Low Atrial Fibrillatory Rate Is Associated With Poor Outcome in Patients With Mild to Moderate Heart Failure

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Background—Atrial fibrillatory rate (AFR) is a measure of atrial remodeling caused by atrial fibrillation (AF), and its acceleration negatively affects outcome of interventions for persistent AF. However, the prognostic value of AFR in patients with congestive heart failure (CHF) has not been studied. We sought to evaluate whether AFR can predict outcome in patients with mild to moderate (New York Health Association II–III) CHF.

Methods and Results—High-resolution 20-minute long Holter ECGs obtained from 169 CHF patients with AF at enrollment were analyzed. AFR was estimated using spatiotemporal QRST cancellation and time–frequency analysis. The patients were followed for a median of 44 months, with primary end point defined as total mortality and secondary end points as sudden death and heart failure death. Atrial signal quality was sufficient for AFR estimation in 142 patients (mean age 69±11 years, 101 male). Of those, 48 patients died during follow-up, including 18 because of CHF progression. Mean AFR was 390±60 fpm and decreased with age (r=−0.3, P<0.001). Patients with AFR ≥371 fpm (lower tertile) had 44% 3-year mortality as compared with 26% with higher AFR. Lower AFR was an independent predictor of all cause mortality (HR=1.99, 95% CI=1.09–3.63, P=0.025) and CHF death (HR=3.74, 95% CI=1.38–10.14, P=0.010) after adjustment for significant clinical covariates in multivariable Cox analysis.

Conclusions—In CHF patients with AF, reduced AFR assessed using noninvasive approach is associated with increased risk of death because of heart failure progression, and may be considered a predictor of outcome. (Circ Arrhythm Electrophysiol. 2012;5:77-83.)

Key Words: atrial fibrillation ■ electrocardiography ■ atrial fibrillatory rate ■ congestive heart failure ■ risk stratification

Atrial fibrillatory rate (AFR) is a characteristic of atrial substrate in atrial fibrillation (AF) that, in experimental studies, was shown to be a measure of atrial remodeling, and demonstrated acceleration associated with longer duration of the arrhythmic episodes.1 A noninvasive method of AFR assessment, frequency analysis of fibrillatory ECG (FAF-EKG),2,3 has consistently showed that faster AFR is associated with worse prognosis in regard to the sinus rhythm maintenance in patients without significant structural heart disease admitted for cardioversion4–6 or catheter ablation7 of persistent AF. However, FAF-EKG has never been used for systematic assessment of AFR in patients with congestive heart failure (CHF); it is more likely to have advanced structural atrial abnormalities predisposing to AF maintenance. The prognostic impact of AFR on clinical outcome in CHF patients is not known either.

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Therefore, the objective of our research was to evaluate the association of AFR with clinical outcome in the population of patients with mild to moderate CHF included in the MUSIC (MUerte Subita en Insuficiencia Cardiaca) study, with AF at baseline.

Materials and Methods

Patient Population

This analysis involved ambulatory patients with mild to moderate (II–III class according to New York Heart Association [NYHA]) CHF enrolled in the multicenter Spanish MUSIC study. The study included patients with symptomatic heart failure with either depressed or preserved left ventricular ejection fraction (LVEF). The latter were included if they had heart failure symptoms and a prior hospitalization for CHF, or any objective signs of CHF confirmed by

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Clinical Evaluation and Follow-Up
In all the patients, clinical, echocardiographic, ECG, and laboratory data were collected at enrollment. Patients were followed every 6 months on an outpatient basis for a median of 44 months. Primary end point was defined as total mortality. In each case, the cause of death was classified by a MUSIC Study End Points Committee. Total mortality was defined as of cardiac or noncardiac origin. Cardiac deaths were classified either as sudden or caused by heart failure progression. Death was defined as “sudden” if it was (1) a witnessed death occurring within 60 minutes from the onset of new symptoms, unless a cause other than cardiac was obvious, (2) an unwitnessed death within 24 hours of symptoms onset in the absence of preexisting progressive circulatory failure or other causes of death, or (3) a death during attempted resuscitation. Deaths caused by end-stage heart failure were defined as occurring in hospitals as a result of refractory progressive pump failure.

Data Analysis and Signal Processing
At baseline, all subjects underwent 24-hour ambulatory ECG in 3 orthogonal X, Y, and Z leads using SpiderView recorders (ELA Medical). During the initial 20 minutes, ECG was recorded with 1000 Hz resolution while patients were resting in supine position. High-resolution Holter recordings were available in 169 AF patients. Four 60-second long recording segments were retrieved at the 4th, 9th, 14th, and 19th minute of initial resting ECG for off-line automated computerized processing using the AFRtracker software (CardioLund Research AB). The preprocessing needed to analyze surface ECG signals were baseline filtering, pacemaker spike detection and suppression, beat detection and classification, and spatiotemporal QRST cancellation (Figure 1).6 The lead with the highest amplitude of atrial signal was used for further time frequency analysis aimed at estimation of AFR over a period of 60 seconds using the methodology applied earlier.4 The AFR did not demonstrate significant difference between the 4 selected 1-minute long segments. The mean value of AFR calculated from the 4 measurements was used for analysis.

Twenty-seven subjects with AF at baseline were excluded from analysis because of either low amplitude of atrial signal or poor ECG quality preventing reliable AFR assessment. The final data set, therefore, comprised 142 subjects.

Statistical Analysis
The *t* test, Mann-Whitney *U* test, or *χ*² analysis were used for univariate comparisons of data between patient groups. To evaluate the correlation between AFR and clinical covariates, Pearson or Spearman tests were used, where appropriate. Logistic regression analysis was used to assess the strength of the relationships between clinical covariates and AFR group. Cumulative probability of survival was estimated and graphically shown according to the Kaplan-Meier method, with comparisons made using log-rank tests. The Cox proportional-hazards regression model was used in the prediction of the specified end points.

A stepwise selection process was used with Cox proportional-hazards regression to derive a multivariable model, which considered variables that were significantly different between the higher and lower AFR groups at the <0.10 level in univariate analysis, or were viewed clinically important (eg, LVEF). Only variables that were still statistically significant at <0.10 in the multivariable model for the mortality end point were retained. The AFR variable then was added to this final multivariable model. This multivariable model was prespecified to be stratified by amiodarone use because of its effect on AFR, allowing nonparametric adjustment for this therapy through the estimate of separate baseline survival curves. A probability value of <0.05 was considered statistically significant. Data were analyzed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

Clinical Characteristics of Studied Population
Final studied population included 142 patients (104 males), mean age 69±11 years, with CHF in NYHA class II (72%) or III (28%). LVEF ranged from 15% to 70% (mean 40±15%). In the studied group, 28% of the patients had CHF because of ischemic cardiomyopathy, 31% of the patients were diabetics, and 59% of the patients had hypertension. None of the AF patients had rhythm control strategy implemented at the time of enrollment, even though a considerable number of patients received amiodarone for rate control purposes. Detailed clinical characteristics, as well as medication, are shown in Table 1. The clinical and echocardiographical characteristics of patients excluded because of unavailability of AFR measurements did not differ from those of patients included in the analysis.

Baseline Atrial Fibrillatory Rate and Clinical Covariates
AFR ranged from 236 fps to 514 fps (mean 390±60 fps, median 396 fps). AFR was significantly correlated with age (*r* = −0.302, *P* < 0.001), QRS duration (*r* = −0.255, *P* = 0.002), creatinine, and NT-proBNP levels (*r* = −0.187, *P* = 0.026 and *r* = −0.179, *P* = 0.033, respectively).
Table 1. Clinical Characteristics of a Studied Population With Heart Failure and Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studied Group N=142</th>
<th>AFR ≤371 fpm N=47</th>
<th>AFR &gt;371 fpm N=95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69 (72):±11</td>
<td>72 (74):±10</td>
<td>68 (71):±11*</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>104 (73%)</td>
<td>30 (64%)</td>
<td>74 (78%)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>40 (28%)</td>
<td>20 (43%)</td>
<td>20 (21%)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44 (31%)</td>
<td>18 (38%)</td>
<td>26 (27%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84 (59%)</td>
<td>28 (60%)</td>
<td>56 (59%)</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>39 (26%)</td>
<td>17 (36%)</td>
<td>22 (23%)</td>
</tr>
<tr>
<td>LVEF &gt;50%</td>
<td>43 (30%)</td>
<td>16 (34%)</td>
<td>27 (28%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>40 (38):±15</td>
<td>41 (36):±17</td>
<td>40 (38):±14</td>
</tr>
<tr>
<td>Left atrium diameter (mm)</td>
<td>52 (52):±8</td>
<td>53 (53):±8</td>
<td>51 (51):±8</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>117 (110):±29</td>
<td>125 (118):±33</td>
<td>113 (107):±27*</td>
</tr>
<tr>
<td>Mean heart rate</td>
<td>75 (75):±14</td>
<td>74 (71):±17</td>
<td>75 (77):±13</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>112 (106):±32</td>
<td>117 (112):±33</td>
<td>110 (101):±31</td>
</tr>
<tr>
<td>NTproBNP (ng/L)</td>
<td>2854 (1511):±3740</td>
<td>3556 (1874):±4788</td>
<td>2505 (1311):±3068</td>
</tr>
</tbody>
</table>

Medications

| Amiodaron                 | 21 (15%)            | 14 (30%)          | 7 (7%)*           |
| ACE inhibitors or ARB     | 118 (83%)           | 33 (70%)          | 85 (89%)*         |
| Beta blockers             | 81 (57%)            | 24 (51%)          | 57 (60%)          |
| Digoxin                   | 86 (61%)            | 29 (62%)          | 57 (60%)          |
| Diuretics                 | 127 (89%)           | 42 (89%)          | 85 (88%)          |
| Spironolactone            | 60 (42%)            | 21 (45%)          | 39 (41%)          |
| Statins                   | 45 (32%)            | 20 (43%)          | 25 (26%)          |

Data are presented as mean (median)±standard deviation for continuous variables, or as numbers (percentage) for categorical variables.

AFR indicates atrial fibrillatory rate; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*P <0.05 for comparison between groups with lower vs higher AFR.

However, no significant correlations were found for AFR and LVEF, left atrium diameter, and average heart rate. Regarding pharmacotherapy, lower AFR was observed in patients on amiodarone (336 versus 404 fpm, P=0.001), while higher AFR was observed in patients treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor block (ARB; 401 versus 364 fpm, P=0.001). Table 1 shows a comparison of clinical characteristics of studied patients categorized according to AFR values (≤371 versus >371 fpm). Multivariable logistic regression analysis showed that age (odds ratio [OR]=1.05, CI=1.00–1.10, P=0.032) and NYHA class III (OR=2.87, CI=1.23–6.68, P=0.014), as well as amiodarone (OR=8.50, CI=2.70–26.78 P<0.001) or the lack of ACE-inhibitors/ARB use (OR=3.60, CI=1.33–9.69, P=0.021) are associated independently with lower values of AFR.

**AFR and Clinical Outcome**

During follow up period, there were 48 deaths, including 32 cardiac deaths and 16 noncardiac deaths (5 cancer, 3 accidents, 1 ischemic stroke, 1 bleeding, 1 sepsis, 1 pancreatitis, 1 respiratory insufficiency, and 3 surgery-related deaths). Among cardiac deaths, 14 were classified as sudden and 18 as deaths caused by pump failure. There was no statistical difference between the total mortality and different modes of death observed in patients excluded because of unavailability of AFR measurements and the final study population.

Patients with lower AFR (lower tertile AFR ≤371 fpm) had lower survival. According to the Kaplan-Meier analysis, lower AFR was associated with a 2-fold higher total mortality (44% versus 26%, P=0.036; Figure 2A) and cardiac death (37% versus 16%, P=0.014), and nearly 4-fold higher mortality caused by heart failure progression (27% versus 7%, P=0.004; Figure 2B). No significant differences were observed for the sudden death end point.

AFR ≤371 fpm was found to be a significant predictor of total, cardiac, and heart failure death in univariate analysis, and remained an independent risk marker when adjusted for significant clinical covariates, that is, ischemic etiology, NYHA class III, and LVEF <35% and stratified by amiodarone use (hazard ratio [HR]=1.99, CI=1.09–3.63, P=0.025, HR=2.48, CI=1.19–5.18, P=0.015, and HR=3.74, CI=1.38–10.14, P=0.010 for total mortality, cardiac death, and heart failure death, respectively; Table 2). AFR ≤371 fpm remained significantly associated with clinical outcome in patients not treated with amiodarone (HR=2.15, CI=1.01–4.63, P=0.049 and HR=3.06, CI=1.08–8.68, P=0.036 for cardiac death and heart failure death, respectively).

**Discussion**

**Main Findings**

In the post hoc analysis of AF cohort enrolled in the MUSIC study, we have for the first time demonstrated that patients

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with CHF NYHA II–III and low AFR were at higher risk of death, the risk being mostly driven by the excessive mortality related to congestive heart failure. The atrial substrate in patients with mild to moderate CHF is characterized by age-related slowing of AFR associated with biochemical and ECG markers, indicating severity of clinical condition. There was no link between AFR and risk of sudden cardiac death.

**Age-Related AFR Slowing**

The link between faster AFR and increased sustainability of AF is known because of the landmark experimental study of Wijffels et al.\(^1\) It was suggested that the shortening of atrial refractory period following rapid atrial pacing is a manifestation of an atrial remodeling process that results in the shortening of fibrillatory cycle length and prolongation of AF episodes. Clinical observations confirmed these findings,\(^10\) and the link between slower AFR and better outcome of interventions for persistent AF have been reported, both for cardioversion\(^7,11\) and catheter ablation of AF.\(^7,11\) However, refractoriness of atrial myocytes is not the only determinant of AFR. Ablation in the left atrium that creates boundaries hindering propagation of fibrillatory waves prolongs the AF cycle length measured in the right atrial appendage.\(^11\) AFR obtained from surface ECG is a composite measure that reflects fibrillatory process in the atria rather than a local AF cycle length. Slowing of AFR, therefore, can be explained by a combination of factors that include reduced firing of focal AF sources, lower number of circulating wavelets, increase in atrial refractory period, or slowing of atrial conduction.

The age-related AFR slowing earlier has been reported in a population of patients with long-standing persistent AF.\(^12\) The reason for that is likely to be the age-related atrial fibrosis\(^13\) that results in a slowing of atrial conduction observed during sinus rhythm, either as an increased prevalence of fractionated atrial electrograms\(^14\), or abnormal P-wave morphology\(^15\) or duration.\(^16,17\) Conduction slowing, therefore, can lead to less and larger reentry circuits expressed in a slower AFR on surface ECG. The age-related decrease in AFR observed in the MUSIC population is, therefore, well in line with these observations.

A recent study by Swartz et al\(^18\) using similar methodology of noninvasive AFR assessment has provided direct evidence of association between the extent of atrial fibrosis and slower
AFR in patients who develop AF following cardiac surgery, thus further supporting our findings of AFR as a biomarker of advanced cardiac pathology in patients with AF and structural heart disease.

**Decreased AFR and CHF Severity**

Apart from the negative correlation with age, AFR also was related inversely to the biochemical and ECG markers. Even though the correlations are rather weak, they quite consistently indicate the presence of association between the slower AFR and severity of clinical condition in patients with CHF, such as NP-proBNP, creatinine, and QRS duration. Though the association between the CHF and AF is well documented, there is an ongoing discussion in regard to the effect of CHF on atrial electrophysiology. There is data suggesting that atrial conduction is deteriorated in CHF settings, both in animal experiment and in CHF patients without AF history. The causes of that are complex and may be caused by the autonomic imbalance, accumulation of fibroblasts, collagen between atrial myocytes (i.e., fibrosis), and connexin dysfunction. Even atrial refractoriness prolongs as a result of CHF, as suggested by data from electrophysiological studies in CHF patients without AF history. Slowing down of the atrial fibrillatory process, expressed by an AFR decrease that correlates with CHF severity markers observed in our study, is, therefore, the expected net result of these changes. However, we have not been able to demonstrate any association between AFR and LVEF. The reason is likely to be due partly to the relatively low sensitivity of the LVEF as an indicator of CHF severity, and the recent evidence suggesting that biochemical markers such as BNP bear prognostic information independent of the left ventricular systolic dysfunction. Another plausible explanation for the lack of association between LVEF and AFR can be the earlier findings, suggesting that in patients with CHF it is the diastolic dysfunction of the left ventricle associated with increased left atrial filling pressure that is likely to have a causative role for AF development. In that case, MUSIC population with AF included in our analysis may have had advanced diastolic dysfunction at baseline, that independently from LVEF affected the severity of their clinical condition.

While the finding of slower AFR in amiodarone-treated patients is rather expected, the lower AFR in patients not treated with ACE/ARB is intriguing but not surprising. Renin-angiotensin blockade is known to prevent or slow down development of cardiac fibrosis in the settings of heart failure, and data from large-scale trials indicate the effect of ACE/ARB therapy in regard to the new onset of AF in CHF patients. In light of these observations, the lower AFR in 24 patients who were not treated with ACE/ARB (397±59 fpm versus 355±55 fpm, P<0.001) may be another manifestation of the more advanced structural changes in atrial myocardium.

Bollmann et al. have reported a decrease of AFR in response to short-term candesartan treatment in patients with persistent AF scheduled for elective cardioversion in the CAndesartan in the Prevention of Relapsing Atrial Fibrillation [CAPRAF] study, which is in contrast to our findings. However, the patients included in CAPRAF study did not have congestive heart failure, but had AF that persisted for 1 month on average, and the effect was confined to patients with baseline AFR above 420 fpm. This AFR range corresponds to the upper tertile of AFR values in our patients with CHF. However, we have not been able to explore this phenomenon any further, as 96% of patients with AFR above 420 fpm in our nonrandomized study were treated with ACE inhibitors.

**AFR as an Independent Predictor of Increased Mortality**

We demonstrate for the first time that the noninvasive characteristic of atrial fibrillatory process such as AFR bears important prognostic information in patients with CHF and AF. After correction for clinically relevant covariates such as age, gender, LVEF, diabetes, ischemic cardiomyopathy, severity of heart failure (NYHA class III), and the use of amiodarone, which is known to slow down AFR in earlier studies, low AFR appeared to be predictive for increased total mortality (HR=1.99), cardiac death (HR=2.48), and CHF-related death (HR=3.74). In line with earlier discussed significant associations between AFR and indicators of clinical severity, the results of the multivariable analysis suggest that AFR may be considered an important noninvasive ECG indicator of clinical condition in these patients, and its independent prognostic value justifies further studies in well-controlled populations.

**AFR in AF Intervention Studies and Findings in MUSIC AF Cohort**

Our findings on the MUSIC AF cohort are seemingly opposite to the earlier accepted concept that linked lower AFR to less atrial remodeling and better outcome of interventions aimed at restoration and maintenance of sinus rhythm. There is, however, several important observations to be considered.

Firstly, none of the earlier studies that used FAF-ECG technology systematically included patients with structural heart disease or CHF. In one analysis presented by Haïssaguerre et al., patients with structural heart disease admitted for catheter ablation of AF had significantly lower AFR than those with structurally normal hearts, supporting our observation in MUSIC material. Because no information on the AF duration at inclusion in MUSIC study was collected, we have not been able to analyze whether observed AFR values correlate with the duration of the arrhythmia, which is a limitation of our study. Earlier experimental studies suggest that acceleration of AFR is observed at AF onset and during the first hours, and may continue until 24 to 36 months from the onset of AF episode, at which point no additional acceleration in AFR is observed. Our findings suggest that as structural changes in the atria progress further because of age or accompanying CHF, resulting atrial conduction slowing leads to fewer and larger re-entry circuits expressed as slower AFR on surface ECG.

Secondly, it is still unclear what impact AFR may have on the outcome of AF management strategies in CHF population because no such attempt was made in the MUSIC study.
There is an ongoing debate whether AF per se and rhythm control interventions in CHF have impact on survival in patients with CHF. The observed prognostic value of AFR in MUSIC population may, therefore, be completely independent from its link to the outcome of rhythm control interventions reviewed earlier.

Finally, our analysis is the first one that has investigated the impact of AFR on the mortality end point, and to the best of our knowledge no similar study has been published.

Study Limitations
Being a post hoc analysis of data collected for the core MUSIC protocol that was not aimed at detailed evaluation of AF characteristics in patients with CHF, our study lacks potentially important information on AF duration and its clinical course. As shown recently by our group, the AF duration is strongly associated with the extension of atrial fibrosis, and therefore may influence AFR. Nevertheless, our study is hypothesis-generating and warrants further controlled studies in patients with CHF and AF.

Conclusions
Based on the post hoc analysis of MUSIC dataset, our study provides the first clinical evidence of the independent prognostic value of AFR in patients with mild to moderate CHF. Opposite to earlier findings in patients without structural heart disease, in patients with CHF lower AFR is associated with worse prognosis. Age-related decline in AFR associated with an increase in CHF-related mortality most likely is related to an advanced atrial structural remodeling or fibrosis.

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Disclosures
None.

References

CLINICAL PERSPECTIVE
Atrial fibrillatory rate (AFR) is a noninvasive estimate of atrial refractoriness in patients with atrial fibrillation that can be calculated from the surface ECG. Earlier studies have shown that faster AFR is associated with a lower success rate for catheter ablation or cardioversion in patients with recurrent persistent atrial fibrillation without congestive heart failure. However, this novel ECG marker has not been studied for prediction of long-term clinical outcomes. By applying computer-based AFR assessment to ambulatory Holter ECGs recorded in patients with mild to moderate congestive heart failure enrolled in the MuerteSubita en Insuficiencia Cardiaca (MUSIC) study, we found that in the context of heart failure, low AFR is associated with other indices of severity of clinical condition, such as QRS duration, creatinine, and NT-proBNP levels. It is also a strong predictor of a higher risk of death, mainly driven by the excessive mortality related to congestive heart failure. Slowing down of the atrial fibrillatory process in patients with congestive heart failure is likely to reflect the degree of structural remodelling and the extent of atrial fibrosis. The results of our study suggest that AFR can be considered a promising novel ECG marker that reflects modification of atrial substrate in patients with congestive heart failure, and can be considered for inclusion in clinical outcome prediction models in studies on patients with atrial fibrillation.
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