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Abstract
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Reference

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Is atrial fibrillation associated with pulmonary embolism?


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Summary. Background: A pulmonary embolism (PE) is thought to be associated with atrial fibrillation (AF). Nevertheless, this association is based on weak data. Objectives: To assess whether the presence of AF influences the clinical probability of PE in a cohort of patients with suspected PE and to confirm the association between PE and AF. Patients/methods: We retrospectively analyzed the data from two trials that included 2449 consecutive patients admitted for a clinically suspected PE. An electrocardiography (ECG) was systematically performed and a PE was diagnosed by computer tomography (CT). The prevalence of AF among patients with or without a PE was compared in a multivariate logistic regression model. Results: The prevalence of PE was 22.8% (519/2272) in patients without AF and 18.8% (25/133) in patients with AF (P = 0.28). After adjustment for confounding factors, AF did not significantly modify the probability of PE (odds ratio [OR] 0.68, 95% confidence interval [CI] 0.42–1.11). However, when PE suspicion was based on new-onset dyspnea, AF significantly decreased the probability of PE (OR 0.47, 95% CI 0.26–0.84). If isolated chest pain without dyspnea was the presenting complaint, AF tended to increase the probability of PE (OR 2.42, 95% CI 0.97–6.07). Conclusions: Overall, the presence of AF does not increase the probability of PE when this diagnosis is suspected. Nevertheless, when PE suspicion is based on new-onset dyspnea, AF significantly decreases the probability of PE, as AF may mimic its clinical presentation. However, in patients with chest pain alone, AF tends to increase PE probability.

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Introduction

The hypothesis that a pulmonary embolism (PE) can trigger atrial fibrillation (AF) is widely accepted. Many authors report this causal association, which was for example suggested in the ACC/AHA/ESC 2006 guidelines for the management of patients with AF, where a PE is mentioned as a reversible cause of AF [1]. The putative association between AF and PE is mainly based on physiologic hypotheses. On the one hand, a PE can increase the right atrium pressure, elicit stretch injuries or dysfunctions that can in turn trigger AF [1]. On the other hand, some data suggest that AF could itself be a risk factor for PE [2–6]. AF could cause a PE through direct embolization of right atrial thrombi that result from stasis in the atria, or possibly through a hypercoagulable state described in chronic AF [7–9].

Physiologic rationales of the AF–PE association have not yet been confirmed by epidemiologic data and available evidence of this association is sparse and inconsistent. AF was shown to be an uncommon finding in patients with a PE and no prior cardiac or pulmonary disease, the prevalence ranging from 0 to 4% [10,11]. Among all the patients, irrespective of prior cardiopulmonary disease, the prevalence of PE ranged from 3% to 14% [12,13]. Subsequent controlled studies did not find any significant difference in the prevalence of AF between patients with or without a PE [14,15]. Several weaknesses could have limited these studies’ ability to detect an association between AF and PE. First, sample size was probably insufficient given the low prevalence of AF in case of PE. Second, all but one study [15] suffered from a lack of adjustments for main confounding factors. Finally, as these studies included patients with PE suspicion only, selection bias could have occurred.

The question whether a causal association between PE and AF really exist goes beyond mere academic interest. Intuitively, most clinicians integrate this putative association in the diagnostic approach of PE: when this condition is suspected, the presence of AF is commonly thought to increase the pre-
test probability of a PE. Because PE diagnosis is difficult to ascertain on a clinical basis and pre-test probability has a central role in PE diagnosis [16], even small clues such as the presence of AF may therefore significantly influence the diagnostic process. However, the real influence of AF on the likelihood of PE is still unknown. Moreover, AF has not been included in any PE prediction rules [17–19]. Therefore, we analyzed a large cohort of patients with a clinical suspicion of PE to examine whether the presence of AF effectively increases the pre-test probability of the disease and to try to confirm an association between AF and PE.

Methods

Study population

We retrospectively analyzed data from two trials on PE diagnosis, CT-EP3 [20] and CT-EP4 [21]. These two European prospective randomized multicenter studies were conducted between 2002 and 2006 in six teaching hospitals in Switzerland, France and Belgium and compared sequential PE diagnostic strategies. Given that the conception, sites and inclusion criteria were similar, the data of both studies were merged.

All consecutive patients who presented to the emergency department with a clinical suspicion of a PE, defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause, were included. Main exclusion criteria were allergy to iodine contrast agents, creatinine clearance below 30 mL min\(^{-1}\), pregnancy, age <18 years, diagnosis of a PE already established before admission, expected survival time <3 months, refusal or inability to give informed consent and anticoagulant therapy in progress. All patients had an initial electrocardiography (ECG) that informed consent and anticoagulant treatment in progress. All patients had an initial electrocardiography (ECG) that investigators prospectively analyzed for AF presence before knowing the results of tests for a PE. A validated PE diagnosis algorithm was performed for each patient, with all PE diagnosis confirmed by multidetector-row CT. Further details on methodology and data collection are available in the original publications [20,21].

Data analysis

We compared patients’ characteristics between CTEP3 and CTEP4 to check for heterogeneity before merging the data. The \(\chi^2\) test was used to compare categorical variables and Student’s \(t\)-test to compare continuous variables; Mann–Whitney \(U\)-test was used for non-normal data. To adjust for potential confounding factors of the AF–PE association, a multivariate logistic regression model was built. Adjustment covariates were chosen based on a priori decision on available variables and included age, gender, presence of cardiac failure, chronic obstructive pulmonary disease (COPD), a history of a stroke or neoplasm and creatinine clearance. Linearity of continuous variables was verified using a likelihood ratio test to confirm absence of superiority of the categorized form of the variable [22]. Potential effect modification was tested in the same multivariate logistic model using a likelihood ratio test. Goodness-of-fit of the logistic model was tested using the Hosmer and Lemeshow method [23]. Analyses were conducted using Stata version 10.0 (StataCorp, College Station, TX, USA), and statistical significance was defined as a \(P\)-value < 0.05.

Results

In all, 2449 patients were included, 756 in CT-EP3 [20] and 1693 in CT-EP4 [21]. Information on AF presence was available for 2405 patients (98.1%). Forty-four patients for whom an ECG interpretation was not available were excluded from the analysis. Patients’ characteristics are summarized in Table 1. They differed between the two trials in terms of gender distribution, known heart failure or active malignancy and chest pain at admission. However, these differences were very small and data of both trials were merged considering their comparable design and identical setting and inclusion criteria. The mean age was 59.9 years and 43.7% were males. Five hundred and forty-four patients (22.6%) had a confirmed PE, with a similar proportion in both trials (25% in CT-EP3 and 21% in CT-EP4). AF was diagnosed in 133 patients (5.5%). The prevalence of PE was 22.8% (\(n = 519\)) in patients without AF and 18.8% (\(n = 25\)) in patients with AF, a non-significant difference (\(P = 0.28\)). As patients with AF differ from patients without AF in terms of comorbidities, confounding factors can be expected. After adjustment in a multivariate logistic regression model for age, gender, cardiac failure, COPD, a history of a stroke, neoplasm and creatinine clearance, there was a non-significant trend for patients with AF to be less likely to have a PE, with an adjusted odds ratio (OR) of 0.68 (95% confidence interval [CI] 0.42–1.11, \(P = 0.122\), Table 2). We

<table>
<thead>
<tr>
<th>Table 1 Characteristics of the study population</th>
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<tbody>
<tr>
<td>Overall ((n = 2449))</td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Age, mean (SD), year</td>
</tr>
<tr>
<td>Male gender, (n) (%)</td>
</tr>
<tr>
<td>Known heart failure, (n) (%)</td>
</tr>
<tr>
<td>Chronic obstructive lung disease, (n) (%)</td>
</tr>
<tr>
<td>Active malignancy, (n) (%)</td>
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<tr>
<td>Stroke history, (n) (%)</td>
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<tr>
<td>Dyspnea at presentation, (n) (%)</td>
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<tr>
<td>Chest pain at presentation, (n) (%)</td>
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</table>

*Significance of the comparison between the two studies.
also assessed the association between PE and AF in subgroups with a lower probability of non-PE-related AF, such as younger patients and patients without heart failure (Table 2). AF remained unassociated with PE among patients aged < 65 years (OR 0.86, 95% CI 0.35–2.12) and in the absence of heart failure (OR 0.63, 95% CI 0.37–1.06).

The inclusion criteria for this population were a clinical suspicion of PE defined as new-onset dyspnea and/or chest pain without another obvious cause. These inclusion criteria can be expected to influence the prevalence of AF, as dyspnea is a common manifestation of AF and chest pain is not. Patients with AF manifesting as acute dyspnea may have been included in the cohort as PE suspicion, creating a selection bias. Therefore, we explored whether the clinical presentation prompting PE suspicion influenced the effect of AF on the probability of PE. Indeed, when new-onset dyspnea was one of the symptoms leading to PE suspicion (n = 1724), the presence of AF significantly decreased the probability of PE (adjusted OR = 0.47, 95% CI 0.26–0.84, P = 0.010, Table 3). In this subgroup, the prevalence of PE in patients without AF was 26.8% (434/1620), and 17.3% (18/104) in patients with AF. On the contrary, when the suspicion of PE was raised because of chest pain alone (n = 681), the presence of AF tended to increase the likelihood of PE (adjusted OR = 2.42, 95% CI 0.97–6.07, P = 0.059), approaching statistical significance in spite of a very low number of patients with AF in this setting. In these non-dyspneic patients, PE was found in 13% (85/652) of patients without AF, and in 24.1% (7/29) in patients with AF. The influence of dyspnea on the PE–AF association was highly significant (P-value for effect modification = 0.003).

In order to confirm the hypothesis that dyspnea influenced the association between AF and PE, we explored if a similar effect modification existed in the association between PE and COPD and between PE and heart failure, two conditions that can manifest as new onset dyspnea (Table 3). In patients suspected of PE based on new-onset dyspnea, the presence of COPD or heart failure significantly decreased PE probability. However, in the absence of new-onset dyspnea, these two conditions did not significantly influence the probability of PE.

### Discussion

When we analyzed the entire population of patients suspected of PE, our data did not support the common belief that AF increases the pre-test probability of PE. After adjustment for potential confounding factors, the presence of AF even tended to decrease the likelihood of finding a PE, but this did not reach significance. This was equally observed in subgroups of patients where AF could have been caused by an acute and transient condition such as PE, such as younger patients (age < 65 years) or patients without heart failure. The absence of influence of AF on the probability of PE in patients suspected for this condition is consistent with the fact that none of the commonly used prediction schemes include AF presence to estimate PE probability.

The analyzed cohort is a selection of patients suspected of PE. Any disease or health condition that shares a similar clinical presentation with PE might be over-represented in this population. In particular, AF can manifest as new-onset dyspnea, which was one of the criteria to suspect PE. Therefore, we hypothesized that patients with AF could be over-represented in the subgroup of patients included because of new-onset dyspnea, which could modify the association between AF and PE. We explored this hypothesis by

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**Table 3** Effect of dyspnea at presentation on the association between pulmonary embolism (PE) and atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD) or heart failure

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 2405)</th>
<th>Dyspnea (n = 1724)</th>
<th>No dyspnea (n = 681)</th>
<th>Interaction with dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>133 (5.5%)</td>
<td>104 (6.0)</td>
<td>29 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Association with PE, OR*</td>
<td>0.68 (0.42–1.11)</td>
<td>0.47 (0.26–0.84)</td>
<td>2.42 (0.97–6.07)</td>
<td>P = 0.003</td>
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<tr>
<td>COPD</td>
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</tr>
<tr>
<td>n (%)</td>
<td>246 (10.2)</td>
<td>216 (12.5)</td>
<td>30 (4.4)</td>
<td></td>
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<tr>
<td>Association with PE, OR*</td>
<td>0.43 (0.28–0.65)</td>
<td>0.32 (0.20–0.51)</td>
<td>1.40 (0.51–3.87)</td>
<td>P = 0.009</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>143 (5.9)</td>
<td>134 (7.8)</td>
<td>9 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Association with PE, OR*</td>
<td>0.53 (0.31–0.88)</td>
<td>0.43 (0.25–0.73)</td>
<td>1.80 (0.36–8.99)</td>
<td>P = 0.095</td>
</tr>
</tbody>
</table>

CI, confidence interval. *Adjusted for age, gender and the presence of AF, heart failure, chronic obstructive pulmonary disease (COPD), stroke or cancer in the past and creatinine clearance.
Introducing dyspnea as an effect modification term in our multivariate models. Our results showed that in patients with suspected PE based on new-onset dyspnea (71.6% of all PE suspicion), the presence of AF significantly decreased the pre-test probability of PE. On the contrary, in the remaining 28.4% of patients in whom PE suspicion was based on chest pain alone, AF tended to increase the probability of PE. Therefore, while AF does not influence the probability of PE in the overall population of patients suspected for this condition, it might influence it according to the presenting complaint that leads to a suspicion of PE: AF decreases the probability of PE in dyspneic patients and tends to increase it in non-dyspneic patients.

The absence of an association between AF and PE in our cohort should not be considered as a proof of absence of a causal relationship between these two conditions. Our cohort of patients suspected of PE is not representative of the general population and is subject to selection biases which can spuriously affect any association analysis. Indeed, we showed that the presenting symptoms leading to the suspicion of PE influenced dramatically the association between AF and PE, in particular the complaint of new-onset dyspnea. This suggests a selection bias owing to the fact that AF can manifest as dyspnea, misleading to inclusion in this cohort of PE suspicions. As supportive evidence, we found that dyspnea similarly influenced the association between PE and COPD or heart failure, two conditions that can also manifest as a new onset dyspnea. Therefore, the subgroup of patients included for acute dyspnea is not accurate to analyze the association between AF and PE. In contrast, the subgroup of patients suspected of PE because of chest pain without dyspnea is free of this bias, as AF does not commonly manifest with chest pain and may be more appropriate to assess the association between AF and PE. Among these patients, AF presence tended to be associated with PE (adjusted OR 2.42, 95% CI 0.97–6.07, \( P = 0.059 \)). The observed trend towards an association is strong (OR 2.42) and a lack of power could have limited the ability to reach statistical significance as the number of patients with AF in this setting was small (only 29). Consequently, these data may suggest a true association between these two conditions, in support of existing pathophysiological hypotheses.

Is this clinically helpful? As we already stressed, our findings do not affect the validity of the existing clinical prediction rules for PE that are used in all patients with a suspected PE, whatever the clinical presentation. However, it might help the clinician to decide in which patient PE should be suspected. Indeed, not all patients with dyspnea and/or isolated chest pain are investigated for PE and clinicians exclude patients with those complaints from PE investigation when another diagnosis is obvious, such as for instance acute left heart failure or pneumonia. In our experience, AF by itself often prompts an investigation for PE. Our findings support that if AF is found in the presence of a dyspnea that is explainable, for example by heart failure or COPD, the presence of AF itself should not be the only reason for the clinician to look for PE. On the other hand, PE should probably be evoked and searched for in a patient with AF, chest pain and no obvious diagnosis, as about one-quarter of these patients could have PE.

Limitations

The present study had several limitations. First, as it had an observational design, residual confounding could not be excluded. Second, AF duration was not recorded in this population. However, duration of AF in non-anticoagulated patients is mostly unknown or unreliable in daily practice, and chronic AF was certainly underrepresented in our cohort, because patients on ongoing anticoagulation \( (n = 182) \) were excluded. Third, in spite of the fact that criteria for PE suspicion were clearly defined, our population is still heterogeneous, as a result of the variety of presenting symptoms of PE. Awaiting a prospective study in which all patients with new-onset AF would be investigated for PE, we believe that our data provide valuable information. Finally, in spite of the fact that the present study is the largest available attempt to demonstrate the commonly accepted association between AF and PE, a lack of power could have limited our ability to demonstrate significance in the subgroup analyzes.

Conclusion

The presence of AF does not increase the probability of PE in patients suspected of this diagnosis. On the contrary, when PE is suspected on the ground of new-onset dyspnea, the presence of AF significantly decreases PE probability, as AF may mimic its clinical presentation. However, when PE suspicion emerges from chest pain alone, the presence of AF tends to increase PE probability. Because this subgroup of patients is free of any bias linked to dyspnea, this strong trend may suggest a true association between these two conditions.

Addendum

G. Gex and E. Gerstel had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. They equally contributed to conception, design, data analysis and interpretation, manuscript draft, and critical revision. M. Righini, G. Le Gal, D. Aujesky, P.-M. Roy, O. Sánchez, F. Verschuren and O.T. Rutschmann contributed to collecting the data and critical revision of the manuscript. T. Perneger contributed to analysis and interpretation of the data and critical revision of the manuscript. A. Perrier contributed to conception, design, data analysis and interpretation, and critical revision.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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