevención de muerte súbita. Se revisa la literatura y se analizan las relaciones fisiopatológicas existentes entre la disyunción del anillo mitral, los complejos ventriculares prematuros y el riesgo de muerte súbita.

Palabras clave: Ablación por catéter. Fibrilación ventricular. Muerte súbita. Taquicardia ventricular. Válvula mitral.

Introduction

Mitral annulus disjunction (MAD) was described three decades ago by Bharati et al.¹, who documented the case of a 45-year-old doctor with a previous history of palpitations, mid-diastolic click, frequent premature ventricular complexes, and episodes of non-sustained ventricular tachycardia, who died suddenly. Postmortem pathological findings revealed a redundant myxomatous mitral valve with posterior leaflet atrial insertion.

In an autopsy report of 900 hearts, a prevalence of mitral valve degeneration of 3% was found, out of which 92% had MAD. Typically, patients were young, which is why the development of connective tissue degeneration was suggested to be secondary to mitral fibrous annulus dysfunction². Eriksson et al.³ evaluated patients undergoing mitral valve repair due to myxomatous degeneration using a transesophageal echocardiographic protocol, and observed an annular disjunction (mean value of 10 mm) at the basal portion of the posterior leaflet in 98% of patients with advanced disease; they demonstrated that its recognition by this imaging modality modified the repair technique for optimizing long-term results.

Since then, there has been growing interest in the investigation of the relationships between mitral valve apparatus anatomical abnormalities and their arrhythmogenic potential.

Mitral annulus posterior region abnormal movement secondary to leaflet abnormal insertion favors a curvilinear movement during ventricular systole, without any anterior component and sub-valvular apparatus hypermobility, which results in a “curly” appearance when evaluated on two-dimensional echocardiographic images⁴. Loss of movement synchrony has been associated

with the development of left ventricular fibrosis, due to excessive mobility and continuous traction. This phenomenon increases valve-adjacent myocardial cells stress, mainly affecting the chordae tendinae and papillary muscles. Such fibrous compromise has been demonstrated in histopathological studies and by tissue characterization with magnetic resonance imaging, mainly with late-enhancement sequences after gadolinium administration.

Fibrosis generated by continued stress not only alters ventricular geometry, but constitutes a substrate for electrical instability and is a trigger of life-threatening arrhythmias. The combination of the substrate (fibrosis) and continuous mechanical stress promotes the genesis of premature ventricular complexes of the papillary muscles or fascicles, which can trigger ventricular fibrillation, basically for being associated with Purkinje fibers compromise⁵⁻⁷. Catheter ablation of arrhythmogenic foci plays an important role in reducing arrhythmia burden and decreasing appropriate and inappropriate defibrillator discharges⁸.

Case presentation

This case is about a 30-year-old woman with no prior relevant pathological or family history. She had a history of several years with palpitations that occurred suddenly, unrelated with physical exertion and that resolved spontaneously, with no evidence of syncope. She attended a quaternary care center, specialized in the management of cardiovascular diseases. On physical examination, her vital signs were within normal parameters, with a holosystolic murmur on basal areas as only pathological finding.

Initial evaluation included a 12-lead electrocardiogram and 24-hour Holter monitoring in which premature

ventricular beats of several morphologies separately arranged were observed, with periods of bigeminism, trigeminism, doublets and monomorphic and pleomorphic ventricular tachycardia of up to six beats, with an initial arrhythmia burden of 6% and with normal atrio-ventricular and intraventricular conduction. Transthoracic echocardiogram showed a myxomatous mitral valve, with 6-mm thick mobile and redundant leaflets, with segments A2 and P2 prolapse, segment A2 0.6-cm displacement and segment P2 0.5-cm displacement beyond the valve plane, which generated moderate regurgitation. Color Doppler showed a regurgitation flow towards the posterior wall and up to the left atrial roof, with a vena contracta width of 0.5 cm. The left atrium and ventricle were considerably dilated, with left ventricular end diastolic diameter of 3.8 cm/m², normal global and segmental myocardial contractility, and ejection fraction of 60% evaluated by Simpson's method.

Pharmacological management was started with a beta-blocker, but the symptoms persisted and an increase in arrhythmia burden to up to 20% was observed. Performing an electrophysiological study with 3D mapping (NavX® Ensite®, St. Jude Medical, St. Paul, MN, USA) and ablation was decided. During the procedure, three extrasystole morphologies were documented, whose origin was located towards mitral-aortic and paraseptal continuity. Modulation of the arrhythmic substrate with radiofrequency energy was practiced.

During ambulatory follow-up, the patient persisted with symptoms, although without syncope being documented. Propafenone was started at appropriate doses, with good pharmacological adherence. Diagnostic workup was expanded with a cardiac magnetic resonance that showed a discordance between mitral valve annulus insertion (Fig. 1 A and B) and a 15-mm atrial displacement of the leaflet insertion points, consistent with MAD. In addition, late-enhancement foci with mesocardial, non-coronary distribution were observed (Fig. 2 C). A new 12-lead Holter was performed, where the extrasystoles morphology was observed (Fig. 2 A).

Given the persistence of symptoms, refractoriness to medical management, high arrhythmia burden and malignant potential, performing a new electrophysiological study with 3D mapping and ablation with radiofrequency energy was decided.

Under superficial sedation with remifentanyl infusion administered by the cardiovascular anesthesiologist, the study was initiated in sinus rhythm with ventricular extrasystoles of different morphology, with (M1) positive in leads II, III and aVF predominating, with right bundle branch block and negative in leads I and aVL (Fig. 2 B).

Figure 1. Magnetic resonance imaging, three-chamber (A) and four-chamber cine sequences (B). In an image acquired at the level of the left ventricular outflow tract, a dilated left atrium, with an area of 16 cm² is observed. The left ventricle is dilated without hypertrophy, with discordance between the mitral annulus and mitral valve leaflets, secondary to insertion points abnormal displacement towards the left atrium. Distance of 15 mm.

Quadrupolar and decapolar diagnostic electrocatheters (Inquiry® St. Jude Medical, St Paul, MN, USA) were positioned on right ventricle apex and coronary sinus, respectively. Through a puncture in the common femoral artery, the bidirectional ablation catheter with contact sensor (TactiCath® Quartz Contact Force, St. Jude Medical, St Paul, MN, USA) was advanced, and positioned in the left ventricle.

Under fluoroscopic and ultrasound vision, a deflectable sheath (Agilis® St. Jude Medical, St Paul, MN, USA) was advanced, and with a 98-cm Brockenbrough needle (BRK®, St. Jude Medical, St Paul, MN, USA), a trans-septal puncture was performed with no complications. Through it, a high-density mapping catheter (Advisor® HD Grid mapping Catheter, St. Jude Medical, St Paul, MN, USA) was passed, which was also advanced up to the left ventricle, and with a 3D system (Ensite® Precision Cardiac Mapping System, St. Jude Medical, St Paul, MN, USA), a three-dimensional anatomical map of left ventricle activation was generated, with emphasis on the lateral wall, basal portion, corresponding to the first morphology (M1). Simultaneously, a second morphology (M2) was mapped, with axis towards superior and positive in leads I and aVL.

From the most common morphology (M1), obtaining precocity of up to -69 ms (relative to QRS onset) was possible, with fractionated potentials at the lateral and basal region, where the voltage map also showed transitional zones. Purkinje potentials were also observed and highly fractionated potentials on the sites of greater precocity.

Figure 2. **A:** 12-lead Holter registry showing ventricular extrasystoles with three predominant morphologies. **B:** surface electrocardiogram during electrophysiological study in which a clearly predominant morphology is observed. M1: right bundle branch block morphology, positive in leads II, III, aVF and negative in I and aVL. M2: with axis towards superior and positive in leads I and aVL. Arrhythmia burden of 15%. **C:** cardiac magnetic resonance image, late enhancement sequences after gadolinium administration with fibrotic foci of non-coronary distribution and localization on segments 7 and 8.

Concurrently, on intracardiac echocardiogram (Viewflex® intracardiac Echo Probe, St. Jude Medical, St Paul, MN, USA), two hyperechoic, refringent areas were observed, suggestive of homogeneous scar, one throughout the entire length of the anterior papillary muscle and the other on the mesocardial region at the basal portion of the posterior papillary muscle. Applying radiofrequency energy was decided in order to homogenize the anterior muscle scar, starting in the area of highest precocity and completely surrounding it for consolidation. During one of the applications, a monomorphic ventricular tachycardia did develop that degenerated into ventricular fibrillation (Fig. 3) and required defibrillation, returning to sinus rhythm. Once in basal conditions, the stimulation protocol was completed from the ventricle with up to three extra stimuli and two cycle lengths, without inducing any arrhythmia being achieved. In addition, dobutamine infusion at a rate of 15 µg/kg/min was used, and under its effect, the ventricular stimulation protocol was repeated. Clinical arrhythmia non-inducibility and ventricular

extrasystoles disappearance were the end points for ablation.

The patient was considered to be at high risk of lethal arrhythmias, with ventricular fibrillation induction during the procedure, with cardiac structural pathology involving the mitral valve complex and especially the papillary muscles (most possibly the Purkinje network given that ventricular fibrillation was so easily induced), and with significant fibrosis, which constitute an arrhythmogenic substrate, which is why implanting a cardioverter defibrillator for sudden death primary prevention was decided.

Discussion

The mitral valve is developed from endocardial cushions. Its proper functioning requires perfect interaction of its components: mitral annulus, leaflets, sub-valvular apparatus and papillary muscles. The mitral annulus is a three-dimensional saddle-shaped structure with passive conformational changes during the cardiac cycle. Mobility of the annulus is determined by

Figure 3. Polygraph registry during radiofrequency application. The presence of two ventricular extrasystoles is observed, followed by sinus rhythm and four ventricular tachycardia beats that degenerate into ventricular fibrillation.

atrial and ventricular adjacent muscles contraction and relaxation⁹. The leaflets are articulated from the fibrous annulus; however, there are significant differences in the arrangement of the articulation in the aortic (anterior) and mural segments (posterior)¹⁰. The anterior leaflet is articulated along the area of fibrous continuity thickened by the aortic valve trigons. This anchoring ensures mitral-aortic continuity within the left ventricle, and confers this part of the mitral annulus greater attachment and support. In addition, it makes for the probability of dilatation of this segment to be infrequent. Conversely, the annulus mural portion (which supports the posterior leaflet) is articulated to the left atrioventricular junction parietal region. Posterior annulus configuration is varied even in hearts without anatomical alterations, and varies from a firm fibrous cord to replacement by fibro-adipose tissue instead of a real ring. Such configuration makes this portion of the structure much more susceptible to degeneration¹¹.

Mitral valve prolapse is defined as a superior displacement of the mitral valve of at least 2 mm during systole and mitral valve leaflets myxomatous degeneration, which results in thickening of at least 5 mm during diastasis. One of the multiple consequences of

this condition is the probability of sudden death due to sustained ventricular arrhythmias, with an estimated annual risk that ranges from 0.2% to 1.9%¹². MAD is a structural abnormality of uncertain origin consisting of an abnormal separation between the mitral valve annulus (which is where the valve is inserted) and the basal region of ventricular myocardium posterolateral wall, which is the region it should normally be implanted in. It is a localized abnormality that affects the ventricular myocardium, which is located just below the mitral valve posterior leaflet, typically around the scallops called P1 and P2. This condition may or may not be accompanied by mitral prolapse in its classic presentation¹³.

MAD was described more than 30 years ago in autopsy reports of approximately 900 hearts. Ninety-two percent of patients with mitral valve prolapse were shown to have MAD as well². In a systematic review of recent literature, several findings were identified: first, in patients with mitral valve myxomatous disease and mitral prolapse, MAD is common and, therefore, in these patients it is highly important to carefully examine the annulus posterior portion looking for disjunction; second, MAD is associated with the presence of life-threatening ventricular arrhythmias; therefore, when

detected, thorough studies are necessary in order to more accurately determine malignant potential; and third, there is growing evidence that, in patients who survive sudden death without a clearly identified cause, MAD should be actively sought, since this can be the cause of the arrhythmic event¹⁴.

MAD mainly affects mitral valve posterior leaflet hinge point, and causes a wide separation between the atrium and left ventricular free wall¹⁵. This condition can be evaluated with multimodal non-invasive imaging modalities, such as 2D echocardiography on parasternal long axis view during end of systole. 3D echocardiography has been recently incorporated in order to evaluate the paradoxical annular dynamics with systolic expansion and flattening secondary to annular-ventricular function uncoupling¹⁶. Left ventricular basal and mediolateral segments hyper-contractile state and abnormal curvilinear movement during systole have been documented in Doppler tissue studies, where an increase in systolic velocities is observed, which represent greater strain of the subvalvular apparatus and adjacent papillary muscles during systole. This energetic movement has been postulated to be able to favor the generation of premature ventricular complexes and polymorphic ventricular tachycardia associated with sudden death^{17,18}.

The presence of ventricular arrhythmias is common and proportional to the distance and the compromised circumferential area. In terms of clinical relevance, a distance > 8.5 mm has been associated with non-sustained ventricular tachycardia (OR: 10; 95% CI: 1.3-78.1)¹⁹.

Continuous abnormal movement and the stress generated by the anatomical abnormality lead to the development of fibrosis, which would represent a later phase in the evolution of the pathology²⁰. Moreover, it would also be related to the connective tissue degeneration that subsequently gives the leaflet its myxomatous appearance, alters its coaptation plane and favors prolapse. Presence of mitral valve prolapse has been documented in up to 78% of patients with MAD²¹.

In the presented case, tissue characterization on cardiac magnetic resonance did not document myocardial perfusion disorders at rest. However, late gadolinium enhancement foci with non-coronary distribution and localization in the inferoseptal and inferolateral basal segment at the mid-ventricular level (segments 7 and 8) were found, which were closely related to papillary muscles insertion. Such changes were also observed on intracardiac echocardiography. In addition, during

the electrophysiological study, these zones were clearly related to the areas of interest for electrical potentials characteristics. Papillary muscles and left ventricular inferobasal region fibrosis has been observed in histopathological studies of patients with sudden death²². Furthermore, there is evidence that late gadolinium enhancement in papillary muscles and longitudinal MAD distance in posterolateral wall are predictors of life-threatening arrhythmic events¹⁹.

Pharmacological treatment with beta-blockers, calcium channel blockers and other antiarrhythmic agents has been described, but with little impact on current survival and disease progression reduction^{8,23,24}. Mapping and ablation techniques are feasible in symptomatic patients and in those who are refractory to pharmacological management. Often, premature ventricular complexes promote ventricular fibrillation in these patients.

Ablation techniques can reduce symptoms and defibrillator appropriate discharges. However, the percentage of arrhythmia recurrence (including life-threatening arrhythmia) is not yet established, and current evidence supports that foci may arise from the territory where initial ablation has not been performed²⁵.

Pro-arrhythmic potential during or immediately after ablation has been described^{26,27}. Syed et al. reported a patient who developed arrhythmic storm after ablation and several others who developed ventricular fibrillation during the procedure.²⁸ In their study, electrophysiological results of patients with mitral valve abnormalities (prolapse and MAD) who have suffered a previous cardiac arrest are compared with those of patients who are free of events²⁹. In this study, patients with a history of cardiac arrest were characterized by the presence of ventricular extrasystoles arising from diseased Purkinje tissue, and late, mid-diastolic and fractional potentials were documented, similar to what was described in our patient. Ventricular extrasystole foci constant localization and abnormal tissue with slow conduction suggest an association between Purkinje fibers structural alteration and abnormality.

The risk of sudden death in patients with mitral valve apparatus structural abnormalities has been reported from its initial description in the 1980s to current date^{1,8,22}. The mechanisms involved in the genesis of arrhythmias include reentry mechanisms and triggered activity, although successful mapping and ablation of arrhythmias of focal origin is described in the literature³⁰. Thanks to technological advances and multimodal imaging studies integration has the pathophysiological process that triggers lethal

arrhythmias been better understood, as well as the evolutionary sequence of events. This favors strategic planning and a comprehensive, individualized approach to each patient.

Surgical correction of myxomatous mitral valve disease in patients with ventricular arrhythmias that are refractory to pharmacological treatment (even without severe mitral regurgitation) remains a controversial topic. However, another series found that a decrease in arrhythmia burden allowed a reduction or discontinuation of pharmacological treatment^{22,31-33}. However, another series found that arrhythmia burden decrease depended on the time of surgical intervention on the valve. Patients who had a reduction of 10% in general tended to be younger, which suggests that early intervention could modify the electrophysiological substrate³⁴.

Defibrillator implantation is considered in patients with malignant characteristics (high risk of sudden death), who experience episodes of sustained ventricular tachycardia or ventricular fibrillation. This, despite current limited availability of data on the use of these devices as primary prevention. So far, the role of ventricular extrasystole foci ablation or mitral valve surgical intervention with regard to the risk of sudden death has not been clearly defined. Studies that allow determining whether any of these interventions can be generally considered in this group of patients are necessary.

Conclusion

MAD is a structural abnormality of uncertain origin consisting of an abnormal separation between the mitral valve annulus and ventricular myocardium posterolateral basal wall, which is strongly associated with the presence of life-threatening ventricular arrhythmias. When detected, thorough studies are needed in order to more accurately determine malignant potential. Ablation of clinically dominant ventricular extrasystole foci could improve symptoms and reduce cardioverter-defibrillator appropriate discharges; however, long-term follow-up is necessary, since new foci can arise.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare no patient data appear in this article.

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