

# Triggers for new-onset atrial fibrillation in critically ill patients

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## BACKGROUND

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Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is characterised by loss of coordinated atrial contraction, and an irregularly irregular ventricular rhythm. New-onset atrial fibrillation (NOAF) is AF occurring in a patient with no known history of chronic or paroxysmal AF. It is common in patients admitted to an intensive care unit (ICU), occurring in around 14% of all patients, with higher rates in patients with septic shock (Wetterslev et al., 2019).

NOAF during an ICU admission is associated with increased hospital mortality (Bedford et al., 2020). NOAF during critical illness also carries a long-term burden, increasing the risk of heart failure, stroke, and death at five years (Walkey et al., 2014).

Sustained AF is dependent on triggering events occurring in abnormal atrial tissue. Spontaneous initiation of AF often occurs by focal ectopy and initiation of re-entry, where electrical activation forms a self-sustaining circuit. Often the focus lies within the pulmonary veins (PVs), though non-PV foci are frequently identified (Haïssaguerre et al., 1998). Once triggered, AF is maintained by atria that have undergone electrical or structural remodelling, or both. Remodelling can occur gradually in the context of chronic illness, or rapidly in the context of critical illness. This remodelling alters the mechanical and anatomic structure of the atria (the substrate) such that its propensity for development and maintenance of AF is increased (an arrhythmogenic substrate). Numerous risk factors contribute to the development of NOAF during critical illness, with multiple mechanisms that encourage remodelling and ectopy (Bedford et al., 2021).

## DEVELOPMENT OF AN ARRHYTHMOGENIC SUBSTRATE

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Many comorbidities associated with AF contribute to atrial structural remodelling leading to an arrhythmogenic substrate, including ageing, and conditions leading to chronic atrial stretch such as systemic and pulmonary hypertension, obesity, and congestive heart failure (Bosch et al., 2019).

Resultant remodelling is characterised by fibrosis, slowing of conduction, and spatial heterogeneity of refractoriness.

During the development of critical illness, systemic inflammation increases the risk of AF. Inflammatory mediators encourage myocardial myofibroblast differentiation and subsequent accelerated fibrosis (Friedrichs et al., 2011). Moreover, inflammatory cascades and bacterial endotoxins can alter ion channel function, resulting in shortened action potential durations and increased risk of arrhythmia (Aoki et al., 2012). Furthermore, reactive oxygen species (ROS) are elevated during critical illness and increase atrial ectopic activity. ROS also promote an arrhythmogenic atrial substrate by altering the function of connexins responsible for intercellular electrical coupling (Dobrev et al., 2019).

Consequently, the older, more comorbid patient is at higher risk of sustained NOAF during critical illness due to pre-existing remodelled substrate. This risk is compounded by the severity of their acute illness, which, through mechanisms outlined above, often outweighs comorbidities in contribution of overall risk (Bosch et al., 2019).

## TRIGGERS DURING CRITICAL ILLNESS

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Various triggering mechanisms can initiate AF through inducing focal ectopy and promoting re-entrant circuits. AF is then sustained due to the underlying remodelled substrate. Multiple potential triggering events may occur in the context of critical illness. This process is outlined in Figure 1.

The autonomic nervous system plays an important role in AF initiation and maintenance. There is a dynamic relationship between the sympathetic and parasympathetic nervous systems, with changes in autonomic balance evoking rapid firing from PVs and atria. Whilst mainly non-modifiable, measures such as optimal analgesia, and management of ventilator dyssynchrony may mitigate some autonomic drivers of arrhythmogenesis.

After cardiac surgery, withholding beta blockers from patients previously treated with beta blockers (beta blocker withdrawal) increases post-operative AF risk (Mathew et al., 2004). Administration of catecholamines such as adrenaline and noradrenaline also increases the risk of NOAF. Consequently, patients with higher blood pressure targets are at increased risk. Catecholamine-sparing vasopressors e.g. vasopressin may reduce AF risk and may be considered in high-risk patients where clinically appropriate (McIntyre et al., 2018).

Volume overload is common in critically ill patients and can lead to atrial stretch which increases rapid firing from PVs due to stretch-dependent ion channels. Positive fluid balance is associated with increased NOAF risk in critically ill patients (Shaver et al., 2015). This association may also reflect that more unwell patients (who are at higher NOAF risk due to illness severity) often receive larger volumes of intravenous fluid.

High-normal concentrations of plasma potassium are often targeted with the aim of NOAF prevention or as part of a NOAF treatment regimen (Chean et al., 2017). Hypokalaemia leads to increased risk of atrial arrhythmia by slowing intra-atrial conduction and shortening the effective refractory period, thereby increasing the risk of re-entrant circuits. Hypokalaemia has been associated with NOAF in patients post-MI and has led to guidelines suggest targeting a plasma  $[K^+]$  in the upper range of normal in these patients (Antman et al., 2004). This practice is often applied to the general critically ill population, although optimal target potassium levels are yet to be determined.

Pulmonary artery (PA) catheters may increase NOAF risk. Randomised trials of PA catheters have not compared rates of NOAF between intervention and control groups, however dysrhythmias during insertion are reported in 3-18% of patients (Rajaram et al., 2013). AF may be induced by myocardial irritation from malpositioned central catheters or by guidewires inserted into the atrium during catheter insertion. It remains unclear whether central venous catheters pose an increased NOAF risk when well positioned. Where there are benefits to a superior vena caval location (for

example for flow rates during renal replacement therapy), based on current evidence these are likely to outweigh any risks of new arrhythmia.

## SUMMARY

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Multiple risk factors for NOAF during critical illness have been identified, and some of the underlying mechanisms have been outlined above. However, it is not yet clear how modifying these may reduce NOAF risk and improve outcomes.

In the absence of robust evidence for NOAF prevention strategies, no specific interventions can be recommended at present. Further research is required to develop and validate tools to identify patients at high risk of NOAF who may benefit most from preventative strategies. Randomised studies in high risk cohorts will then guide our ability to prevent this common and important problem. Whilst further research is awaited, pragmatic approaches may reduce the risk of NOAF in critically ill patients, including considered electrolyte replacement, earlier use of catecholamine-sparing agents, targeting euvolaemia, and considering restarting pre-admission beta-blockers when possible.

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## FIGURE LEGENDS

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Figure 1 – Potential mechanisms for new-onset atrial fibrillation during ICU admission. An arrhythmogenic substrate (a structurally and electrically remodelled myocardium) can develop prior to acute illness or surgery due to ageing and comorbidities. Further accelerated remodelling can then occur during critical illness or in the perioperative period. Electrical remodelling (changes in

ion handling and connexin expression) occurs alongside structural remodelling (atrial stretch and fibrosis). Factors such as high sympathetic drive, fluid overload and systemic inflammation promote remodelling such that on arrival to the ICU, there is an elevated predisposition to new-onset AF (NOAF). Arrhythmogenic potential will depend on the combined effects of comorbidities and acute-illness-related factors on the myocardium and will vary considerably from patient to patient. Each factor is not uniquely required, but adds to an accumulated risk. Exposure to triggering events may then initiate AF through multiple mechanisms, which is then sustained due to underlying remodelled tissue.

CCF = congestive cardiac failure; COPD = Chronic obstructive pulmonary disease; AF = atrial fibrillation.