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ORIGINAL RESEARCH ARTICLE

Mechanical and electrical uncoupling: the role of cardiac magnetic resonance imaging in arrhythmogenic cardiomyopathy. Proof of concept

Desacoplamiento mecánico y eléctrico: el papel de la resonancia magnética cardiaca en la miocardiopatía arritmogénica. Prueba de concepto

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Abstract

Objectives: *Arrhythmogenic cardiomyopathy (ACM) is a complex cardiac disorder associated with ventricular arrhythmias. Understanding the relationship between mechanical uncoupling and cardiac structural changes in ACM patients is crucial for improved risk stratification and management.* **Methods:** *In this study, we enrolled 25 ACM patients (median age 34 years, 72% men) based on the 2019 Modified Task Force and Padua criteria. Patients were categorized by the presence or absence of clinically relevant ventricular tachycardia (crVT), necessitating emergency interventions. Right ventricular-arterial coupling (VAC) was assessed using echocardiography. Low-rank regression splines were employed to model left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) in relation to VAC.* **Results:** *Positive associations were observed between VAC and LVEF (ρ = 0.472, p = 0.023), RVEF (ρ = 0.522, p = 0.038), and right ventricular (RV) indexed stroke volume (ρ = 0.79, p < 0.001). Patients with crVT exhibited correlations with RV shortening, reduced RVEF (39.6 vs. 32.2%, p = 0.025), increased left ventricular (LV) mass (38.99 vs. 45.55, p = 0.045), and LV end-diastolic volume (LVEDV) (56.99 vs. 68.15 mL/m^2, p = 0.045). Positive associations for VAC were noted with LVEDV (p = 0.039) and LV mass (p = 0.039), while negative correlations were observed with RVEF by CMR (p = 0.023) and RV shortening by echocardiography (p = 0.026).* **Conclusions:** *Our findings underscore the significance of right VAC in ACM, demonstrating correlations with RV and LVEF, RV stroke volume, and clinically relevant arrhythmias. Insights into RVEF, LV mass, and end-diastolic volume provide valuable contributions to the understanding of ACM pathophysiology and may inform risk assessment strategies.*

Keywords: *Arrhythmogenic cardiomyopathy. Right ventricular-arterial coupling. Ventricular tachycardia. Echocardiography.*

Resumen

Objetivos: *La miocardiopatía arritmogénica (MCA) es un trastorno cardíaco complejo asociado con arritmias ventriculares (AV). Comprender la relación entre el desacoplamiento mecánico y los cambios estructurales cardíacos en pacientes con MCA es crucial para una estratificación de riesgos y una gestión mejorada.* **Métodos:** *En este estudio, reclutamos a 25 pacientes con MCA (edad media 34 años, 72% hombres) basándonos en los criterios del Task Force 2019 y los criterios*

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de Padua. Los pacientes se clasificaron según la presencia o ausencia de taquicardia ventricular clínicamente relevante (crVT), que requería intervenciones de emergencia. Se evaluó el acoplamiento ventricular derecho-arterial (VAC) mediante ecocardiografía. Se utilizaron low-rank regression splines para modelar la fracción de eyección del ventrículo izquierdo (FEVI) y la fracción de eyección del ventrículo derecho (FEVD) en relación con el VAC. **Resultados:** *Se observaron asociaciones positivas entre el VAC y la FEVI (ρ = 0.472, p = 0.023), la FEVD (ρ = 0.522, p = 0.038) y el volumen de eyección indexado del ventrículo derecho (ρ = 0.79, p < 0.001). Los pacientes con crVT mostraron correlaciones con acortamiento del ventrículo derecho, disminución de la FEVD (39.6 vs. 32.2%, p = 0.025), aumento de la masa ventricular izquierda (38.99 vs. 45.55, p = 0.045) y volumen diastólico final del ventrículo izquierdo (VDVI) (56.99 vs. 68.15 mL/m^2, p = 0.045). Se observaron asociaciones positivas para el VAC con el VDVI (p = 0.039) y la masa ventricular izquierda (p = 0.039), mientras que se observaron correlaciones negativas con la FEVD por RMC (p = 0.023) y el acortamiento del ventrículo derecho por ecocardiografía (p = 0.026).* **Conclusiones:** *Nuestros hallazgos subrayan la importancia del VAC derecho en la MCA, demostrando correlaciones con la FEVD y FEVI, el volumen de eyección del ventrículo derecho y arritmias clínicamente relevantes. Las percepciones sobre la FEVD, la masa ventricular izquierda y el volumen diastólico final proporcionan contribuciones valiosas para comprender la fisiopatología de la MCA y pueden informar estrategias de evaluación de riesgos.*

Palabras clave: *Miocardiopatía arritmogénica. Acoplamiento ventricular-arterial derecho. Taquicardia ventricular. Ecocardiografía.*

Introduction

For many years, arrhythmogenic cardiomyopathy (ACM), known as arrhythmogenic right ventricular (RV) dysplasia, has a significant potential for sudden cardiac death. Its prevalence is 1 in 5,000 and represents an important cause of sudden cardiac death in people younger than 60 years old. ACM is characterized by replacing normal myocardium with fibro-adipose tissue, mainly at the anterior infundibulum, RV apex, and the diaphragmatic area of the right ventricle[1].

Cardiac magnetic resonance imaging (CMR) is important in diagnosing and managing patients with ACM. The diagnostic criteria focus on RV volume and ejection fraction (EF), and only the Padua consensus considers late gadolinium enhancement[2,3].

Simulations show abnormal deformation patterns of ACM not by changing the electrical properties of the system but only when altered mechanical characteristics are altered by reducing contractility and increasing stiffness[4,5]. Thus, the ventricular-arterial coupling (VAC) can be useful by being related to efficiency (RV and left ventricular [LV] EF) in RV echocardiography. TAPSE/pulmonary arterial systolic pressure (sPAP) index can reflect the length-force relationship is a useful RV function evaluation and is not affected by the grade of LV dysfunction[6].

CMR is an important tool that allows stratification and prognosis of ACM. VAC might play an important role in ACM prognosis based on mechanical and structural abnormalities related to the structural information provided by CMR.

We aimed to describe and correlate mechanical uncoupling by echo with CMR findings and clinically relevant arrhythmias in patients with ACM.

Methods and study population

We retrospectively screened 97 patients with suspicion of ACM at Instituto Nacional de Cardiología, in Mexico City from January 2008 to November 2021 with a follow-up of 12 months. Our exclusion criteria were pregnancy/postpartum period, infectious, autoimmune, hepatic, or neoplastic diseases, previous dialysis, transplant, coronary syndromes, or not fulfilling the criteria mentioned earlier. Fifty-seven were excluded as they did not meet the clinical and imaging definition and 12 for other reasons. Therefore, 28 were diagnosed using the 2019 Modified Task Force Criteria for arrhythmogenic ventricular cardiomyopathy (ACM) and Padua criteria. Moreover, three patients were eliminated as they did not have CMR and echo at the time of diagnosis (Fig. 1).

The RV function variables were obtained from echocardiography reports conducted by trained personnel. The TAPSE was calculated through the systolic excursion of the tricuspid annulus assessed by M-mode and expressed in centimeters.

We explored two critical pathophysiological factors in ACM: right VAC as the ratio of TAPSE to echocardiographic derived sPAP (TAPSE/SPAP) and clinically relevant ventricular tachycardia (need for emergency

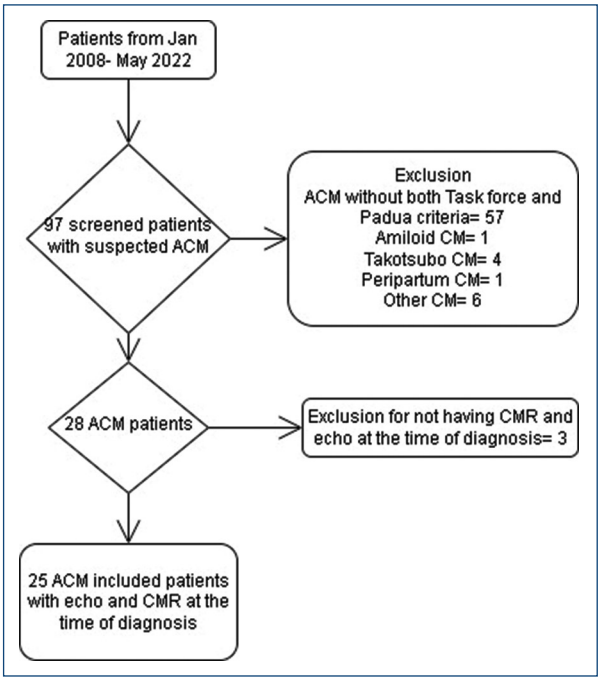

Figure 1. Flow chart of the study.

electrical or pharmacological cardioversion) compared with clinical data, electrocardiographic findings and multi-imaging with transthoracic echocardiogram; plus CMR as the gold standard.

Patients were managed under the Declaration of Helsinki. They provided written informed consent, and the current registry was approved by the Research Committee and the Ethics in Research Committee of the Instituto Nacional de Cardiología.

Statistical analysis

Statistical data analysis of clinical and imaging parameters was expressed as median and interquartile ranges. A Spearman's rank test was used to obtain correlations. The Fisher's exact test was used to compare nominal characteristics, and exact Mann-Whitney U-tests for group comparisons were performed.

In preconceived regression models of left and RV function with VAC were conceived in the frame of low-rank regression splines, generalized additive models and fitted to penalized likelihood estimation (restricted by 5 knots) were performed (GAMPL in SAS) to produce flexible nonparametric regressions. A $p < 0.05$ was considered statistically significant. The analysis was done in SPSS version 22 and SAS-University-Edition©.

Ethics approval statement

The current registry was approved by the Research and the Ethics in Research Committee of the Instituto Nacional de Cardiología.

Results

The median age of our cohort was 34 years old, 72% were men, two patients had hypothyroidism (12%), 36% had a family history, and the median body mass index was 25.39 kg/m^2.

Electrocardiographic abnormalities were present across the cohort, with 52% having incomplete right bundle branch block (iRBBB) and T wave inversion, 68.2% having Epsilon waves, and 52% having wide QRS (> 120 ms).

The echocardiography parameters had a median LVEF of 55% and RV shortening of 34%. The calculated VAC (TAPSE/sPAP) was 0.63. The CMR showed a median LVEF of 47% and right ventricular ejection fraction (RVEF) of 34.45%, with 19 patients (76%) with late gadolinium enhancement (Table 1).

VAC

At the Spearman regression, we found a positive relation with LVEF by echo $\rho = 0.461$ ($p = 0.027$) and by CMR $\rho = 0.472$ ($p = 0.023$), RVEF by CMR $\rho = 0.522$ ($p = 0.038$); TAPSE $\rho = 0.498$ ($p = 0.022$); and the RV indexed stroke volume $\rho = 0.79$ ($p < 0.001$) and a negative with the tricuspid regurgitation gradient $\rho = -0.489$ ($p = 0.033$) and sPAP $\rho = -0.772$ ($p < 0.001$).

Low-rank regression splines showed a mainly positive association of LVEF (df = 3 F = 20.75 $p < 0.001$) and RVEF (df = 4 F = 24.34 $p < 0.001$) with VAC. Furthermore, a positive linear association was seen when VAC was compared against the RV-indexed stroke volume (df = 1 F = 31.67 $p < 0.001$).

When evaluating RVEF and LVEF against VAC (df = 3 F = 13.04 $p < 0.001$) in a contour model, it showed an overall positive correlation between EFs and coupling in the patients with ACM (Fig. 2).

Ventricular tachycardia

Differences were seen in patients with ventricular tachycardia; a tendency where older patients had more events (33 vs. 45 years. $p = 0.057$); more use of an ICD (33.3 vs. 87.5%, $p = 0.01$). Echocardiography demonstrated lower fractional RV shortening (39.9 vs. 22%,

Table 1. Clinical, electrocardiographic, and multi-imaging characteristics

Cohort (n = 25)	Value
Age (years)	34 (26-50)
Men (%)	18 (72)
BMI (kg/m^2)	25.39 (20.2-28.7)
Weight (kg)	70 (55-85)
Height (cm)	167 (160-172)
Body surface area (m^2)	1.78 (1.59-1.96)
IRBBB (%)	13 (52)
Inverted T wave (%)	13 (52)
QTc Bazzet (ms)	430 (420-480)
Epsilon wave (%)	17 (68.2)
Wide QRS > 120 ms (%)	13 (52)
Implantable cardiac defibrillator (%)	17 (68)
Ventricular tachycardia or fibrillation	16 (64)
Echocardiography	
LVEF (%)	55 (40-56)
RV shortening (%)	34 (20-40)
TAPSE mm	18 (16-20)
sPAP mmHg	31 (25-41)
VAC (TAPSE/sPAP)	0.63 (0.55-0.8)
Cardiac magnetic resonance	
LVEF	47 (40.7-55)
RVEF	34.45 (30.35-39.6)
Mass (g/m^2)	44.89 (36.81-54.50)
LV final diastolic volume (mL/m^2)	64.88 (55.79-73.73)
LV final systolic volume (mL/m^2)	37.02 (28.1-41.45)
LV beat volume (mL/m^2)	29.05 (24.21-36.09)
RV final diastolic volume (mL/m^2)	86.85 (66.25-113.76)
RV final systolic volume (mL/m^2)	55.35 (34.21-68.81)
RV beat volume (mL/m^2)	29.05 (24.21-36.09)
Gadolinium enhancement	19 (76)

Values in interquartile ranges unless stated otherwise. IRBBB: incomplete right bundle branch block; LV: left ventricle; RV: right ventricle; EF: ejection fraction; sPAP: pulmonary arterial systolic pressure; VAC: ventriculo-arterial coupling.

p = 0.033), and CMR showed that they had lower RVEF (39.6 vs. 32.2% p = 0.025) and higher LV mass (38.99 vs. 45.55, p = 0.045) and final diastolic LV volume (56.99 vs. 68.15 mL/m^2, p = 0.045). No differences were seen in ECG findings, LVEF by echo or CMR, and no difference in RV volumes (Table 2).

Correlations with ventricular tachycardia

Positive associations were seen with final diastolic LV volume $\rho = 0.454$ p = 0.039, LV mass $\rho = 0.454$ p = 0.039, and negative with RV EF by CMR $\rho = -0.505$ p = 0.023 and RV shortening in echo $\rho = 0.508$ p = 0.026.

Discussion

Our study demonstrated that in ACM, VAC correlates with lower RVEF and LVEF and the RV stroke volume, suggesting increased fibrofatty replacement; furthermore, end-diastolic LV volumes, RVEF, and shortening correlate with electrical outcomes measured by CMR and echo, respectively (Fig. 3).

Over the past decade, there has been increasing appreciation for the importance of RV coupling, which provides a valuable method for assessing performance by describing the energy transfer between ventricular contractility and arterial afterload (vascular stiffness)[7]. We found that VAC, measured by echocardiogram, correlates with CMR-measured LVEF, RVEF, and RV stroke volume, confirming the relationship between mechanical RV performance, possibly suggesting an increased RV involvement and poor RV performance in these patients[8].

The RV EF is an essential parameter to define morphofunctional abnormalities in ACM patients, as well as for outpatient patient monitoring. Although CMR imaging remains the gold standard for defining this variable, limited availability in non-cardiovascular centers, the time required for proper image acquisition (not suitable for hemodynamically unstable patients), and the cost associated with magnetic resonance imaging hinder its widespread use in ACM patients. As a result, the existence of a non-invasive parameter that can be easily performed at the patient's bedside, with fast availability, such as VAC, becomes a useful tool.

In our study, the right VAC provides a suitable correlation with CMR-measured RVEF without replacing this study in the in-depth analysis of RV function.

Previous studies have addressed the presence of VT in ACM but did not explore LV volumes[9]. In our study, we found that increased diastolic LV volumes and low RVEF are associated with the presence or development of VT; interestingly, although RVAC correlated with RVEF, we did not find a statistically significant association with VT; the low number of patients could explain this but also that the presence of VT could be driven by other factors not explored. These findings are relevant since no studies have correlated the presence of an increased volume and electrical outcomes in ACM. A possible explanation is that the global disturbance of the cardiomyocytes and electrical uncoupling in ACM are more prominent in individuals with LV involvement, having a higher risk of VT. Overload RV induces increased Cx43 heterogeneity, thus translating in the clinical setting to a reduced RV fractional shortening and probably the development of electrical instability[5,10].

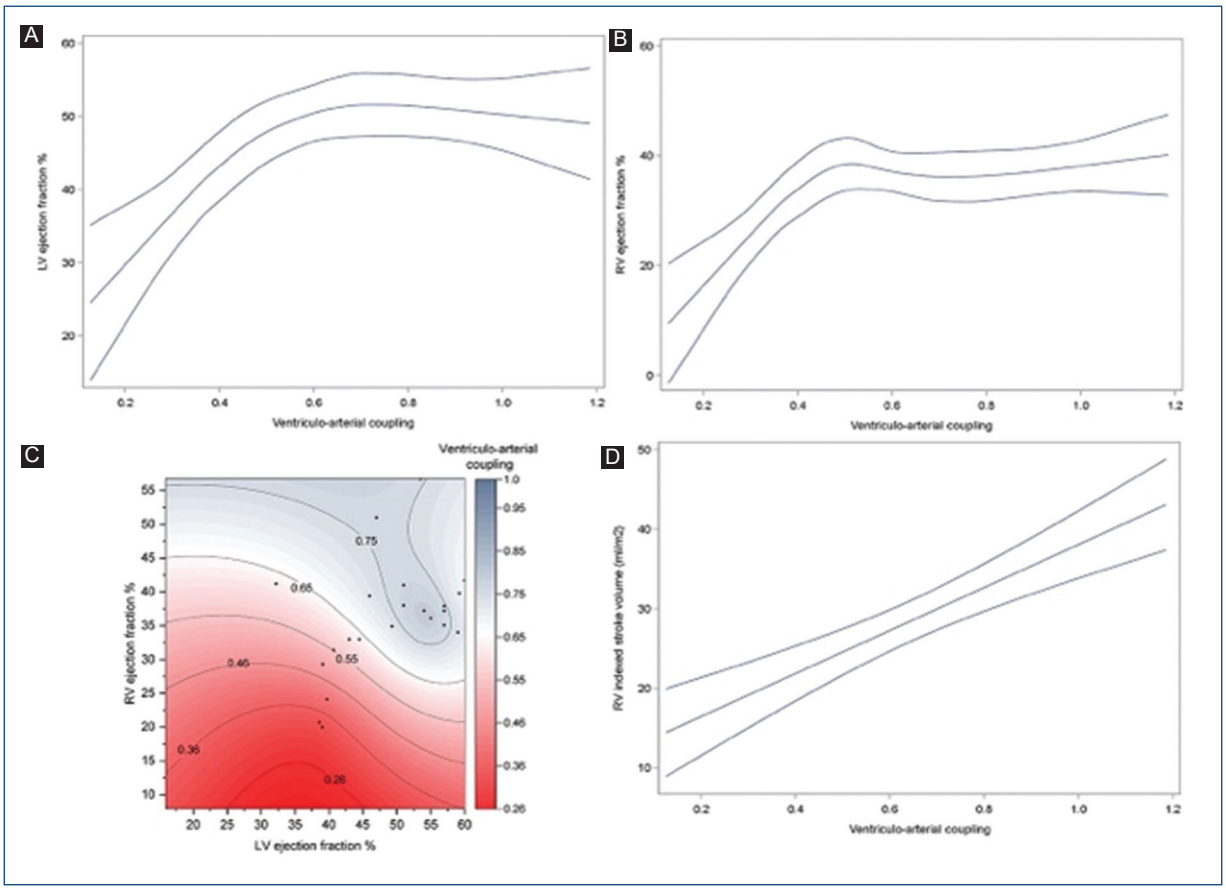

Figure 2. Low-rank regression splines. **A:** ventriculo-arterial coupling (VAC) vs. LV ejection fraction. **B:** VAC vs. RV ejection fraction. **C:** RV and LV ejections fractions vs. VAC. **D:** VAC vs. RV indexed stroke volume. LV: left ventricle; RV: right ventricle.

Table 2. Clinical and demographic characteristics of arrhythmogenic cardiomyopathy cohort divided by the presence of ventricular tachycardia

Variables	Ventricular tachycardia		
	No (n = 9)	Yes (n = 16)	p-value
Men (%)	6	12	0.673
Age (years)	33 (20-34)	45 (28-55)	0.057
Weight (kg)	80 (55-99)	70 (60-81)	0.637
Height (cm)	165 (162-172)	168 (158.5-171.5)	0.978
BMI (kg/m^2)	28.3 (20.2-29.8)	27.2 (21.4-27.6)	0.522
BSA (m^2)	1.9 (1.59-2.06)	1.78 (1.6-1.91)	0.718
Incomplete RBBB (%)	4 (44)	9 (56.3)	0.688
T wave inversion	4 (44)	9 (56.3)	0.688
Corrected QT ms	430 (424-470)	438 (418-480)	0.846
Epsilon wave	7 (77.8)	10 (62.5)	0.661
Wide QRS (> 120 ms)	5 (55.6)	8 (50)	1

(Continues)

Table 2. Clinical and demographic characteristics of arrhythmogenic cardiomyopathy cohort divided by the presence of ventricular tachycardia *(continued)*

Variables	Ventricular tachycardia		
	No (n = 9)	Yes (n = 16)	p-value
ICD (%)	3 (33.3)	14 (87.5)	0.01
Echocardiography			
LVEF	54.5 (49.2-55.5)	55 (38-57)	0.776
RV shortening	39.9 (27.5-41.5)	22 (13-35)	0.033
TAPSE (mm)	18.5 (14-26.5)	18 (16.20)	0.75
Tricuspid gradient (mmHg)	18 (13-30)	18 (16-20)	0.395
sPAP (mmHg)	30 (24-40.5)	31 (25-41)	1
VAC (TAPSE/sPAP)	0.65 (0.38-1.04)	0.63 (0.58-0.67)	0.916
Cardiac magnetic resonance			
LVEF	47 (46-53.5)	46.2 (39.4-57)	0.718
RVEF	39.6 (36.2-46)	32.2 (26.7-36.1)	0.025
Mass (g/m2)	38.99 (29.02-45.41)	45.55 (44.87-57.43)	0.045
LV final diastolic volume (mL/m^2)	56.99 (55.5-60.83)	68.15 (64.88-74.54)	0.045
LV final systolic volume (mL/m^2)	29.11 (26.85-33.59)	39.27 (35.71-43.62)	0.14
LV beat volume (mL/m^2)	27.17 (25.69.34.43)	30.22 (26.7-39.52)	0.301
RV final diastolic volume (mL/m^2)	90.29 (74.07-113.76)	85.78 (49.38-103.53)	0.656
RV final systolic volume (mL/m^2)	48.24 (31.29-68.81)	55.35 (37.47-68.60)	0.717
RV stroke volume (mL/m^2)	29.61 (28.17-44.95)	25.63 (11.92-34.07)	0.126
Gadolinium enhancement	6 (66.7)	13 (81.3)	0.63

Values in interquartile ranges unless stated otherwise. IRBBB: incomplete right bundle branch block; LV: left ventricle; RV: right ventricle; EF: ejection fraction; sPAP: pulmonary arterial systolic pressure; VAC: ventriculo-arterial coupling.

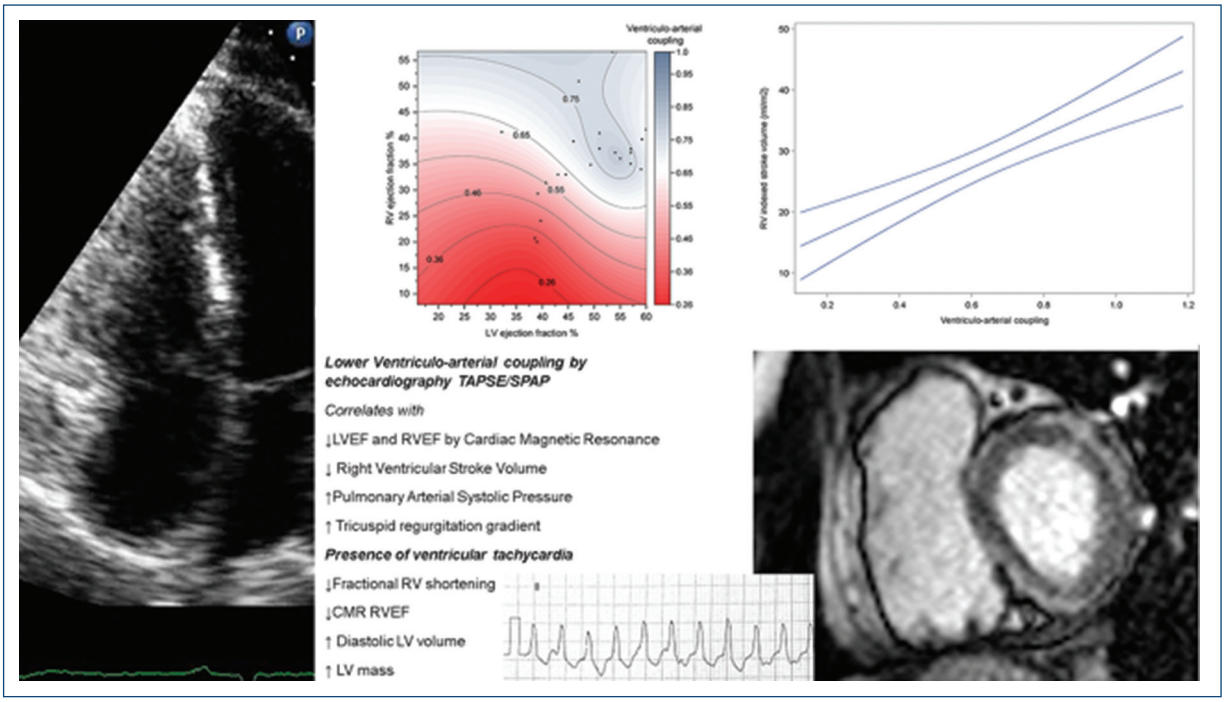

Figure 3. Illustrates the relationship between venoarterial coupling (TAPSE/sPAP) and the presence of ventricular tachycardia, with echocardiogram and cardiac magnetic resonance parameters.

Future perspective includes a more extensive study of VAC as it would allow to set up the prognosis in ACM, identifying patients at risk of electromechanical complications in a non-invasive way by the relationship with RV and LVEF also if the LV diastolic volume predicts the development of clinically important arrhythmias in ACM rather than RV volumes.

Limitations

Limitations in this study were the lower prevalence of the confirmed disease by two criteria although this gives the study a higher specificity. Despite the compelling data, this study proves that echo and CMR might be key in predicting electromechanical coupling in ACM. A more extensive population must be studied to confirm these findings.

Conclusions

This study remarks that in multi-imaging evaluation in recognition of electric-mechanical outcomes, we found that right VAC by echo correlates with RVEF and LVEF by CMR and RV stroke volume in patients with ACM. RVEF, LV mass, and end-diastolic volume correlate with clinically relevant arrhythmias highlighting that ACM has a biventricular involvement that is not limited to RV.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

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

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 that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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