Clinical characteristics of patients with arrhythmic mitral valve prolapse in a single tertiary center: prevalence of electrocardiographic and myocardial abnormalities

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INTRODUCTION

Mitral valve prolapse (MVP) related sudden cardiac death (SCD) occurs with an estimated annual risk of 0.2%–1.9% and affects also young and otherwise healthy MVP patients with trivial or absent mitral regurgitation (MR) [1–3]. Several characteristics of the arrhythmogenic MVP (AMVP) were found, including bileaflet MVP, female sex, T-wave inversions (TWI), mitral annular disjunction (MAD), focal fibrosis of papillary muscles (PMs) and adjacent inferobasal LV wall, and frequent/complex ventricular arrhythmias (VA) [1, 3, 4]. The cohorts studied in the MVP series included SCD victims [2, 4, 6], survivors of cardiac arrest (CA) [3], patients with frequent and complex VA referred for catheter ablation [7, 8], or imaging studies for MR [9]. Little is known, however, about the characteristics of patients diagnosed with AMVP in real-life settings. Given the paucity of data, we aimed to characterize consecutive patients from our institution, in whom features of AMVP were found.

METHODS

Patients referred to our tertiary center between October 2016 and March 2020 were screened for the presence of AMVP defined as MVP, MAD, curling, and frequent and/or complex VA. Patients underwent a cardiovascular evaluation that included history, physical examination, 12-lead ECG, transthoracic echocardiography, 24-hour Holter monitoring, exercise testing, and LGE-CMR unless contraindicated. Additionally, all patients implanted with an ICD and diagnosed with idiopathic ventricular fibrillation (IVF), i.e., negative for ischemia, cardiomyopathy, and channelopathy, were systematically re-screened, and included in the study group, if signs of AMVP were present. The patients were divided into two groups based on the occurrence of CA in the past medical history and followed prospectively. The institutional review board approved the study and all patients gave informed consent.

Statistical analysis

All calculations were done using Statistica 13PL (StatSoft, Tulsa, OK, USA). Continuous data were presented either as median (range) or median (IQR); categorical data were given as n (%). The normality of continuous data was tested with W Shapiro-Wilk test. U Mann-Whitney test was used for intergroup comparisons. Fisher's exact test was used for categorical data comparisons. $P < 0.05$ was adopted as significant.

RESULTS AND DISCUSSION

Twenty-six patients met the study criteria (Table 1). Twelve (46%) patients were diagnosed with MVP and/or VA in childhood, at the median age of 9 years. A total of 23 (89%) patients reported symptoms such as palpitations, dizziness, and fatigue. Among 23 patients implanted with an ICD due to IVF, in 7 (30%, 2 males) AMVP was subsequently diagnosed. The median age of CA was 28 (range 17–37) years. In all patients, the sentinel VF event occurred while not on

β-blockers: at leisure activity (n = 7), and night (n = 1). In men, CA occurred in the daytime and was not associated with stress/exercise. In 3 women CA occurred in relation to pregnancy or postpartum period, i.e., in the 8th week of pregnancy, two and six months post-delivery. Noteworthy, all but one CA patient were consulted by a cardiologist for a median period of 7 (range 0–16) years before CA. Upon observation, in 3 patients (two males) appropriate ICD therapies occurred, with recurring electrical storms in one.

In the non-CA group the most common referral diagnoses were: frequent /complex VA (n = 14/18, 78%), either alone (n = 7) or with MVP (n = 5) and/or a suspicion of NC cardiomyopathy (n = 2), a suspicion of the long QT syndrome (n = 1); a cardiac murmur and palpitations (n = 1), syncope (n = 1), or arterial hypertension (n = 1).

All patients had bileaflet MVP with curling, MAD and preserved LVEF. In 13 (50%) mild/minimal MR, in 12 (46.2%) moderate, and one patient (3.8%) severe MR was found. CMR was performed in 12 (46%), and in 8/12 (67%) patients criteria for LVNC were fulfilled, with a median NC/C ratio of 3.2 (range 1.4–5.5). The NC pattern was associated with thinning of the compact myocardial layer to 2–4 mm in the anterior and/or lateral wall**,** and an abnormal structure/fragmented (trabeculated) base of PMs. In 9/12 (75%) subtle dispersed LGE was identified in the basal inferolateral wall and/or mid-inferolateral segments or PMs.

In all patients complex VA was recorded with >1 (median 3) PVCs morphology predominantly of the RBBB pattern from the posterior PM. In 15/26 (58%) patients three-beat nonsustained VT (nsVT), and in 14/26 patients nsVT lasting >3 beats occurred. In Holter recordings, PVCs occurred predominantly at night in two, and during the daily activity in the remaining patients. Of the 19 individuals who underwent exercise stress treadmill testing, an increase in frequency and VA complexity was observed in 3, resolution of VA in 6, VA onset in recovery stage in 3, and persistent VA with no/minimal change in 4 patients.

TWI was observed in the inferior leads in 20 (77%) patients, in 15 (58%) both normal ECGs and TWI were found. Among a total of 165 ECGs (6 strips/patient), 87 (53%) ECGs were normal, the remaining showed TWI in different configurations in ≥2 inferior leads. Only one CA survivor presented with normal ECG in all strips when compared to 5/18 nonCA patients (12.5% vs 28%; $P = 0.378$).

Twenty-four (92%) patients were treated with betablockers (bisoprolol, metoprolol, nadolol), which did not prevent malignant VA in ICD patients. Class Ic antiarrhythmics (propafenone or flecainide) alone or with betablocker were used in 2 patients with modest efficacy. One patient underwent mitral valve repair for significant MR 3 years after CA, with no VTA during follow-up.

The CA and non-CA patients differed for heart rate 68 (64–71) vs 76 (64–85) bpm; $P = 0.04$, E/e'ratio — 7.7 (6.5–9.2) vs 5.9 (5.4–6.7); $P = 0.04$, and the fastest rate of nsVT — 220 (181– 279) vs 178.5 (150–200) bpm; $P = 0.04$ (Table 1).

The presence of LV non-compaction in AMVP patients seems to contrast with the results of the studies reporting MVP as the only cardiac abnormality in SCD or out-of-hospital CA series [2–4]. In these studies, however, patients with any cardiomyopathy were *a priori* excluded. Recently, Garbi et al. showed that 81% of SCD cases with „lone" MVP had microscopic LV fibrosis associated with hypertrophy and degeneration of the myocytes, and 11% also had RV fibrosis [10]. The diffuse LV fibrosis was also demonstrated in AMVP by reduced post-contrast T1 times on CMR imaging [11]. Lastly, in MVP patients, VA arise from fascicles, LV outflow tract or septal aspect of the mitral annulus, RV outflow tract and free wall [3, 7] indicating the presence of more extensive arrhythmogenic substrate. In this context higher E/e'ratio, which is a noninvasive insight into diastolic LV pressures, might reflect more extensive disease (fibrosis) in CA patients. Various mechanisms for VA in the setting of MVP were postulated, with focal fibrosis (positive LGE) and consequent regions of conduction block promoting re-entry arrhythmia, and interstitial fibrosis (abnormal T1) resulting in spontaneous diastolic depolarization and abnormal automaticity [11]. To the best of our knowledge, E/e' ratio was not previously discussed in AMVP patients in the context of SCD risk.

Interestingly, inferior TWI was present in 77% of patients, with intermittent TWI in 58% of AMVP cases. This finding is of importance since TWI is considered a part of the diagnostic tetrad in AMVP [3, 4, 9]. The observed variability, however, may be also related to cardiac memory.

Our study showed that almost all patients were consulted by a cardiologist before CA, moreover, half of them was supervised since childhood/adolescence. Thus, patients with malignant MVP are under the specialist care for a long time, while their SCD risk goes unrecognized. In this context, the observed differences between CA and nonCA patients with regard to the rate of nsVT and E/e'ratio seem to be interesting, however, they need to be validated in larger groups of AMVP patients, preferably the multi-center registry, to establish risk stratification algorithms for SCD in MVP.

Finally, in women CA tends to occur in pregnancy or after delivery, pointing to a possible relation of hormonal status to VA. Similarly, Syed et al. found that in 2 of 6 females, pregnancy and a menstrual cycle were triggers for appropriate ICD shocks [7].

CONCLUSIONS

AMVP is a clinical syndrome characterized by intermittent TWI and myocardial abnormalities, such as LV non-compaction. AMVP patients after CA differ by faster rates of nonsustained VT and higher E/e' ratio from non-CA patients. We support the view that patients with IVF should be systematically reassessed for the presence of new arrhythmogenic conditions, including AMVP, which may constitute 30% of IVF cases.

Table 1. Characteristics of the study patients and group comparisons

Variables	Overall AMVP group (n = 26)	Non-CA group (n = 18)	CA group[a] (n = 8)	P-value
Age, years, median (IQR)	36 (33.5–46)	36.5 (35–48)	36.5 (29.5–44)	0.44
Women, n (%)	18 (69)	12 (67)	6 (75)	0.523
Follow-up, months, median(IQR)	27.5 (21–103)	24.5 (18–64)	108 (40–177)	0.009
Weight, kg, median (IQR)	65 (60–71)	64 (56–71)	65 (63–75)	0.36
Height, cm, median (IQR)	173 (170–179)	174 (170–180)	168.5 (166–178)	0.08
Body mass index, kg/m^2, median (IQR)	21 (20–23)	20.5 (20–23)	22.4 (22–25.5)	0.08
Age of first symptoms, years, median (IQR)	18 (9–28)	18 (8–26)	17.5 (9.5–29.5)	0.98
Symptomatic PVCs, n (%)	23 (89)	16 (89)	7 (88)	0.686
Syncope, n (%)	4 (15)	3 (17)	1 (13)	0.64
β-blockers, n (%)	24 (92)	16 (89)	8 (100)	0.471
Pacemaker, n (%)	1 (4)	0	1 (12.5)	0.31
ICD, n (%)	9 (35)	2 (11)	7 (88)	0.0004
ECG data				
No of PVCs, median (IQR)	3250 (1803–8675)	3000 (1800–9200)	3250 (1737–4500)	0.98
The shortest coupling interval, ms, median (IQR)	400 (360–440)	420 (370–440)	360 (330–440)	0.11
The longest coupling interval, ms, median (IQR)	480 (480–543)	520 (480–550)	480 (460–516)	0.11
Max VT rate, bpm, median (IQR)	188 (170–207)	178.5 (150–200)	220 (181–279)	0.04
HR, bpm, median (IQR)	75 (65–85)	75.5 (64–85)	67.5 (64–71)	0.04
PR, ms, median (IQR)	150 (130–160)	150 (130–160)	170 (150–195)	0.13
QRS, ms, median(IQR)	90 (90–110)	100 (90–100)	95 (85–100)	0.86
QT, ms, median (IQR)	400 (380–420)	400 (360–430)	420 (380–440)	0.43
QTc, ms, median (IQR)	437 (420–455)	440 (420–456)	439 (427–452)	0.98
Inferior TWI, n (%)	20 (77)	13 (72)	7 (88)	0.38
Intermittent TWI, n (%)	14 (54)	9 (50)	5 (63)	0.44
Echocardiographic data				
Curling distance, mm, median (IQR)	6 (5–7)	6 (4–7)	7 (5–8)	0.35
MAD, mm, median (IQR)	11 (9–12)	10 (9–12)	11 (8–13)	0.97
LVEF, %, median(IQR)	60 (55–60)	60 (55–60)	58 (53–63)	0.93
GLS, %, median (IQR)	–21 (–22.5–[–20])	–21.5 (–24.5–[–20])	–20.5 (–22–[–19])	0.26
LVESD, mm, median(IQR)	32 (28–35)	32 (30–35)	29.5 (26–37)	0.68
LVEDD, mm, median (IQR)	51 (47–55)	51 (49–55)	50 (46–55)	0.74
LA diameter, mm, median (IQR)	37 (34–42)	37 (35–43)	36 (32–42)	0.52
LAVI, ml/m^2, median (IQR)	31 (23–40)	27 (23–41)	36 (22–45)	0.9
e', median (IQR)	0.11 (0.1–0.12)	0.11 (0.1–0.12)	0.11 (0.09–0.14)	0.97
E/e', median (IQR)	6.2 (5.6–6.8)	5.9 (5.4–6.7)	7.7 (6.5–9.2)	0.04

[a]The patient with symptomatic polymorphic VT/VF and DDD pacemaker was also included in this group.

Abbreviations: GLS, global longitudinal strain; HR, heart rate; ICD, implantable cardioverter-defibrillator; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MAD, mitral annular disjunction; MVP, mitral valve prolapse; PVCs, premature ventricular contractions; TWI, T-Wave inversion; VT, ventricular tachycardia

Article information

Conflict of interest: None declared.

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