Clinical Medicine Insights: Cardiology

ORIGINAL RESEARCH

Prevalence and Prognostic Significance of Left Ventricular Dysfunction in Patients Presenting Acutely with Atrial Fibrillation

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Condensed Abstract: The prevalence and prognostic importance of CM occurring as a consequence of AF is poorly defined. This study investigated the incidence of CM in patients with AF, its clinical features and long-term outcomes. We demonstrated that CM is common in patients presenting acutely with newly diagnosed rapid AF, and carries a worse long-term prognosis. Systolic dysfunction was reversible in an important proportion of patients, suggesting a greater prevalence of rate-related CM in AF than has previously been postulated. This underscores the importance of appropriate rhythm management strategies and repeat imaging studies.

Summary

Background: Atrial fibrillation (AF) may precipitate LV dysfunction, potentially leading to cardiomyopathy (CM). The prevalence and prognostic importance of CM occurring as a consequence of AF is poorly defined. We investigated the incidence of CM in patients with AF, its clinical features and long-term outcomes.

Methods: We reviewed 292 consecutive patients (average age 72 ± 13yrs) presenting acutely with AF and tachycardia over a 3 year period from June 2004. Clinical details were obtained from medical records. CM was defined as ejection fraction (EF) ≤ 50% on index admission.

Results: Echo was performed 93% of patients at index admission, and 69 (24%) had CM (average EF% = 37 ± 11), 60 of which were newly diagnosed. Patients with CM had significantly higher presenting heart rate (141 ± 19 vs. 132 ± 23 bpm), larger end-diastolic (5.7 vs. 5.2 cm) and end-systolic (4.5 vs. 3.2 cm) dimensions, and larger left atrial size (4.6 vs. 4.3 cm) ($P < 0.05$ for all). They were also statistically more likely ($P < 0.05$) to be male, present with breathlessness, have a history of coronary disease, and be treated with digoxin and warfarin. Follow-up echo between 6 and 12 months was performed in 46% of patients with new CM, and average EF rose to 53 ± 12%. At an average follow-up of 2.5 years, there was a significant increase in mortality in CM patients (16% vs. 9.5%, $P < 0.05$).

Conclusion: CM is common in patients presenting acutely with newly diagnosed rapid AF, and carries a worse long-term prognosis. Systolic dysfunction was reversible in an important proportion of patients, suggesting a greater prevalence of rate-related CM in AF than has previously been postulated. This underscores the importance of appropriate rhythm management strategies and repeat imaging studies.

Keywords: atrial fibrillation, cardiomyopathy, prevalence, prognosis

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Introduction

Atrial fibrillation is associated with significant morbidity and mortality,[1] and has been reported to be the most common cardiac arrhythmia.[2] Its prevalence markedly increases with age, more than doubling for every successive decade of life.[1] Similarly the prevalence of congestive heart failure (CHF) is increasing and is also strongly associated with age.[3] AF and CHF are closely linked, but to what extent AF is a cause or consequence of ventricular systolic or diastolic dysfunction is unclear.[4] AF is a frequent complication of cardiomyopathy (CM) and heart failure, but animal studies and clinical reports have also indicated its potential to induce systolic dysfunction.[5] AF results in loss of atrial contribution of ventricular filling, and inappropriately rapid and irregular ventricular contractions, potentially precipitating left ventricular dysfunction.[6] Moreover, it has been demonstrated that CM in the setting of AF may be reversible, either with pharmacologic ventricular rate control,[7] cardioversion to sinus rhythm,[8] or AV junction ablation and permanent ventricular pacing.[9] However, the burden of CM occurring as a consequence of AF and its prognostic importance is poorly defined.[6] The purpose of this study was to investigate the incidence and clinical correlates of CM in patients presenting acutely with newly diagnosed AF, and to assess the importance of a rate-related aetiology in this setting.

Methods

We reviewed the clinical records of all patients presenting with atrial fibrillation to the General Medical Service at North Shore Hospital, Waitemata Health, Auckland, New Zealand, for the period 2004–2007. Waitemata Health is the sole provider of publicly funded medical services for a population of approximately 500,000 people, through two district general hospitals. The General Medical service at North Shore Hospital assesses an average of 16,000 acute referrals for inpatient admission annually. Patients were included in this analysis if: (a) this was their first documented presentation to the service with atrial fibrillation and (b) if their ventricular response rate was recorded to be greater than 100 beats per minute on presentation. Those patients with a clinical presentation consistent with an acute coronary syndrome were excluded. The resulting analysis included 292 consecutive patients. All clinical information including mortality was obtained from record and database review, and patients underwent follow-up either at our institution or with their community provider after hospital discharge, as determined by the responsible clinician. In particular details of the index admission and convalescent echocardiograms, if available, were documented. CM was defined as ejection fraction (EF) $\leq$50% on index echocardiogram. Ejection fraction was assessed both visually and objectively using bi-plane Simpsons rule or the Teichholz formula.

Statistics

Analysis was undertaken using SPSS 17.0. Data are expressed as a mean ± standard deviation (SD). The baseline characteristics of the groups were compared using students t-test for continuous variables, and Chi-square or Fisher Exact tests for categorical variables. Survival estimates and event rates were compared by the Kaplan-Meier method. The log-rank test was used to compare the Kaplan-Meier survival curves. A P value of <0.05 was considered significant.

Results

The baseline clinical characteristics of the cohort are presented in Table 1. Of the 292 patients reviewed, 69 (24%) were found to have an EF $\leq$ 50% on index echocardiogram, of which only 9 had a known pre-existing CM. Normal LV systolic function was noted in 207, and only 13 (7%) patients did not have an echocardiogram performed in association with their index admission. They were excluded from the subsequent analysis. Therefore overall 23% of patients with acute AF were found to have previously undiagnosed CM. Those patients found to have reduced systolic function had a significantly higher baseline heart rate (141 ± 19 vs. 132 ± 23 bpm, $P < 0.05$), a greater likelihood of breathlessness being the primary presenting symptom (72% vs. 47%, $P < 0.05$), and a trend towards an increased incidence of hypotension (10% vs. 5%, P = ns). A greater proportion of patients with CM received Digoxin (49% vs. 24%, $P < 0.05$) and Warfarin (62% vs. 47%, $P < 0.05$). Use of other antiarrhythmic drugs did not differ significantly between the two groups, but it is notable that Class 1 antiarrhythmic use was negligible.

Table 1. Baseline characteristics of the study cohort.

	CM	NO CM
Number of patients	69	207
Patient Characteristics (n,%):		
Age (years) (Mean ± SD)	72 ± 11	72 ± 13
Sex (Male%)	67%	48%
Known Cardiomyopathy	9 (13%)	7 (3%)*
Ischaemic Heart Disease	28 (41%)	60 (29%)
Hypertension	30 (43%)	90 (44%)
Valvular Heart Disease	7 (10%)	25 (12%)
Primary symptom on admission (Mean ± SD)		
Palpitations	23 (33%)	127 (61%)*
Breathlessness	50 (72%)	97 (47%)*
Chest pain	19 (28%)	80 (39%)
Clinical findings on admission		
Resting heart rate (Mean ± SD)	141 ± 19	132 ± 23*
Hypotension (BP < 100 mmHg systolic)	7 (10%)	11 (5%)
Medication at discharge (n,%):		
Beta-blockers	44 (64%)	123 (59%)
Calcium channel blockers	37 (54%)	96 (46%)
Digoxin	34 (49%)	49 (24%)*
Amiodarone	15 (22%)	48 (23%)
Class I antiarrhythmic	1 (1%)	13 (6%)
Aspirin	47 (68%)	132 (64%)
Warfarin	43 (62%)	98 (47%)*

Values are means ± SD, or numbers of patients (percentages).
*$P < 0.05$.

The echocardiographic data at index admission and subsequent follow-up is presented in Table 2. In the CM group the average index EF% was 37 ± 11%, as compared with 67 ± 8% in the patients without CM. The average end-diastolic dimension was increased in the CM group, but not significantly greater than in those without CM (5.7 vs. 5.2 cm, P = ns). However end-systolic dimension (4.5 vs. 3.2 cm) and left atrial size (4.6 vs. 4.3 cm) ($P < 0.05$ for both) were significantly greater in the CM group.

Follow-up echocardiography was obtained between 6 and 12 months after index presentation in 57 patients, 26 (43%) of whom had been found to have a newly diagnosed CM in association with AF. These patients had a significant increase in resting systolic function at repeat scanning, with the average EF rising to 53 ± 12%. This was associated with a normalisation in end-systolic dimensions (4.5 to 3.9 cm) and a small reduction in average left atrial size (4.6 to 4.4 cm). Figure 1 demonstrates graphically the outcome for all 26 patients of the initial 60 with newly diagnosed CM who underwent follow-up echocardiography, confirming that nearly all made significant gains in systolic function. Indeed 13 (50%) normalised their EF. At clinical follow-up, 11 (42%) of those patients

Table 2. Echocardiography results.

	CM	NO CM
Echocardiography data on admission (Mean ± SD)		
LVEDD (cm)	5.7 ± 0.9	5.2 ± 3.3*
LVESD (cm)	4.5 ± 0.9	3.2 ± 1.7*
Ejection Fraction (%)	37 ± 11	67 ± 8*
LA Size (cm)	4.6 ± 0.9	4.3 ± 0.8*
Echocardiography data at 6 months (Mean ± SD)		
LVEDD (cm)	5.7 ± 0.7	5.0 ± 1.0
LVESD (cm)	3.9 ± 0.8	3.4 ± 0.9
Ejection Fraction (%)	53 ± 12	62 ± 13
LA Size (cm)	4.4 ± 0.8	4.5 ± 0.6

Values are means ± SD, or numbers of patients (percentages).
*$P < 0.05$.

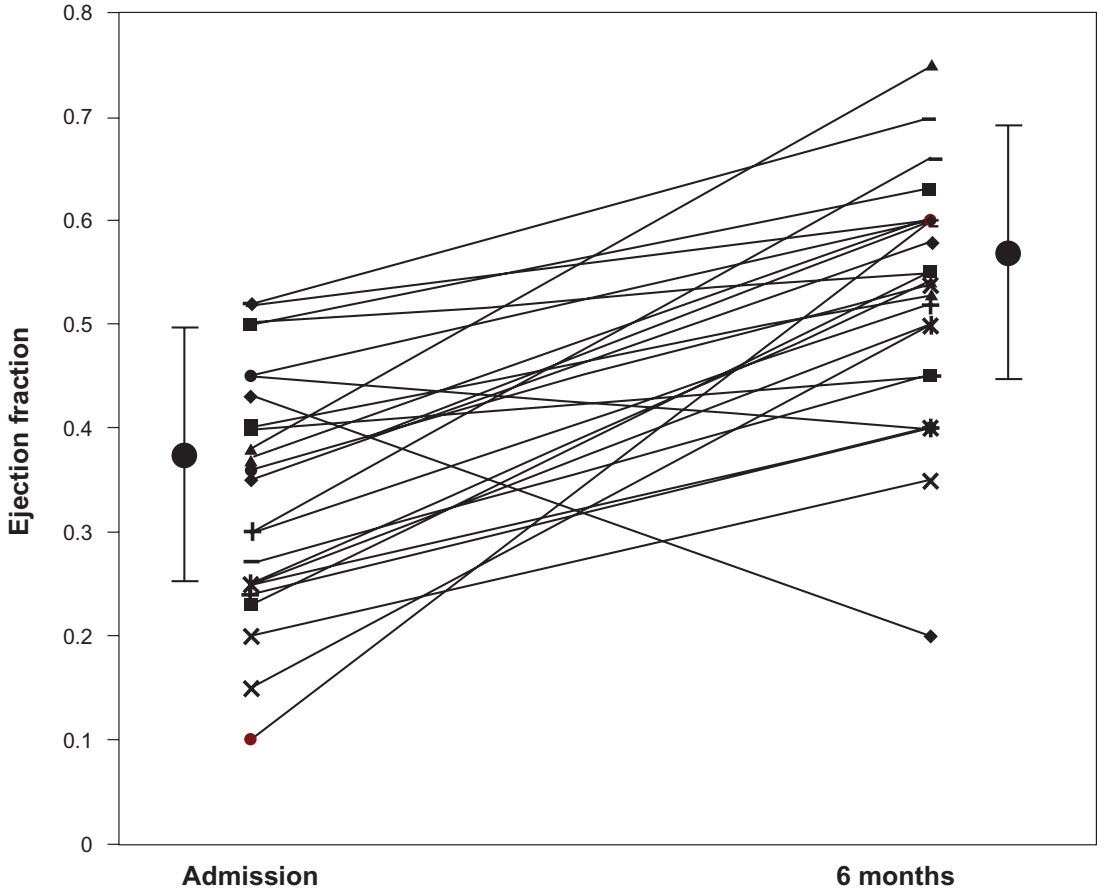

Figure 1. Graphical representation of the index and follow-up EF for all 26 patients of the initial 60 with newly diagnosed CM who underwent follow-up echocardiography, confirming that nearly all made significant gains in systolic function. Note that 13 (50%) normalised their EF.

with newly diagnosed CM undergoing follow-up echocardiogram were in sinus rhythm, 1 was paced, and the average heart rate of those who remained in AF was 82 ± 17 bpm, suggesting acceptable rate control in the majority.

In the entire cohort there were 30 deaths over an average follow-up period of 2.5 years. Deaths were significantly higher in the CM group (16% vs. 9.5%) and this is illustrated in Figure 2, showing the significantly worse mortality in those patients with newly diagnosed CM in the setting of acute AF and tachycardia.

Discussion

This study identifies that previously unsuspected CM is common in patients presenting acutely with newly diagnosed rapid AF, and that patients with CM in this setting have a worse long-term prognosis. Furthermore we have demonstrated that in an important proportion of patients this systolic dysfunction is reversible. This suggests a potentially greater prevalence of rate-related CM in AF than has previously been postulated.

Reversible LV dysfunction associated with rapid AF has been recognised for decades, and was first discussed in detail by Phillips and Levine in 1949.[10] However the evidence confirming this relationship and defining the causal link is surprisingly scant. Grogan et al[7] reported a small series of 10 patients initially considered to have idiopathic dilated CM who had a gain in median ejection fraction from 25% to 52% after adequate rate control or restoration of sinus rhythm. Similarly Kieny et al[8] reported 12 patients with chronic AF and average EF of 32% who were successfully restored to sinus rhythm. This was associated with a 20.8% average improvement in EF, and 6 (50%) of the patients returned to normal systolic function. More recently improvement

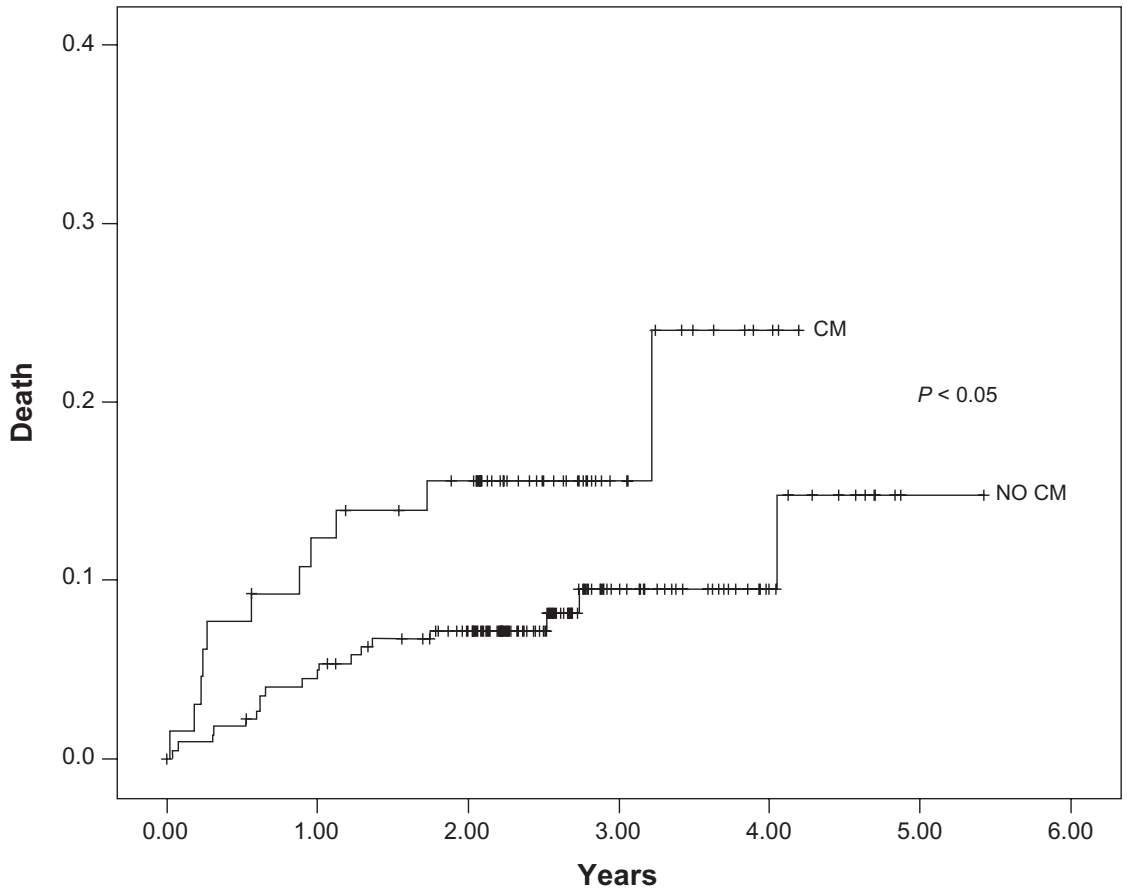

Figure 2. Kaplan-Meier analysis showing the significantly worse mortality ($p < 0.05$) in those patients with newly diagnosed CM in the setting of acute AF and tachycardia, as compared with patient with no CM.

in cardiac function of a similar magnitude has been seen in patients with CM and AF refractory to therapy who were treated either with AV node ablation and pacemaker implantation,[9] or who underwent catheter ablation.[11] From this later work, Cha et al postulated that the prevalence of AF-induced CM was 10% in this challenging group.[4]

Our study reviewed a considerably larger cohort of patients with AF than those studies cited thus far, and focussed on those presenting acutely to an emergency department with tachycardia. Overall 23% of patients with acute AF were found to have previously undiagnosed CM. However the causes of CM in our group are likely heterogeneous, and include (but are not limited to) idiopathic dilated CM, myocarditis and rate-related CM. In particular in this study the duration of AF prior to presentation to the emergency department is unclear. The development of a tachycardia-related myopathy requires an element of chronicity to the dysrhythmia, further suggesting that not all cases of impaired LV function in our series are related solely to rapid AF. However the finding that 50% of those patients with newly diagnosed CM in the setting of AF returned to normal systolic function at follow-up replicates Kieny's results, and supports the hypothesis that this group indeed had AF-induced CM. The CM group in our series also had a higher average presenting heart rate, but no information can be gleaned on whether this was a cause for, or a consequence of, the systolic dysfunction. It should be noted however that patients seen at follow-up were almost uniformly in well rate-controlled AF or sinus rhythm. Furthermore it is interesting to note that the average end diastolic dimension in our patients with CM was only marginally about the upper limit of normal, supporting the concept of an acute rate-related dysfunction without marked LV dilation.

There is a limited understanding of the mechanisms underlying tachycardia-induced myopathy. The majority of our understanding is derived from animal studies of pacing-mediated CM. Morrison et al[6] summarise the evidence and hypotheses in three categories: structural changes, cellular changes and increased sympathetic nerve activity. Changes in extracellular collagen distribution and increased myocardial stiffness are noted, along with depletion of myocyte energy stores and abnormal calcium metabolism. Unfortunately our study does not provide any further insights into the mechanisms of myopathy.

Framingham study data have demonstrated that AF is an independent predictor of mortality in men and women of all ages.[1] Furthermore the subsequent development of CHF in patients with known AF was associated with increased mortality for both men (HR 2.7; 95% CI, 1.9 to 3.7), and women (HR 3.1; 95% CI, 2.2 to 4.2).[12] Similarly our study suggested that, at an average follow-up of 2.5 years, there was an increase in mortality for those patients with acute AF and newly diagnosed CM patients (16% vs. 9.5%). Patients whose LV function improved (LVEF $>$ 45%) after atrioventricular node ablation have been shown to have a comparable survival to age-and sex-matched controls, and better than that noted in patients with persistent LV dysfunction.[9] None of the patients in our study who normalised their LV function died during follow-up, but the numbers available for analysis were very limited.

Limitations

This is a retrospective clinical review and suffers the major limitations associated with this type of study. Most notable in our series is the lack of consistent clinical follow-up and echocardiography, even in patients with confirmed systolic dysfunction on index admission. This reduces the reliability of the data regarding recovery of LV function, but does not impact the information gained on prevalence or prognostic importance of CM in this setting. A further potential limitation is the challenge in assessing LV systolic function in the setting of tachycardia, especially fast AF. Echocardiographic may result in spuriously low estimations of EF%. We are unable to further clarify this issue, but would note that echocardiograms were performed in the days following admission to an inpatient service—at a time when rate control was likely to have improved over that on presentation to the emergency department. Although a very small number of patients underwent cardiac magnetic resonance imaging in convalescence, there was no rigorous assessment to exclude or confirm myocarditis. It is therefore not possible to resolve the true proportion of CM that was induced by AF alone. Similarly it is not feasible to account for the potential effect of optimal pharmacologic therapy for systolic dysfunction on the subsequent improvement in EF seen in the follow-up echocardiograms.

Conclusions

We have demonstrated that CM is common in patients presenting acutely with newly diagnosed rapid AF, and carries a worse long-term prognosis. Systolic dysfunction is reversible in an important proportion of patients, suggesting a greater prevalence of rate-related CM in AF than has previously been postulated. This underscores the importance of appropriate rhythm management strategies and repeat imaging studies.

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