ORIGINAL ARTICLE

Determinants of new-onset atrial fibrillation in a multidisciplinary critical care unit

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Abstract

Background: The presence of New-onset Atrial Fibrillation (NOAF) during critical illness increases morbidity, mortality, and hospital costs, as well as the incidence of complications such as heart failure and thromboembolic disorders. We aimed to determine the incidence and the risk factors associated with NOAF in Intensive Care Units (ICU). *Material and Methods:* A nested case control study of patients admitted to ICU was conducted to determine the risk factors associated with NOAF. Occurrence of potential risk factors were noted once in eight hours. Frequency, percentage, and odds ratio were calculated. Multiple logistic regression was done to find the risk factors associated with NOAF. *Results:* We followed up 271 individuals of both genders, among whom 29 cases of new onset of AF were observed (10.7%). The risk of getting NOAF was higher for those who were on renal replacement therapy (OR: 7.9 (95% CI: 3.2-19.2)), suspected sepsis (OR: 4.2 (95% CI: 1.7-10.2)) and had hypokalemia (OR: 4 (95% CI: 1.2-12.9)). *Conclusion:* Prompt diagnosis and treatment of hypokalaemia and sepsis may significantly reduce the risk of NOAF in ICU. Other independent risk factors were suspected sepsis and renal replacement therapy.

Keywords: Atrial Fibrillation, Critical Care, New-onset Atrial Fibrillation, Hypokalaemia ,Sepsis

Introduction

Atrial Fibrillation (AF) is one of the most common heart arrhythmias in the intensive care unit (ICU) [1-2]. AF affects 1 % of people under the age of 60 and 8% over the age of 80 [3]. In the intensive care setting, it has been reported that older age, male sex, electrolyte abnormalities, history of arrhythmias, volume overload, and use of inotropes, as well as cardiac surgery, mechanical ventilation for longer than 24 hours, congestive heart failure, and hypertension, are risk factors for developing AF [4]. Studies have shown that new-onset arrhythmias are related to severe morbidity, higher in-hospital mortality, longer Intensive Care Unit (ICU) Length of Stay (LOS), and increased hospital LOS. Additionally, ICU patients with sepsis may be at risk for AF [1, 2, 5]. Observational data indicate that up to 46% of individuals with septic shock and 4.5%-15% of people in the ICU experience new-onset AF [6-7]. Patients with critical illness may be sensitive to new-onset AF because of baseline comorbidity, acute metabolic, ischemic or neuro-hormonal stressors, or other pathophysiological changes during acute illness. Uncertainty exists regarding the role of AF as a measure of illness severity or as a potential independent cause of poor outcomes [8]. However, considering the negative consequences of AF on cardiac output and filling pressures, it is possible that the arrhythmia itself contributes to higher mortality [9]. Among critically ill patients, New-onset Atrial Fibrillation (NOAF) is the most common sustained arrhythmia [10]. The high

mortality associated with NOAF may be reduced by adhering to emerging AF management strategy such as targeting risk factors [11].

Prior studies have established that factors associated with NOAF include demographics, pre-existing cardiovascular disease, acute renal and respiratory failure, severity of illness, trauma, sepsis and use of vasopressors [12-13]. However, only a handful of these are modifiable risk factors. Therefore, this study aims to estimate the risk associated with both modifiable and other risk factors of new onset of AF in a Multi-Disciplinary Critical Care Unit (MDCCU).

Material and Methods

This is a nested case control study where all patients admitted to the MDCCU unit were followed up till discharge or death over a period of 2 months. The study subjects included all the critically ill patients of both genders, admitted in the ICU. Patients with known arrhythmia episodes in the past were excluded from the study. A structured questionnaire was used to collect the data from ICU. Occurrence of potential risk factors were noted once every eight hours. Data collected included sociodemographic data (age, gender, lifestyle habits like smoking, alcohol), medical history of co-morbidities, reason for ICU admission, number of days in the ICU, medications (digoxin, diuretic, antibiotics) and details of medical interventions in the ICU (electrolyte correction, vasopressor use, renal replacement therapy and central venous catheter placement). Data regarding left ventricular function, suspected sepsis, occurrence of NOAF and recurrence of AF in these patients were also collected. Although, the data collected was as per routine protocol, informed consent was obtained from each patient or relative and approval was obtained from the Institutional Ethics Committee (Ref.No 60/2019)

Statistical analysis

Data analysis was performed using SAS University Edition. Descriptive statistics included proportion of males, average age, incidence, and recurrence of AF. Logistic regression model was built using only those factors that had a significant odds ratio on univariate analysis.

Results

In the study, 272 people admitted to ICU were followed up till discharge or death over a period of two months. Of these, only one person was excluded because of history of AF prior to admission, reducing the final study sample size to 271. The incidence of AF in this sample was 10.7%. That is, 29 of 271 patients had NOAF, among whom 14 (48.2%) had recurrent episodes of AF. Among those with recurrence, 11 (78.5%) patients had single recurrence of AF and 3 (21.5 %) had more than one.

On examining the potential risk factors, those related to demography and lifestyle were not statistically significant. Suspected sepsis {defined as the quick Sepsis-related Organ Failure Assessment (qSOFA) score >1} was associated with a 4.2 times (95% CI: 1.8-9.5) higher risk of developing NOAF. In addition, organ failure, dyselectrolytemia and need for certain interventions were also associated with NOAF. As shown in Table 1, patients who had renal failure had 6.3 times higher risk (95% CI: 1.7-23.7), those with respiratory failure had 3.3 times higher risk (95% CI: 1.5-7.4) and those who had poor Left Ventricular (LV) function had 3.7 times higher risk (95% CI: 1.1-12.7) of developing NOAF. Similarly, the risk of developing NOAF was 3.2

times higher (95% CI: 1-3.8) for those who had hypocalcaemia and 3 times higher (95% CI: 1-8.8) for those with hypokalaemia. Additionally, the risk of developing AF for those who were on Renal Replacement Therapy (RRT) was 5.9 times higher (95% CI: 2.6-13.3), the risk in those who required vasopressor support was 3.6 times higher (95% CI: 1.6-7.8) and those who had a Central Venous Catheter (CVC) placement was 4.5 times higher (95% CI: 1.9-10.4). Diuretic therapy carried 2.2 times higher risk (95% CI: 1.0-4.8) of NOAF. As shown in Table 2, after adjusting for all other factors, the independent risk factors were use of RRT (adjOR: 7.9 (95% CI: 3.2-19.2)), sepsis (adjOR: 4.2 (95% CI: 1.7-10.2)) and hypokalemia (adjOR : 4.0 (95% CI: 1.2-12.9)).

Table 1: Risk factors associated with NOAF in critically ill patients in ICU

Characteristics	Numbers, N(%) (Total N=271)	Crude odds ratio
Gender		
Male	169 (62.4%)	1.4 (0.6-3.2)
Age group		
< 60	131 (48.4%)	1.0
60-75	112 (41.3%)	2.4 (0.9-6.3)
≥75	28 (10.3%)	1.6 (0.5-5.1)
Lifetsyle habits		
Smoker	8 (3.0%)	3.1 (0.6-16)
Alcohol	15 (5.5%)	1.4 (0.3-6.6)
Co-morbidities		
Sepsis	47 (3.3%)	4.2* (1.8-9.5)
Hypertension	156 (57.6%)	1.3 (0.3-6.2)
Diabetes mellitus	161 (59.0%)	1.6 (0.3-7.1)
Chronic kidney disease	47 (17.0%)	1.6 (0.3-8.7)
Chronic liver disease	29 (10.7%)	0.8 (0.1-6.3)
Chronic obstructive pulmonary disease	24 (8.9%)	2.2 (0.4-13.3)
Coronary artery disease	48 (17.7%)	1.3 (0.2-7.1)
Dyslipidemia	54 (19.9%)	1.4 (0.3-7.4)
Others	155 (57.2%)	1.2 (0.3-5.5)
Any comorbidity	247 (91.1%)	1.4 (0.3-6.1)

Continued...

Characteristics	Numbers, N(%) (Total N=271)	Crude odds ratio
Organ Failure		
Cardiovascular system	20 (7.4%)	1.1 (0.1-9)
Respiratory system	89 (32.8%)	3.3* (1.5-7.4)
Gastrointestinal tract	8 (3.0%)	2.9 (0.3-26.5)
Central nervous system	2 (0.74%)	-
Renal system	10 (3.7%)	6.3* (1.7-23.7)
Investigations		
Echocardiography		
Poor left ventricular function	14 (5.2%)	3.7* (1.1-12.7)
Electrolyte		
Potassium	186 (68.6%)	3.0* (1-8.8)
Sodium	29 (10.7%)	0.9 (0.3-3.3)
Calcium	52 (19.2%)	3.2* (1.3-8)
Magnesium	160 (59.0%)	0.5 (0.2-1.2)
Phosphorus	36 (13.3%)	0.7 (0.2-2.3)
Interventions		
Diuretic	122 (46.1%)	2.2* (1.0-4.8)
Vasopressor	78 (29.5%)	3.6* (1.6-7.8)
Renal replacement therapy	52 (19.2%)	5.9* (2.6-13.3)
Central venous catheter	40 (14.8%)	4.5* (1.9-10.4)

Table 2: Independent risk factors of NOAF

Characteristics	Adjusted odds ratio (95 % CI)*
Renal replacement therapy	7.9 (3.2-19.2)
Sepsis[#]	4.2 (1.7-10.2)
Potassium	4.0 (1.2-12.9)

Discussion

New-onset Atrial fibrillation (NOAF) in the ICU not only has an impact on morbidity and mortality, but also results in increased healthcare use and cost. Prior studies have identified several socio-economic and disease severity-related factors associated with developing NOAF. However, data on modifiable risk factors that could prevent NOAF in the general adult ICU population is limited [12-13]. Moreover, most of the studies include patients restricted to those with sepsis or from cardiac ICUs [14-15]. Very few have addressed this question in a non-cardiac multi-disciplinary ICU, like ours.

The incidence of NOAF in our study is low with only 10.7% of the critically ill developing it. However, according to prior studies the incidence varied from 4.5% [16] to 31.9% [17]. The incidence of NOAF in a subset of patients with sepsis or suspected sepsis admitted to the ICU in our study was found to be about 25.5%. This is lower than prior studies who have estimated it to be 30 to 50% [18-19].

More than half of the 25 studies in a systematic review showed increasing age to be a significant predictor of NOAF [13]. Our study, on the other hand, had a little more than half (51.7%) elderly, but did not show a significant association of age with NOAF. Similarly, a majority of our study subjects were males (62.3%). However, gender was not a significant predictor of NOAF. In the systematic review cited above, two studies [20-21] showed a significant association with male gender. Of these, one [22] did not compare AF with non-AF patients and the other showed gender as a significant risk factor only in the univariate analysis [28]. In contrast, an earlier systematic review of 17 studies concluded there is strong evidence that men are at higher risk of NOAF [28]. This conflict in conclusion is because of the definition of 'strong evidence' given by these authors [12]. Moreover, only one [20] of the two studies quoted are the same in those two reviews. In fact, the second study actually does not claim gender to be a risk factor [23].

Similarly, almost all patients (91.1%) had at least one comorbidity, and a majority had hypertension (57.6%) and diabetes (59.0%). Most of the earlier studies did not find comorbid conditions to be significant risk factors either. Not many studies considered lifestyle habits such as smoking, alcohol as potential risk factors. Those who did not find them to be associated [13]. These factors were not statistically significant in our study either. However, smoking had 3.1 times and alcohol 1.4 times higher risk in the univariate analysis which is suggestive of a trend towards developing NOAF. The lack of statistical significance is probably due to the very low prevalence of these abusive habits among our study subjects. Pre-existing condition at admission such as sepsis, and other organ failures such as renal and respiratory failure were associated with NOAF.

Sepsis is the most common cause of NOAF, according to prior studies. Moreover, an increase in the severity of sepsis has been shown to be associated with an increase in incidence of NOAF [20]. However, we had very few cases with sepsis (3.3%) at admission. On the other hand, we had many more patients (14%) who were suspected to have sepsis. Patients with sepsis were defined as those with confirmed blood cultures in addition to other laboratory investigations while suspected sepsis cases were defined as patients with a

qSOFA score of at least one. This group of patients, which included both sepsis and suspected sepsis, had 4.2 times higher risk of developing NOAF than others.

Organ failure at admission that were significantly associated with NOAF were renal failure, respiratory failure and cardiovascular failure (LV dysfunction). Almost a third (32.8%) of our patients had respiratory failure and were on mechanical ventilation. They had 3.3 times higher risk of NOAF in the ICU than those who did not have respiratory failure. A similar finding was seen in several other studies too [10, 12, 16, 24-30]. The most likely explanation for this finding is that mechanical ventilation induces changes in intra pleural or intrathoracic pressure and lung volumes which can in turn affect the key determinants of cardiovascular performance like atrial filling, heart rate and myocardial contractility which then can cause atrial fibrillation.

Only few (5.2%) of the study subjects had poor LV function on echocardiography. Those who had poor LV function with an ejection fraction (EF) of less than 0.35 had 3.7 times higher risk of NOAF compared to those who had higher EF. Other studies also found similar associations [12, 24]. Now it is well known that Heart Failure with reduced Ejection Fraction (HFrEF) can promote structural, ultrastructural, and neuroendocrine processes leading to AF.

Renal failure is often associated with hypertension which causes LV diastolic dysfunction leading to stress on atrial myocytes causing atrial fibrillation. Another mechanism is activation of renin angiotensin aldosterone system which can lead to negative remodeling of atria. In our study, patients with renal failure (3.7%) had 6.3 times higher risk of NOAF compared to those who did not. This association is corroborated by a systematic review on this topic [13]. Interventions such as RRT and CVC; medications such as diuretics and vasopressors; and electrolyte imbalances such as hypokalemia and hypocalcemia were significant risk factors in our study.

Major causes of NOAF include the interventions and medications used in the ICU. Almost half (46.1%) were on diuretics and had 2.2 times higher risk of developing NOAF compared to those who were not on diuretics. Medications such as furosemide can cause hypokalemia by increasing potassium excretion which explains the increased risk of atrial fibrillation. Similarly, about a third of the patients (29.5%) were on vasopressors and had 3.6 times higher risk of NOAF. Vasopressors such as vasopressin, and exogenous catecholamines (dobutamine, noradrenaline) administered in the ICU stimulates both α1- and β1- adrenergic receptors that increase the risk of arrhythmia. Although vasopressors are also used as therapeutic strategy for hemodynamic instability after AF, here we considered its use before the incidence of AF. Several prior studies have also shown such association [13, 26-30]. An intervention that could trigger NOAF is RRT. Changes in electrolytes produced during dialysis, especially the abrupt decrease in potassium concentration could increase the incidence of NOAF. In our study we found that those on RRT (19.2%) had 5.9 times higher risk of NOAF than those who were not. Only one other study found this association [26].

Arrhythmias due to CVC insertion can occur due to mechanical irritation of the endocardium or right atrium by the catheter tip. We found that those who had a CVC (14.8%) had a 4.5 times higher risk of developing NOAF. Two other studies have shown the same [10, 29].

Other triggers of NOAF are electrolyte imbalances. As explained above, with respect to both RRT and diuretic, hypokalemia is expected among those with NOAF. More than two thirds (68.6%) of our study subjects had hypokalemia and had 3 times the risk of developing NOAF than those who did not. Only one other study has shown the same [24]. Imbalance of magnesium was also found in more than half (59.0%) the subjects. However, it wasn't significantly associated with NOAF. On the other hand, hypocalcemia was found only in a fifth (19.2%) of the subjects and had 3.2 times higher risk of NOAF compared to those who did not have hypocalcemia. We did not find any study of risk factors of NOAF in ICU that included hypocalcemia as a risk factor. However, Denham *et al.* [30] explains in their review that hypocalcemia can cause AF by salt and water retention thus exacerbating heart failure which in turn can cause AF. He also postulates that hypocalcemia can determine the progression of AF from short lived paroxysmal AF to longer duration of persistent AF. In our study we found that 42% of those with hypocalcemia had persistent AF lasting for more than 1 day, but only 23.5% of those without hypocalcemia. Whether it progressed from paroxysmal AF or not could not be verified.

As explained above, many of the risk factors are interrelated and therefore a multivariate analysis was undertaken. The independent risk factors of NOAF were hypokalemia (4 times risk), sepsis (4.2 times risk) and RRT (7.9 times risk). Therefore, close monitoring to prevent hypokalemia is an important factor that could prevent NOAF in the ICU. Similarly, predisposing factors that need RRT must be investigated to prevent NOAF in the ICU. Although our study had very few patients with confirmed sepsis, we had several with suspected sepsis as per qSOFA at admission. Therefore, such patients must be closely monitored.

Conclusion

The incidence of NOAF in a non-cardiac MDCCU was found to be 10.7%. Of these at least one recurrent episode was seen in 38%. Independent risk factors of NOAF in the ICU include hypokalemia, RRT and sepsis. Therefore, regular monitoring and correction of serum potassium levels in the ICU and close monitoring of those with suspected sepsis can prevent NOAF. Moreover, predisposing factors that need RRT must be investigated further to prevent new onset of AF in the ICU.

Limitations

The limitation of our study includes the relatively small sample size which may have limited the statistical power of some clinical factors of lower prevalence. Increasing the time period in which the study was conducted could have given us a larger study sample. Moreover, other potential triggers of AF in ICU such as systemic inflammation, circulating stress hormones, autonomic dysfunction, and volume shifts which coexist in most of these patients were not studied.

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