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Risk factors and outcomes associated with new-onset atrial fibrillation during acute respiratory distress syndrome☆,☆☆

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ABSTRACT

Purpose: Outcomes and risk factors associated with new-onset atrial fibrillation (AF) during acute respiratory distress syndrome (ARDS) are unclear. We investigated mortality and risk factors associated with new-onset AF during ARDS.

Materials and methods: We obtained data from the ARDS Network Albuterol for Treatment of Acute Lung Injury trial, which prospectively identified new-onset AF among patients with ARDS as an adverse event. We determined Acute Physiology and Chronic Health Evaluation III–adjusted associations between new-onset AF and 90-day mortality. We also examined associations between new-onset AF and markers of inflammation (interleukin 6 and interleukin 8), myocardial injury (troponin I), autonomic activation (epinephrine), and atrial stretch (central venous pressure) as well as other clinical characteristics.

Measurements and main results: Of 282 patients (mean age, 51.6 years; 45% women; 77% white) enrolled in Albuterol for Treatment of Acute Lung Injury, 28 (10%) developed new-onset AF during the study. We did not identify associations between new-onset AF and baseline central venous pressure, plasma levels of troponin I, epinephrine, interleukin 6, or interleukin 8. New-onset AF during ARDS was associated with increased 90-day mortality (new-onset AF, 43% vs no new-onset AF, 19%; Acute Physiology and Chronic Health Evaluation–adjusted odds ratio, 3.09 [95% confidence interval, 1.24-7.72]; $P = .02$).

Conclusion: New-onset AF during ARDS is associated with increased mortality; however, its mechanisms require further study.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia to affect the critically ill, with an estimated incidence of 8% to 10% among intensive care patients [1,2]. New-onset AF among critically ill patients may be associated with poor outcomes, for example, patients with severe sepsis who develop new-onset AF have increased short-term [3] and long-term [4] risks for stroke and death. New-onset AF during critical illness may potentially be on the etiologic pathway to mortality through hemodynamic compensation [5] or thromboembolic complications; [3] alternatively, new-onset AF may merely be a marker of increased severity of illness. Few studies have prospectively identified new-onset AF during critical illness and assessed outcomes in the context of baseline illness severity.

Unfortunately, optimal management strategies for AF during critical illness are unclear [6]. Insights into mechanisms of AF during critical illness may enable a more rational approach to prediction, prevention, and treatment. Prior studies using population-based [2,3], single-center [7-9], or trial [10] data have shown that acute factors (eg, choice of vasopressor, acute organ failures, mechanical ventilation, and right heart catheterization), rather than preexisting cardiovascular comorbidities [11,12] are associated with increased risk for new-onset AF during critical illness. Thus, new-onset AF during critical illness may have different underlying mechanisms as compared with AF that develops in the community. However, triggers of new-onset AF during critical illness are poorly understood. Potential contributing factors have been hypothesized to include autonomic activation, inflammation, atrial stretch, and/or myocardial injury [13].

☆ Author contributions:
DBA: statistical analysis, interpretation of findings, and drafting manuscript.EJB: revising manuscript for intellectual content.EKB and KAH: biomarker analysis.AJW: conceptualizing study, statistical analysis, and revising manuscript for intellectual content.

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We conducted an exploratory post hoc analysis to investigate outcomes and risk factors associated with new-onset AF during ARDS using data prospectively collected during the multicenter ARDS Network Albuterol for Treatment of Acute Lung Injury (ALTA) trial [14]. We investigated the hypothesis that new-onset AF is associated with increased risk of death among patients with ARDS after adjusting for baseline severity of illness. To better understand potential mechanisms for new-onset AF during critical illness, we also investigated the hypothesis that increased baseline epinephrine, interleukin 6, interleukin 8, central venous pressure, and troponin (surrogate measures for autonomic activation, inflammation, atrial stretch, and myocardial injury, respectively) would be associated with incident AF.

2. Materials and methods

2.1. Data source

We used data from the ALTA trial, which enrolled 282 patients with ARDS and randomized 152 to nebulized albuterol and 130 to nebulized saline placebo to determine the effect of albuterol treatment on outcomes over 90 days. Patients were enrolled within 48 hours of ARDS onset. Further details regarding patient selection, definitions, and study protocol used in ALTA can be found in the original manuscript (www.clinicaltrials.gov; registry no. NCT00434993) [14]. Briefly, the ALTA investigators found no significant difference in ventilator-free days, mortality, or incidence of AF between albuterol and placebo groups; and the study was terminated due to futility.

2.2. Covariates

We examined the association between baseline interleukin 6, interleukin 8, endogenous epinephrine (R&D Systems, Minneapolis, MN), high-sensitivity troponin I (Siemens Vista, Munich, Germany), and central venous pressure with the incidence of new-onset AF. Plasma for biomarker measurement was collected upon study trial enrollment, before administration of albuterol.

In addition to the above a priori hypothesized AF triggers, we explored the association between new-onset AF; and the following variables were measured at the time of study enrollment (baseline): demographics (age, sex, and race), comorbid conditions (diabetes mellitus, hypertension, chronic pulmonary disease, chronic dialysis, cancer, chronic liver disease, history of cardiovascular disease [myocardial infarction, congestive heart failure, stroke, or peripheral vascular disease]), and dementia. We also explored association of new-onset AF with baseline vasopressor use, hemodynamics (mean arterial pressure and heart rate), and laboratory values (plasma values for sodium, potassium, bicarbonate, creatinine, total bilirubin, magnesium, glucose, and hemoglobin level).

Finally, we examined association between AF incidence and choice of vasopressor administered at baseline (dopamine vs norepinephrine).

2.3. Outcomes

New-onset AF was recorded prospectively as an adverse event and was defined per study protocol as the development of AF between trial enrollment and intensive care unit discharge; other details regarding timing of AF onset were not recorded. We excluded 24 patients who did not have AF data available. Among 28 subjects with new-onset AF during the aforementioned time frame, 4 had a remote history of AF, and 3 had AF on hospital admission (but not at trial enrollment). Mortality was defined as death before hospital discharge, within 90 days.

2.4. Statistical analysis

We compared continuous variables based on AF status using Wilcoxon-Mann-Whitney tests and categorical variables with Fisher exact tests or χ^2 tests as appropriate. Because of skewed distributions, we used natural log-transformed values of interleukin 6, interleukin 8, epinephrine, central venous pressure (CVP), and troponin, reported in summary statistics as geometric means. Clinical variables that were significantly associated with new-onset AF in univariable testing were subsequently analyzed with an age-adjusted logistic regression model. We used Acute Physiology and Chronic Health Evaluation (APACHE) III [15]–adjusted logistic regression to investigate the association between new-onset AF and 90-day mortality. We also performed sensitivity analysis using a nested case-control design with 4:1 matching (case = new-onset AF and control = no AF) within ± 10 points of APACHE III scores and conditional logistic regression to determine association between new-onset AF and mortality.

Given 282 participants enrolled in ALTA and a 10% prevalence of AF in this sample, we estimated 80% power to detect odds ratios (ORs) of 2.5 or greater for associations between independent variables and new-onset AF. We used SAS software version 9.3 (SAS Institute Inc, Cary, NC) with a 2-tailed α threshold of .05 for statistical significance in logistic regression models. All study procedures were approved by the ARDS Network Natural History Committee and the Boston University Medical Campus Institutional Review Board.

3. Results

Of the 282 patients with ARDS enrolled in ALTA, 28 (10%) had new-onset AF, and the median duration of AF was 1.5 days (interquartile range, 1-2). As previously reported [14], AF incidence did not differ by ALTA trial albuterol randomization group. Patients had a mean age of 51.6 years, 45% were women, and 77% were white. Table 1 demonstrates similar demographics, APACHE scores, and hemodynamic parameters regardless of AF status. We did not identify associations between new-onset AF and a priori–hypothesized factors interleukin 6, interleukin 8, epinephrine, troponin, or CVP in either primary or the case-control sensitivity analysis (Table 1) Appendix A. With the exception of higher baseline serum sodium levels (no AF, 139 ± 6 vs new-onset AF, 141 ± 6 meq/L; age-adjusted OR, 1.08; 95% confidence interval [CI], 1.01-1.16; $P = .02$), we did not identify other variables associated with new-onset AF. New-onset AF during ARDS was associated with increased risk for 90-day mortality (new-onset AF, 43% vs without new-onset AF, 19%; $P = .006$; APACHE III–adjusted OR 3.09 [95% CI, 1.24-7.72; $P = .02$]). Our case-control APACHE III–matched sensitivity analysis yielded similar results (OR = 2.81; 95% CI [1.07-7.42]; $P = .04$). New-onset AF was not associated with vasopressor choice (norepinephrine, 11/68 [16.1%]; dopamine, 1/15 [6.67%]; $P = .36$].

4. Discussion

We investigated risk factors and outcomes associated with the development of new-onset AF among patients with ARDS. Patients with new-onset AF in the setting of ARDS had higher 90-day mortality, which persisted after adjustment for baseline APACHE III scores. We did not find evidence to support our hypothesis for increased baseline inflammation (interleukin 6 and interleukin 8), atrial stretch (CVP), myocardial injury (troponin), or catecholamine activation (epinephrine) among patients who subsequently developed new-onset AF during ARDS. Our results were similar in sensitivity analysis using an APACHE III–matched case-control design.

Other studies have not specifically investigated AF in patients with ARDS, but our results support prior findings [3,4] that new-onset of AF in the setting of critical illness is associated with increased mortality. Determining whether new-onset AF may be in the etiologic pathway to poor outcomes or is a merely a marker of illness severity is methodologically difficult. In addition to our observation of increased mortality risks despite adjustment for baseline severity of illness (APACHE III), data from other studies support a potential etiologic association between new-onset AF and poor outcomes. In a systematic review of 4

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