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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 (ALTA) trial, which prospectively identified new-onset AF among patients with ARDS as an adverse event. We determined APACHE 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, 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 ALTA, 28 (10%) developed new-onset AF during the study. We did not identify

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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%, APACHE-adjusted odds ratio: 3.09 (95% CI 1.24–7.72), p=0.02].

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

Keywords

atrial fibrillation; cytokines; interleukins; troponin; epinephrine; mortality; mechanism

Introduction

Atrial fibrillation (AF) is the most common arrhythmia to affect the critically ill, with an estimated incidence of 8–10% 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, newonset 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 (e.g., choice of vasopressor, acute organ failures, mechanical ventilation, right heart catheterization), rather than pre-existing 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 to 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]

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. In order 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.

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Materials and Methods

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 in order 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 Number 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.

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, prior to 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 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, heart rate), and laboratory values (plasma values for: sodium, potassium, bicarbonate, creatinine, total bilirubin, magnesium, glucose, and hemoglobin).

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

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 ICU discharge; other details regarding timing of AF onset was not recorded. We excluded 24 patients who did not have AF data available. Among 28 subjects with new-onset AF during the above-mentioned time frame, four had a remote history of AF and three had AF on hospital admission (but not at trial enrollment). Mortality was defined as death prior to hospital discharge, within 90 days.

Statistical Analysis

We compared continuous variables based on AF status using Wilcoxon-Mann-Whitney tests and categorical variables with Fisher exact tests or Chi square tests, as appropriate. Due to skewed distributions, we used natural log-transformed values of interleukin-6, interleukin-8, epinephrine, CVP, and troponin, reported in summary statistics as geometric means. Clinical

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variables that were significantly associated with new-onset AF in univariable testing were subsequently analyzed with an age-adjusted logistic regression model. We used 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; 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 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, North Carolina) with a 2-tailed α threshold of 0.05 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.

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 (inter-quartile range: 1–2). As previously reported,[14] AF incidence did not differ by ALTA trial albuterol randomization group. Patients had a mean age 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). 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% CI 1.01–1.16, p=0.02), 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=0.006; APACHE III-adjusted OR 3.09 (95% CI 1.24–7.72, p=0.02)]. Our case-control APACHE IIImatched sensitivity analysis yielded similar results: (OR=2.81, 95% CI (1.07–7.42), p=0.04). New-onset AF was not associated with vasopressor choice [norepinephrine: 11/68 (16.1%), dopamine 1/15 (6.67%); p = 0.36).

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, 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.

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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 etiological 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 etiological association between new-onset AF and poor outcomes. In a systematic review of four clinical trials consisting of critically ill patients with AF, Kanji et al. observed that new-onset AF is temporally associated with hemodynamic decompensation and acute organ failure. Specifically, 37% of these patients with new-onset AF developed hemodynamic instability within two hours after AF onset, 7% developed myocardial infarction and 4% had acute pulmonary edema within 48 hours of admission.[5] Although our results did not find associations between choice of vasopressor at baseline (ie. dopamine vs. norepinephrine) and AF incidence during ARDS, meta-analysis of randomized trials comparing dopamine to norepinephrine for septic shock have shown that dopamine increases incidence of new-onset AF and results in increased mortality,[16] further suggesting that AF may not simply be a marker of severity of illness. Prospective studies investigating clinical trajectories after onset of AF during critical illness may improve understanding of a potential etiologic role for AF in critical illness outcomes.

Multiple factors may potentially explain the lack of association observed between markers of inflammation, atrial stretch, myocardial injury, or catecholamine activation and newonset AF. First, our study sample provided power to detect AF risk factors with large effect sizes (i.e., odds ratios >2.5). Second, the time-varying nature of biomarkers during critical illness and lack of granular information regarding timing of AF after trial enrollment does not rule out the possibility that measurement of similar risk factors more temporally proximal to AF onset would have yielded different findings. Other markers of inflammation (such as c-reactive protein),[9,17] more direct measurements of atrial stretch (e.g., echocardiography or B-type natriuretic peptides), or alternative measurements of autonomic function (e.g., heart rate variability) may also have yielded different results and deserve further study.

In exploratory analyses, we did find significant age-adjusted association between newonset AF and higher serum sodium levels. Sodium is an important contributor to myocardial cell membrane potential,[18] and emerging evidence[19,20] supports the existence of atrial specific sodium channels which contribute to AF pathogenesis. However, the role of serum sodium in the development of new-onset AF is not well understood, and prior evidence from small observational studies is conflicting.[9,21] Our findings of association between serum sodium and risk of AF are based on exploratory analyses among multiple hypothesis tests and should be viewed as hypothesis-generating findings requiring further study.

Our study had additional strengths and limitations. The prospective nature of outcome and exposure ascertainment served to minimize misclassification of AF status and AF risk factors, as might occur in prior retrospective studies using administrative data. However, we are unable to exclude the possibility that patients experienced silent AF prior to ARDS onset.[23] Our results derive from patients enrolled in a clinical trial subject to exclusion criteria and thus may not be generalizable to all patients with ARDS. Finally, because

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patients must have been alive long enough to develop new-AF (immortal time bias) the association between new-AF and mortality may be stronger than what we report.[24]

Conclusion

In a secondary analysis of clinical trial data among patients with ARDS, we found that patients with new-onset AF during ARDS had higher APACHE-adjusted mortality. We did not identify associations between hypothesized markers for acute inflammation, myocardial injury or autonomic activation and subsequent incidence of AF. Our study provides additional evidence that new-onset AF during critical illness is associated with poor outcomes. However, risk factors and mechanisms for the development of AF during critical illness remain unclear and require further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Non-Standard Abbreviations

ALTA	Albuterol for Treatment of Acute Lung Injury
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
AF	Atrial Fibrillation
CVP	central venous pressure
NHLBI	National Heart Lung and Blood Institute

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- We performed a secondary analysis of clinical trial data to identify patients who developed atrial fibrillation (AF) during ARDS.
- We examined factors and outcomes associated with development of atrial fibrillation during ARDS.
- Development of new-onset AF during ARDS was associated with significantly greater mortality, even after adjustment for severity of illness.
- We did not identify associations between new-onset AF and *a priori*-hypothesized AF triggers interleukin-6, interleukin-8, epinephrine, troponin, or elevated CVP.

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Table 1

Characteristics of study sample stratified by atrial fibrillation status

Baseline Variable	No AF (N= 230)	New-Onset AF (N= 28)	P-value
Age, years (mean ± SD)	52 ±16	52 ± 16	0.94
Sex, women N (%)	104 (45)	13 (46)	1.0
Race/ethnicity N (%)			0.87
White	176 (77)	22 (79)	
Black	38 (17)	5 (21)	
Other	16 (5)	1 (4)	
Body mass index (kg/m^2) (mean ± SD)	28 ± 7	30 ± 10	0.75
Direct lung injury N (%)	138 (60)	16 (57)	0.84
Comorbidities N (%)			
Hypertension	86 (38)	14 (50)	0.22
Diabetes mellitus	52 (23)	4 (14)	0.47
Cardiovascular disease	18 (8)	5 (18)	0.09
Pulmonary disease	11 (5)	1 (4)	1.0
Liver disease	11 (5)	1 (4)	1.0
Cancer	8 (3)	0	0.60
Dialysis	7 (3)	2 (7)	0.25
Dementia	6 (3)	2 (7)	0.21
APACHE III score (mean ± SD)	91 ± 28	97 ± 32	0.25
ARDS Precipitant N (%)			0.85
Pneumonia	93 (43)	12 (44)	
Sepsis	57 (26)	8 (30)	
Aspiration	45 (21)	4 (15)	
Trauma	17 (7.9)	2 (7.4)	
Transfusion	4 (1.9)	1 (3.7)	
Vasopressor requirement N (%)	107 (47)	18 (64)	0.11
Vital Signs (mean ± SD)			
Temperature (°C)	37.4 ± 0.9	37.1 ± 0.9	0.22
Mean arterial pressure (mmHg)	75.6 ± 14	77.1 ± 14	0.56
Heart rate (bpm)	98 ± 21	92 ± 18	0.18
SpO2 (% saturation)	96 ± 3	96 ± 3	0.43
Total fluid balance, 24 hours prior to randomization (mL)	1690 ± 3300	1980 ± 3000	0.65
Central Venous Pressure (cmH_2O)	11.5 ± 5.0	12.5 ± 5.4	0.15
Ventilator Settings (mean ± SD)			
Tidal volume (mL/kg IBW)	7.1 ± 1.7	7.0 ± 1.3	0.80
Positive end expiratory pressure (cmH_2O)	9.2 ± 3.6	8.5 ± 3.2	0.25
Fraction inspired O_2	0.58 ± 0.2	0.54 ± 0.2	0.40
Plateau Pressure (cm H_2O)	23.9 ± 5.5	22.3 ± 7.5	0.14
Oxygenation Index	0.14 ± 0.1	0.16 ± 0.1	0.20

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Baseline Variable	No AF (N= 230)	New-Onset AF (N= 28)	P-value
Days of Mechanical Ventilation prior to enrollment	1.49 ± 2.4	1.32 ± 0.72	0.62
Laboratory Values (mean ± SD)			
Sodium (meq/L)	139 ± 6	141 ± 6	0.01
Potassium (meq/L)	4.0 ± 0.6	4.0 ± 0.6	0.76
Bicarbonate (meq/L)	22.7 ± 5.5	22.3 ± 5.5	0.62
Magnesium (mg/dL)	1.9 ± 0.4	2.0 ± 0.3	0.10
Phosphorous (mg/dL)	3.5 ± 1.5	3.7 ± 1.6	0.68
Glucose (mg/dL)	129 ± 56	124 ± 51	0.36
Albumin (g/dL)	2.2 ±0.6	2.5 ± 0.7	0.12
Bilirubin (mg/dL)	1.7 ± 2.0	1.6 ± 1.2	0.30
Hemoglobin (g/dL)	10.4 ± 2.3	10.1 ± 1.4	0.89
Plasma biomarkers (median +/− IQR)			
Interleukin-6 (pg/mL)	500 ± 915	346 ± 496	0.20
Interleukin-8 (pg/mL)	320 ± 978	160 ± 228	0.87
High Sensitivity Troponin-I (μg/dL)	316 ± 869	156 ± 293	0.66
Epinephrine (ng/mL)	163 ± 549	124 ± 125	0.57