Effects of Atrial Fibrillation on Intensive Care Unit Outcomes in Patients with Respiratory Failure

Atrial Fibrilasyonun Solunum Yetmezliği Hastalarının Yoğun Bakım Sonuçlarına Etkisi

Müge Aydoğdu[1], Çiğdem Hanazay[1], Yağmur Aldağ[1], Ayşe Baha[1], Salih Bilgin[2], Gül Gürsel[1]

[1]Department and Critical Care Unit, Gazi University School of Medicine, Ankara, Turkey
[2]Clinic of Pulmonary Diseases, Medicana International Hospital, Samsun, Turkey

Author Contributions: Concept – M.A., G.G., Y.A., A.B., Ç.H., S.B.; Design – M.A., G.G., Y.A., A.B., Ç.H., S.B.; Supervision – M.A., G.G.; Data Collection and/or Processing – Y.A., Ç.H., A.B., S.B.; Analysis and/or Interpretation – M.A., G.G.; Literature Search – M.A., G.G., Y.A., Ç.H., A.B., S.B.; Writing Manuscript – M.A., G.G.; Critical Review – M.A., G.G., Y.A., A.B., Ç.H., S.B.

Yazar Katkıları: Fikir – M.A., G.G., Y.A., A.B., Ç.H., S.B.; Tasarım – M.A., G.G., Y.A., A.B., Ç.H., S.B.; Denetleme – M.A., G.G.; Veri Toplanması ve/veya İşlemesi – Y.A., Ç.H., A.B., S.B.; Analiz ve/veya Yorum – M.A., G.G.; Literatür Taraması – M.A., G.G., Y.A., Ç.H., A.B., S.B.; Yazıyı Yazan – M.A., G.G.; Eleştirel İnceleme – M.A., G.G., Y.A., A.B., Ç.H., S.B.

Cite this article as:
Aydoğdu M, Hanazay Ç, Aldağ Y, Bilgin S, Gürsel G.
Effects of Atrial Fibrillation on Intensive Care Unit Outcomes in Patients With Respiratory Failure. Yoğun Bakım Derg 2017; 8: 32-8.

Abstract

Objective: A negative impact of atrial fibrillation (AF) on clinical outcomes has been well defined in surgical intensive care unit (ICU) patients. However, some questions remain unanswered regarding the relationship between AF and ICU outcomes in patients with respiratory failure (RF). This study aims to determine the incidence of AF and its effects on ICU outcome among RF patients. In addition, the effects of bronchodilators on AF control, and cardiac medications on RF control, were also assessed.

Material and Methods: In this retrospective observational cohort study, electrocardiographs of all included RF patients were evaluated for AF. Patients were divided into two groups both for AF and mortality, and they were compared for demographics, diagnosis, comorbidities, risk factors, ICU outcomes, and cardiac and bronchodilator therapies.

Results: A 25% incidence of AF was found in a cohort of 147 patients (mean age 68±15years), and among them, 3% was newly diagnosed. There was no significant difference between the groups with respect to demographics, diagnoses, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of both groups. The incidence of heart failure and cerebrovascular event was found to be higher in patients with AF ($p<0.05$). There was no significant difference in sepsis, duration of mechanical ventilation, and ICU stay, but mortality and acute kidney injury were more common in AF patients (36% vs. 21% and 44% vs. 15% respectively, $p<0.05$). The mortality risk increased 3 times with AF [OR(%95CI):3.09(0.91–10.3)]. There were no significant effects of bronchodilators on AF control and cardiac medications on RF control detected.

Conclusion: AF should be diagnosed and treated appropriately in RF patients. Bronchodilator and cardiac medications should not be avoided or withheld when indicated to prevent negative ICU outcomes.

Keywords: Atrial fibrillation, respiratory failure, intensive care unit, mortality, outcome

Received: 08.05.2017 **Accepted:** 27.11.2017

ÖZ

Amaç: Atrial fibrilasyon (AF) ve klinik sonuçlar arasındaki olumsuz ilişki cerrahi yoğun bakım ünitesi (YBÜ) hastalarında iyi tanımlanmıştır. Ama özellikle solunum yetmezliği hastalarında eşlik eden AF'nin prognoza etkileri henüz kesinlik kazanmamıştır. Bu çalışmada amaç solunum yetmezliği ile izlenen YBÜ hastalarında AF insidansını belirlemek ve AF varlığının YBÜ sonuçlarına etkisini değerlendirmektir. Ek olarak solunum yetmezliğinde kullanılan bronkodilatör tedavilerin AF kontrolüne; AF kontrolünde kullanılan kardiyak tedavilerin de solunum sistemine etkileri araştırılmıştır.

Gereç ve Yöntemler: Bu retrospektif, gözlemsel kohort çalışmasında solunum yetmezliği ile YBÜ'ye yatan tüm hastaların elektrokardiyografileri AF varlığı açısından değerlendirilmiştir. Hastalar AF ve mortaliteye göre gruplandırılmış ve demografik özellikleri, tanıları, komorbiditeleri, risk faktörleri, kardiak ve bronkodilatör tedavileri ve YBÜ sonuçları açısından karşılaştırılmışlardır.

Bulgular: Yaş ortalamaları 68±15 yıl olan, 147 hastalık çalışma kohortunda %25 AF insidansı saptanmıştır; bunların sadece %3'üne yeni AF tanısı konmuştur. AF'si olan ve olmayan hasta gruplarının demografik verileri, yatış tanıları ve APACHE II skorları arasında anlamlı farklılık saptanmamıştır. Kalp yetmezliği ve serebrovasküler olay AF (+) hasta grubunda anlamlı derecede yüksek bulunmuştur ($p<0.05$). Yoğun bakım sonuçları açısından değerlendirildiğinde iki grup arasında sepsis,mekanik ventilasyon ve YBÜ yatış süresi açısından anlamlı farklılık saptanmazken mortalite ve akut böbrek hasarı AF (+) hasta grubunda anlamlı derecede yüksek bulunmuştur (sırasıyla %36 vs. %21 and %44 vs.%15, $p<0,05$).Yapılan regresyon analizinde diğer faktörlerin yanı sıra,AF varlığının mortalite riskini 3 kat artırdığı belirlenmiştir [OR(%95CI):3,09(0,91-10,3)].İlaçlar değerlendirildiğinde bronkodilatörlerin AF kontrolü üzerine ve kardiak tedavilerin solunum yetmezliği üzerine olumsuz etkileri saptanmamıştır.

Sonuç: Atrial fibrilasyon solunum yetmezliği ile YBÜ'lerde izlenen hastalarda mortaliteyi olumsuz etkilemesi nedeniyle dikkatle tanınmalı ve tedavi edilmelidir. Bu hastaların tedavisinde bronkodilatör ve kardiak ilaçların kullanımından kaçınılmamalıdır.

Anahtar kelimeler: Atriyal fibrilasyon, solunum yetmezliği, yoğun bakım ünitesi, mortalite, sonuçlar

Geliş Tarihi: 08.05.2017 **Kabul Tarihi:** 27.11.2017

European Respiratory Journal/Abstracts-22nd Annual Congress, 1-5 September 2012, Vienna-ERS Silver sponsorship.
This study was presented 8th Congress of the Turkish Society of Medical and Surgical Intensive Care Medicine; 16:S02 pp., Ankara, Turkey, November 2011.

European Respiratory Journal/Bildiriler-22. Yıllık Kongresi, 1-5 Eylül 2012, Viyana, ERS-Gümüş sponsorluk.
Bu çalışma Türk Dahili ve Cerrahi Yoğun Bakım Derneği 8. Yıllık Kongresi'nde sunulmuştur, Kasım 2011; 16: S02 pp., Ankara, Türkiye.

Address for Correspondence / Yazışma Adresi: Müge Aydoğdu, e.mail: mugeaydogdu@yahoo.com
DOI: 10.5152/dcbybd.2017.1482

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).
Informed Consent: The institutional review board waived the need for informed consent since the study was based on the evaluation of medical recordings and did not evaluate additional variables compared to those used in clinical practice and did not influence clinical treatment.
Peer-review: Externally peer-reviewed.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Yazarlar çalışmanın World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013) prensiplerine uygun olarak yapıldığını beyan etmişlerdir.
Hasta Onamı: Sadece medikal dosya taramasını içeren bu çalışma için etik kurul hasta onamı alınmasına gerek görmemiştir. Hastaların klinik durumlarında, tedavilerinde değişiklik yapılmamış, mevcut durumları dosyalarından değerlendirilerek raporlanmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Introduction

Although atrial fibrillation (AF) is one of the most frequent arrhythmias in critically ill patients, its effects on the prognosis of respiratory failure (RF) are still unknown (1-6). During AF, the loss of atrio-ventricular synchrony and decrease in diastolic filling time will lead to a decrease in cardiac output. Consequently, this low cardiac output may aggravate tissue hypoxia and might affect the intensive care unit (ICU) outcomes of RF patients (7-9).

Critically ill patients suffering from acute, chronic, or acute-on-chronic RF have an increased tendency to develop AF. There seems to be a wide variety of reasons for AF, such as advanced age, male gender, smoking history, airway inflammation, hypoxia, hypercapnia, electrolyte imbalance, pulmonary hypertension, associated comorbidities as cardiovascular diseases, diabetes, sleep-related disorders, presence of sepsis, and the use of various drugs (inhaler β2-adrenergic agonists, steroid, aminophylline, and catecholamines) (10-13). In clinical practice, due to fear of worsening AF, the use of bronchodilators, anti-inflammatory medications, and vasopressors can sometimes be avoided. On the other hand, this might not be appropriate, since these bronchodilators and anti-inflammatory medications may relieve bronchospasm and resolve hypoxia; thus, instead of worsening AF, they may facilitate the heart rate control.

Another controversial issue is using β-blocker agents for AF rate control in RF. The β-blockers, especially the selective ones, have been confirmed to be safe and favorable in patients with both chronic obstructive pulmonary disease (COPD) and coronary artery disease when the risk–benefit ratio was considered (14, 15). But, in spite of this confirmed beneficial effect, there were reports about an increased airway hyper-responsiveness with both selective and nonselective β-blocker agents in COPD patients (16).

In many studies, the worse relationship between newly developing AF in ICU and clinical outcomes has been shown. But there are still undefined issues regarding the effects of medications used for RF and AF and the ICU outcomes. So, the primary goal of this study was to determine the incidence of AF in RF patients and its relationship with their ICU outcomes. The secondary goal was to assess the influence of bronchodilators on AF control, and cardiac medications on RF.

Material and Methods

A retrospective, observational cohort study, was performed in a tertiary care adult medical ICU. The ethics approval was obtained from the local ethics committee, and they concluded that informed consent was not required since the study was based on the analysis of medical records only. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study Design

The inclusion criteria of the study were as follows:

1. Patients who were older than 18 years of age and followed up in ICU due to RF between January 2012 and January 2013
2. Patients who stayed in the ICU longer than 48 hours and were treated either with invasive or noninvasive mechanical ventilation (MV)
3. Patients who had complete medical records, including all the necessary data required for this study

The patients' age, gender, APACHE II score, admission diagnosis, and comorbidities were recorded. If their smoking history included more than 10 packets of cigarettes a year, then it was accepted as positive smoking history. Types and causes of RF and use of long-term oxygen therapy at home were recorded. All the bronchodilator, cardiac, and anticoagulant medications used by the patients for at least 1 week before the ICU admission and during the ICU stay were noted.

The admission and previous electrocardiographs (ECG) of all included patients were evaluated for AF both by an intensivist and a cardiology consultant physician. During ICU stay, all patients had cardiac monitorization, and if there was a sudden increase in heart rate (>110 beats/min), 12-lead ECG was ordered. This was again evaluated with an intensivist and a cardiology consultant physician. If AF was diagnosed, treatment was decided according to European Cardiology Society 2010 Guidelines for the management of AF (17). Anticoagulant therapies were chosen as standard heparin, low-molecular-weight heparin (LMWH), or warfarin, if anticoagulation was not contraindicated. Patients were grouped according to the presence of AF and mortality: as AF (+) and AF (–), and mortality (+) and mortality (–). They were compared for demographics, diagnosis, comorbidities, risk factors, ICU outcomes, and cardiac and bronchodilator therapies.

Definitions

Atrial fibrillation is a supraventricular arrhythmia characterized by disorganized atrial depolarizations without effective atrial contractions. It is diagnosed by a 12-lead ECG, typically with a high-frequency fibrillation wave at rates of 350–600/min and an irregular ventricular response and with the lack of *P*-waves (17).

Sepsis and septic shock were defined as stated by International Sepsis Conference's definitions (18). Again, the consensus guidelines were used to define underlying causes of sepsis such as community-acquired pneumonia (CAP), ventilator-associated pneumonia (VAP), hospital-associated pneumonia (HAP), catheter infections, blood stream infections, bacteremia, urinary infections, and abdominal and wound infections (19, 20).

Acute kidney injury (AKI) was defined in line with the KDIGO 2012 guideline. The worst of either serum creatinine (sCr) or urine output criteria was taken into consideration (21).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS for Windows 15.0 software; Chicago, IL, USA) was used for the statistical analysis of the results. Normally distributed quantitative variables were defined as mean±standard deviation (SD). Qualitative variables were expressed as

percentages. For the comparison of categorical variables, chi-squared test was used. For the comparison of continuous variables, the independent samples t-test and Mann–Whitney U tests were used. Correlations of various factors with mortality were determined using Pearson's or Spearman's correlation analyses. The independent risk factors for mortality were evaluated with multivariate linear regression analysis among the significant parameters of univariate analysis, which were not associated with each other. Results are presented as mean±SD, percentiles, or median (range) values. P value <0.05 was accepted as statistically significant.

Results

A total of 147 patients (mean age 68±15 years) were included in the study. Among them, 76 (52%) were male, and their admission diagnosis was acute RF in 51 (35%) patients, pneumonia in 27 (18%) patients, cardiogenic pulmonary edema in 14 (10%) patients, and pulmonary thromboembolism in 10 (7%) patients. The remaining 96 patients were admitted with acute-on-chronic RF, among which 60 (40%) had COPD exacerbation, 12 (8%) had bronchiectasis exacerbation, 20 (14%) had a sleep-related disorder, and 4 (3%) had lung carcinoma. Atrial fibrillation was found in 36 (25%) patients. Among these AF patients, 33 (92%) had previous diagnosis. The cause of newly developing AF was hypoxia in 1 patient and sepsis in 2 patients.

No significant difference was identified for demographics, APACHE II scores, home long-term oxygen therapy use, and admission diagnoses of AF (+) and AF (–) patient groups (Table 1). On the other hand, there were more comorbidities in AF (+) group (%100 vs. %85, p=0.006). The incidence of congestive heart failure (61% vs. 35%, p=0.007), cardiac valvular disease (11% vs. 2%, p=0.047), and previous cerebrovascular event (CVE) (25% vs. 5%, p=0.002) was significantly higher in AF (+) group (p<0.05) (Table 1).

For the medications known to be aggravating AF, such as theophylline and short- and long-acting β-agonists, no significant difference was identified in their use before ICU admission. During ICU stay, theophylline was not preferred in AF (+) patients (4% vs. 25%, p=0.013) (Table 2). No difference was identified for pre-ICU admission use of β-blockers and calcium channel blockers, but digoxin use was more common in AF (+) patients (31% vs. 2%, p=0.001) (Table 2). During ICU stay, no difference was identified in β-blocker use between the two groups, but calcium channel blockers and digoxin were used more commonly in AF (+) patients (p<0.05) (Table 2). Among AF (+) group, when pre-ICU admission anticoagulation and antithrombotic medications were analyzed, 13 (39%) of them were using warfarin, 13 (39%) were using acetylsalicylic acid, and no one was using LMWH (Table 2).

Among their ICU follow-up characteristics, AKI was significantly higher among the AF (+) patients (44% vs. 15%, p=0.001). No significant difference was found in VAP, HAP, and sepsis development, and duration of invasive and noninvasive MV and duration of ICU stay between the two groups. But mortality was significantly higher in AF (+) patients (36% vs. 21%, p=0.047) (Table 3). The APACHE II score, previous cerebrovascular event, pneumonia as admission diagnosis, sepsis, AF, and length of invasive MV were independent predictors of mortality. Atrial fibrillation was found to be increasing the mortality risk for 3 times [OR (%95 CI): 3.09 (0.91–10.3)]. Among the medications, theophylline and long-acting β2-agonists were found to be significantly and negatively correlated with mortality, but they were not identified significant in multivariate analysis (Table 4).

Table 1. Comparison of the demographical characteristics, comorbidities, intensive care unit (ICU) admission diagnosis, and severity scores of patients with and without atrial fibrillation (AF)

Characteristics	AF (+) (N=36,%)	AF (-) (N=111,%)	p
Age (years) (mean±sd)	71±10	67±10	0.275
Gender (male)	14 (39)	62 (56)	0.057
APACHE II (mean±sd)	20±7	20±7	0.340
BMI* (kg/m^2) (mean±sd)	31±11	29±10	0.225
Smoking	14 (39)	58 (52)	0.115
Long-term oxygen therapy use	12 (33)	42 (39)	0.362
Comorbidities	36 (100)	94 (85)	0.006
Hypertension	24 (67)	59 (62)	0.366
Congestive heart failure	22 (61)	34 (35)	0.007
Cardiac valvular disease	4 (11)	2 (2)	0.047
Coronary arterial disease	12 (33)	20 (21)	0.104
Previous cerebrovasvular event	9 (25)	6 (5)	0.002
Previous PTE/DVT**	4 (11)	7 (7)	0.331
Alzheimer's	2 (6)	8 (8)	0.453
Diabetes mellitus	10 (28)	28 (25)	0.459
Thyroid disease	4 (11)	7 (7)	0.348
ICU Admission Diagnosis			
COPD exacerbation***	12 (33)	48 (43)	0.181
Pneumonia	8 (22)	19 (17)	0.481
Sleep disorders and obesity hypoventilation syndrome	4 (11)	16 (15)	0.418
Cardiogenic pulmonary edema	6 (17)	8 (7)	0.092
Lung carcinoma	1 (3)	3 (3)	0.071
Pulmonary thromboembolism	3 (8)	7 (6)	0.461
Bronchiectasis	2 (6)	10 (9)	0.399

*Body mass index; **Pulmonary thromboembolism/Deep venous thrombosis;
***Chronic obstructive pulmonary disease; sd: standard deviation

Discussion

This study is important since in the literature, there are many studies about newly developing AF in ICUs, especially in cardiovascular surgery patients; however, studies about medical patients are scarce in number. And as far as we know, there were no such a study evaluating the incidence and effects of AF in RF critical care patients.

This study revealed a 25% incidence of AF in RF patients, and among them, 3% was newly diagnosed. In surgical intensive care populations, the incidence of AF was reported between 4.4% and 6.7% (22-24). A much higher incidence, between 10% and 65%, was defined in cardiovascular and cardiac surgery patients (25, 26). Our relatively high incidence is most probably related to our study population, as RF patients who had an increased risk of AF were included. A study that was performed in medical and coronary ICU by Reinelt et al. (27), reported an AF rate of 29.8%, which is similar to our study.

Table 2. Comparison of the bronchodilator and cardiac treatments of the patients received before and during intensive care unit (ICU) stay for their effects on atrial fibrillation (AF)

Medical Treatments	AF (+) (N=36,%)	AF (-) (N=111,%)	p
Bronchodilator Treatments Before ICU Admission			
Theophylline	3 (8)	18 (16)	0.056
Long-acting bronchodilator (β2-agonists, anticholinergics)	16 (44)	38 (34)	0.557
Short-acting β2-agonists	5 (14)	13 (12)	0.362
Short-acting β2-agonists + Short-acting anticholinergics	13 (36)	32 (29)	0.465
Bronchodilator Treatments During ICU Stay			
Theophylline	1 (3)	28 (25)	0.013
Long-acting bronchodilator (β2-agonists, anticholinergics)	6 (17)	34 (31)	0.061
Short-acting β2-agonists	2 (5)	12 (11)	0.284
Short-acting β2-agonists + Short-acting anticholinergics	19 (53)	61 (55)	0.557
Cardiac Treatments Before ICU Admission	33 (92)	54 (49)	0.001
β-blocker	10 (28)	16 (14)	0.408
Calcium channel blocker	18 (50)	28 (25)	0.232
Digoxin	11 (31)	2 (2)	0.001
Warfarin	14 (39)	3 (3)	0.001
Acetylsalicylic acid	15 (42)	19 (17)	0.151
LMWH*	0 (0)	5 (5)	0.103
Cardiac Treatments During ICU Stay	36 (100)	88 (79)	0.007
β-blocker	8 (22)	16 (14)	0.100
Calcium channel blocker	19 (53)	26 (23)	0.011
Digoxin	10 (28)	3 (3)	0.001
Warfarin	14 (39)	2 (2)	0.001
Acetylsalicylic acid	17 (47)	33 (30)	0.194
LMWH*	22 (61)	79 (72)	0.084

*Low-molecular-weight heparin

Table 3. Comparison of the intensive care unit (ICU) outcome variables of patients with and without atrial fibrillation (AF)

Parameter	AF (+) (N=36,%)	AF (-) (N=111,%)	p
Ventilator-associated pneumonia	3 (8)	7 (7)	0.483
Hospital-acquired pneumonia	6 (17)	15 (14)	0.449
Acute kidney injury	16 (44)	17 (15)	0.001
Sepsis	10 (28)	25 (23)	0.362
Length of IMV* (days) (mean±sd)	3±6	5±13	0.770
Length of NIMV** (days) (mean±sd)	6±7	6±6	0.662
Length of ICU stay*** (days) (mean±sd)	12±9	13±10	0.723
Mortality	13 (36)	23 (21)	0.047

*Invasive mechanical ventilation; **Noninvasive mechanical ventilation; ***Intensive care unit

In this study, we observed no difference in age, gender, APACHE II score, body mass index, and smoking history of patients with AF (+) and AF (–). In most of the studies evaluating the risk factors for AF development, age was identified as an independent risk factor (27, 28). This was not true for our study since we choose a specific patient group with RF, most of them were elderly, having chronic RF, and 92% had previously diagnosed AF. Since our patient group was mostly composed of patients with chronic AF, instead of development risk factors of AF, we evaluated factors affecting the control of AF and the ICU outcomes of patients with AF.

Although the demographic characteristics of AF (+) and (–) patients were similar, comorbidities, especially the cardiac ones (coronary arterial disease, valvular problems), were more frequent in AF (+) patients. It is well known and accepted that structural changes on the right atrium and ventricular functions are important predisposing factors for AF. In RF patients, in addition to hypoxia, this enlargement in right heart will be an important cause of atrial arrhythmias (29). As a limitation, since it is a retrospective study, we couldn't reach the ECG results of most of our patients and could not evaluate the right heart dimensions. Previous CVE was also more prominent in AF (+) patients. This indicates one of the most important complications of AF as an increased incidence of thromboembolic events and points out the importance of anticoagulation in these patients. Among the 33 patients with previously diagnosed AF, 100% of them had been receiving heart rate-limiting medication. But, as for anticoagulation, warfarin was being used by 39% of patients and acetylsalicylic acid by 42% of them. None of them was receiving LMWH, and due to the timing of the study, no patient was receiving new oral anticoagulants. Anticoagulation is not required for AF of less than 48 hours according to the recent guidelines on antithrombotic therapy from the American College of Chest Physicians (30). On the other hand, if AF has been presenting for more than 48 hours or with unknown duration, then full anticoagulation should be given (30). The cardioembolic risk was evaluated by two scoring systems: CHADS2 (31) and the newer CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) scores (32). Although these scores are not validated for critical illness, they may help clinicians in deciding antithrombotic therapy. As a limitation, since it was not one of the scopes of our study and since this was a retrospective study, we did not calculate CHADS2 and CHA2DS2-VASc scores and evaluated the cardioembolic risk.

Another important result of our study is that there was no significant difference for the use of theophylline and short- and long-acting β-2 agonists (LABA) at pre-ICU admission period among patients with AF (+) and AF (–). This result made us think that those medications have no direct effect on AF development. But, as a clinical practice, during ICU stay, theophylline was preferred less among patients with AF (+). Theophylline is not a first-choice medication for COPD and asthma exacerbation, so it is being used less during clinical practice, preferred just for difficult, unresponsive bronchospasms. It was shown to cause tachycardia, arrhythmia, and especially AF when its blood level is not in the therapeutic range (13, 33, 34). So, as far as it is in the therapeutic range, clinicians should not question the use of theophylline in nonresponsive bronchospasm cases due to the fear of AF triggering. In con-

Table 4. Assessment of factors affecting mortality

Characteristics	Mortality (+) (N=36,%)	Mortality (-) (N=111,%)	p	r	OR (%95 CI)
Age (years) (mean±sd)	73±15	67±15	0.033	0.176	
Gender (male)	21 (58)	55 (50)	0.235		
*APACHE II (mean±sd)	25±8	18±6	0.001	0.398	1.1 (1.0-1.21)
BMI* (kg/m^2) (mean±sd)	22±11	31±9	0.006	-0.319	
*Long-term oxygen therapy use	6 (17)	48 (44)	0.003	-0.245	
Comorbidities	31 (86)	99 (89)	0.405		
Hypertension	19 (59)	64 (64)	0.394		
Congestive heart failure	13 (39)	43 (43)	0.438		
Cardiac valvular disease	0 (0)	6 (6)	0.182		
Coronary arterial disease	7 (22)	25 (25)	0.460		
*Previous cerebrovasvular event	7 (22)	7 (7)	0.017	0.207	4.5 (0.94-21.6)
Previous PTE/DVT**	2 (6)	9 (9)	0.467		
Alzheimer's	3 (9)	7 (7)	0.454		
Thyroid disease	2 (6)	9 (9)	0.474		
ICU Admission Diagnosis					
COPD exacerbation***	12 (33)	48 (43)	0.181		
*Pneumonia	13 (36)	14 (13)	0.007	0.222	4.1 (1.2–14.6)
*Sleep disorders	1 (3)	19 (17)	0.028	-0.182	
Cardiogenic pulmonary edema	1 (3)	13 (12)	0.092		
*Lung carcinoma	3 (3)	1 (1)	0.046	0.196	
PTE	2 (6)	8 (7)	0.539		
Bronchiectasis	4 (11)	8 (7)	0.332		
ICU Follow-Up Characteristics					
*VAP	6 (17)	4 (4)	0.017	0.220	
*Acute kidney injury	15 (42)	17 (16)	0.002	0.270	
*Sepsis	23 (64)	12 (11)	0.001	0.533	4.05 (1.26-13.01)
*Atrial fibrillation	13 (36)	23 (21)	0.032	0.154	3.09 (0.91-10.3)
***Length of IMV (days) (mean±sd)**	13±21	2±5	0.001	0.408	1.14 (1.05-1.25)
Length of NIMV (days) (mean±sd)	5±7	7±6	0.144		
*Length of ICU stay (days) (mean±sd)	18±12	11±8	0.001	0.310	
Bronchodilator Treatments Before ICU Admission*	14 (39)	57 (51)	0.134		
Theophylline	3 (18)	18 (29)	0.282		
Long-acting bronchodilator	10 (59)	44 (70)	0.557		
Short-acting β2-agonists	1 (6)	17 (27)	0.068		
Short-acting β2-agonists + Short-acting anticholinergics	10 (63)	35 (56)	0.417		
Bronchodilator Treatments During ICU Stay	21 (58)	76 (69)	0.180		
*Theophylline	1 (4)	20 (26)	0.017	-0.227	
*Long-acting bronchodilator	3(13)	37 (49)	0.002	-0.307	
Short-acting β2-agonists	1(4)	13(17)	0.111		
Short-acting β2-agonists + Short-acting anticholinergics	20(87)	60 (78)	0.264		

Table 4. Assessment of factors affecting mortality (continued)

Cardiac Treatments Before ICU Admission	15 (44)	70 (66)	0.020	-0.192	
β-blocker	6 (38)	20 (26)	0.264		
Calcium channel blocker	6 (43)	40 (53)	0.352		
Digoxin	3 (21)	10 (13)	0.333		
Warfarin	1 (7)	16 (22)	0.163		
*Acetylsalicylic acid	10 (67)	24 (32)	0.015	0.264	
Low-molecular-weight heparin	0 (0)	5 (7)	0.379		
Cardiac Treatments During ICU Stay	26 (74)	96 (90)	0.007	-0.191	
β-blocker	8 (32)	16 (18)	0.100		
Calcium channel blocker	6 (24)	39 (42)	0.078		
Digoxin	4 (16)	9 (10)	0.283		
Warfarin	1 (4)	15 (16)	0.100		
Acetylsalicylic acid	13 (52)	37 (40)	0.192		
Low-molecular-weight heparin*	25 (96)	76 (79)	0.031	0.184	

*The parameters that were used in logistic regression analysis

BMI: Body mass index; PTE/DVT: Pulmonary thromboembolism/Deep venous thrombosis; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; NIMV: Noninvasive mechanical ventilation

trast to our results, although not performed among critical care patients, a meta-analysis performed by Salpeter AR et al. found that the β-2 agonist use in patients with obstructive airway disease leads to an increased risk for adverse cardiovascular events. This is especially important and more prominent in patients with previous cardiac disorders (12). But, in Goodman et al. (35) study, similar to our results, inhaled β2-agonist use was compared among patients with no AF, new-onset AF, and previous AF, and no difference was identified among the groups. In a study performed by Hanrahan et al. (36), a high proportion (40%) of COPD patients with no or stable cardiac comorbidities was detected to have atrial tachycardia before treatment, which increased by 2%–5% with LABA treatment. There were no more serious arrhythmias that increased with inhaled LABA therapy. Although not performed among critically ill patients, similar to our study, LABA therapy caused no increase in heart rate.

The presence of AF may affect the ICU outcome of the patients. It may lead to a prolonged ICU and hospital stay and may increase mortality (22, 24, 27). In our study, although duration of MV and ICU stay was similar; AKI development and mortality were higher in AF (+) patients. The AKI was higher in AF (+) patients most probably due to hypotension and low cardiac output occurring during AF. In a study performed by Goodman S et al., similar to our results, AKI incidence (46% and 16%) and mortality (16% and 54%) were higher in patients with both newly and previously diagnosed AF, when compared with patients who had no AF (35).

In our study, the independent risk factors for mortality were identified as APACHE II, previous CVE, pneumonia, sepsis, AF, and the length of MV. Atrial fibrillation was found to be one of the important determinants of mortality, increasing the risk for 3 times. In a recent study of Shaver et al. (37), similar to our result, any AF was identified as a significant and independent risk of mortality (OR: 1.62; %95 CI, 1.14–2.29; p=0.007). They reported that during critical illness, both the previous and the newly diagnosed AF lead to similar risk of mortality.

In our study, AF (+) patients received β-blockers, calcium channel blockers, and digoxin for heart rate control. Since there were no difference in the length of MV and ICU stay among patients with AF (+) and AF (–), it might be thought that those cardiac medications would not increase bronchospasm and deteriorate RF. Salpeter AR et al. reported a similar result in their meta-analysis that in patients with obstructive lung disease, the β-blocker use was safe and that it might even lead to significant reductions in cardiovascular mortality (12). Kargın et al. (38) found similar results with our study: In COPD patients with acute RF and AF, the β-blocker use is associated with similar duration of ICU stay and mortality incidence when compared with the use of another heart rate-limiting drug.

Study Limitations

In addition to the limitations mentioned previously in discussion, one of the greatest limitations of this study is that it is a single-center retrospective study with a low number of participants. However, we believe that it is still important since it was conducted with a selected group of patients, that is, RF patients with an increased risk of AF. In addition, since there are not many studies about medical critical care patients, it represents a good foundation for future, more comprehensive prospective studies. Since data for this study were collected between 2012 and 2013, and the use of new oral anticoagulants has become more common in our country after 2014, we couldn't evaluate the use and effects of new oral anticoagulants in this study. Furthermore, there was no significant risk factors identified as disturbing AF control; so, no multivariate regression analysis can be made to identify independent risk factors of AF deterioration in critical care units. However, it would be possible to identify possible risk factors for AF deterioration, if a larger cohort, including patients having different medical causes of ICU admission, can be evaluated.

Conclusion

As a conclusion, AF must be cautiously diagnosed and treated in critically ill RF patients since it is associated with an increased incidence of heart failure, renal failure, cerebrovascular event, and mor-

tality. The bronchodilator therapies and cardiac medications especially the β-blockers, can be used with close follow-up in RF patients with AF without affecting the ICU outcome.

References

1. Annane D, Sebille V, Duboc D, et al. Incidence and prognosis of sustained arrhythmias in critically ill patients. Am J Respir Crit Care Med 2008; 179: 20-5. [CrossRef]
2. Seguin P, Launey Y. Atrial fibrillation is not just an artefact in the ICU. Crit Care 2010; 14: 182. [CrossRef]
3. Artucio H, Pereira M. Cardiac arryhtmias in critically ill patients: epidemiologic study. Crit Care Med 1990; 18: 1383-8. [CrossRef]
4. Meierhenrich R, Steinhilber E, Eggermann C, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. Crit Care 2010; 14: R108. [CrossRef]
5. Walkey AJ, Wiener RS, Ghobial JM, et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA 2011; 306: 2248-54. [CrossRef]
6. Chen AY, Sokol SS, Kress JP, et al. New-onset atrial fibrillation is an independent predictor of mortality in medical intensive care unit patients. Ann Pharmacother 2015 May; 49: 523-7 [CrossRef]
7. Malik A, Candilio L, Hausenloy DJ. Atrial fibrillation in the intensive care setting. J Intensive Care Soc 2013; 14: 141-9. [CrossRef]
8. Arora S, Lang I, Nayyar V, et al. Atrial fibrillation in a tertiary care multidisciplinary intensive care unit–incidence and risk factors. Anaesth Intensive Care 2007; 35: 707-13.
9. Christian SA, Schorr C, Ferchau L, et al. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. J Crit Care 2008; 23: 532-6. [CrossRef]
10. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013; 162: 237-51. [CrossRef]
11. Tongyoo S, Permpikul C, Haemin R, et al. Predicting factors, incidence and prognosis of cardiac arrhythmia in medical, non-acute coronary syndrome, critically ill patients. J Med Assoc Thai 2013 ; 96: S238-45.
12. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004; 125: 2309-21. [CrossRef]
13. Huerta C, Lanes SF, García Rodríguez LA. Respiratory medications and the risk of cardiac arrhythmias. Epidemiology 2005; 16: 360-6. [CrossRef]
14. Minor DS, Meyer AM, Long RC, et al. Beta blockers and chronic obstructive pulmonary disease: Inappropriate avoidance. J. Clin Hypertension 2013; 15: 925-30. [CrossRef]
15. Du Q, Sun Y, Ding N, et al. Beta-Blockers Reduced the Risk of Mortality and Exacerbation in Patients with COPD: A Meta-Analysis of Observational Studies. PLoS ONE 2014; 9: e113048. [CrossRef]
16. van der Woude HJ, Zaagsma J, Postma DS, et al. Detrimental effects of beta-blockers in COPD: a concern for nonselective beta-blockers. Chest 2005; 127: 818-24. [CrossRef]
17. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, A.J. Camm, P. Kirchhof, G.Y. Lip, U. Schotten, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Eur Heart J 2010; 31: 2369-429. [CrossRef]
18. Calandra T, Cohen J. For the international sepsis forum definition of infection in the ICU consensus conference. Crit Care Med 2005; 33: 1538-48. [CrossRef]
19. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community Acquired Pneumonia in Adults. Clinical Infectious Diseases 2007; 44: S27-72. [CrossRef]
20. American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416. [CrossRef]
21. Kidney Disease Improving Global Outcomes (KDIGO). Acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements 2012; 2: 1-13.
22. Seguin P, Signouret T, Laviolle B, et al. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. Crit Care Med 2004; 32: 722-6. [CrossRef]
23. Bender JS. Supraventricular tachyarrhythmias in the surgical intensive care unit: an under-recognized event. Am Surg 1996; 62: 73-5.
24. Brathwaite D, Weissman C. The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest 1998; 114: 462-8. [CrossRef]
25. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001; 135: 1061-73. [CrossRef]
26. Hogue Jr CW, Hyder ML. Atrial fibrillation after cardiac operations: risks, mechanisms, and treatment. Ann Thorac Surg 2000; 69: 300-6. [CrossRef]
27. Reinelt P, Karth GD, Geppert A, et al. Incidence and type of cardiac arrhythmias in critically ill patients: a single center experience in a medical-cardiological ICU. Intensive Care Med 2001; 27: 1466-73. [CrossRef]
28. Seguin P, Laviolle B, Maurice A, et al. Atrial fibrillation in trauma patients requiring intensive care. Intensive Care Med 2006; 32: 398-404. [CrossRef]
29. Liu T, Li GP, Li LJ. Atrial Dilatation and Atrial Fibrillation: A Vicious Circle? Medical Hypotheses 2005; 65: 410-1. [CrossRef]
30. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141: e531-75.
31. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285: 2864-70. [CrossRef]
32. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010; 137: 263-72. [CrossRef]
33. Bittar G, Friedman HS. The arrhythmogenicity of theophylline. A multivariate analysis of clinical determinants. Chest 1991; 99: 1415. [CrossRef]
34. Sessler CN, Cohen MD. Cardiac arrhythmias during theophylline toxicity. A prospective continuous electrocardiographic study. Chest 1990; 98: 672. [CrossRef]
35. Goodman S, Shirov T, Weissman C. Supraventricular arrhythmias in intensive care unit patients: short and long-term consequences. Anesth Analg 2007; 104: 880-6. [CrossRef]
36. Hanrahan JP, Grogan DR, Baumgarten RA, et al. Arrhytmias in patients with chronic obstructive pulmonary disease (COPD). Occurrence, frequency and the effect of treatment with the inhaled long acting beta2 agonists arformoterol and salmeterol. Medicine 2008; 87: 319-32. [CrossRef]
37. Shaver CM, Chen W, Janz DR, et al. Atrial fibrillation is an independent predictor of mortality in critically ill patients. Crit Care Med 2015; 43: 2104-11. [CrossRef]
38. Kargın F, Takir HB, Salturk C, et al. The safety of beta-blocker use in chronic obstructive pulmonary disease patients with respiratory failure in the intensive care unit. Mutidiscip Respir Med 2014; 9: 8. [CrossRef]