Impact of Atrial Fibrillation on the Clinical Course of Hypertrophic Cardiomyopathy

Iacopo Olivotto, MD; Franco Cecchi, MD; Susan A. Casey, RN; Alberto Dolara, MD; Jay H. Traverse, MD; Barry J. Maron, MD

Background—Clinical impact of atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM) is largely unresolved. Thus, we analyzed the prognostic implications of AF in a large, community-based HCM population assembled from Italian and US cohorts.

Methods and Results—Occurrence of AF and outcome were assessed in 480 consecutive HCM patients (age at diagnosis, 45±20 years; 61% male) who were followed up for 9.1±6.4 years. AF occurred in 107 patients (22%; incidence, 2%/y) and was independently predicted by advancing age, congestive symptoms, and increased LA size at diagnosis. Patients with AF had increased risk for HCM-related death (OR, 3.7; $P<0.002$) because of excess heart failure–related mortality but not sudden, unexpected death. This risk associated with AF was substantially greater in patients with outflow obstruction or with earlier development of AF (≤50 years of age). AF patients were also at increased risk for stroke (OR, 17.7; $P=0.0001$) and severe functional limitation (OR for NYHA class III or IV, 2.8; $P<0.0001$). Compared with those with exclusively paroxysmal AF, patients developing chronic AF showed higher combined probability of HCM-related death, functional impairment, and stroke ($P<0.0001$). In a subgroup of 37 patients with AF (35%), the clinical course was largely benign in the absence of stroke and severe symptoms.

Conclusions—In a community-based HCM population, AF (1) was common, with 22% prevalence over 9 years; (2) was associated with substantial risk for heart failure–related mortality, stroke, and severe functional disability, particularly in patients with outflow obstruction, those ≤50 years of age, or those developing chronic AF; and (3) was nevertheless compatible with benign outcome in 35% of patients. **(*Circulation*. 2001;104:2517-2524.)**

Key Words: cardiomyopathy ■ fibrillation ■ prognosis

Atrial fibrillation (AF) is a commonly reported complication of hypertrophic cardiomyopathy (HCM).[1–14] However, studies regarding long-term prognosis of AF in HCM patients have been sparse and often conflicting, with some reports suggesting a generally unfavorable prognosis associated with this arrhythmia[5–9] and others indicating a relatively benign course.[10,11] Thus, many crucial issues regarding the determinants and clinical impact of AF on HCM patients remain unresolved; therefore, the present investigation was undertaken in our community-based population, including the largest series of HCM patients with AF assembled to date.

Methods

Patient Selection

Two HCM patient cohorts were combined for this analysis; both represent regional populations consecutively enrolled and prospectively followed up at their respective institutions, ie, Azienda Ospedaliera Careggi; Florence, Italy (n=202 patients), and Minneapolis (Minn) Heart Institute (n=278 patients). Therefore, the final study group comprised 480 patients. Selected data from these populations have been previously reported.[4,5]

Follow-up was 9.1±6.4 years. Mean age at diagnosis was 45±20 years (range, 1 to 87 years); 292 patients (61%) were male; and 125 (26%) had basal left ventricular (LV) outflow obstruction ≥30 mm Hg. Maximal LV thickness was 22±5 mm.

Management Strategies

Over the extended period of clinical practice encompassed by the present study (>20 years), treatment of AF in the 2 participating centers was not designed to follow a systematic protocol, involved a number of treating clinicians, and thereby reflected changes in standard practice guidelines.[4,5] In general terms, in patients presenting with recent-onset AF, restoration of sinus rhythm was attempted by pharmacological treatment (class IA, IC, or III agents such as quinidine, propafenone, and amiodarone) or DC cardioversion after optimal anticoagulation with warfarin. Conversely, patients with chronic AF were usually treated aggressively to achieve optimal ventricular rate control with verapamil (29%), β-adrenergic blocking agents (37%), or both (22%). Moreover, amiodarone was often administered in combination with either of these drugs (37%). Warfarin was often used to prevent embolic complications in patients with both paroxysmal and chronic AF.[15]

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From Cardiologia S. Luca, Azienda Ospedaliera Careggi, Florence, Italy (I.O., F.C., A.D.), and the Minneapolis Heart Institute Foundation, Minneapolis, Minn (S.A.C., J.H.T., B.J.M.).

Correspondence to Dr Iacopo Olivotto, Via Jacopo Nardi 30, Florence, 50132, Italy. E-mail jacoli@flownet.it

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Definitions

Hypertrophic Cardiomyopathy

Diagnosis of HCM was based on echocardiographic identification of a hypertrophied, nondilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.[1]

Atrial Fibrillation

Documentation of AF was based on ECG recordings obtained either after acute onset of symptoms or fortuitously during routine medical examination in asymptomatic patients. AF was defined as paroxysmal when it was either self-terminating or successfully cardioverted to sinus rhythm; AF was considered chronic when it became established.

Mode of Death

For survival analysis, 3 modes of HCM-related death were defined[16]: (1) sudden and unexpected death, in which the collapse occurred in the absence or <1 hour from the onset of symptoms in patients who previously experienced a relatively stable or uneventful course (including resuscitated cardiac arrest and appropriate implantable defibrillator interventions); (2) heart failure–related death, which was in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase (including patients with heart transplantation); and (3) stroke-related death, which occurred in patients who died as a result of ischemic stroke.

Echocardiography

Echocardiographic studies were performed with Hewlett Packard and Toshiba instruments. M-mode left atrial end-systolic dimension (LA) was measured from the parasternal long-axis view. The extent and magnitude of LV hypertrophy were assessed as previously described.[17] Peak instantaneous LV outflow tract basal gradient was estimated with continuous-wave Doppler.[17]

Statistical Analysis

Student's *t* test was used for the comparison of normally distributed data. The χ^2 test was used to compare noncontinuous variables expressed as proportions. ORs and 95% CIs were calculated by use of univariate and multivariate Cox proportional-hazard regression models.

Because AF was more common in older and more symptomatic patients, direct comparison of AF patients (n=107) with the overall group of HCM patients in sinus rhythm would have exaggerated the impact of AF on HCM prognosis. Therefore, to make our observations regarding the consequences of AF in HCM more accurate, in each of our survival analyses, the 107 HCM patients with AF were matched to HCM control patients in sinus rhythm with similar baseline features—ie, the same sex, age (±2 years), and NYHA functional class at HCM diagnosis. Thus, 86 patients with AF could be matched to a single sinus rhythm control patient. However, for 21 AF patients, 2 or 3 potential sinus rhythm patients were identified as equally deserving control subjects. To avoid selection bias, each of these potential control subjects was included in the matched control group. Therefore, the final number of control patients in sinus rhythm was 133 for the 107 AF patients.

Results

Clinical Manifestations of AF

Occurrence

Of the 480 patients, 25 (5%) developed AF before the initial HCM diagnosis, including 18 in whom AF constituted the initial manifestation of HCM and led to the diagnosis. Of the remaining 455 patients, 82 (17%) developed AF 2 months to 29 years after initial HCM diagnosis, with an annual rate of 9 new cases over a 9-year follow-up (incidence, 2%/y). Overall, AF was documented in 107 patients, with a prevalence of 22%.

Clinical Profile

AF presented as paroxysmal in 77 patients (with subsequent progression to chronic AF in 32) and as chronic AF in 30 other patients (Table 1). Patients with paroxysmal AF had 4±3 documented episodes, ≤3 in 35 patients (45%) and ≥10 in 8 (10%). The average progression time from paroxysmal to chronic AF was 5.1±3.5 years (range, 4 months to 14 years).

Age

Development of AF occurred over a wide age range, from 19 to 82 years (average, 55±15 years). Although occurrence increased progressively with age and was predominant in patients >60 years of age, AF was frequently documented at relatively early ages; ie, 39 patients (36%) developed AF at ≤50 years of age (Figure 1).

Determinants of AF

The strongest predictor of AF was increased LA size, independent of age and NYHA functional class (Table 2 and Figures 2 and 3). LA dimension was 49±9 mm in patients who developed AF compared with 41±8 mm in those remaining in sinus rhythm ($P<0.001$). LA size ≤45 mm appeared to represent the threshold value associated with substantial risk of subsequent AF development, which was evident even in asymptomatic patients (NYHA class I; Figure 2, bottom), although it doubled when associated with congestive symptoms (NYHA classes II through IV).

Among the 107 AF patients, a subset of 13 (12%) with normal LA dimension (≤40 mm) was identified. These patients, compared with AF patients with LA >40 mm, were similar in age, degree of functional limitation, and prevalence of outflow obstruction at diagnosis. Moreover, patients with LA ≤40 mm and >40 mm were similar with respect to the prevalence of chronic AF (23% versus 29%; $P=0.3$) and stroke (31% versus 27%, $P=0.4$).

Maximum LV thickness was greater in patients with AF (23±5 mm) than in patients in sinus rhythm (22±5 mm; $P<0.01$), but outflow obstruction showed similar frequency (32% versus 25%, respectively; $P=0.1$) and therefore was not predictive of AF. Moderate to severe mitral regurgitation was present in only a minority of AF patients (n=16; 15%).

Outcome and Functional Status

Mortality

During follow-up, 74 patients died of HCM-related causes, including 38 (35%) among the 107 AF patients (sudden death in 13, heart failure–related death in 17, and stroke-related death in 8; Table 1). When AF patients were compared with 133 matched control subjects in sinus rhythm, AF was associated with markedly increased risk for HCM-related death (Figure 3). Annual HCM-related mortality was 3% in AF patients compared with 1% among control patients in sinus rhythm ($P<0.001$; Figure 3). This increased risk was explained by an excess stroke- and heart failure–related mortality ($P<0.001$). Conversely, no association was evident between AF and sudden death ($P=0.2$). HCM-related mortality was similar among patients with ≤2 episodes of

TABLE 1. Clinical Features of 107 Patients With HCM and AF

	Exclusively Paroxysmal	Paroxysmal to Chronic	Exclusively Chronic	Total
n	45	32	30	107
Female, n (%)	23 (51)	11 (34)	12 (40)	46 (43)
Age at diagnosis, y	43±19*	46±16*	56±14	50±17
Age at end of follow-up, y	60±15	61±13	67±11	62±14
Duration of follow-up, y	12±8	15±6	11±8	12.6±7.7
Family history of HCM, n (%)	9 (20)	14 (44)	9 (30)	32 (30)
NSVT on Holter ECG, n (%)	13 (29)	13 (41)	16 (53)	42 (39)
LV outflow obstruction ≥30 mm Hg, n (%)	21 (47)*	8 (25)	5 (17)	34 (32)
Symptoms at diagnosis, n (%)	37 (82)	25 (78)	23 (77)	85 (79)
Syncope, n (%)	3 (7)	2 (6)	4 (13)	9 (8)
LVMM or mitral valve replacement, n (%)	6 (13)	5 (16)	4 (13)	15 (14)
Pacemaker implantation, n (%)	8 (18)	5 (16)	3 (10)	16 (15)
AF				
No. at diagnosis (%)	9 (20)	6 (19)	10 (33)	25 (23)
Age at development of AF, y	55±15	52±15	59±13	56±15
Total paroxysmal AF episodes, n	3.0±2.7	5.8±0.7	NA	4.1±3.2
Self-terminating AF episodes, n	2.2±3.5	2.8±3.0	NA	2.1±3.1
AF episodes requiring treatment, n	1.4±1.2	3.1±1.8	NA	2.0±1.8
Symptomatic status, n (%)				
NYHA class III or IV at diagnosis	7 (16)	6 (19)	3 (10)	16 (15)
NYHA class III or IV at last evaluation	15 (33)*†	21 (66)	18 (60)	54 (51)
End-stage phase	3 (7)*	4 (12)	8 (27)	15 (14)
Echocardiographic findings at diagnosis				
LA, mm	47±9*	49±8	53±10	50±9
Maximum LV thickness, mm	24±6	23±4	23±4	23±5
LV end-diastolic dimension, mm	44±7	46±7*	41±10	44±7
LV shortening fraction, %	38±13	39±11	39±9	38±11
Moderate to severe mitral regurgitation, n (%)	4 (9)	4 (12)	8 (27)	16 (15)
Outcome, n (%)				
Total HCM deaths	17 (38)	10 (32)	11 (36)	38 (35)
Sudden, unexpected	7 (16)	5 (16)	1 (3)	13 (12)
Heart failure–related	6 (13)	5 (16)	6 (20)	17 (16)
Stroke-related	4 (9)	0	4 (13)	8 (7)
Nonfatal ischemic stroke	5 (11)	5 (16)	5 (17)	15 (14)
Treatment before AF, n (%)	28 (62)	18 (56)	16 (53)	62 (58)
β-Blockers	14 (31)	10 (31)	10 (33)	34 (32)
Verapamil	12 (26)	8 (25)	7 (23)	27 (25)
Quinidine, propafenone, flecainide	25 (56)	16 (50)	16 (53)	57 (53)
Amiodarone	1 (2)†	5 (15)	1 (3)†	7 (6)
Treatment after development of AF, n (%)	44 (98)	31 (97)	30 (100)	105 (98)
β-Blockers	31 (67)	15 (47)	11 (37)	57 (53)
Verapamil	22 (50)	17 (53)	17 (57)	56 (52)
Quinidine, procainamide	4 (9)	7 (22)	1 (3)	10 (9)
Propafenone, flecainide	4 (9)	5 (16)	1 (3)	7 (6)
Amiodarone	22 (49)	21 (66)*	11 (37)	52 (49)
Digoxin	9 (20)	9 (29)	13 (43)	31 (29)
Warfarin	6 (23)*†	29 (93)	24 (86)	59 (69)

NSVT indicates nonsustained ventricular tachycardia; LVMM, LV myotomy-myectomy.
*$P<0.05$ vs chronic only AF; †$P<0.05$ vs paroxysmal to chronic AF.

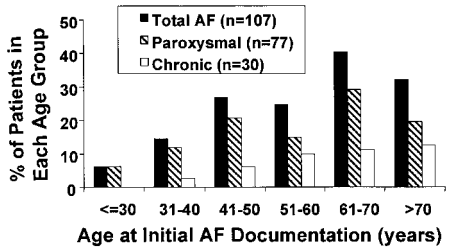

Figure 1. Age at development of AF in 107 HCM patients. Bars express proportion of patients in each age group with paroxysmal or chronic AF. Patients evolving from paroxysmal to chronic AF are considered paroxysmal.

paroxysmal AF and ≥3 episodes or chronic AF (37% versus 36%, respectively).

Independent determinants of HCM-related mortality identified with multivariate analysis were AF (OR, 3.7; 95% CI,1.7 to 8.1; $P<0.0001$); NYHA class III or IV at diagnosis (OR, 2.2; 95% CI,1.2 to 4.1; $P=0.01$), and older age (>50 years) at diagnosis (OR, 2.0; 95% CI,1.2 to 3.5; $P=0.01$). Of note, the association of AF and outflow obstruction (≥30 mm Hg) significantly increased the risk of HCM-related death compared with nonobstructive AF patients (OR, 2.6; 95% CI,1.3 to 5.0; $P<0.01$; Figure 4).

Symptomatic Status

AF produced variable consequences in symptomatic status. Over the short term, AF onset produced new or worsening clinical manifestations in most of the 107 patients (n=90; 84%), including dyspnea and/or chest pain (n=54), heart failure, and pulmonary edema (n=16), and impaired consciousness, including syncope (n=20). In a minority of patients (n=17; 16%), new symptoms did not occur after development of AF, which was identified fortuitously during routine outpatient examination. Over the long term, AF was associated with substantial functional deterioration (OR for NYHA class III or IV at the end of follow-up, 2.8; 95% CI,1.8 to 4.5; $P<0.0001$) compared with 133 control HCM patients in sinus rhythm (Figure 5).

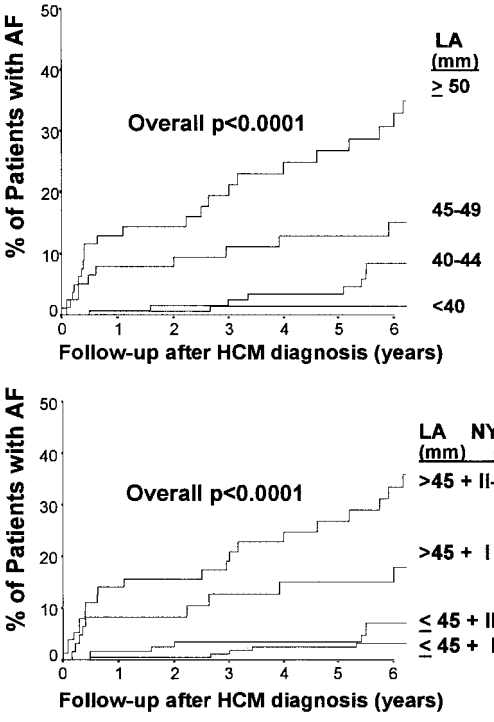

Figure 2. LA size and NYHA functional class at HCM diagnosis and risk of AF for 455 HCM patients in sinus rhythm at initial evaluation. Top, Probability of developing AF with respect to LA size. Bottom, Probability of developing AF with respect to LA size and NYHA functional class. Twenty-five patients who developed AF before initial HCM diagnosis were excluded.

Stroke

Ischemic strokes were 8 times more frequent among AF patients than among those in sinus rhythm (21% versus 2.6%), occurring after an average of 3.5±3.4 years after AF development and causing death in 8 patients and permanent disability in 11. The prevalence of stroke was independent of whether AF was exclusively paroxysmal or chronic AF (22% versus 27%, respectively; $P=0.54$) and of the number of AF

TABLE 2. Predictors of AF Among 455 Patients With HCM in Sinus Rhythm at Initial Diagnosis*

	Univariate Analysis		Multivariate Analysis	
Variable at Diagnosis	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	1.1 (0.7–1.7)	0.71	NI	
Age at diagnosis >50 y†	2.8 (1.8–4.5)	<0.0001	2.3 (1.4–3.7)	<0.001
Family history of sudden death†	1.5 (0.9–2.6)	0.12	NI	
NYHA class II at diagnosis‡	2.5 (1.6–4.1)	0.0001	1.7 (1.1–2.8)	0.02
NYHA class III or IV at diagnosis‡	3.8 (1.8–8.0)	<0.0005	2.8 (1.3–6.1)	<0.005
LA dimension ≥45 mm†	3.6 (2.6–5.7)	<0.0001	3.4 (2.2–5.5)	<0.0001
Maximum LV thickness ≥20 mm†	1.2 (0.7–2.1)	0.28	NI	
LV outflow obstruction† (gradient ≥30 mm Hg)	1.3 (0.8–2.0)	0.26	NI	

NI indicates not included in multivariate analysis. OR was calculated by Cox regression analysis.

*25 patients who developed AF before initial HCM diagnosis were excluded from this analysis.

†The group of patients without the indicated feature represent the reference category for calculation of risk.

‡Patients in NYHA class I represent the reference category for calculation of risk.

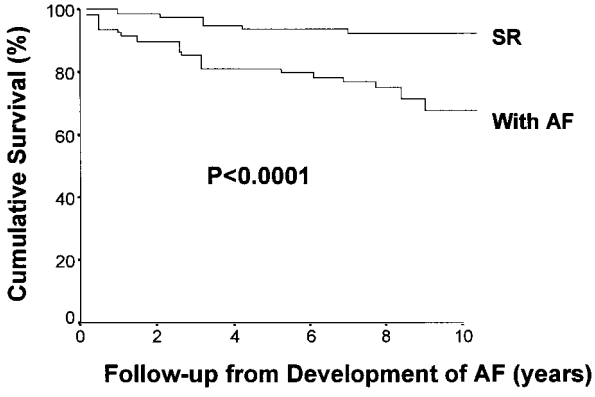

Figure 3. Impact of AF on overall HCM-related mortality. Cumulative survival of 107 patients with HCM and AF is compared with 133 matched HCM patients in sinus rhythm (SR).

paroxysms (1 only compared with ≥2, 23% versus 18%, respectively; $P=0.6$).

Compared with 133 matched patients in sinus rhythm, the independent OR for stroke in AF patients was 17.7 (95% CI, 4.1 to 75.9; $P=0.0001$). Of note, patients developing AF ≤50 years of age were at greater risk (Figure 5); however, fatal strokes occurred only in patients developing AF at >50 years of age (n=8).

Patient Subgroup Analysis

Younger age at AF development was associated with a more unfavorable prognosis. Indeed, patients with early (≤50 years) compared with later (>50 years) development of AF showed a 1.7-, 3.6-, and 1.5-fold independent increase in HCM-related mortality, stroke prevalence, and progression of symptoms, respectively, at 5 years of follow-up (Figure 5). In addition, compared with patients developing exclusively paroxysmal AF, those developing chronic AF showed a higher combined probability of HCM-related death, functional impairment, and stroke ($P<0.0001$; Figure 6). However, heart failure–related mortality did not differ between patients with chronic or

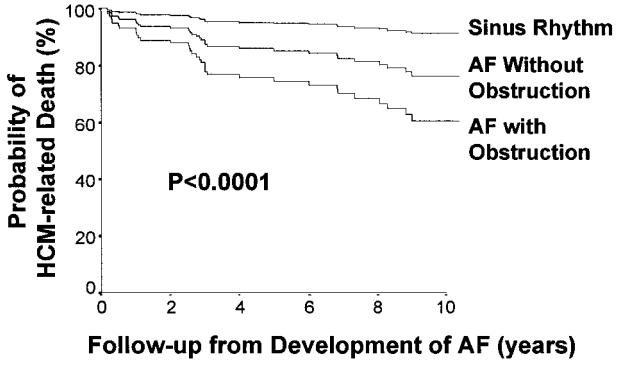

Figure 4. Combined impact of AF and basal outflow obstruction (gradient, ≥30 mm Hg) to overall HCM-related mortality in 107 patients with HCM and AF compared with 133 matched HCM patients in sinus rhythm. Hazard plot is based on multivariate Cox regression analysis including age, sex, and NYHA functional class.

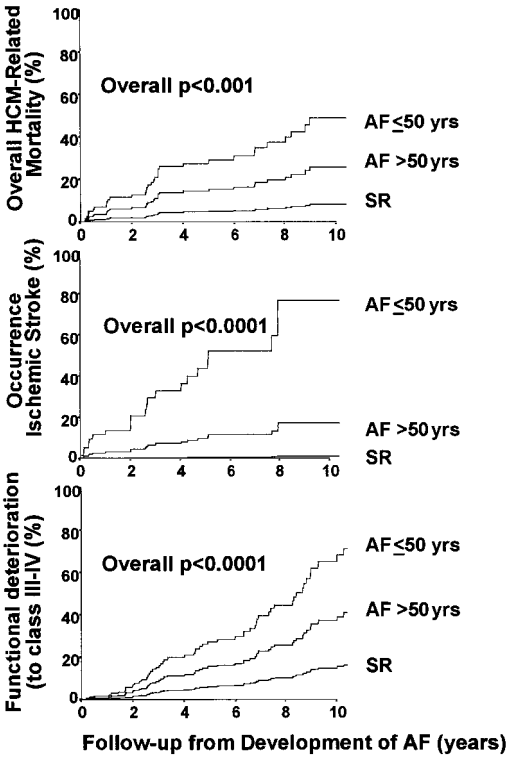

Figure 5. Relation of early (≤50 years of age, n=39) vs late (>50 years of age, n=68) development of AF to overall HCM-related mortality (top), ischemic stroke (middle), and progression to NYHA class III or IV (bottom) compared with 133 matched HCM patients in sinus rhythm (SR). Hazard plot is based on multivariate Cox regression analysis including age, sex, and NYHA functional class.

paroxysmal AF at the end of follow-up (13% versus 18%, respectively; $P=0.4$).

Finally, comparison of the 2 HCM cohorts making up the study population showed that the patients from Florence and Minneapolis were similar with regard to most clinical features, including the proportion of patients with severe symptoms (NYHA functional classes III and IV); family history of HCM-related sudden death; or treatment with drugs, dual-chamber pacemakers, implantable defibrillators, or

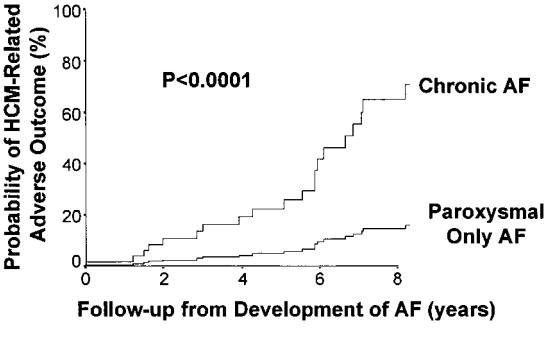

Figure 6. Cumulative risk for adverse outcome in HCM patients with exclusively paroxysmal (n=45) and chronic (n=62) AF. Adverse outcome was defined as combined end point including HCM-related death, progression to NYHA class III or IV, or stroke. In this analysis, patients evolving from paroxysmal to chronic AF are considered chronic.

myotomy-myectomy. Moreover, the 2 cohorts showed similar outcome in terms of overall HCM-related mortality, death caused by heart failure or stroke, sudden death, and incidence of stroke. However, Florence patients were somewhat younger (age at diagnosis, 41±17 versus 47±22 years for Minneapolis patients), less often had outflow obstruction (basal gradient ≥30 mm Hg; 20% versus 34%), showed a higher prevalence of AF (28% versus 18%), and more often received amiodarone (25% versus 17%).

Variability in Prognosis

Of the 107 patients with AF, 37 (35%) had a largely benign outcome; ie, they survived free of stroke with no or only mild symptoms (NYHA class I or II) until the end of follow-up. Conversely, the remaining 70 patients (65%) died of HCM-related causes (n=38), incurred stroke-related disability (n=11), or progressed to NYHA class III or IV (n=21). These patients with adverse prognosis more frequently had chronic AF than those with benign outcome (60% versus 38%; $P<0.05$) but were otherwise similar with respect to age, initial NYHA class, LA dimension, and follow-up duration (all $P>0.6$).

Treatment

Prevention of Stroke

After development of AF, 79 of the 107 patients were treated for prevention of thromboembolic complications with warfarin (n=59) or antiplatelet agents (aspirin or ticlopidine; n=20), and 28 did not receive prophylactic treatment. Indeed, stroke was less common among warfarin-treated patients (n=6; 10%) compared with other patients (39% among untreated and 30% among patients on antiplatelet agents; $P=0.001$ and $P<0.05$, respectively, versus warfarin).

Pharmacological Maintenance of Sinus Rhythm

Among the 77 patients who experienced paroxysmal AF, 43 received low-dose amiodarone (200 mg/d) for prevention of recurrences (Table 1). However, the duration of sinus rhythm and survival after the first episode of AF were not different in patients with and without amiodarone treatment ($P=0.4$ and $P=0.8$, respectively), even after correction for age at AF development, NYHA class, and LA size.

Discussion

Historical Perspective

Studies addressing the prognostic significance of AF in HCM patients are limited and present conflicting conclusions.[6–11] Early observational studies (confined largely to patients with obstruction) emphasized the association of AF onset with severe acute clinical deterioration.[6,7] Conversely, a more recent study reported no difference in mortality among patients with AF compared with an HCM control group in sinus rhythm.[10] However, the latter investigation was based largely on highly selected patients at a tertiary referral center,[4,5] and the deleterious impact of AF may have been obscured by the low survival rate in control patients with sinus rhythm.[10] Our large, community-based patient cohort with HCM provided a unique opportunity to assess the prognostic impact of AF in a population largely free of such patient selection bias.

AF Prevalence and Age

AF was common in our study population, with a prevalence of 22% and incidence of 2% new cases annually. Thus, HCM patients appear to have a 4- to 6-fold-greater likelihood of developing AF compared with the general population.[15,18] AF prevalence increased progressively with age and was predominant in patients >60 years of age. However, it was not rare in younger patients (≤50 years of age), in whom it was associated with higher risk for clinical deterioration and HCM-related death.

Predictability of AF

AF proved to have a measure of predictability as a HCM complication. We identified several predictors of AF, the most powerful of which, in addition to age and functional class, was LA size. Modest LA enlargement (ie, 40 to 45 mm) is common in HCM, probably the consequence of impaired diastolic function associated with thickened and noncompliant ventricular chambers.[19,20] However, the determinants of more marked LA enlargement ultimately predisposing to AF are unresolved. Neither mitral regurgitation nor presence of outflow obstruction reliably predicted the development of AF; indeed, moderate to severe mitral regurgitation was present only in a minority of AF patients (ie, 15%), and outflow obstruction occurred with similar frequency among patients with and without AF.[21]

It is possible that specific HCM-causing mutations may increase predisposition to AF, eg, by causing an intrinsic atrial myopathy associated with prolonged and fragmented atrial conduction or presently undefined hemodynamic alterations.[13] Such a hypothesis could also explain the development of AF in the absence of LA dilatation in a minority of patients (12% with LA ≤40 mm in our study group).

Impact of AF on HCM-Related Mortality

The present study identifies AF as a key determinant of HCM-related mortality and limiting symptoms. Development of AF may indeed represent a clinical turning point, often dominating the clinical picture and decisively influencing long-term outcome. Over a 9-year follow-up, patients with AF showed an ≈4-fold increase in the risk of HCM-related death compared with matched control subjects in sinus rhythm, reflecting significant increases in heart failure and stroke-related mortality. Conversely, we found no relation between clinically evident AF and the occurrence of sudden unexpected death. Therefore, although a causal link between AF and potentially lethal ventricular arrhythmias has been suggested in individual patient reports,[7,22] our data do not support AF as a consistent trigger of sudden death in HCM.

HCM-related mortality was not uniformly distributed among our AF cohort but appeared to preferentially affect certain patient subgroups, such as those with early AF development (≤50 years). Although the more severe consequences associated with development of AF in

younger HCM patients have not been explained satisfactorily, AF may represent a marker of generally more aggressive disease.[7] In addition, the combination of AF and basal outflow obstruction proved to be particularly adverse,[6] suggesting that obstructive patients may rely on LA contraction for LV filling more than nonobstructive patients and thus may be more prone to long-term deterioration after development of AF.[19,20]

Clinical Heterogeneity

The impact of AF on long-term prognosis shows substantial heterogeneity among individual HCM patients and should not be regarded as invariably unfavorable. Indeed, although AF was strongly associated with HCM-related mortality and clinical deterioration in our overall study population, 35% of AF patients were alive and free of stroke or severe symptoms at the end of follow-up. The likelihood of a benign outcome was significantly higher in patients with exclusively paroxysmal AF compared with those progressing to chronic AF. These observations imply that therapeutic efforts aimed at preventing or delaying the transition from paroxysmal to chronic AF could improve patient outcome.[2,15]

Given the retrospective nature of the present study, it was not possible to specifically address in precise terms the importance of ventricular rate control in our patients with chronic AF. However, it is unlikely that inadequate rate control represented a major determinant of HCM-related mortality because of the aggressive management with β-adrenergic blocking agents, calcium channel blockers, and amiodarone at both institutions. Furthermore, heart failure–related mortality did not differ between patients with chronic or paroxysmal AF at the end of follow-up, whereas an excess mortality in the chronic AF group would probably have been expected in the presence of persistently elevated ventricular rates.

The question of whether the clinical importance of AF may be explained primarily by its hemodynamic impact on LV filling or an underlying cardiomyopathic process remains unresolved. The substantial clinical heterogeneity observed in our study cohort, however, suggests that multiple variables may contribute differently to determine the final outcome in the individual patient with AF.[1,4,5]

AF and Stroke

In the present study, HCM patients with AF showed an 8-fold increase in risk of ischemic stroke (presumably of cardioembolic origin in most patients) compared with control patients in sinus rhythm.[6,8,9,16] Of note, the risk of stroke was comparable between patients with chronic and paroxysmal AF and, among the latter, was not related to the number of documented AF episodes. Specifically, patients with a single AF paroxysm had a prevalence of stroke similar to those with multiple episodes. Oral anticoagulation with warfarin in patients with AF provided protection against stroke, which, however, was not absolute even when international normalized ratio values were maintained in the target range.[15] Such observations agree with a wide range of clinical studies on AF in patients with heart diseases other than HCM,[15] indicating that the threshold for initiation of anticoagulant treatment in HCM should be low.[2] Our data suggest that warfarin treatment should be considered for primary prevention of stroke, regardless of the number of documented AF episodes; nevertheless, this clinical decision needs to be tailored in the individual patient with due consideration for risk of hemorrhagic complications, lifestyle modification, and expected compliance.[15]

Finally, although we could not establish an efficacy for amiodarone in maintaining sinus rhythm after the development of paroxysmal AF in this retrospective study, we do not wish to dismiss the possibility that long-term low-dose amiodarone may be effective in maintaining sinus rhythm in HCM patients, as has been shown prospectively in other cardiac conditions.[15,23]

Conclusions

AF was a common occurrence in a community-based HCM population, often representing a turning point in the clinical course by virtue of HCM-related mortality, symptomatic deterioration, and risk of stroke. However, the long-term consequences of AF were not uniformly unfavorable, and about one third of the patients experienced an uneventful course, particularly if progression to chronic AF did not ensue. Nevertheless, the powerful independent association of AF with HCM-related mortality and morbidity underlines the necessity for aggressive therapeutic strategies.

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