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New Onset Atrial Fibrillation in Critically Ill Patients

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1. Introduction

New onset atrial fibrillation is the most common rhythm disturbance in critically ill patients. Although it is frequently seen in critically ill patients, data regarding the aetiology and treatment are scarce. Extrapolating treatment regimes from non-critically ill patients is not recommended since there is a difference in aetiology of the arrhythmia. In this chapter we will discuss the pathophysiology and treatment strategies of new onset atrial fibrillation in medical- and non-cardiac surgery critically ill patients, based on the latest available evidence.

2. Pathophysiology

In critically ill patients the underlying mechanism for developing atrial fibrillation might differ from the outpatients clinic. Electrolyte disorders, rapid fluid changes like bleeding on one site and fluid overload by rapid filling in case of sepsis on the other site are present in excess and perfect triggers that induce atrial fibrillation. Reduced left ventricular function is also associated with atrial fibrillation. In critically ill patients, especially patients with sepsis, myocardial depression can occur, therefore inducing heart failure and, as a consequence, a higher risk of atrial fibrillation. Also underlying cardiac ischemia, for example the results of tremendous physically exercise which sepsis is, but also as a results of previously known or unknown coronary artery disease, can induce atrial fibrillation.
Recent studies have shown that elevated inflammatory biomarkers are associated with the development of atrial fibrillation. Inflammatory markers like C-reactive protein (CRP), high-sensitivity CRP (hs-CRP) an interleukin-6 are elevated in both patients with paroxysmal as persistent atrial fibrillation (Chung et al 2001 Dernellis et al 2001, Gaudino et al 2003). Atrial fibrillation is also common in septic patients, (Salman et al 2008, Christians et al 2008) the incidence is even higher in patients with septic shock. 46% of patients with septic shock developed new onset atrial fibrillation, often with an increase in C-reactive protein (CRP) levels before the onset of atrial fibrillation. (Meierhenrich et al 2010) As most critically ill patients have elevated inflammatory markers, they, therefore might be at risk for the development of atrial fibrillation (Sequin et al 2006). Furthermore, atrial fibrillation is also associated with local inflammation like pericarditis and myocarditis.

3. Treatment

Evidence for the best treatment strategy in critically ill patients is scarce. There are only 4 randomized controlled trials and furthermore 3 prospective follow-up studies who included mainly non-cardiac surgery and medical critically ill patients (table 1). However, since there is heterogeneity in not only patient selection, but also type of atrial arrhythmia and definition of treatment goals, these trials are not comparable and therefore the best treatment strategy based on these trials cannot be recommended. Even the question whether to treat or not critically ill patients with new onset atrial fibrillation has not been answered yet. Placebo controlled trials are lacking and, furthermore, spontaneous conversion is common in new onset atrial fibrillation, even in the setting of critically ill patients.

RCT trials	**Number of patients**	***Rhythm***	**Intervention**
Chapman 1993	24	AT	Amiodarone vs Procainamide
Barranco 1994	30	SVT	Flecainide vs Verapamil
Moran 1995	42	SVT	Magnesium vs Amiodarone
Balser 1998	64	SVT	Esmolol vs Diltiazem
Prospective			
Holt 1989	10	SVT	Amiodarone
Mayr 2003	37	SVT	Direct current cardioversion
Sleeswijk 2008	29	NAF	Magnesium Amiodarone

AT= atrial tachycardia
SVT= supraventricular tachycardia
PSVT= paroxysmal atrioventricular nodal reentrant tachycardia
NAF= new onset atrial fibrillation
A.fib= atrium fibrillation
A.flut= atrium flutter

Table 1.

Despite the lack of evidence, it is common practice to treat atrial fibrillation in the ICU setting. Many physicians feel the need to restore sinus rhythm in critically ill patients with either electrical cardioversion, chemical conversion or a combination of these treatment strategies. These feelings are predominantly based on their experience in non-critically ill patients. However, critically ill patients differ from the general population, therefore, extrapolating treatment regimes and results are not justified and may even harm. For example, DC electrical cardioversion in patients with new onset atrial fibrillation has a success rate of over 90%, while the only study investigating DC electrical cardioversion in critically ill patients yields an initial success rate of 35 % and only 13,5% after 48 hours, (Mayr et al 2003) which data are comparable to control group e.g. spontaneous conversion. Guidelines recommend immediate cardioversion in hemodynamic unstable patients.

Although critically ill patients are often hemodynamic unstable, this is in most cases not directly the results of atrial fibrillation, but on the contrary, atrial fibrillation is often the result of hemodynamic instability. Therefore an approach with direct DC electrical cardioversion may not be suitable in the ICU setting.
Although data are lacking, as mentioned before, most physicians tend to treat atrial fibrillation with rapid ventricular response in some way, therefore, the three cornerstones of treatment for atrial fibrillation include corrections of the underlying condition, rhythm or rate control and prevention of thrombo-embolic complications

3.1 The underlying condition

Whether treatment of the underlying condition may restore sinus rhythm or prevent recurrent atrial fibrillation, is not exactly known. However, treatment of the underlying disease and correction of precipitating factors such as electrolyte disturbances, volume imbalance or hypoxia are part of the general treatment in the ICU setting and are treated anyway. By "simply" treating sepsis lots of triggers that may induce atrial fibrillation will be eliminated and in most cases the arrhythmia will convert spontaneously to sinus rhythm by correcting electrolyte disorders and major fluid changes. However, in some of these patients, atrial fibrillation direct contribute to further hemodynamic deterioration of the patient and therefore should be treated as soon as possible. Since, as mentioned before, triggers are available in excess and also cannot always be removed, conversion to sinus rhythm might be a rather optimistic treatment goal, which means, conversion might be possible, but subsequently remaining sinus rhythm might be the Achilles' heel of this treatment strategy. Therefore, a goal that might be easier to achieve might be rate control to an acceptable ventricular frequency.

3.2 Rhythm or rate control

Based on the studies performed in the general population, (Van Gelder et al 2002, Wyse et al 2002) and postoperative atrial fibrillation, (Soucier et al 2003) and given the fact that a rhythm strategy with DC electrical cardioversion in critically ill cardiac surgery patients failed to show any benefit (Mayr et al 2003) and furthermore, chemical conversion is often accompanied by severe side effects or is contra-indicated, a rhythm control strategy is not recommend in critically ill patients, with the exception of those patients with life threatening cardiovascular collapse due to atrial fibrillation or in a setting of acute coronary syndrome. In these cases it is recommended to add an anti-arrhythmic drug in order to maintain sinus rhythm.
This might introduce another problem, while most anti-arrhythmic drugs lower pressure or are contra-indicated in ischemic heart failure.
Experience with rather new Vaughan-Williams class III anti arrhythmic drugs like ibutilide or nifekalant for chemical conversion is scarce. Ibitulide has been used in a few studies, (Bernard et al 2003, Hennersdorf et al 2002, Varriale et al 2000) but for the fact of limited safety data, we cannot recommend treatment with ibitulide in the ICU setting.
Few studies in critically ill patients have shown that just lowering ventricular rate by drugs that lower AV conduction and thereby contributing to more hemodyamic stability is effective for conversion to sinus rhythm. Amiodarone intravenously is the most common used anti-arrrhythmic drug in this setting.
Amiodarone, a type III anti-arrhythmic drug with also class II and IV effects , is well tolerated in hemodynamic unstable patients. Even patients with compromised left ventricular function can be safely treated with amiodarone. (Kumar 1996) However, the

high rate of serious adverse reactions makes amiodarone very unpopular. These adverse reactions are usually seen in prolonged administration although, amiodarone-induced pulmonary toxicity (Daniels et al 1997, Donaldson et al 1997, Laprinsky et al 1993, Van Mieghem et al 1994) and acute liver failure (Bravo et al 2005) may also present within days or weeks. These short terms adverse reactions of amiodarone are not well studied and may be underdiagnosed in clinical trials, especially in critically ill patients, since these patients often have more than one reason to develop (multi) organ failure.

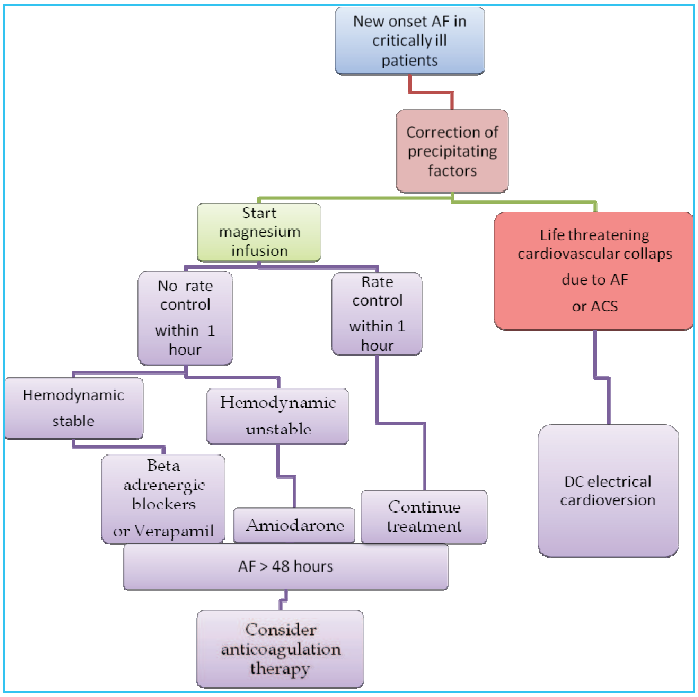
Beta adrenergic receptor blockers or nondihydropyridine calcium channel blockers like verapamil are also widely used for lowering ventricular rate, however, in ICU setting, these drugs may further compromise hemodynamic state in critically ill patients.

The use of magnesium has shown some promising results both in critically ill patients (Sleeswijk et al 2008, Moran et al 1995) as also in the general population presenting with new onset atrial fibrillation. (Gullenstad et al 1993) However, the anti-arrhythmic effect of magnesium is not completely understood. A normal serum level of magnesium does not rule out an absolute magnesium deficiency since magnesium is mainly located intracellular. So, it is difficult to establish whether the anti-arrhythmic effects of magnesium are mainly due to repletion of intracellular hypomagnesiaor the result of the presumed effect on Na-K-ATP-ase (Dyckner 1980, Ebel 1983) or the effect of blocking of calcium channels. (White et al 1989) However, magnesium seems to be effective in patients with both a low and normal level of serum magnesium. (Eray et al 2000) The optimal dosage of magnesium has not yet been establish. There are different regimens used in clinical trials, which may explain the difference in success of the treatment.

The facts that hypomagnesia is frequently seen in critically ill patients (Ryzen et al 1985) and that hypomagnesia is associated with increased mortality (Chernow et al 1989), in combination with the positive effects of magnesium seen on both ventricular and supraventricular arrhythmia, (Toraman et al 2001, Gullenstad et al 1993, Sleeswijk et al 2008, Moran et al 1995, Chiladakis et al 2001, Hays et al 1994, Jensen et al 1997) in the absence of serious adverse effects, and furthermore combined with the low cost, the prophylactic effect on pro-arrhythmia, (Caron et al 2003), the synergistic effect with anti-arrhythmic drugs (Kalus et al 2003) and the reduction for the need of potential toxic anti-arrhythmic, (Sleeswijk et al 2008) justify its use in all critically ill patients with atrial fibrillation. Of course, serum levels should be monitored, especially in those with renal failure, to prevent toxicity of hypermagnesia. Although there are different regimes used in clinical trials, we suggested a treatment regime with a bolus magnesium of 0.037 gram/kg body weight within 15 minutes followed by a continuous infusion of 0.025 gram/kg body weight / hour. (Sleeswijk et al 2008, Moran et al 1995)

Digoxin is one of the oldest anti-arrhythmic drugs with positive inotropic and negative dromotropic effect. However, its dromotropic effect is very disappointing, especially in the critically ill patients probably because the enhanced adrenergic state which is seen in these patients. (Falk et al 1987, Clemo et al 1998, Goldman et al 1975) Furthermore, digoxin has several serious side effects and the combination of rather ineffectiveness with safety matters makes digoxin not recommended in critically ill patients.

Since inflammation plays an important crucial role in the pathophysiology of new onset atrial fibrillation in critically ill patients, it is tempting to use anti-inflammatory agents for the treatment and prevention of atrial fibrillation. Glucocorticoids, (Whitlock et al 2008) statins, angiotensin converting enzyme inhibitor and 3 fatty acids (Guglin et al 2008) may have shown to be effective in preventing or termination atrial fibrillation by modulating the substrate. Due to the limited evidence and safety concerns these agents cannot yet be recommended for the treatment of new onset atrial fibrillation in critically ill patients.



AF= atrial fibrillation
ACS= acute coronary syndrome

Fig. 1. Treatment algorithm for new onset atrial fibrillation in critically ill patients.

In summarize, the treatment of new onset atrial fibrillation in critically ill patients should start with the correction of precipitating factors and is further primarily aimed at a rate control strategy, starting with the infusion of magnesium. If rate control is not achieved we recommend amiodarone for the unstable patients and in hemodynamic stable patients a beta adrenergic receptor blocker of verapamil can be started. With this regime conversion to sinus rhythm will occur within 24 hours in most patients.

4. Prevention of thrombo-embolic complications

The risk for thrombo-embolic complication is increased in patients with atrial fibrillation lasting for more than 48 hours. Critically ill patients are at risk for thrombo-embolic complications due to their underlying disease and immobility. The formation of thrombi in atrial fibrillation is the result of the combination of blood coagulation status, vessel wall related factors and reduced blood flow. All these 3 factors are altered in favor of more easily development of thrombi in critically ill patients. Furthermore, inflammation, usually present in critically ill patients, might enhance development of thrombosis. However, critically ill patients also have a high risk of bleeding complications due to coagulation disorders (Levi et al 2006) or the need for invasive procedures during their stay in the ICU.
In each patient the benefit of stroke prevention must be weighed against the risk of bleeding. Although data are lacking, we tend to mention that the CHADS2 risk calculator for thrombo-embolic complication in atrial fibrillation cannot be applied in the critically ill.

In case of persistent atrial fibrillation for at least 48 hours, one should consider starting anticoagulant therapy in critically patients. Due to the high bleeding risk we recommend treatment with unfractionated heparin or short acting low molecular weight heparin.

5. Prognosis

Treatment with magnesium and or drugs that lower AV node conduction is in most case effective to restore sinus rhythm within 24 hours. Recurrence rate and long term outcome has not been studied in critically ill patients. New onset atrial fibrillation in critically ill patients is associated with increased mortality, morbidity and prolonged ICU stay. (Sleeswijk et al 2007) However, a causal link between atrial fibrillation and mortality has not yet been found. Atrial fibrillation may simply be a marker of severity of illness rather than an independent contributor of mortality.

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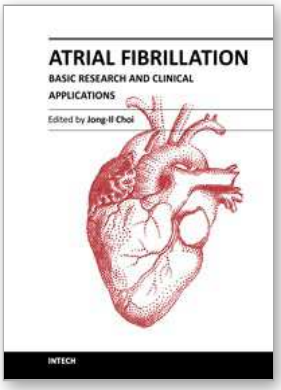

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Atrial Fibrillation-Basic Research and Clinical Applications is designed to provide a comprehensive review and to introduce outstanding and novel researches. This book contains 22 polished chapters and consists of five sections: 1. Basic mechanisms of initiation and maintenance of atrial fibrillation and its pathophysiology, 2. Mapping of atrial fibrillation and novel methods of signal detection. 3. Clinical prognostic predictors of atrial fibrillation and remodeling, 4. Systemic reviews of catheter-based/surgical treatment and novel targets for treatment of atrial fibrillation and 5. Atrial fibrillation in specific conditions and its complications. Each chapter updates the knowledge of atrial fibrillation, providing state-of-the art for not only scientists and clinicians who are interested in electrophysiology, but also general cardiologists.

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