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Prognostic Significance of Atrial Fibrillation is a Function of Left Ventricular Ejection Fraction

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Summary

Background: Atrial fibrillation (AF) has been reported to be associated with decreased survival in population-based studies. Its prognostic importance in end-stage heart failure is not clear.

Methods and Results: We investigated the prognostic implications of AF as function of left ventricular (LV) ejection fraction (EF) in 8,931 consecutive patients undergoing echocardiography at our medical center between 1990 and 1999. Patient characteristics were: age 66 ± 13 years, EF 51 ± 15, AF in 1,203 patients. There were 1,911 deaths over a mean follow up of 913 days. The prevalence of AF was 11% in patients with normal left ventricular ejection fraction (LVEF) (EF $\geq$ 55%, n = 5, 130), and 18% each in those with mild (EF 41–54%, n = 1209), moderate (EF 26–40%, n = 1183) and severe reductions in left ventricular ejection fraction (LVEF) (EF $\leq$ 25%, n = 961). The 5-year survival rate was 72% for those in sinus rhythm compared to 56% for those in AF ($p < 0.0001$). The effect of AF on 5-year survival was most pronounced in those with normal LVEF (62 vs 78%, $p < 0.0001$) followed by those with mild reduction in LVEF (57 vs 72%, $p = 0.02$). It was not a predictor of survival in those with moderate (5-year survival 55 vs 61%, p = ns) or severe LV dysfunction (5-year survival 47 vs 45%, p = ns). Using the Cox regression model, AF was an independent predictor of mortality after correcting for age and LVEF in the entire cohort and in those with normal LVEF, but not in those with reduced LVEF. Among the other co-morbidities analyzed, an independent effect of AF on mortality was present in those with QTc $\geq$ 450, raising a possibility of enhanced susceptibility of these patients.

Conclusions: The effect of AF on mortality diminishes with worsening LV function and is absent in those with severe LV dysfunction. Susceptibility of patients with QT prolongation to AF mortality warrants further attention.

Key words: atrial fibrillation, ejection fraction, mortality, echocardiogram, electrocardiogram

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Atrial fibrillation (AF) is a common rhythm disorder, being present in 1% of the general population and 10% of octogenarians.[1,2] Population based studies have shown increased mortality with AF.[3–5] However, most of these are clinical observations and lack comprehensive echocardiographic and electrocardiographic data. It is possible that patients developing AF have underlying myocardial dysfunction and AF may have been a manifestation of the underlying disorder. The effect of AF on mortality in patients with advanced degrees of LV dysfunction is uncertain as well.[6–10] Independent prognostic significance of AF in heart failure patients was reported by Dries *et al*.[6] However, this was not supported by data from the VHeft studies or heart failure patients awaiting cardiac transplantation.[7–9] Data from a heart failure clinic population indicated that AF could be prognostically unimportant in those with greater hemodynamic derangement.[10] There are no published data investigating the effect of AF on survival at different levels of left ventricular ejection fraction (LVEF).

Methods

Study Population

This single center retrospective study included patients from the Loma Linda VA Medical Center between July 1990 and June 1999 who had an echocardiographic examination. It was our laboratory policy to perform 12 lead electrocardiograms routinely at the time echocardiographic examinations. Removal of duplicate examinations resulted in 8,931 consecutive patient who formed the study cohort.

Echocardographic Data

All patients had standard two-dimensional and Doppler echocardiographic examinations. LVEF was assessed visually by a level III trained echocardiographer and entered into the database at the time of the examination. Visual estimate of EF by an experienced interpreter has been shown to correlate very closely with that obtained by radionuclide ventriculography and equivalent to or superior to other quantitative echocardiographic methods.[11–13] Anatomic measurements were performed according to the recommendations of the American Society of Echocardiography.[14]

ECG Analysis

Digitally stored ECG data on the MUSE system was used for analysis. The intervals were digitally measured by this system. Conduction problems, atrial fibrillation and myocardial infarctions were interpreted by the computer and verified by a cardiologist. Atrial fibrillation diagnosis was made when the P waves were absent and the RR intervals were irregular.

Follow-up and Mortality Data

Follow-up data was gathered by using VA Hospital administrative records. The endpoint of this study was all cause mortality as determined by mortality records. Different causes of mortality were not identified. Alive status was confirmed by prescription refills or clinic visits. Only 3% of the patients were lost to follow-up and hence were censored on the day of echocardiographic examination.

Database Management

All the data was entered into the computer in Microsoft Excel program. Data management was accomplished in Microsoft Excel and Access programs.

Statistical Analysis

Kaplan–Meier survival curves of patients with and without atrial fibrillation were compared using the log rank statistic using StatView 5.01 (SAS Insitute Inc, Cary, NC). A p-value ≤ 0.05 was considered to be significant. Cox regression model was used to correct for the effect of covariates and to calculate the hazard ratio.

Results

Baseline Patient Characteristics

Most of the patients were men (96%), typical of VA population. The mean age was 66 ± 13 years and LVEF $51 \pm 15\%$. Eighty-one percent were Caucasians, 10% African-Americans and 7% were of Hispanic origin. There were 1,203 patients with AF. LVEF assessment was possible and available in 8483 patients. Measurements on LV size and wall thickness were available in 5,136 patients. By using 2-tailed Student's '*t*' test, compared to those in SR, patients with AF were older, had a lower EF, greater LV wall thickness and size, a marginally faster heart rate, longer QT interval and a greater prevalence of left bundle branch block (Table 1). However, both groups were similar in terms of height, weight, and QRS duration. There were 1,911 deaths over a mean follow up of 913 days.

AF Prevalence in EF Subgroups

The prevalence of AF was 11% in patients with normal LVEF ($EF \geq 55\%$, $n = 5,130$), and 18% each in those with mild (EF 41–54%, $n = 1,209$), moderate (EF 26–40%, $n = 1183$) and severe reductions in LVEF ($EF \leq 25\%$, $n = 961$).

AF and Mortality

The 5-year survival rate was 72% for those in SR compared to 56% for those in AF ($p < 0.0001$, Fig. 1). As shown in Fig. 2, the effect of AF on 5-year survival was most pronounced in those with normal LVEF (62 vs. 78%, $p < 0.0001$) followed by those with mild reduction in LVEF (57 vs. 72%, $p = 0.02$). It was not a predictor of survival in those with moderate (5-year survival 55 vs. 61%, p = ns) or severe LV dysfunction (5-year survival 47 vs. 45%, p = ns).

Using the Cox regression model, AF was an independent predictor of mortality after correcting for age and LVEF in the entire cohort and in those with normal LVEF, but not in those with reduced LVEF (Table 2). However, when corrected for group differences such as age, EF, left bundle branch block, LV wall thickness and size and heart rate, AF was not a predictor of mortality either in the entire cohort or any of the EF subsets including those with normal EF.

TABLE 1 Patient characteristics of patients in sinus rhythm (SR) and atrial fibrillation (AF)

Variable	SR (n = 7, 728)	AF (n = 1, 203)	p-value
Age (years)	65 ± 13	72 ± 10	<0.0001
Male gender (%)	96	97	0.28
Height (cm)	176 ± 11	176 ± 9	0.26
Weight (Lbs)	189 ± 40	190 ± 39	0.33
EF (%)	52 ± 15	47 ± 17	<0.0001
Heart rate (bpm)	76 ± 18	77 ± 20	0.026
QRS duration (ms)	100 ± 21	100 ± 21	0.32
Left bundle branch block (%)	4	9	<0.0001
QT interval (ms)	373 ± 46	405 ± 50	<0.0001
Ventricular septum thickness (mm)	11.6 ± 2.4	12.1 ± 2.6	<0.0001
LV free wall thickness (mm)	11.6 ± 2.0	11.8 ± 2.1	0.015
LV end-diastolic diameter (mm)	49 ± 9	52 ± 10	<0.0001
LV end-systolic diameter (mm)	36 ± 11	39 ± 12	<0.0001
Left atrial diameter (mm)	39 ± 7	46 ± 8	<0.0001

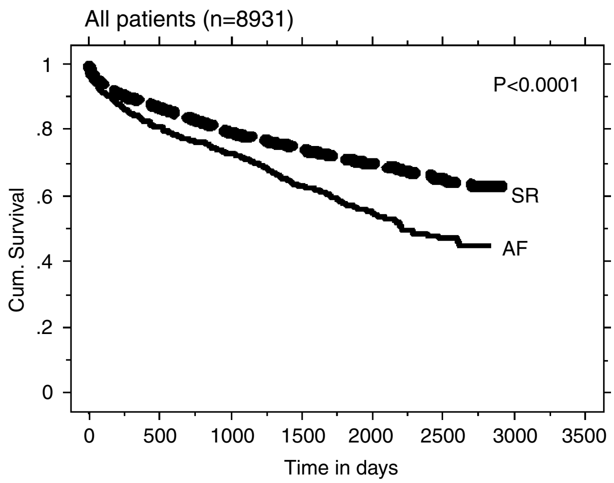

FIG. 1 Kaplan–Meier analysis showing the effect of atrial fibrillation (AF, n = 1, 203) in survival compared to those in sinus rhythm (SR, n = 7, 728) in all the study patients.

Effect of AF on Mortality in other Patient Subsets

Table 3 summarizes the prevalence and prognostic significance of AF in different subsets of patients both by Kaplan–Meier analysis as well as by Cox regression analysis adjusted for age and EF. This table also gives insight into the interaction between AF and the variables on which subsets are based. Compared to the AF prevalence of 14% in the whole cohort, it was markedly increased in those with left bundle branch block (LBBB) (28%), right bundle branch block (RBBB) (24%) and 3–4+ MR (29%) and TR 37%). The prevalence was marginally increased in the elderly, those with AS and those with left ventricle hypertrophy (LVH) or MI on ECG, but not in those with QT interval prolongation.

By univariate analysis, AF was associated with a higher mortality in most of the subsets except those with LBBB, AS, and those with LVH on ECG and 3–4+ MR (Fig. 3). However, this did not persist after adjusting for age and EF in any of the groups except those with QTc ≥450. Interestingly, in these patients, AF was an independent predictor of mortality after adjusting for age and EF raising the possibility of a deleterious interaction between AF and increased QTc in terms of a mortality impact.

Discussion

The three important findings of our study are: (i) The effect of AF on mortality is absent in those with moderate and severe LV dysfunction; (ii) AF is a predictor of higher mortality even in those with normal EF after adjusting for co-morbidities and (iii) There may be an enhanced sensitivity to AF in those with QT prolongation in terms of mortality. This is the only study, we are aware of, which has analyzed the effects of AF on survival as a function of EF and various electrocardiographic and echocardiographic variables which may have prognostic importance. In addition, size of the study population is very large compared to other published studies.

Patients with Normal and Abnormal LV Function

Review of literature suggests that AF may be prognostically important in subjects with no other known cardiac disease. Data from New York life insurance suggests that for patients with AF, the hazard ratio for death is about 3.[3] However, data on LV function and other co-morbidities are lacking and AF might have been a manifestation of underlying heart disease which might have determined the prognosis. Framingham Heart Study supports these observations as well.[4] Being a community based study, it has a predominance of subjects with normal LV function. A study of 3,983 male air crew recruits

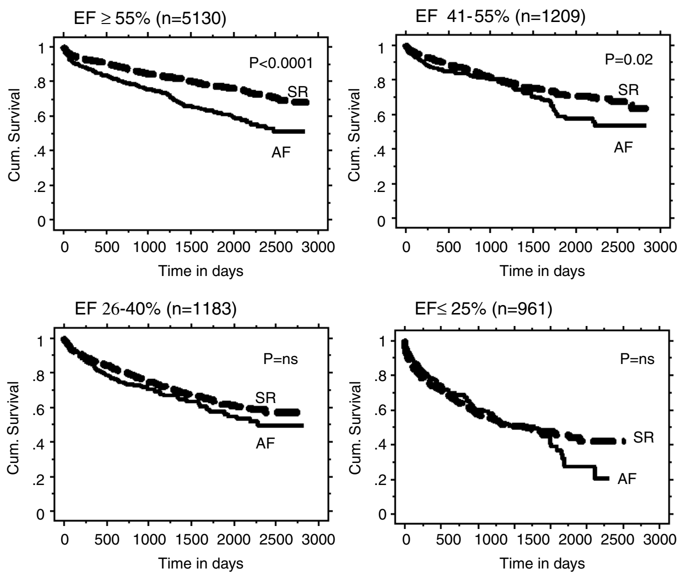

FIG. 2 Graph showing the effect of AF on mortality stratified by the level of LV ejection fraction.

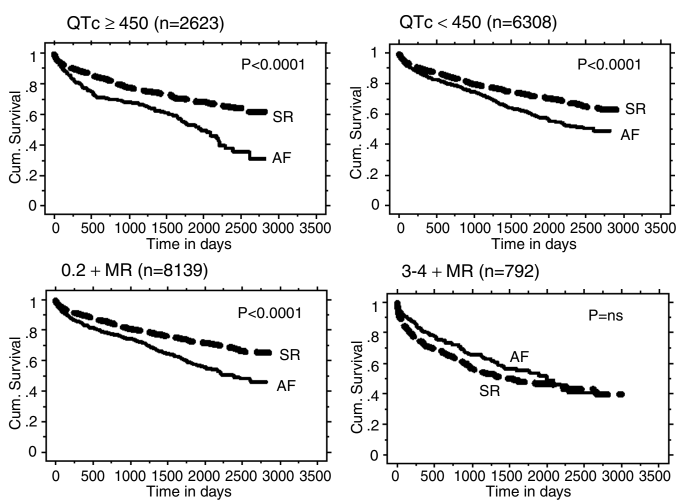

FIG. 3 Graph showing the effect of AF on mortality in subsets based mitral regurgitation severity and QTc interval.

observed for 44 years concluded that AF is associated with a slightly increased mortality (RR 1.31), but less than the other reports.[5]

Data in patients with congestive heart failure (CHF) is mixed, but seems to indicate that AF is prognostically unimportant in those with more severe disease. Mahoney *et al*. based on a study of 234 consecutive patients referred for cardiac transplantation, concluded that AF is not associated with a decrease in survival.[8] Independent predictors of event-free survival were New York Heart Association (NYHA) class and pulmonary artery wedge pressure.[8] In a study of 409 CHF patients, AF was an univariate predictor of mortality, but not a predictor after correcting for covariates.[9] In a study of 390 patients from a CHF clinic, 19% had AF.[10] AF was an independent predictor of mortality in the whole cohort and those with pulmonary artery wedge pressure of <16 mmHg, but not in those with a higher filling pressure. AF was not an independent predictor of higher mortality in either SCD-HeFT or the COMET trial.[15,16]

These data and our own results indicate that AF may be prognostically important in patients with no or mild LV dysfunction. When CHF or LV dysfunction is more severe, mortality from the disease process itself is high and addition of AF as a co-morbidity makes little difference in terms of prognosis.

AF in MI Patients

Eldar *et al*. reported an increase in mortality with AF in 2,866 patients with acute MI, attributable to worse risk profile.[17] In our series, prevalence of AF in those

TABLE 2 Cox regression model for in different corrected for age and EF

Variable	Hazard ratio (95% CI)	Chi-square	P-value
All patients (n = 8, 931)			
Age (per year)	1.041 (1.037–1.045)	282.4	<0.0001
LVEF (per %)	0.979 (0.977–0.981)	196.8	<0.0001
AF	1.128 (1.010–1.246)	5.3	0.02
Patients with normal EF (= >55%, n = 5130)			
Age (per year)	1.039 (1.033–1.045)	130.4	<0.0001
LVEF (per %)	1.023 (1.011–1.035)	15.5	<0.0001
AF	1.290 (1.112–1.468)	14.2	0.0002
Patients with reduced EF (<55%, n = 3353)			
Age (per year)	1.044 (1.038–1.050)	154.7	<0.0001
LVEF (per %)	0.969 (0.963–0.975)	141.3	<0.0001
AF	0.983 (0.825–1.141)	0.04	0.83
Patients with mildly reduced EF (41 to 54%, n = 1209)			
Age (per year)	1.050 (1.036–1.064)	—	<0.0001
LVEF (per %)	1.004 (0.952–1.030)	—	0.87
AF	1.151 (0.861–1.341)	—	0.26
Patients with moderately reduced EF (26–40%, n = 1183):			
Age (per year)	1.043 (1.027–1.059)	—	<0.0001
LVEF (per %)	0.991 (0.933–1.049)	—	0.74
AF	0.950 (0.661–1.290)	—	0.78
Patients with severely reduced EF (= <25%, n = 961)			p-value
Age (per year)	1.041 (1.031–1.051)	—	<0.0001
LVEF (per %)	0.965 (0.955–0.975)	—	<0.0001
AF	0.890 (0.654–1.116)	—	0.34

Abbreviations: LVEF = left ventricular ejection fraction; AF = atrial fibrillation.

with electrocardiographic Q waves was 18%. Though AF was associated with increased mortality in the univariate analysis, it did not persist after correcting for age and EF.

Patients with Electrical Abnormalities

As summarized on Table 3, AF was not an independent predictor of mortality in patients with any of the conduction disturbances. To our knowledge, there are no similar studies in the literature to compare. The most interesting and alarming interaction was between AF and QTc prolongation. While, QTc prolongation did not predispose to AF, AF seemed to make them vulnerable to death in an independent fashion. These is no such report in the literature. We speculate that varying cycle lengths that occur in AF may make these patients vulnerable to torsades de pointes through long-short coupling sequences.

Strengths of the Study

Ours is a very large study with 1,203 patients with AF at all levels of LV function. We also have comprehensive echo and electrocardiographic data. Because of the size of the population, we have been able to analyze the impact of AF at different levels of LV function and in different patient subsets based on echo and electrocardiographic data.

Study Limitations

One of the study limitation is its retrospective nature. The study population was also predominantly male and the conclusions of this study may not be applicable to women. Clinical data such as causes of LV dysfunction, the details of medical therapy and their functional class were not available. These factors have important

TABLE 3 Effect of AF on mortality in various patient subsets by Kaplan–Meier method with log rank p-value and Cox proportional hazards model

Patient subsets (n)	AF: n (%)	Log rank p-value AF	Cox proportional hazards model p-value AF	Age	EF
Age >66 years (n = 4,682)	897 (19%)	<0.0001	NS	<0.0001	<0.0001
MI on ECG (n = 2,623)	469 (18%)	<0.0001	NS	<0.0001	<0.0001
LVH on ECG (n = 1,456)	256 (18%)	0.066	NS	<0.0001	<0.0001
LBBB (n = 408)	113 (28%)	NS	NS	<0.0001	<0.0001
RBBB (n = 693)	165 (24%)	0.005	NS	<0.0001	<0.0001
QRSd >110 ms (n = 1,622)	236 (15%)	0.0001	NS	<0.0001	<0.0001
QRSd ≥130 ms (n = 720)	104 (14%)	0.003	NS	<0.0001	<0.0001
QTc ≥450 (n = 2,623)	469 (18%)	<0.0001	0.01	<0.0001	<0.0001
Any MR (n = 4702)	847 (18%)	<0.0001	NS	<0.0001	<0.0001
3 or 4+ MR (n = 792)	227 (29%)	0.09	NS	<0.0001	<0.0001
Any TR (n = 4132)	770 (19%)	<0.0001	NS	<0.0001	<0.0001
3 or 4+ TR (n = 574)	214 (37%)	0.04	NS	<0.0001	<0.0001
Any AS (n = 650)	110 (17%)	0.054	NS	<0.0001	<0.0001
Moderate/severe AS (n = 251)	46 (18%)	NS	NS	<0.0001	<0.0001

LBBB = left bundle branch block, RBBB = right bundle branch block, NS = not significant, MR = Mitral regurgitation, TR = Tricuspid regurgitation, AS = Aortic stenosis.

prognostic implications. Despite these limitations, the findings of this study may have important clinical implications.

Conclusions and Clinical Implications

This study establishes the fact that AF increases mortality in those with normal, but not in those with impaired LV function. Independent mortality effect of AF in patients with QT prolongations warrants further attention.

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