First-degree atrioventricular block in hypertrophic cardiomyopathy patients: an easy and worthy prognostic marker?

Ana Filipa Amador,[1,2] Catarina Martins da Costa,[1,2] João da Silva Santos,[2] Cláudia Camila Dias,[2] Elisabete Martins[1,2]

[1]Department of Cardiology, São João University Hospital Center, Porto; [2]Faculty of Medicine, University of Porto, Portugal

Correspondence: Ana Filipa Amador, Department of Cardiology, São João University Hospital Center, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal.
Tel.: +351933176428.
E-mail: a.filipa.amador@gmail.com

Key words: hypertrophic cardiomyopathy, first-degree atrioventricular block, atrial fibrillation, outcomes, E/e' ratio.

Contributions: AFA, CMC, were responsible for the acquisition, analysis, and interpretation of the data, as well as drafting the paper; JS, was responsible for data acquisition and contributed to the paper draft; CCD, was responsible for the data analysis, and revision of the paper; EM, was responsible for the design of the work and reviewed the paper critically for important intellectual content. All authors finally approved the submitted version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: the research protocol was approved by the Hospital do São João Ethics Committee (reference number: CE-275-22) and patients' consent was acquired. The study was performed according to the recommendations of the Helsinki Declaration.

Informed consent: adquired.

Patient consent for publication: obtained.

Availability of data and materials: raw data were generated at Hospital Universitário de São João, Porto. Derived data supporting the findings of this study are available from the corresponding author CC on request. Data was collected anonymously.

Funding: none.

Received: 1 December 2023.
Accepted: 15 February 2024.
Early view: 6 March 2024.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Monaldi Archives for Chest Disease 2025; 95:2860
doi: 10.4081/monaldi.2024.2860

Abstract

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease. Recently, a connection has been observed between the presence of first-degree atrioventricular block (FDAVB) and cardiovascular outcomes, although the pathophysiology of this association remains poorly understood. Considering the period 2000-2023, we retrospectively included HCM patients at sinus rhythm at the first appointment and sought possible interactions of FDAVB (defined as PR interval >200 ms) with different clinical and imaging variables and with the occurrence of cardiovascular events, including atrial fibrillation (AF). A total of 97 patients were included, of whom 57 (58.8%) were men, with a mean age of 51±19 years, and 14 (14.4%) had FDAVB. During a median of 4.29 (percentile 25 1.92, percentile 75 7.67) years of follow-up, 35 cardiovascular events occurred, including 13 *de novo* diagnoses of AF, 8 hospitalizations due to heart failure, 8 new-onset strokes, 4 myocardial infarctions, and 2 implantations of cardio defibrillators in secondary prevention; no HCM-related death occurred. We did not find any association between outcomes and the presence of FDAVB. The role of FDAVB as a prognostic marker in HCM patients requires further investigation. We found that FDAVB patients were older, more frequently reported dyspnea, had a larger QRS duration, a higher ratio of early mitral inflow velocity to mean early diastolic mitral annular velocity (E/e'), and lower maximal left ventricle wall thickness by magnetic resonance ($p<0.05$). After multivariable analysis, FDAVB was independently associated with a higher echocardiographic E/e' ratio ($p=0.039$) (odds ratio=1.588). This is the first paper to document an independent association between FGAVB and a higher E/e' ratio in HCM patients.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common monozygotic inherited cardiomyopathy, affecting 1:500 to 1:200 of the general population; it is mainly associated with autosomal dominant mutations in proteins of the contractile myofilaments of the cardiac sarcomere and Z-disc. The pathophysiology of HCM is complex, involving morphofunctional alterations in cardiomyocytes and intercellular junctions, microvascular coronary disease, silent myocardial ischemia, and systemic inflammation, ultimately resulting in myocardial hypertrophy and fibrosis. These alterations collectively contribute to an elevated risk of arrhythmic events and diastolic dysfunction in HCM patients [1-5].

Atrial fibrillation (AF) emerges as the most common arrhythmia in HCM patients, with a multifactorial etiology. Fibrosis-related reentry circuits play a significant role, along with left atrial (LA) hypertrophy and dilation due to high left ventricle (LV) filling pres-

sure, diminished ventricular relaxation, mitral regurgitation, and outflow tract obstruction. AF is associated with major cardiovascular events, including higher mortality, among HCM patients [6-9].

The clinical expression of HCM is highly heterogeneous, spanning from an asymptomatic state or a benign course to severe cardiovascular events such as advanced heart failure and sudden cardiac death (SCD). Stratifying the risk of life-threatening events and guiding the management of HCM accordingly remains a challenge [3,10,11].

Traditionally considered as benign and lacking prognostic relevance for cardiovascular events, first-degree atrioventricular block (FDAVB), defined as the prolongation of the PR interval exceeding 200 milliseconds (ms), has recently been recognized in numerous studies as a significant predictor of future adverse cardiac outcomes in diverse populations, both in healthy individuals and those with different cardiac diseases [12-21].

Recently, Higuchi *et al.* were the first to document in a cohort of HCM patients an association of FDAVB with a higher prevalence of HCM-related death, AF, and heart failure hospitalizations. However, the understanding of how FDAVB can predict adverse cardiovascular events remains limited [22].

In this study, our objective was to further explore the associations of FDAVB with clinical and imaging characteristics and focusing on outcomes, particularly the development of AF, in a HCM patient cohort.

Materials and Methods

Study design

This retrospective cohort study involved an initial population of 108 patients with HCM monitored at the Myocardiopathy Consultation of the Cardiology Department at Centro Hospitalar e Universitário São João in Oporto, Portugal, spanning from April 2000 to January 2023. Patients were included based on a diagnosis of HCM, established by evidence of non-dilated LV hypertrophy with a wall thickness ≥15 mm in transthoracic echocardiogram (TTE), in the absence of any other cardiac or systemic conditions justifying loading conditions [10,11].

From the initial sample of 108 patients, 11 were excluded due to the presence of AF at the time of the first appointment electrocardiogram (ECG). One patient had a missing value for the PR interval and was only included in the descriptive statistics. Patients were categorized based on the presence of FDAVB.

Data information

We collected clinical, 12-lead ECG, Holter ECG monitoring, TTE, and magnetic resonance imaging (MRI) data from the informatics system. The initial evaluation encompassed the first clinical assessment, during which an ECG was performed. Data related to TTE, MRI, and Holter monitoring were extracted from the respective exams conducted closest to the date of the initial consultation. Outcomes were assessed from the first appointment until January 2023.

Relevant electrocardiogram and echocardiographic definitions

The duration of intervals on the ECG was automatically determined at acquisition and then manually confirmed. We utilized the ECG from the first appointment date to diagnose the presence of FDAVB in our population, defining FDAVB as a PR interval greater than (>) 200 ms. The echocardiographic ratio between early diastolic transmitral flow and mean early diastolic mitral annular velocity (E/e'), employing tissue Doppler imaging, was calculated using the mean values of both e´ at the septal and lateral sides of the mitral annulus

Outcomes definitions

In our study, we considered as outcomes: cardiovascular death (including SCD, heart failure-related death and stroke-related death), implantable cardioverter-defibrillator (ICD) placement for secondary prevention of SCD, ventricular appropriate ICD shocks, *de novo* AF, hospitalization due to heart failure, myocardial infarction and new onset stroke.

Statistical analysis

Categorical variables were presented as absolute frequencies (n) and relative frequencies (%). Means with standard deviation or medians with percentiles 25 (P25) and 75 (P75) were used for continuous variables, accordingly to their distribution.

When testing a hypothesis about continuous variables, the parametric independent samples *t*-test or the nonparametric Mann-Whitney test were used as appropriate, taking into account normality assumptions and the number of groups compared. When testing a hypothesis about categorical variables, a chi-square test and Fisher's exact test were used, as appropriate. To have a more thorough understanding of the factors associated with increased PR interval (dependent variable), bivariate and multivariate logistic regression modeling was used. Model goodness-of-fit was assessed using the Hosmer-Lemeshow statistic, and discriminative power was evaluated by receiver-operating characteristic curve analysis. The significance level used was 0.05. Statistical analysis was performed using the software Statistical Package for the Social Sciences v. 27.0 (IBM, Chicago, IL, USA).

Results

Baseline hypertrophic cardiomyopathy patients' characteristics

A total of 97 HCM patients were included, consisting of 57 men (58.8%) with a mean age of 51±19 years. A total of 44 patients (45.4%) had a family history of HCM and 41 (42.2%) had a positive genetic test with a mutation on *MYBPC3*, *MYH7*, *TNNT2* or other genes [13 (31.7%), 12 (29.3%), 9 (22.0%) and 7 (17.1%) patients, respectively]. Additionally, 28 (28.9%) patients had a familiar history of sudden death.

The median PR duration at first visit was 160 (P25 145, P75 187) ms, and 14 (14.4%) patients had FDAVB at the first evaluation. No patient had an implanted pacemaker. At TTE, 90 (92.7%) had normal LV systolic function, while 5 (5.2%) and 2 (2.1%) had mild and moderate systolic dysfunction, respectively; all patients had normal right ventricular systolic function. Median E/e' ratio was 8.99 (P25 7.35, P75 11.00) and median septal thickness was 16 (P25 13, P75 19) mm; basal or after Valsalva obstructive gradients were present in 7 (7.2%) patients. On MRI, 63 (64.9%) patients had the presence of late gadolinium enhancement (LGE) in at least one segment. On Holter monitoring, 6 (6.2%) patients showed episodes of non-sustained ventricular tachycardia, and 3 (3.1%) had paroxysmal AF.

Follow-up

During a median follow-up of 4.29 (P25 1.92, P75 7.67) years, two patients died from oncological causes; no cardiovascular death nor appropriate ICD shock were documented. A total of 35 cardiovascular events were recorded: 13 patients had *de novo* AF (3 diagnoses on Holter monitoring and 10 through ECG performed at a medical contact), 8 hospitalizations due to heart failure, 8 new onset strokes, 4 myocardial infarctions, and 2 ICD implantations for secondary prevention.

Comparisons between patients with and without first-degree atrioventricular block

Among the 14 patients with FDAVB, the majority were men (64.3%), with a median age of 67 years at the time of the first consultation. Clinical characteristics of the FDAVB and the non-FDAVB groups of patients are summarized in Table 1.

In bivariate analysis, significant differences were found in age at diagnosis (FDAVB patients were older, with median age of 67 *vs.* 55 years old in the non-FDAB group, p=0.005), dyspnea (more

Table 1. Clinical characteristics and data from electrocardiogram, transthoracic echocardiogram, magnetic resonance imaging, and 24h-Holter of the first-degree atrioventricular block (FDAVB) group and non-FDAVB group.

	Non-FDAVB group (n=82)	FDAVB group (n=14)	p
Age at the first consult, median (P25-P75)	55 (32-65)	67 (66-67)	0.005[3]
Gender - male, n (%):	48 (58.5)	9 (64.3)	0.686[1]
Symptoms, n (%)			
Tiredness	22 (26.8)	6 (42.9)	0.223[1]
Dyspnea	5 (6.1)	4 (28.6)	0.0081
Thoracic pain	17 (20.7)	3 (21.4)	>0.999[2]
Palpitations	14 (17.1)	0 (0.0)	0.211[2]
Syncope	6 (7.3)	0 (0.0)	0.588[2]
Family history of sudden death n (%)	23 (28.0)	4 (28.6)	0.889[2]
Family history of HCM n (%)	40 (48.8)	3 (21.4)	0.521[2]
Cardiovascular Risk Factors, n (%)			
Hypertension	32 (39.0)	7 (50.0)	0.440[1]
Dyslipidemia	35 (42.7)	6 (42.9)	0.990[1]
Diabetes mellitus	12 (14.6)	2 (14.3)	>0.999[2]
Smoking habits	7 (8.5)	2 (14.3)	0.615[2]
Cardiovascular medication at first consult, n (%)			
ACE inhibitors or ARB	31 (38.3)	5 (35.7)	0.855[1]
β-blocker	49 (60.5)	11 (78.6)	0.195[1]
Calcium channel blocker	6 (7.4)	3 (21.4)	0.125[2]
Loop diuretics	3 (3.7)	1 (7.1)	0.477[2]
Thiazidic diuretics	16 (19.8)	3 (21.4)	>0.999[2]
Vitamin K antagonist	3 (3.7)	1 (7.1)	0.477[2]
Anticoagulant	2 (2.5)	1 (7.1)	0.384[2]
Aspirin	16 (19.8)	4 (28.6)	0.484[2]
Statin	33 (40.7)	9 (64.3)	0.101[1]
Oral antidiabetic	5 (6.2)	1 (7.1)	>0.999[2]
Eletrocardiogram at first consult			
Resting heart rate (bpm), median (P25-P75)	66 (58-75)	68 (60-75)	0.556[1]
PR duration (ms), median (P25-75)	157 (143-174)	222 (208-236)	<0.001[3]
QTc duration (ms), median (P25-P75)	427 (411-443)	431 (412-455)	0.449[3]
QRS duration (ms), median (P25-P75)	99 (90-118)	121 (100-141)	0.0223
Sokolow-Lyon criteria for left ventricle hypertrophy (mm), median (P25-P75)	34 (25-44)	36 (31-44)	0.593[3]
Cornell criteria for left ventricle hypertrophy (mm), median (P25-P75)	25 (18-36)	29 (14-38)	0.839[3]
Right bundle Brunch block, n (%)	22 (26.8)	2 (14.3)	0.506[1]
Left bundle Brunch block, n (%)	6 (7.3)	1 (7.1)	0.999[1]
Pathologic Q waves, n (%)	32 (39.0)	4 (11.1)	0.455[1]
Transthoracic Echocardiography closer to first consult			
Left atrial diameter (mm), median (P25-P75)	39 (31-43)	37 (24-53)	0.619[3]
Index left atrial volume, median (P25-P75)	44 (32-56)	46 (43-52)	0.585[3]
Diastolic left ventricle diameter (mm), median (P25-P75)	47 (43-50)	47 (41-54)	0.718[3]
Septal thickness (mm), median (P25-P75)	16 (13-19)	16 (13-18)	0.734[3]
Posterior Wall thickness (mm), median (P25-75)	10 (9-12)	11 (10-12)	0.194
Left ventricle ejection fraction (%), median (P25-P75)	65 (60-68)	62 (59-64)	0.094[3]
E/e' ratio, median (P25-P75)	8.3 (7.3-10.6)	11.0 (9.3-22.0)	0.039[3]
Cardiac magnetic resonance closer to first consult			
Index systolic volume of left ventricle (mL/m^2), median (P25-P75)	24 (20-30)	28 (18-35)	0.781[3]
Index diastolic volume of left ventricle (mL/m^2), median (P25-P75)	73 (60-86)	78 (58-85)	0.525[3]
Maximum left ventricular thickness (mm), median (P25-P75)	19 (16-21)	16 (14-17)	0.011[3]
Left ventricle ejection fraction (%), median (P25-P75)	67 (62-70)	62 (47-72)	0.397[3]
Right ventricle ejection fraction (%), median (P25-P75)	69 (63-72)	68 (57-72)	0.788[3]
Presence of late gadolunium enhancement, any localization, n (%)	56 (68.2)	8 (57.1)	0.630[2]
Presence of early gadolunium enhancement, any localization, n (%)	1 (1.2)	1 (7.1)	0.242[2]
Holter closer to first consult			
Mean Heart rate (bpm), median (P25-P75)	70 (61-75)	63 (61-66)	0.136[3]
Paroxysmal atrial fibrillation, n (%)	2 (2.4)	1 (7.1)	>0.999[2]
Non sustained ventricular tachycardia, n (%)	4 (4.4)	2 (2.2)	>0.999[2]

[1]Chi-square test; [2]Fisher exact test , [3]Mann Whitney U test; FDAVB, first-degree atrioventricular block; P25, percentile 25; P75, percentile 75; HCM, hypertrophic cardiomyopathy; bpm, beats per minute; ms, miliseconds; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.

frequent in the FDAVB group of patients, 28.6% *vs.* 6.1% on the non-FDAVB group, p=0.008), QRS duration (larger in the FDAVB group, with median 121 ms *vs.* 99 ms in non-FDAVB group, p=0.022), echocardiographic E/e' ratio (greater in the FDAVB group, with a median value of 11. *vs.* 8.3 in non-FDAVB group, p=0.039) and LV maximal septal thickness (LVMWT) at MRI (greater in the FDAVB group, with a median of 16 mm *vs.* 13 mm in non-FDAVB, p=0.011).

In multivariable logistic analysis, we found an association between a higher E/e' ratio and the presence of FDAVB (odds ratio of 1.588, p=0.041). No relation was stablished with other variables, namely maximum LV wall thickness and QRS interval duration (Table 2).

No association was found between the presence of LGE and the E/e' ratio (median E/e' ratio of 6.4 in the LGE group and median 3.5 in the group with no LGE, p=0.456).

First-degree atrioventricular block and outcomes

We did not find any association between FDAVB and the occurrence of at least one outcome: 24 (29.2%) patients in the group of non-FDAVB *vs.* 3 (21.4%) patients in the FDAVB group had at least one event (p=0.751). The same was found for AF: in the group of non-FDAVB, there were 12 (14.6%) *de novo* AF diagnoses *vs.* 1 (7.1%) in the FDAVB group (p=0.684) (Table 3). Dividing the patients accordingly to the development of AF during follow-up, there was not a statistically difference regarding the PR interval: patients who had *de novo* AF had a median PR of 170 (P25 134, P75 180) ms and patients who did not had median PR of 160 (P25 91, P75 187), p=0.202.

Discussion

First-degree atrioventricular block and outcomes

In our cohort of HCM patients, no relation was found between the presence of FDAVB and the new onset of AF or other cardiovascular events during follow-up, contrary to the findings of Higuchi *et al*. [22]. The limited size of our population and the subsequent scarcity of events might have influenced the obtained results, potentially overlooking a possible association.

In the latter paper, the authors advanced two possible explanations for the documented association: i) FDAVB leads to inappropriate atrioventricular coupling with pressure and volume overload, potentially contributing to the dilation of left atrium, which is a risk factor for atrial arrhythmogenesis and SCD [23-25]; ii) FDAVB might be a manifestation of advanced structural and electrical remodeling in a HCM heart, with higher risk of arrhythmia and death. The higher frequency of LA dilation in the FDAVB group substantiated the first hypothesis; the other alternative explanation was not as supported, as there was no difference in LV dimensions, LV ejection fraction, or E/e' ratio between the FDAVB and the non-FDAVB groups, and there was no data regarding fibrosis.

In our sample, the duration of PR interval in FDAVB and non-FDAVB was similar compared to the one in the referred study, but contrary to it, no significant difference was found regarding LA dimensions and the presence of FDAVB. Whether this lack of association could elucidate why FDAVB failed to predict outcomes in our cohort of patients remains uncertain.

However, despite the substantial body of literature indicating FDAVB as a predictor of cardiovascular events across diverse populations (including healthy individuals of different ethnicities, patients with coronary disease, arrhythmogenic right ventricular cardiomyopathy, and acute heart failure, among others) [12-21], there are still neutral findings in some studies [26,27]. Indeed, even within an HCM population, a prior study by Claeys *et al*., examining ECG-derived risk factors for SCD, did not establish a link between FDAVB and SCD [28].

Additional research is essential to evaluate the potential link between the presence of FDAVB and outcomes in HCM patients.

Table 2. Logistic multivariable regression for first-degree atrioventricular block.

	OR	95% CI		p
Median E/e' ratio	1.588	1.020	2.473	0.041
QRS duration (ms)	1.079	0.964	1.208	0.186
Left ventricular maximum wall thickness (mm)	0.771	0.439	1.354	0.366

OR, odds ratio; CI, confidence interval; Hosmer-Lesmeshow p=0.966; area under the curve, 0.920 [0.813-1.000]

Table 3. Outcomes during the follow-up in patients with and without first-degree atrioventricular block.

Outcomes, n (%)	Patients without FDAVB (PR≤200 ms) n=82)	Patients with FDAVB (PR>200 ms) (n=14)	p
Cardiovascular death	0 (0.0)	0 (0.0)	-
De novo atrial fibrillation	12 (14.6)	1 (7.1)	0.684[2]
New onset stroke	7 (8.5)	1 (7.1)	>0.999[2]
Placement of ICD for secondary prevention	2 (2.4)	0 (0.0)	>0.999[2]
Hospitalization related to HCM	7 (8.5)	1 (7.1)	>0.999[2]
Myocardial Infarction	4 (4.6)	0 (0.0)	-
Patients with at least one of the following events (stroke/atrial arrhythmia/secondary ICD implantation/hospitalization related to cardiovascular cause/myocardial Infarction)	24 (29.3)	3 (21.4)	0.751[2]

[1]Chi-square test; [2]Fisher exact test; ICD, implantable cardio-defibrillator, HCM, hypertrophic cardiomyopathy.

First-degree atrioventricular block and hypertrophic cardiomyopathy findings

We found an association between the presence of FDAVB and age, which could merely represent the physiological process of age-related degeneration in the conduction system. An association of FDAVB and a larger QRS interval on ECG was also documented. In theory, both the aging degeneration and more advanced remodeling occur in the entire conduction system, including not only the AV node, but also the bundle branches. Delcrè *et al.* showed that the severity of ECG abnormalities in HCM patients, involving a total of 9 criteria, including QRS duration, is directly related to the degree of phenotypic expression by CMR (both LV mass index and presence/extent of LGE) [29]. This association of FDAVB and larger QRS duration could be explained by a higher degree of remodeling and fibrosis of the electric system of the HCM patients. It is noteworthy that no differences were documented between the group with FDAVB and the group of patients with normal PR regarding cardiovascular medications, particularly β-blockers.

Surprisingly, we documented that FDAVB patients had a lower LVMWT at MRI compared to non-FDAVB patients. While it is established that higher LVMWT is genotype dependent and an important variable for SCD score risk in HCM patients, there seems to be no consistent relationship with the presence of FDAVB [10,22,30]. Nonetheless, it is important to highlight the role of FDAVB as a red flag for hypertrophy phenocopies, as Fabry cardiomyopathy and amyloidosis [31]. One possible explanation for FDAVB and lower LVMWT is that more remodeled hearts could have a less hypertrophic and more fibrotic phenotype. Interestingly, although there was no difference in LGE presence in both groups, identifying replacement fibrosis, we did not have data on interstitial fibrosis (through myocardial T1 mapping) [32]. Additional investigation is needed on this topic.

First-degree atrioventricular block and E/e' ratio

The E/e' ratio is a well-established marker of LV diastolic dysfunction, a parameter that correlates well with LV end-diastolic pressure [33,34].

Impaired LV diastolic function is a major finding in HCM patients and is attributed to myocardial hypertrophy, myofibers disarray, and fibrosis, as well as sarcomeric contraction impairment and silent ischemia. A thickened and noncompliant LV results in under relaxation and abnormal diastolic filling, promoting LA remodeling and AF, both prognosis markers in HCM [3,9,10].

Badran *et al*. discovered that the E/e' ratio is a significant predictor of all-cause mortality in HCM patients. Those with an E/e'>13.5 exhibited the poorest cardiovascular outcomes, facing over twice the risk of events compared to individuals with an E/e'<6.5 [35].

In our study, we found that HCM patients with FDAVB had a higher median E/e' ratio compared to those without FDAVB and, probably as a consequence, more dyspnea. To the best of our knowledge, this is the first time that the association of FDAVB and E/e' ratio has been documented in a cohort of HCM patients, and it remained significant after adjustment for confounders, QRS duration, and LVMWT, markers of dyssynchrony and degree of morphological alterations. The crucial question is whether this association of FDAVB and higher E/e' solely reflects underlying advanced structural and electrical remodeling or if there could be a direct harmful impact of FDAVB on cardiac diastolic function.

Supporting the first hypothesis is the fact that FDAVB patients were older with larger QRS duration; on the other hand, we did not find differences considering the LA dimensions or the presence of LGE between the FDAVB and non-FDAVB patients. According to Adis *et al*., we observed no association between the presence of LGE and the E/e' ratio. Nevertheless, this observation might have overlooked interstitial fibrosis, a significant contributor to HCM pathophysiology [36].

With the abnormal delay of electric conduction within the atrioventricular node, FDAVB can alter the synchronization between atrial contraction and ventricular relaxation. This asynchrony can potentially result in inadequate ventricular filling since its atrial contribution becomes impaired, leading to diastolic dysfunction over time. In non-compliant HCM LV, the contribution to ventricular filling through the rapid diastolic filling phase is reduced while that from atrial systole is increased. Therefore, patients with HCM and FDAVB may experience additionally compromised atrial kick, further exacerbating diastolic dysfunction, and potentially explaining a lower E/e' ratio [37,38].

It is relevant to note that e' measurement can be attained by different methods and has inter-operator variability, with implications for different studies' results. The E/e' ratio is also affected by some physiological factors such as age, gender and ethnicity [39].

Though the identified association between FDAVB and E/e' ratio in HCM patients may lack direct clinical implications, it does open the door to a new area of investigation worth exploring, as FDAVB obtained through a simple ECG may assist in detecting early stages of asymptomatic diastolic dysfunction.

Limitations

This is an observational, retrospective, single-center study with its inherent limitations. It included a small number of patients, with a shorter follow-up time and fewer events, when compared with previous studies. It is worth noting that findings attained in echocardiogram, as the E/e' ratio, are operator dependent and those were different between patients, given the retrospective nature of the study. All these considerations must be considered when interpreting the obtained results. On the other hand, it is the first study about FDAVB in a cohort of Portuguese HCM patients, with collection of important clinical and multi-imaging data, and the first to document a relation between FDAVB and E/e' ratio.

Conclusions

In our HCM cohort of patients, FDAVB was independently associated with E/e' ratio, a surrogate of diastolic dysfunction. As such, it may help to identify HCM patients at the pre-clinical phase, when subtle changes in LV filling appear.

Contrary to previous literature, no association was found with outcomes. FDAVB is a controversial parameter of worse prognosis in HCM patients. There are still few studies that analyzed this issue in HCM patients, and it should be a topic of further investigation in the future, with prospective, large scale and multicenter studies.

References

1. Maron BJ, Desai MY, Nishimura RA, et al. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2022;79:372-89.
2. Medical Masterclass contributors, Firth J. Cardiology: hypertrophic cardiomyopathy. Clin Med (Lond) 2019;19:61-3.
3. Popa-Fotea NM, Micheu MM, Bataila V, et al. Exploring the

continuum of hypertrophic cardiomyopathy-from DNA to clinical expression. Medicina (Kaunas) 2019;55:299.
4. Maron BJ, Desai MY, Nishimura RA, et al. Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2022;79:390-414.
5. Zampieri M, Berteotti M, Ferrantini C, et al. Pathophysiology and treatment of hypertrophic cardiomyopathy: new perspectives. Curr Heart Fail Rep 2021;18:169-79.
6. Dragasis S, Vlachos K, Kariki O, et al. Atrial fibrillation in hypertrophic cardiomyopathy - a contemporary mini-review. Hellenic J Cardiol 2022;67:66-72. Parte superior do formulário
7. Alphonse P, Virk S, Collins J, et al. Prognostic impact of atrial fibrillation in hypertrophic cardiomyopathy: a systematic review. Clin Res Cardiol 2021;110:544-54.
8. Arunachalam K, Maan A, Chu A. Atrial fibrillation in hypertrophic cardiomyopathy: evidence-based review about mechanism, complications and management. Crit Pathw Cardiol 2020;19:87-9.
9. Masri A, Kanj M, Thamilarasan M, et al. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. Cardiovasc Diagn Ther 2017;7: 36-44.
10. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
11. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation 2020;142:558-631.
12. Cheng S, Keyes MJ, Larson MG, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA 2009;301:2571-7.
13. Crisel RK, Farzaneh-Far R, Na B, Whooley MA. First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study. Eur Heart J 2011;32:1875-80.
14. Schumacher K, Buttner P, Dagres N, et al. Association between PR interval prolongation and electro-anatomical substrate in patients with atrial fibrillation. PLoS One 2018;13:e0206933.
15. Chan YH, Hai JJ, Lau KK, et al. PR interval prolongation in coronary patients or risk equivalent: excess risk of ischemic stroke and vascular pathophysiological insights. BMC Cardiovasc Disord 2017;17:233.
16. Liu M, Du Z, Sun Y. Prognostic significance of first-degree atrioventricular block in a large Asian population: a prospective cohort study. BMJ Open 2022;12:e062005.
17. Aro AL, Anttonen O, Kerola T, et al. Prognostic significance of prolonged PR interval in the general population. Eur Heart J 2014;35:123-9.
18. Kimura Y, Noda T, Matsuyama TA, et al. Heart failure in patients with arrhythmogenic right ventricular cardiomyopathy: what are the risk factors?. Int J Cardiol 2017;241:288-94.
19. Kimura Y, Fukuda K, Nakano M, et al. Prognostic significance of PR interval prolongation in adult patients with total correction of tetralogy of fallot. Circ Arrhythm Electrophysiol 2018;11: e006234.
20. Kwok CS, Rashid M, Beynon R, et al. Prolonged PR interval, first-degree heart block and adverse cardiovascular outcomes: a systematic review and meta-analysis. Heart 2016;102:672-80.
21. Nielsen JB, Pietersen A, Graff C, et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. Heart Rhythm 2013;10: 1249-56.
22. Higuchi S, Minami Y, Shoda M, et al. Prognostic implication of first-degree atrioventricular block in patients with hypertrophic cardiomyopathy. J Am Heart Assoc 2020;9:e015064.
23. Nistri S, Olivotto I, Betocchi S, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for hypertrophic cardiomyopathy). Am J Cardiol 2006;98:960-5
24. O'Mahony C, Jichi F, Pavlou M, et al; Hypertrophic cardiomyopathy outcomes investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-20.
25. Minami Y, Haruki S, Yashiro B, et al. Enlarged left atrium and sudden death risk in hypertrophic cardiomyopathy patients with or without atrial fibrillation. J Cardiol 2016;68:478-84.
26. Holmqvist F, Thomas KL, Broderick S, et al. Clinical outcome as a function of the PR-interval-there is virtue in moderation: data from the Duke Databank for cardiovascular disease. Europace 2015;17:978-85.
27. Hisamatsu T, Miura K, Fujiyoshi A, el at. NIPPON DATA80 research group. Long-term outcomes associated with prolonged PR interval in the general Japanese population. Int J Cardiol 2015;184:291-3.
28. Patel SI, Ackerman MJ, Shamoun FE, et al. QT prolongation and sudden cardiac death risk in hypertrophic cardiomyopathy. Acta Cardiol 2019;74:53-8.
29. Delcrè SD, Di Donna P, Leuzzi S, et al. Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: a cardiac magnetic resonance study. Int J Cardiol 2013;167:1038-45.
30. Lopes LR, MS Rahman, and P.M. Elliott, A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. Heart 2013;99:1800-11.
31. Gossios T, Savvatis K, Zegkos T, et al. Deciphering hypertrophic cardiomyopathy with electrocardiography. Heart Fail Rev 2022;27:1313-23.
32. Mewton N, Liu CY, Croisille P, et al. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891-903.
33. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
34. Haland TF, Edvardsen T. The role of echocardiography in management of hypertrophic cardiomyopathy. J Echocardiogr 2020;18:77-85.
35. Badran HM, Soltan G, Almeleigi R, et al. Prognostic significance of left ventricular end diastolic pressure using E/E' in patients with hypertrophic cardiomyopathy. Echocardiography 2019;36:2167-75.
36. Alis D, Guler A, Asmakutlu O, et al. The association between the extent of late gadolinium enhancement and diastolic dysfunction in hypertrophic cardiomyopathy. Indian J Radiol Imaging 2021;31:284-90.
37. Laurent G, Eicher JC, Wolf JE. First-degree atrioventricular block and pseudopacemaker syndrome. Arch Cardiovasc Dis 2013;106:690-3.
38. Bonow RO, Frederick TM, Bacharach SL, et al. Atrial systole and left ventricular filling in hypertrophic cardiomyopathy: effect of verapamil. Am J Cardiol 1983;51:1386-91.
39. Sunderji I, Singh V, Fraser AG. When does the E/e' index not work? The pitfalls of oversimplifying diastolic function. Echocardiography 2020;37:1897-907.