Review Article

Atrial Fibrillation In Critically Ill Patients

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Abstract

Atrial fibrillation (AF) is a common arrhythmia in critically ill patients and is associated with significant mortality. The pathophysiology of development of AF is multifactorial.Advanced age is the most common risk factor for development of AF. The initial therapeutic strategy should depend on the identification and correction of underlying modifiable risk factor. Unfortunately there are limited data for therapeutic strategies for AF in critically ill patients. Present review summarizes the risk factors, pathophysiology, management of haemodynamically unstable as well as stable patients and anticoagulation therapy in critically ill patients.

Key Words: Atrial fibrillation, Critically ill, Mortality.

Introduction

Atrial fibrillation is a supra ventricular arrhythmia characterized by disorganized atrial depolarization without effective atrial contractions. It is the most common arrhythmia among patients in intensive care units (ICU)[1,2,3] and is associated with worst prognosis and longer ICU stay.[3] Atrial fibrillation can be paroxysmal (terminates spontaneously), persistent (persists beyond seven days) or permanent (if conversion to sinus rhythm cannot be achieved). The incidence of new onset atrial fibrillation in critically ill patients ranges from 5% to 46%.[4] Observational studies done in critically ill patients have identified many epidemiological and disease severity related factors that are associated with development of new onset AF.[5] The increased mortality in AF may be due to its detrimental effect on cardiac output and filling pressures. Thromboembolic complications may further worsen the outcomes.[2] There are limited data on therapeutic strategies for AF in critically ill population in intensive care setting compared to non-critically ill population.[4] This review discusses the predictors and management of atrial fibrillation in ICU.

Risk factors for Atrial fibrillation

AF can be attributed to many causes and the risk factors vary between general population and ICU patients.[6] Risk factors for development of AF in ICU patients include increasing age, presence of comorbidities, sepsis, renal failure, ICU interventions including vasopressor use,use of pulmonary artery catheters and renal replacement therapy.There is also an increased risk of developing new onset AF with increasing disease severity.

The incidence and prevalence rises with age i.e., 1% if age more than 60 years and 5-15% if age more than 80 years.[1] In case of patient with sepsis, the incidence of new onset atrial fibrillation correlates with that of severity of sepsis.[1] A prospective study done by Rainer M et al showed 7.8% of sepsis patients developed new onset AF and 46% of septic shock patients developed new onset AF.[5]

The incidence reported based on studies range between 27 and 40% and the peak incidence during first 2-4 days.[1,5] Prospective observational study done by Joseph P Mathew et al showed that significant independent predictors of postoperative atrial fibrillation were advanced age, history of atrial fibrillation and withdrawal of Beta blockers and ACE inhibitors. They found reduced incidence of atrial fibrillation in patients treated with beta blockers pre and post operatively.[8] Seguin and colleagues in their study of AF on a surgical ICU reported incidence of new-onset AF of 5.3%[9] The risk factors associated with development of atrial fibrillation in ICU patients is given in table 1.

Patient factors	Intensive care unit - admission diagnosis	Interventions
Advanced age Obesity Gender - Male Fluid overload Hypotension Hypoxemia Anemia Severity of illness Electrolyte abnormalities Acid-base abnormalities	SIRS Shock Ischemia Cardiac failure Trauma to chest Thoracic surgery	Use of Vasopressor Pulmonary artery catheterisation

Table 1 : Risk factors for the development of atrial fibrillation in Intensive care patients

Pathophysiology

Studies show that the cause of AF is multifactorial.[9] To understand the various treatment options, some basic pathophysiologic concepts leading to development of atrial fibrillation are discussed below. Research in the recent decades has disclosed an interaction between the initiation triggers and the maintenance factors as mechanism of development of AF.[1] The underlying mechanism for development of AF in older subjects is related to the increased length and dispersion of atrial refractoriness, dampening the recovery of atrial excitability in the older atrium.[6]

In case of sepsis, the exotoxins and endotoxins may contribute to the onset of arrhythmia. Exotoxins like streptolysin or pneumolysin have cardiotoxic potential leading to septic cardiomyopathy whereas endotoxins like lipopolysaccharides of some gram negative bacteria through its Toll-like receptor mediated action may contribute to onset of arrhythmia.[10] AF may be precipitated by elevated levels of circulating proinflammatory cytokines, catecholaminergic stress, electrolyte imbalances, and altered volume status during sepsis.[11] Various studies such as Meierhenrich et al as well as Chung et al found a relationship between elevated levels of CRP and onset of AF suggesting a role of inflammation in initiation and maintenance of AF.[6]

Another subgroup of ICU patients at risk of developing AF are post cardiac surgery patients. Cardiac surgeries involving sutures on the atria induce structural remodelling of the atria resulting in inflammation, myocyte alteration and tissues fibrosis which promote AF. After the onset of AF,there is an electrical remodelling process which involves ion channel function and intracellular calcium homeostasis which leads to shortening of refractory periods of atrial cardiomyocytes. These changes occur within a few minutes and contributes to the persistence of AF. Subsequently, alteration in the intracellular calcium homeostasis, contractile remodelling, dysfunction and further dilatation of atria occurs.[1]

Increased sympathetic tone secondary to operative stress can initiate and sustain atrial automatic potential by lowering atrial refractory period.[6]

In critically ill patients,untreated atrial fibrillation can lead to hypotension, myocardial ischemia, heart failure,shock and organ dysfunction.The mechanism of complications are secondary to loss of atrial contraction and high ventricular rate which inturn leads to impaired ventricular filling.[1]

Management

Management varies between ICUs, as there are no sufficient data regarding the treatment strategy.[6, 7] Intensivists adapt treatment modality based on their experience. The first priority in management of atrial fibrillation is to identify and to correct modifiable risk factors such as electrolyte abnormalities, hypoxemia, fluid overload and dehydration that predisposes the patient to develop atrial fibrillation.[4] Management of underlying conditions such as ischemia by revascularization, appropriate antimicrobials for sepsis patients and treating endocrine conditions such as hyperthyroidism are to be done. Adrenergic over stimulation may lead to development of new onset atrial fibrillation. Avoidance or minimisation of adrenergic overstimulation helps in management or resolution. Some of the mechanisms for development of AF and their managements are mentioned in table 2.

Mechanism/Etiology	Management
Myocardial stretch secondary to fluid overload/mitral valve disease	Restriction of fluid, Valvuloplasty
Impaired oxygen delivery to myocardium due to myocardial ischemia, hypovolemia, anaemia	Revascularisation, Fluid resuscitation, Blood transfusion
Electrolyte disturbances such as hypokalemia, hypomagnesemia	Correction of electrolytes according to the goal
Inflammation due to surgery leading to structural remodelling of atria, sepsis	Steroids, Antimicrobial therapy
Adrenergic overstimulation due to inotropic support or stress	Reduction of inotropes, sedation, analgesia, beta blockers
Endocrine disorders such as hyperthyroidism, phaeochromocytoma	Betablockers, Thyrostatic drugs, Alpha and beta blockers.

Table 2 : The underlying mechanism and management of Atrial Fibrillation

Hemodynamically Stable Patient

Rate Versus Rhytm Control

Factors that favour rate control are (i) age above 65 years (ii) Persistent AF (iii) Fewer symptoms (iv) Hypertension (v) Concomitant coronary artery disease (vi) no history of heart failure (vii) contraindication and unsuitability for cardioversion.

Factors that favour rhythm control are (i) Symptomatic patients (ii) Age less than 65 years (iii) Presenting for the first time with lone AF (iv) no hypertension (v) have congestive heart failure (vi)tachycardia mediated cardiomyopathy and (vi) difficulty in achieving rate control.[4,6]

Rate control can be achieved with drugs like beta blockers, digoxin, calcium channel blockers (diltiazem, verapamil) or amiodarone. Since there are no literature evidence on the optimal pharmacological treatment of AF for ICU patients, the clinician should choose the appropriate agent depending on the potential adverse effect.[1] Each drug group has certain advantages and disadvantages for use in critically ill patients.[12]

Drugs with a low risk profile and short half-life is initially recommended.[1] Beta blockers are mostly used to control rate in AF especially in post myocardial infarction and with stable heart failure cases.[6] Selective beta-1 receptor antagonists slower heart rate (chronotropic), delay conduction in the atrioventricular node (Dromotropic) and reduces myocardial excitability (bathmotropic). Esmolol has very short half-life of 7-10 minutes as it is eliminated by unspecific esterases and hydrolyses and can be given intravenously.[1] Metoprolol was found to be well tolerated in septic shock patients with AF.[10]The adverse effect of beta blocker is that it can potentially worsen haemodynamic status because of negative inotropic activity on myocardium.[1,12]

Digoxin has direct effect on atrioventricular node and may slow down the nodal conduction and reduces heart rate. Digoxin should not be used as first line therapy for rate control due to its slow onset of action.[1,4,12] The benefit of digoxin decreases with adrenergic stress, limiting its efficacy in critically ill patients. Digoxin may be beneficial for patients with heart failure in view of positive inotropic effects. Electrolyte disturbances such as hypokalemia, hypomagnesemia and hyperkalaemia exacerbate digoxin toxicity. Digoxin can cause ventricular as well as supra ventricular arrhythmias. The extra cardiac manifestations of digoxin toxicity are blurred vision, flashing lights, nausea, vomiting. In life threatening digoxin toxicity, the administration of digoxin immune Fab is highly effective. In patients with normal kidney function, the plasma half-life ranges from 20-50 hours and in end-stage renal disease upto 4-6 days.[1, 12]

Nondihydropyridine calcium channel blockers such as diltiazem and verapamil are used in patients with contraindications for beta blocker. In patients with new onset AF and fast ventricular response, intravenous calcium channel blocker diltiazem found to be more successful.The main adverse effects are increased incidences of hypotension.

Amiodarone has less negative inotropic effects compared to beta-blockers and calcium channel blocker and it is one of the commonly used drug in the ICU setting for the treating atrial fibrillation. The adverse cardiac event most commonly seen is prolonged QT interval while Tosades de pointes can be rarely seen. The common extra cardiac side effects are hypo and hyperthyroidism.

In patients with impaired left ventricular function, digoxin or amiodarone is the pharmacological agent.[13] Multicenter risk index for atrial fibrillation found high incidence of postoperative atrial fibrillation (approximately 32%) and showed episode occurred within first 3 days after CABG and recurrences within 2 days after initial episode. Further it showed administration of amiodarone or digoxin were associated with a lower risk of recurrence.[8] A retrospective study by Liu et al found that beta blockers and amiodarone were most commonly used in new onset AF in sepsis patients followed by non DHP CCB.[14]

Magnesium sulphate has been found to be effective in controlling rate and conversion to normal sinus rhythm.[4] Mechanism of action of magnesium are calcium antagonism, membrane stabilisation and regulation of energy transfer. IV magnesium has high therapeutic index and minimal negative inotropic effects. Prophylactic use of IV magnesium may reduce the occurrence of atrial fibrillation after cardiac surgery.[13] Magnesium sulfate has synergistic effect when combine with digoxin in controlling ventricular rate.[4]

Dronedarone and dofetilide may be useful for cardioversion. Dronedarone is an oral multichannel blocker with reduced lipophilicity and no iodine components when compared to amiodarone. The risk of increased mortality in patients with heart failure and risk of severe hepatotoxicity and nonavailability for IV administration limit its use in ICU settings. Vernakalant targets atrial specific channels and is approved for pharmacological cardioversion of AF of less than 7 days duration. It can be given intravenously.The safety and efficacy data for use in critically ill patients is lacking.[1, 12]

A prospective study conducted on septic patients with atrial fibrillation showed that majority reverted to sinus rhythm with either electrical cardioversion or medical therapy with amiodarone, beta-blockers, digitalis glycosides or a combination of these.[9]

Substances	Recommended dose
Esmolol	1.0 mg/kg in boluses of 10–20 mg iv, followed by continuous infusion (start with 0.05 mg/kg/min, increase dose every 30 minutes if necessary)
Diltiazem	0.25 mg/kg iv over 2 minutes, followed by continuous infusion (10–15 mg/h) if necessary
Amiodarone	150–300 mg iv, followed by a continuous infusion (900–1200 mg daily) up to 0.1 g/kg Maintenance dose 200 mg daily
Digoxin	0.25–0.5 mg iv every 4–8 h up to 1 mg, followed by maintenance dose of 0.25 mg daily

Table 3 : Commonly used intravenous antiarrythmic substances in ICU and the recommended dose.

Haemodynamically Unstable

In patients with dyspnea, acute chest pain or haemodynamic instabilty,sinus rhythm must be immediately restored by synchronised electrical cardioversion.[15] The aim is to determine whether the cause of instability is arrhythmia or underlying condition.

The initial management include (i) restoration of adequate perfusion with fluids, vasopressors and / or inotropes depending upon the aetiology, (ii) to ensure patient comfort with sedation and analgesia, (iii) to reduce sympathetic activation and maintaining sufficient oxygen supply to myocardium. Synchronised cardioversion is unlikely to provide benefit if tachycardia is a compensatory mechanism. The success rate is inversely proportional to chest wall impedance, left atrial size and duration of atrial fibrillation. Biphasic waveforms and anterior-posterior electrode placement provide higher success rates than lateral electrode positioning and monophonic waveforms. Due to wound dressing and chest tubes in post cardiac surgery patients, studies recommend single shock of 200 joules to be given to increase success rate in view of high impedance. Based on studies it is proposed that high initial energy reduces the incidence of tachyarrhythmic complications. To restore sinus rhythm in patients with pacemakers or internal cardioverter/ defibrillators (ICD) an internal overdrive pacing and or cardioversion may be attempted by cardiologists.[1]

Long Term Treatment After Haemodynamic Stabilisation

Anticoagulation

Presence of AF increases the risk of stroke and thus the priority of long term AF management is prevention of stroke. A retrospective study which evaluated association of atrial fibrillation and hospital mortality in critically ill patients showed 5.5% of incidence of stroke associated with atrial fibrillation. Walkey et al showed that patients with severe sepsis had a six-fold increased risk for in-hospital stroke as compared with hospitalized patients without severe sepsis.[16] The one year thromboembolic stroke and bleeding risk are assessed with CHADS-VASc and HAS-BLED but not validated in ICU populations. Anticoagulation poses a challenge in critically ill due to the potential need for urgent surgery or procedures and risk for coagulopathy.[4] In view of short half-life and reversibility with protamine, unfractionated heparin is the drug of choice for ICU patients. In view of ongoing inflammation and procoagulatory state,the risk is even higher in critically ill patients. Short term anticoagulation is accomplished with unfractionated heparin. After an overlap and INR of target range, heparin is stopped and initiated with oral coumarins for long term anticoagulation. Due to lack of evidence in critically ill patients, newer anticoagulants such as thrombin inhibitors and oral factor Xa inhibitors are not recommended.[1]

Discussion

Atrial fibrillation is the most common arrhythmia in critically ill patient. The risk factors for development of atrial fibrillation in intensive care unit are old age, use of vasopressors, use of pulmonary artery catheter and disease severity.[2] Severity of illness (APACHE II, SAPS II, shock, SIRS) organ failures and sepsis were all reported risk factors for development of atrial fibrillation.[17]

Atrial fibrillation in critically ill patient is associated with worst prognosis and longer stay in hospital.[3] Though AF is a common arrhythmia and associated high mortality and potential long term consequences, a thorough research on treatment of AF in critically ill patients is lacking. As there are no treatment guidelines, the treatment decision depends on treating clinician's experience. Haemodynamically unstable patients need synchronised cardioversion but the conversion rate in critically ill patients is lower (35%) compared to outpatients (90%). The decision for rate control versus rhythm control in haemodynamically stable patients should be based on various patient factors and underlying conditions. Evidences are lacking to substantiate one approach over the other. Studies show in haemodynamically stable patients, first option being rate control with beta blocker or calcium channel blocker, if beta blockers are contraindicated. In cases refractory to beta blockers or calcium channel blockers, amiodarone should be used. In view of highly variable conversion rates, no pharmacologic strategy was identified as superior to another.[4] Further studies are needed to determine the attributable morbidity and evidence to substantiate optimal therapy. Future research should aim for development of risk prediction tools to favour AF prevention in the ICU and for developing therapeutic strategy in critically ill ICU patient.

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