Clinical Profile and Prognostic Significance of Atrial Fibrillation in Hypertrophic Cardiomyopathy

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Key Words

Hypertrophic cardiomyopathy · Atrial fibrillation · Prognosis

Abstract

Objectives: The clinical outcomes of hypertrophic cardiomyopathy (HCM) are largely unpredictable. This study aimed to investigate the relationship between atrial fibrillation (AF) and its prognostic implications in Chinese patients with HCM. **Methods:** From 1999 to 2011, 654 unrelated HCM patients were consecutively recruited at Fuwai Hospital. Medical history, including electrocardiographic and echocardiographic data, was analyzed. **Results:** AF was documented in 158 patients (24%). During follow-up of 4.2 ± 2.8 years, Kaplan-Meier analysis revealed that the presence of AF was associated with an increased risk for all-cause death ($p = 0.001$), cardiovascular death ($p < 0.001$), severe heart failure ($p < 0.001$) and ischemic stroke ($p < 0.001$). Multivariate analysis identified AF as an independent predictor of stroke-related death (HR 6.71, 95% CI 1.23–38.58, $p = 0.03$), advanced heart failure (HR 1.83, 95% CI 1.04–3.22, $p = 0.04$) and ischemic stroke (HR 9.98, 95% CI 4.06–24.53, $p < 0.001$). Furthermore, enlarged left atrial diameter was positively related to all-cause death (HR 1.09, 95% CI 1.05–1.13, $p < 0.001$), cardiovascular death (HR 1.08, 95% CI 1.04–1.20, $p < 0.001$) and

development of advanced heart failure (HR 1.05, 95% CI 1.01–1.10, $p = 0.01$). **Conclusions:** AF predicts poor outcomes for patients with HCM. Left atrial dilation is also related to an adverse prognosis and provides additional prognostic information.

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Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiac disorders, with marked heterogeneity in clinical manifestations and outcomes [1, 2]. Although HCM generally has a relatively benign prognosis in an unselected population [3, 4], some patients suffer from end-stage heart failure, stroke or premature sudden cardiac death (SCD) [5–7]. Consequently, identification of patients at high risk has great clinical significance for initiating early prevention and improving the prognosis of HCM. At present, some risk factors associated with SCD in HCM patients have been established [8]. A risk-stratification algorithm based on these factors is

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useful in identifying high-risk subjects for lifesaving intervention with an implanted cardioverter-defibrillator (ICD). However, risk factors related to heart failure and stroke in HCM patients are not well developed.

Atrial fibrillation (AF) is reported to occur in approximately 1% of the general population [9], but 20–30% of the HCM population [4, 10–13]. Some studies suggest that AF is associated with adverse outcomes in patients with HCM and other cardiovascular diseases [11, 14, 15]. However, no prospective data have been reported in the Chinese HCM population. This study was therefore undertaken to investigate the prognostic value of AF in Chinese HCM patients.

Methods

Population

A total of 654 unrelated patients with HCM were consecutively recruited at Beijing Fuwai Hospital, Chinese Academy of Medical Sciences, from 1999 to 2011. All of the patients gave informed consent to participate in this research project, which was approved by the ethics committee of Fuwai Hospital. The diagnosis of HCM was based on a hypertrophied left ventricle with wall thickness ≥ 15 mm (or ≥ 13 mm with an HCM family history) on echocardiography (or echocardiography and cardiac magnetic resonance imaging) in the absence of other cardiac or systemic diseases responsible for the hypertrophy (e.g. cardiac valve disease, uncontrolled hypertension or congenital heart disease) [8, 16]. AF was documented based on ECG recordings obtained when patients presented with acute onset of symptoms or during routine examination on admission or based on 24-hour Holter monitoring. Three cardiologists independently reviewed all clinical data.

Follow-Up

The primary end points were all-cause death and cardiovascular death (including SCD, heart failure-related death and stroke-related death). SCD was defined as sudden, unexpected natural death from a cardiac cause occurring within 1 hour after the onset of symptoms in a person without any prior fatal condition. Potentially lethal cardiovascular events in which patients were either successfully resuscitated from cardiac arrest or received appropriate defibrillation from an implanted ICD were regarded as equivalent to SCD. Heart failure-related death was defined as death occurring in the context of long-term cardiac decompensation with progression of disease over the preceding year. Stroke-related death was defined as death occurring in patients who died of ischemic or hemorrhagic stroke.

The other end points included development of advanced chronic heart failure [New York Heart Association (NYHA) functional class deterioration from I/II to III/IV] or ischemic stroke. Chronic heart failure was diagnosed according to typical shortness of breath at rest or during exertion and/or fatigue, signs of fluid retention such as ankle swelling and objective evidence of an abnormality of the structure or function of the heart at rest [17].

Follow-up duration was calculated from the initial evaluation for patients with AF at enrollment, and from the time of onset of AF for patients with sinus rhythm at enrollment who developed AF during follow-up.

Statistical Analysis

Statistical analysis was performed with SPSS version 18.0 software (SPSS Inc., Chicago, Ill., USA). All data were expressed as mean $\pm$ standard deviation or frequency. Differences in continuous variables were assessed using the Student *t* test, and the Wilcoxon rank-sum test was used when the distributions were asymmetric. The χ^2 test was used for comparisons between noncontinuous variables, and if the patient number in any group was <5 , the Fisher exact test was used. The Kaplan-Meier method was used to calculate survival time free from the end point events. A log-rank test was used to compare survival curves among different patient groups. The Cox proportional hazard regression model was performed to identify variables associated with the end points. All statistical tests were two-sided and a *p* value of <0.05 was considered to be statistically significant.

Results

Baseline Clinical Characteristics

Of the 654 patients with HCM at enrollment, 112 (17%) had AF. Of these, 86 (77%) were identified during acute onset of symptoms, 19 (17%) during routine examination on admission and 7 (6%) during electrocardiography with Holter monitoring. Patients with AF were older (56 ± 15 vs. 49 ± 14 years, $p < 0.001$) and had more severe heart failure (NYHA functional class III/IV, 21 vs. 10%, $p < 0.001$) than patients with sinus rhythm. Echocardiographic findings showed that patients with AF had a more dilated left atrium (45 ± 8 vs. 39 ± 6 mm in diameter, $p < 0.001$) and larger left ventricular (LV) end-diastolic diameter (46 ± 6 vs. 45 ± 7 mm, $p = 0.02$) (table 1).

Clinical Outcomes

New development of AF was identified in 46 patients during follow-up. Of these patients, 37 (80%) were identified because of symptom onset, 7 (15%) during routine medical examinations and 2 (4%) during Holter monitoring. Overall, AF was documented in 158 (24%) patients throughout the study. New occurrence of AF was independently predicted by aging (HR 1.04, 95% CI 1.02–1.07, $p = 0.001$), severe heart failure (HR 2.32, 95% CI 1.10–4.89, $p = 0.03$) and dilated left atrium (HR 1.08, 95% CI 1.03–1.13, $p = 0.002$). See online supplementary table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000354953).

During a follow-up of 4.2 ± 2.8 years (range 0.1–12.2 years), 57 patients died. Twenty-three deaths (15%, 23/158), including 8 SCDs, 7 heart failure-related deaths, 7 stroke-related deaths and 1 noncardiovascular death occurred in patients with AF. Thirty-four deaths (7%, 34/496), including 11 SCDs, 15 heart failure-related

Table 1. Baseline characteristics of the study population

	All patients (n = 654)	Patients with AF (n = 112)	Patients with SR (n = 542)	p value
Male	463 (71)	81 (72)	382 (71)	0.70
Age, years	50±15	56±15	49±14	<0.001
Dyspnea	395 (60)	78 (70)	317 (59)	0.03
Chest pain	271 (41)	41 (37)	230 (42)	0.25
Palpitation	274 (42)	71 (63)	203 (38)	<0.001
Unexplained syncope	128 (20)	23 (21)	105 (19)	0.78
NYHA III/IV	76 (12)	24 (21)	52 (10)	<0.001
Family history of HCM	166 (25)	31 (28)	135 (25)	0.54
Family history of SCD	95 (15)	20 (18)	75 (14)	0.27
Heart rate at rest, bpm	71±13	72±17	71±12	0.25
Systolic blood pressure, mm Hg	122±18	122±20	121±17	0.70
Diastolic blood pressure, mm Hg	75±11	75±12	75±10	0.88
Echocardiography				
Left atrial diameter, mm	40±7	45±8	39±6	<0.001
LV end-diastolic diameter, mm	45±7	46±6	45±7	0.02
Left ejection fraction	66±9	64±10	67±9	0.001
Maximal LV wall thickness, mm	20±6	20±5	20±6	0.50
LV outflow obstruction at rest	240 (37)	34 (30)	206 (38)	0.13
Electrocardiography				
Pathological Q wave	166 (25)	34 (30)	132 (24)	0.18
ST-segment depression	437 (67)	66 (59)	371 (69)	0.06
Flat or inverted T-wave	455 (70)	76 (68)	379 (70)	0.67
Drug therapy				
Beta blockers	551 (84)	99 (88)	452 (83)	0.19
Calcium-channel blockers	253 (39)	45 (40)	208 (38)	0.72
ACEIs/ARBs	179 (27)	30 (27)	149 (28)	0.88
Diuretics	80 (12)	28 (25)	52 (10)	<0.001
Digoxin	9 (1.4)	6 (5)	3 (1)	0.001
Amiodarone	36 (6)	22 (20)	14 (3)	<0.001
Warfarin	17 (3)	16 (14)	1 (0)	<0.001
Invasive therapy				
Surgical septal myectomy	15 (2.3)	2 (2)	13 (2)	1.00
Alcohol septal ablation	99 (15)	11 (10)	88 (16)	0.09
ICD implantation	3 (1)	0 (0.0)	3 (1)	1.00

Figures in parentheses are percentages. ACEIs = Angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; SR = sinus rhythm.

deaths, 2 stroke-related deaths and 6 noncardiovascular deaths occurred in the patients with sinus rhythm. The annual incidence of cardiovascular death was 1.8% in the entire cohort. Kaplan-Meier analysis showed that the patients with AF had a higher risk for all-cause mortality ($p = 0.001$) and cardiovascular death ($p < 0.001$) (fig. 1). As for cardiovascular death, the presence of AF was related to an increased risk for SCD ($p = 0.04$) and stroke-related death ($p < 0.001$), but not to heart failure-related death ($p = 0.26$).

Multivariate Cox regression analysis identified AF as an independent risk factor for cardiovascular death (HR

2.02, 95% CI 1.10–3.70, $p = 0.02$) and stroke-related death (HR 11.21, 95% CI 2.22–56.65, $p = 0.003$) after adjustment for age, gender, unexplained syncope, NYHA function class (III/IV vs. I/II), maximal LV wall thickness, LV outflow tract obstruction (gradient ≥ 30 mm Hg) at rest, LV end-diastolic diameter and a family history of SCD (online suppl. table S2). However, AF was just an independent predictor for stroke-related death (HR 6.71, 95% CI 1.23–38.58, $p = 0.03$) after left atrial diameter was included in the multivariate analysis. Conversely, dilated left atrial diameter was significantly associated with all-cause death (HR 1.09, 95% CI 1.05–1.13, $p < 0.001$) and

Table 2. Multivariate Cox proportional hazards models for the end points of death

Variables	All-cause death		Cardiovascular death		SCD		Heart failure-related death		Stroke-related death	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Female gender	1.74 (0.95–3.19)	0.08	1.58 (0.82–3.05)	0.17	1.14 (0.40–3.28)	0.81	2.39 (0.84–6.83)	0.11	1.70 (0.37–7.80)	0.50
Age ^a	1.01 (0.99–1.03)	0.20	1.01 (0.99–1.03)	0.47	0.98 (0.95–1.01)	0.18	1.03 (1.00–1.06)	0.06	1.03 (0.97–1.09)	0.31
Unexplained syncope	1.30 (0.68–2.48)	0.43	1.29 (0.65–2.57)	0.47	2.24 (0.85–5.92)	0.10	0.99 (0.29–3.36)	0.98	0.47 (0.05–4.21)	0.50
NYHA III/IV at registration	1.94 (1.00–3.77)	0.05	2.05 (1.01–4.14)	0.04	2.53 (0.84–7.65)	0.10	2.82 (1.03–7.76)	0.04	0.40 (0.04–3.91)	0.43
Left atrial diameter ^b	1.09 (1.05–1.13)	<0.001	1.08 (1.04–1.20)	<0.001	1.02 (0.96–1.09)	0.53	1.13 (1.07–1.20)	<0.001	1.10 (1.00–1.20)	0.04
LV end-diastolic diameter ^b	1.03 (0.99–1.08)	0.14	1.05 (1.01–1.09)	0.02	1.02 (0.95–1.11)	0.56	1.08 (1.02–1.15)	0.01	1.02 (0.92–1.14)	0.72
Maximal LV wall thickness ^c	1.01 (0.96–1.06)	0.72	1.01 (0.96–1.07)	0.64	1.00 (0.91–1.09)	0.96	0.98 (0.90–1.07)	0.61	1.08 (0.95–1.23)	0.24
LV outflow tract obstruction	0.51 (0.26–1.01)	0.06	0.58 (0.28–1.18)	0.13	0.72 (0.24–2.17)	0.55	0.29 (0.07–1.13)	0.07	1.08 (0.21–5.65)	0.92
Family history of SCD	1.22 (0.60–2.48)	0.59	1.34 (0.65–2.79)	0.43	2.30 (0.85–6.19)	0.10	1.49 (0.43–5.22)	0.53	–	–
AF	0.98 (0.52–1.84)	0.95	1.21 (0.62–2.37)	0.57	1.80 (0.60–5.38)	0.29	0.39 (0.13–1.18)	0.09	6.71 (1.23–38.58)	0.03

^a Each 1-year increase in age. ^b Each 1-mm increase in diameter. ^c Each 1-mm increase in wall thickness.

Fig. 1. AF contributed to a higher risk for all-cause death (a) and cardiovascular death (b) than did sinus rhythm (SR).

cardiovascular death (HR 1.08, 95% CI 1.04–1.20, $p < 0.001$) (table 2).

The association of AF with the development of advanced chronic heart failure was analyzed in 549 patients after exclusion of patients with a history of NYHA functional class III/IV at enrollment. Kaplan-Meier analysis showed that patients with AF had a higher risk of advanced heart failure ($p < 0.001$) (fig. 2a). Multivariate

analysis recognized both AF (HR 1.83, 95% CI 1.04–3.22, $p = 0.04$) and left atrial diameter (HR 1.05, 95% CI 1.01–1.10, $p = 0.01$) to be predictors for this event (online suppl. table S1).

The relationship between AF and the occurrence of ischemic stroke was analyzed in 640 patients after eliminating those with a history of ischemic stroke at enrollment. Kaplan-Meier analysis revealed that patients with

Fig. 2. AF contributed to a higher risk for advanced heart failure (a) and ischemic stroke (b) than did sinus rhythm (SR).

AF were at a higher risk for ischemic stroke than those with sinus rhythm ($p < 0.001$) (fig. 2b). Multivariate analysis showed that AF (HR 9.98, 95% CI 4.06–24.53, $p < 0.001$) and aging (HR 1.03, 95% CI 1.00–1.06, $p = 0.04$) were the independent risk factors for this type of thromboembolic event (online suppl. table S1).

Discussion

Thus far, research focusing on AF in HCM patients has been sparse and the sample size of most studies is small. Therefore, the prognostic significance of AF in HCM patients needs to be clarified further. In this study, AF was documented in nearly a quarter of 654 unrelated patients in a Chinese HCM cohort. The independent predictors of AF included advancing age, dilated left atrium and severe chronic heart failure. Follow-up study showed that AF was a predictor for stroke-related death, advanced heart failure and ischemic stroke. Furthermore, a dilated left atrium was also associated with adverse outcomes of HCM and provided additional prognostic information.

In a relatively large study from Olivetto et al. [11], AF was identified in 22% (107/480) of HCM patients. This prevalence was similar to that in our study results (24%), indicating that AF is a common complication of HCM.

Furthermore, the authors reported that annual HCM-related mortality was 1.7% and that AF was related to increased risk for cardiovascular death, advanced heart failure and ischemic stroke. The reported mortality was consistent with our observation of 1.8%, and the associations of AF with advanced heart failure and ischemic stroke were also confirmed in our study. However, we did not find a significant relationship between AF and cardiovascular death. Interestingly, we identified a dilated left atrium as an additional risk factor for cardiac mortality and stroke-related death. If Olivetto et al. [11] did not integrate the size of the left atrium into the multivariate analysis, this could explain why the findings differed. Recently, a small study of 81 HCM patients indicated that AF was not associated with the combined end point of cardiac death or stroke or hospitalization for heart failure when left atrial size was included in a multivariate analysis [18].

Left atrial enlargement has been considered an indicator of the severity of diastolic dysfunction [19]. Some studies have demonstrated a dilated left atrium to be correlated to increased risk for cardiovascular morbidity and mortality in patients with HCM and other forms of cardiac disease [18, 20–23]. Therefore, integrating left atrial diameter into a multivariate analysis may more accurately evaluate the relationship between AF and prognosis in HCM patients. This hypothesis was confirmed in our

study: the association of AF with elevated risk for cardiovascular death disappeared after left atrial diameter was integrated into a multivariate analysis. However, a dilated left atrium generated a higher risk for all-cause death and cardiovascular death as well as contributing to the deterioration of chronic heart failure. All these findings suggest that a dilated left atrium should be considered an additional risk factor for adverse prognosis in HCM patients. Consequently, more attention should be focused on patients with left atrial enlargement irrespective of the presence or absence of AF.

At present, the relationship between AF and SCD in HCM patients is uncertain [11, 24, 25]. In our study, Kaplan-Meier analysis showed that patients with AF were at a higher risk for SCD than those with sinus rhythm, but a multivariate analysis did not support AF as an independent predictor for this adverse event. Accordingly, the relationship between AF and SCD still needs to be verified in a larger HCM cohort in the future.

Notably, although we highly recommend anticoagulant therapy for the patients with AF who were at high risk for ischemic stroke, only 20% of patients regularly took anticoagulants. A lack of understanding of the risk of stroke from AF may lead to medication noncompliance, so more effective health education is urgently required for Chinese HCM patients with AF. In addition, our patients prefer medication to invasive therapy and ICD implantation because of concerns about the risks of surgery and for financial reasons. Therefore, some adverse cardiovascular events may be associated with fewer patients adopting these therapies, but the results obtained from this

kind of cohort accurately reflect the natural disease course.

Several limitations of this study should be mentioned. First, the subjects in this study were enrolled from a single center. Fuwai Hospital is, however, one of the largest cardiovascular referral hospitals in China, so subjects were representative of a large geographical area. Second, because some patients with AF did not know whether the AF was paroxysmal or persistent during follow-up, they were placed in one AF category without subdividing it. Third, we were unable to explore the influences of duration of AF and degree of rate control on left atrial dilatation and mortality because some patients could not provide detailed information about these factors. In addition, because not all patients in our study were subjected to Holter monitor evaluation (or prolonged monitoring), it may be that we failed to detect some of the asymptomatic, paroxysmal AF cases.

In conclusion, our study demonstrates that AF is a common complication of HCM and predicts poor outcomes in HCM patients. More attention should be focused on patients with left atrial dilatation because of its impact on the adverse prognosis of HCM.

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