Left Atrium Dilatation and Left Ventricular Hypertrophy Predispose to Atrial Fibrillation in Patients With Community-Acquired Pneumonia

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Atrial fibrillation (AF) is one of the most common cardiovascular complications in patients hospitalized with community-acquired pneumonia (CAP). However, predisposing clinical factors associated with AF in CAP patients have not been fully elucidated. We enrolled 545 patients consecutively hospitalized for CAP. Data on demographic characteristics and co-morbidities were collected and all patients underwent ECG, echocardiography, and laboratory measurements. During the in-hospital stay, 9.5% of patients experienced a new episode of AF within 24 to 72 hours from admission. CAP patients who experienced AF had a higher indexed left atrial area (LAAi) and a higher proportion of concentric left ventricular hypertrophy than those not presenting AF. Univariate logistic regression analysis showed that hypertension, history of coronary heart disease, high Pneumonia Severity Index classes, history of paroxysmal AF, systolic heart failure, concentric left ventricular hypertrophy, and an enlarged LAAi were associated with a new episode of AF. A multivariable logistic analysis showed that history of paroxysmal AF (odds ratio [OR] 11.7; 95% confidence interval [CI] 5.8 to 23.7; p <0.001), enlarged LAAi (OR 5.4; 95% CI 2.5 to 11.9; p <0.001), and concentric left ventricular hypertrophy (OR 2.2; 95 CI 1.1 to 4.6; p = 0.034) remained independently associated with AF occurrence. In conclusion, in this large cohort of CAP patients, history of paroxysmal AF, enlarged LAAi, and concentric left ventricular hypertrophy are independent predictors of AF occurrence during the early stages of pneumonia. **(Am J Cardiol 2019;124:723−728)**

Atrial fibrillation (AF) may complicate the early phase of community-acquired pneumonia (CAP).[1−4] We have previously shown that patients with severe infection seem to be at high risk of AF[5] but predisposing clinical factors associated with AF in CAP patients have not been fully elucidated. In other clinical settings, left atrial enlargement or left ventricular hypertrophy, evaluated by echocardiography, have been associated with an enhanced risk of AF[6−8] but the impact of these characteristics on AF risk during pneumonia is unknown. Thus, the aim of this study was to evaluate clinical, laboratory, and echocardiographic factors associated with AF development in a cohort of hospitalized patients with CAP.

Methods

The study was conducted at the University-Hospital Policlinico Umberto I, Rome. All patients with CAP admitted through the emergency department from October 2011 to October 2018 were prospectively recruited and followed up until discharge. Inclusion criteria were: (1) age ≥ 18 years; (2) diagnosis of CAP.[9,10]

Patients were excluded from the study if any of the following criteria applied: preexisting permanent or persistent AF, severe sepsis or immunosuppression, presence of malignancy; pregnancy, or breastfeeding.

The present study was conducted according to the principles stated in the Declaration of Helsinki. The institutional review board approved this observational study, which was registered at ClinicalTrials.gov (Identifier: NCT01773863).

The severity of illness at presentation was quantified by the Pneumonia Severity Index (PSI), a validated prediction score for 30-day mortality in patients with CAP.[11] Immediately after the diagnosis of CAP, routine blood laboratory tests including serum high-sensitivity cardiac troponin T (hs-cTnT) and arterial blood gas test were performed. Thereafter, serum hs-cTnT was repeated every 12 hours and a 12-lead electrocardiography (ECG) was repeated every 24 hours.

Type 2 diabetes mellitus, hypertension, history of coronary heart disease (CHD), dyslipidemia, and chronic obstructive pulmonary disease were defined as previously

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described.[12,13] Persistent, permanent, and paroxysmal AF (PAF) was defined as previously reported.[14]

A new episode of AF was considered a newly recognized episode of AF during the hospitalization in patients that were in sinus rhythm before hospital admission as documented by medical records, ECGs, rhythm strips, and Holter-monitors.[5] Adjudication of AF and AF treatment strategies were performed by cardiologists who did not participate in patient recruitment and follow-up, according to the international guidelines.[15]

Echocardiography was performed according to standardized procedures using a Vivid S6 machine equipped with GE 7S-RS Probe with M-mode, 2-dimensional Doppler.[16] Images were digitally stored, and measurements were made offline by 2 independent echocardiographers (RC and CC) in accordance with guidelines of the American Society of Echocardiography.[16] Ejection fraction was calculated using the biplane Simpson formula.[16]

According to the European Society of Cardiology guidelines,[17] we used 3 cutoffs for left ventricular ejection fraction (LVEF): LVEF < 40% corresponding to heart failure (HF) with reduced ejection fraction; LVEF: 40% to 49%, corresponding to HF with midrange ejection fraction; LVEF >50% corresponding to preserved ejection fraction.

Left ventricular mass (LVM) estimation was calculated according to the American Society of Echocardiography and European Association of Echocardiography joint recommendations [16] and indexed by body surface area (BSA). We defined the presence of left ventricular hypertrophy (LVH) for an LVM indexed by BSA (LVMi) >95 g/m^2 for women and an LVMi >115 g/m^2 for men.[16] The definition of LV remodeling was assessed calculating the relative wall thickness (RWT). In accordance to American Society of Echocardiography/European Association of Echocardiography recommendations[16] patients were categorized into 4 categories of cardiac remodelling: (1) no remodelling (without LVH and with an RWT < 0.42); (2) concentric remodelling, (without LVH and with an RWT > 0.42); (3) eccentric hypertrophy (LVH and an RWT < 0.42); and (4) concentric hypertrophy (LVH and an RWT > 0.42). The left atrial area indexed by BSA (LAAi) was measured in apical 4-chamber and 2-chamber views, obtaining contours orthogonally around the long axis of the left atrium, normal values were reported in guidelines of the American Society of Echocardiography. We defined the presence of left atrial enlargement if LAAi was higher than the cut-off values.[16]

Categorical variables were reported as counts (percentage) and continuous variables were expressed as mean ± standard deviation or median and interquartile range. Differences between percentages were assessed by chi-square test or Fisher exact test. Student unpaired *t* test and Pearson correlation test were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney and Spearman rank correlation test) were employed for all the other variables.

The bivariate and multivariate effects of prognostic factors and treatments on the incidence of intrahospital AF were assessed by means of logistic regression models. Wald confidence intervals were obtained and tests for odds ratios (ORs) and adjusted ORs were computed based on the estimated standard errors.

Only p values <0.05 were regarded as statistically significant. All tests were 2-tailed and analyses were performed using computer software packages (IBM SPSS Statistics 25.0; R version 2.15.2, R Development Core Team, Vienna, Austria).

Results

Five hundred forty-five CAP patients were recruited, after excluding 73 patients with persistent or permanent AF, 472 patients with sinus rhythm were included in the analysis (Figure 1).

During the in-hospital stay, 52 patients (9.5%) experienced an episode of AF; the arrhythmia occurred in the

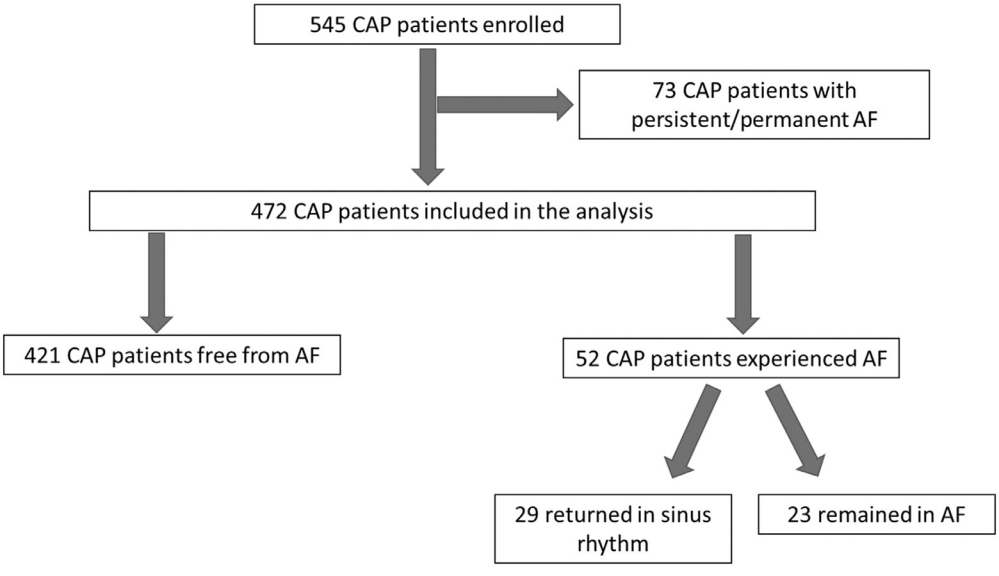

Figure 1. Patients' study flow diagram.

early phase of hospitalization, usually within 24 to 72 hours from hospital admission.

Patients who experienced AF were older, had a higher prevalence of a history of CHD, hypertension, and PAF. Moreover, AF patients showed a higher PSI score and were more likely to be treated with oral anticoagulants and antiplatelet agents at admission. Finally, AF patients showed an increased level of hs-cTnT, a lower LVEF, a larger LAAi, and an increased LVMi (Table 1).

Hs-cTnT levels were found to be inversely associated with the LVEF (Rs = −0.390; p <0.001) and directly associated with LAAi (Rs = 0.443; p <0.001) and with LVMi (Rs = 0.471; p <0.001).

An enlarged LAAi was present in 81% of patients having AF during the in-hospital stay versus 31% of patients that remained with sinus rhythm (p <0.001).

Patients with an enlarged LAAi had higher levels of hs-cTnT than patients with normal LAAi (0.041 [0.021 to 0.085] vs 0.012 [0.010 to 0.030] ng/ml; p <0.001).

LVH was present in 79% of patients having AF during the in-hospital stay and in 39% of patients that remained with sinus rhythm (p <0.001).

In particular, concentric LVH was more prevalent in patients with AF compared with patients without (44% vs 18%; p <0.001); whereas eccentric LVH was not associated to AF presence (35% vs 27%; p = 0.256).

Patients with concentric LVH had higher median values of hs-cTnT compared with those without concentric LVH (0.042 [0.020 to 0.086] vs 0.016 [0.010 to 0.045] ng/ml; p <0.001).

Univariate logistic regression analysis showed that arterial hypertension, history of CHD, high PSI classes, age, history of PAF, ejection fraction (categorized as EF < 40%, indicating HF with reduced ejection fraction, 40% to 49%, indicating HF with midrange ejection fraction and EF ≥ 50%, indicating patients without systolic HF), concentric LVH, and an enlarged LAAi were associated to AF occurrence during the in-hospital stay (Figure 2). The multivariable logistic analysis showed that variables remaining independently associated with AF were a history of PAF, enlarged LAAi, and concentric LVH (Table 2).

The median length of the hospital stay was 11 days (interquartile range, 9 to 15 days); hospital stay was longer

Table 1
Characteristics of the enrolled patients with CAP

Variable	CAP without AF during the intra-hospital stay (n = 420)	CAP with AF during the intra-hospital stay (n = 52)	p Value
Age (years)*	69.3 ± 17.2	79.7 ± 9.6	<0.001
Men	62%	71%	0.212
BMI (kg/m$^{2)}$*	26.4 ± 11.3	26.0 ± 3.9	0.766
Preexisting conditions			
History of CHD	27%	42%	0.024
Previous stroke	10%	18%	0.109
T2DM	27%	22%	0.520
Hypertension	67%	85%	0.012
COPD	31%	31%	0.962
Prior PAF	9%	63%	<0.001
Chronic renal failure	15%	16%	0.888
Dyslipidemia	26%	27%	0.939
Aspirin use	36%	35%	0.880
Thienopyridines	13%	26%	0.047
Heparins	5%	11%	0.119
Oral anticoagulants	6%	16%	0.011
Statins use	32%	31%	0.939
Corticosteroids	22%	32%	0.141
Hs-CRP (mg/dl)*	49.9 [24.4-121.4]	44.4 [20.4-76.3]	0.416
WBC count*	11700 ± 5300	11200 ± 5200	0.463
Hs-cTnT (ng/ml)†	0.016 [0.010 − 0.046]	0.040 [0.018 − 0.074]	<0.001
PS score*	90 ± 35	107 ± 26	<0.001
PSI class II	31%	10%	<0.001
PSI class III	25%	21%	
PSI class IV	33%	46%	
PSI class V	11%	23%	
LVEF (%)*	53.5 ± 9.7	49.1 ± 12.2	0.015
LVMi (g/m^2)*	107 ± 32	131 ± 25	<0.001
LAAi (cm^2)*	9.9 ± 3.4	12.9 ± 3.5	<0.001

BMI = body mass index; CAP = community-acquired pneumonia; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; hs-CRP = high sensitivity C reactive protein; hs-cTnT = high sensitivity cardiac T troponin; LAAi = indexed left atrium area; LVEF = left ventricular ejection fraction; LVMi = indexed left ventricular mass; PAF = paroxysmal atrial fibrillation; PSI = pneumonia severity index; T2DM = type 2 diabetes mellitus; WBC = white blood cells.

* Data are expressed as mean and standard deviation.

† Data are expressed as median and interquartile range.

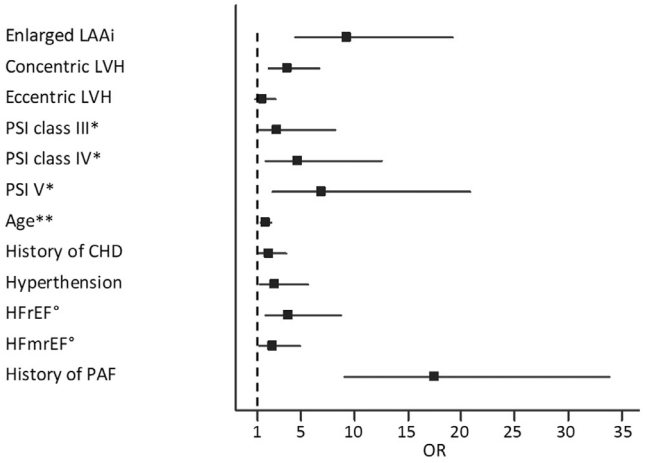

Figure 2. Predictors of atrial fibrillation occurrence at univariate analysis. CHD = coronary heart disease; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAAi = indexed left atrium area; LVH = left ventricular hypertrophy; OR = odds ratio; PAF = paroxysmal atrial fibrillation; PSI = pneumonia severity index.
Boxes represent odds ratios and horizontal lines 95% confidence intervals. *versus PSI class II; **for each decade, versus patients without systolic heart failure.

Table 2
Logistic regression analysis: predictors of AF during the in-hospital stay

	OR	95% CI		p
Enlarged LAAi	5.413	2.458	11.917	<0.001
Concentric LVH	2.205	1.060	4.589	0.034
PAF	11.690	5.769	23.689	<0.001

After adjusting for age, PSI score, hypertension, history of CHD, and ejection fraction.

AF = atrial fibrillation; CHD = coronary heart disease; CI = confidence interval; LAAi = indexed left atrium area; LVH = left ventricular hypertrophy; OR = odds ratio; PAF = paroxysmal atrial fibrillation; PSI = pneumonia severity index.

in the group of patients that experienced AF (13 [8 to 16] vs 10 [7 to 13] days; p <0.001).

Upon discharge, 29 of 52 AF patients (55.8%) re-established sinus rhythm whereas 23 maintained an AF rhythm (Figure 1). Overall, a rhythm control intervention (electrical and/or pharmacological) was applied to 21 of 52 AF patients (40%). Sinus rhythm returned in 62% and 52% of patients who underwent or not cardioversion, respectively.

Patients who maintained AF had a higher LVMi (139 ± 26 vs 124 ± 22 g/m^2; p = 0.032) and LAAi (14.4 ± 3.5 vs 11.7 ± 3.1 cm^2; p = 0.005); in particular, an enlarged LAAi was present in 96% of AF patients who maintained AF versus 69% of patients that returned to sinus rhythm (p <0.001). No clinical differences existed between these 2 groups, even if a tendency for a higher prevalence of PAF was present in patients who maintained AF upon being discharged (74 vs 55%; p = 0.163). A logistic regression analysis showed that the only independent predictor of AF upon discharge, after adjusting for PAF and LVMi, was an enlarged LAAi (OR 9.9; 95% confidence interval 1.1 to 85.2; p = 0.037).

Discussion

This study is the first to show that left atrial enlargement and concentric LVH are independently associated with an increased risk of AF occurrence in patients with CAP.

In our study, we found an incidence of AF occurrence of 9.5% that confirms our previous reports[1,5] and is in accordance with analyses in different cohorts of hospitalized CAP patients.[2,3]

In the present study, advanced age, hypertension, history of CHD, systolic HF, PAF, and higher PSI classes were found to be more prevalent in patients experiencing AF during hospitalization for CAP. These findings suggest that atherosclerotic burden could predispose to the development of AF in the presence of an appropriate trigger such as systemic inflammation. Accordingly, we found that with increasing class of PSI there was an increased incidence of AF, suggesting a relation between the severity of inflammation and AF. Recent systematic reviews and meta-analyses reported an increased risk of new onset of AF according to the increasing grade of sepsis in critically ill patients.[18,19] These findings further reiterate the possibility that the severity of the infection/inflammation could be a trigger for AF. It is noteworthy that, similarly to our report, older age, cardiovascular co-morbidities, such as HF, myocardial infarction, and PAF, were independent risk factors for AF onset in septic patients during ICU stay.[18]

To the best of our knowledge, no study investigated echocardiographic parameters as predictors of AF in patients hospitalized for pneumonia. We demonstrated that CAP patients with an increased LAAi and/or a concentric LVH had a higher risk to develop AF during the hospital stay.

This is in accordance with previous reports showing that increased left atrial size is a predictor of AF recurrence[20] and that left atrial remodeling is strongly and independently associated with PAF[21] and with cardiovascular adverse events.[22] Interestingly, in our study, an enlarged LAAi remained an independent predictor by multivariable logistic regression after adjusting for PAF suggesting that the investigation of left atrium dimensions by echocardiography in CAP patients could be useful to predict AF occurrence/recurrence in this setting.

LVH leading to diastolic dysfunction, which in turn causes elevation of cardiac filling pressures, has a role in eliciting atrial enlargement.[23] It has been postulated that anatomical left atrial remodeling occurs in patients with longstanding concentric LVH,[24] so predisposing to AF occurrence. In a post-hoc analysis of the AFFIRM trial, concentric LVH was associated with an increased rate of AF recurrences in patients treated with a rhythm control strategy.[25] In our study, concentric but not eccentric LVH was an independent determinant of AF occurrence during the early phase of pneumonia.

The exact mechanisms of action through which pneumonia could trigger the onset of AF are still to be fully clarified. One possible mechanism could be a direct myocardial damage; this hypothesis is supported by the fact that we found higher levels of hs-cTnT in patients who experienced in-hospital AF. Of particular interest is the fact that increased troponins were associated with enlarged LAAi and concentric LVH, suggesting that these conditions could

be associated with greater myocardial damage. Oxidative stress may be a common pathway linking myocardial damage with AF in CAP patients. Indeed, we have previously shown that upregulation of Nox2-mediated reactive oxygen species production in CAP is associated with myocardial damage[26] and AF occurrence.[5]

An implication of our study is that patients with left atrial enlargement or LVH should be monitored in the early phases of respiratory tract infections to prevent AF. Furthermore, patients with the above described echocardiographic characteristics or with PAF should be considered for vaccination to lower the AF risk. Finally, approximately 40% of patients experiencing AF did not return in rhythm sinus and displayed a permanent AF, indicating that lung infection is a relevant factor triggering and sustaining AF in patients with left atrial enlargement. We did not know, however, if patients with permanent AF returned or not to sinus rhythm after hospitalization, and further study is necessary to explore this point.

Lack of Holter monitoring or long-term ECG monitoring is the main limitation of the study and, hence, we may have underestimated the real incidence of intra-hospital AF. We did not investigate the underlying mechanisms linking LAA dimensions and concentric LVH to AF occurrence in this setting. Finally, some factors previously showed to be predictors of AF, did not emerge as independent predictors in the multivariable analysis probably due to the relatively small sample size. Larger studies should be performed to better analyze all the possible predictors of AF in this setting.

In conclusion, this prospective large single-center study shows that history of PAF, left atrial dilatation and concentric LVH are independent predictors of AF occurrence during the early stages of pneumonia and should be carefully monitored in the early phase of lung infections.

Disclosures

All the authors state that they have no conflict of interests.

Group Authorship

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