Chapter

Atrial Fibrillation during Septic Shock

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Abstract

Atrial Fibrillation (AF) is an early and common occurrence during septic shock, accounting for 25–30% of admissions. Conventional cardiovascular risk factors do not generally increase its incidence, especially in cases of new-onset AF. Inflammation during the sepsis process has been postulated as a possible trigger. Detrimental effects of AF result in prognosis worsening, even when the probability for a negative outcome has been adjusted for severity of illness. New-onset AF (NOAF) has been associated with greater mortality rate than preexisting chronic AF. Early cardioversion has not uniformly improved hospital outcomes. In this review, the incidence, prognosis and management of AF in septic shock patients are summarized.

Keywords: atrial fibrillation, septic shock, sepsis, antiarrhythmic therapy, cardioversion, critical care

1. Introduction

The term sepsis derives from ancient Greek "sêpsis" ("putrefaction" or "decay of organic matter") and was first used in a medical context in Homer's Iliad more than 2700 years ago. Currently, sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection [1]. Since 2016, the updated operative definition of sepsis no longer considers the presence of systemic inflammatory response syndrome, but requires an infection plus organ dysfunction indicated by an acute change in Sequential Organ Failure Assessment (SOFA) [2] of at least two points (see **Table 1**). Septic shock is defined as sepsis plus circulatory failure with increased risk of death, indicated by hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) 65 mmHg or greater and a serum lactate of greater than 2 mmol/L despite adequate fluid resuscitation [3]. Other indices of tissue hypoperfusion (e.g. altered mental status, oliguria, delayed capillary refill) are acceptable alternatives whenever serum lactate determination is not available.

In high-income countries, sepsis represents approximately 6% of adult hospitalizations and 10–37% of intensive care unit (ICU) admissions. Mortality estimates from sepsis and septic shock vary widely, rounding 15% and 22% respectively [4]. In low-income regions, sepsis and septic shock predictably carry an even higher mortality, up to 50% [5].

Generally speaking, atrial fibrillation (AF) is the most frequently found cardiac arrhythmia in the ICU setting. Previously known AF is significantly prevalent among older patients with chronic conditions who are at risk for critical illness. New-onset AF (NOAF), on the other hand, is frequently triggered by accelerated

System	Score				
	0	1	2	3	4
Respiration PaO_2/FIO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation platelets, $\times 10^3\ \mu L^{-1}$	≥150	<150	<100	<50	<20
Liver bilirubin, mg dL^{-1} (μmol L^{-1})	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>120 (204)
Cardiovascular	MAP ≥70 mmHg	MAP<70 mmHg	Dopamine<5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Central nervous system (CNS)					
Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<6
Renal creatinine, mg dL^{-1} (μmol L^{-1}) < 1.2 (110) 1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)		
Urine output, mL per day				<500	<200

FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.
[a]Catecholamine doses are given as $\mu g kg^{-1}\ min^{-1}$ for at least 1 h.
[b]Glasgow Coma Scale scores range from 3 to 15; higher score indicates belter neurological function.

Table 1.
Sequential organ failure assessment (SOFA) score [2].

atrial remodeling and by concomitant stressors during critical illness, such as electrolyte imbalances and use of vasopressor drugs [6].

In this narrative review, the pathogenesis, risk factors, incidence, prognosis and management of AF in septic shock patients are summarized.

2. Pathogenesis

The negative effects of sepsis on the heart are not limited to the contractile function and ventricular relaxation, but also affect the electric function. Although the precise mechanisms remain to be elucidated, inflammation seems to play an important role. The electrical instability of cardiomyocytes in patients with sepsis has been considered to be due to the use of vasopressor drugs and the presence of electrolyte disturbances. However, according to recent findings, atrial fibrillation (AF) could be the result of the necrosis and fibrosis induced by inflammation [7, 8]. These alterations are supposed to be able to trigger an arrhythmia due to a fluctuation in the myocardial cells' membrane potential [9].

The development of NOAF in septic shock patients depends upon the presence of an arrhythmogenic substrate, the trigger factors and the modulation factors such as autonomic nervous system or inflammation. Triggered activity has been shown in the musculature of the atrium. An imbalance between sympathetic and vagal tone leading to a reduction of heart rate variability has been proposed as an explanation for the development of NOAF in septic patients [10]. Vagal stimulation normally attenuates the inflammatory response [11]. In human atrial cardiomyocytes, partial blockage of the I(f) 'funny' pacemaker current has been observed after exposition to gram-negative bacteria endotoxin [12], which may contribute to a reduced responsiveness to both sympathetic and vagal autonomic stimuli (the name "funny current" arose because of its numerous unusual characteristics, including the mixed Na + and K+ current permeability, activation on hyperpolarization, and

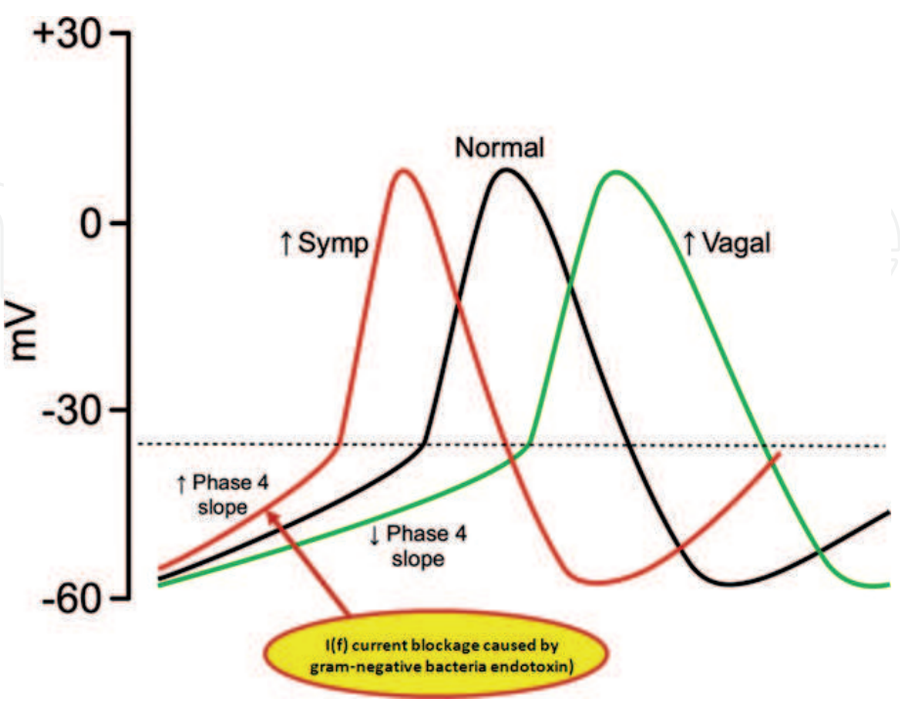

Figure 1.
Schematized transmembrane action potential of sinus node (pacemaker) cells. The black line shows normal slope in sinus rhythm. During gram-negative bacteria induced-sepsis, it has been shown I(f) current blockage, which results in an increased phase 4 slope, triggering sinus tachycardia and facilitating AF onset (red line) [12].

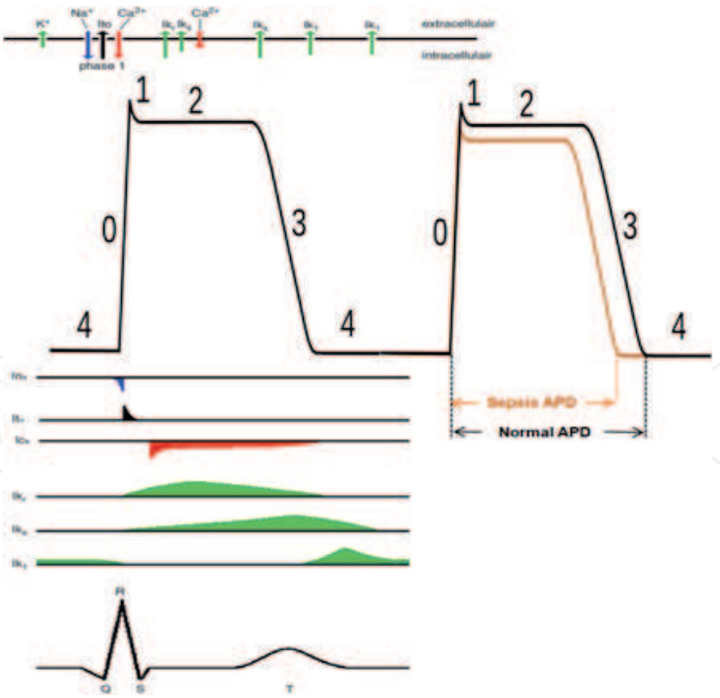

Figure 2.
Schematized transmembrane action potential of atrial myocytes in normal and septic animals. The orange line indicates how sepsis decrease phase 2 (plateau phase) duration and leads to decrease in APD (action potential duration). This is due to a decrease in influx of calcium through the voltage-dependent L-channels, which is at least in part caused by sepsis-induced tachycardia. The decrease in APD (and hence in the atrial refractory period) has been proposed to effectively trigger AF [15].

slow activation and deactivation kinetics [13]) (see **Figure 1**). This would result in a high heart rate output, which is commonly observed in septic patients. Unopposed sustained tachycardia during the will further increase calcium influx through L-type Ca2+ channels, which leads to marked shortening of the atrial refractory period and action potential duration (**Figure 1**) and elicit triggered activity, hence facilitating the onset of AF [14, 15] (see **Figure 2**). This process has been shown to be further enhanced due to beta-adrenergic stimulation after endotoxin application [16], which increases channel activity by prolonging the open time and shortening the close time of Ca2+ channel. These findings might explain the high sensitivity of cardiac pacemaker cells to positive inotropic effect of adrenergic stimulation and most likely development of new AF episode especially in the early stages of sepsis [17].

3. Risk factors

Sepsis itself is a strong risk factor for NOAF in the critical care setting. An extensive retrospective population-based cohort analysis by Walkey et al. revealed that compared to those without severe sepsis, patients with severe sepsis (n = 49,082) exhibited a significantly increased risk of NOAF (odds ratio (OR), 6.82; 95% confidence interval (CI), 6.54–7.11; P < 0.001) [18]. Multiple studies have been shown that the classic risk factors for the development of chronic atrial fibrillation in the general population may differ from those present in septic patients with NOAF. Risk factors for the occurrence of NOAF in septic patients include conditions that are not related to chronic cardiovascular disease, such as increased number of acute organ failures/dysfunction, mechanical ventilation, increased comorbidities, and use of pulmonary artery catheterization [18–22]. NOAF has been also associated with lower EF, older age, higher level of troponin-HS and NT-pro-BNP and longer QRS duration.

Sepsis due to bacterial pneumonia has been associated with a high risk of developing NOAF, while sepsis due to gastrointestinal infections has been related to AF recurrence with worse long-term prognosis [23]. It has been hypothesized that the type and severity of infection could have an impact on the atrial remodeling and the variety of cytokine expression during sepsis. Current evidence suggests that the severity of the inflammatory response in critically ill patients is associated with a higher risk of NOAF, and septic shock patients have in general a heightened probability of developing NOAF than patients with other acute critical illnesses after adjustment for underlying risk factors [21].

In a systematic review that included 11 studies, Kuipers et al. [19] identified independent risk factors with a high level of evidence for NOAF in septic patients. White race, organ failure and pulmonary catheter use were moderately associated with NOAF development, while there was a weak association with age and respiratory tract infection. On the other hand, history of diabetes and urinary tract infections were found to be weak protective factors. In other studies, markers of illness severity (such as the presence of organ failure and shock) as well as several critical care interventions were associated with an increased risk of NOAF in septic patients. Known risk factors for chronic or paroxysmal AF in the general population, such as advanced age, white race, male gender, obesity and (ischemic) heart failure, were in some studies also associated with the development of AF during sepsis [24, 25]. Specific electrocardiographic or echocardiographic features of AF such as P-wave duration or left atrial area, remain to be studied in septic shock patients, although both factors are known to predict the occurrence of AF in the general population [26, 27].

Data regarding risk factors for the occurrence of NOAF in septic shock patients is more limited. Guenancia et al. [26] found that NOAF patients were older and had higher levels of cardiac biomarkers (troponin ($p < 0.01$) and NT-pro-BNP ($p = 0.03$)), lower left ventricular ejection fraction (LVEF), longer duration of the QRS complex and more nonsustained supraventricular arrhythmias (< 30 seconds) on day 1 than patients who maintained sinus rhythm. Age (OR: 1.06; $p = 0.01$) and LVEF <45% (OR: 13.01, $p = 0.03$) were associated with NOAF in their multivariate analysis.

4. Incidence

Atrial fibrillation is a common occurrence in patients with sepsis and septic shock, and its incidence varies widely among investigators. This may be due to the different criteria used to define sepsis and septic shock, or the method used for the diagnosis of AF [28]. In the aforementioned systematic review, Kuipers et al. [19] showed that the mean incidence of new-onset AF was 8% in patients with sepsis and 23% in patients with septic shock. The authors of that study also observed a significant increase in ICU length of stay in this group of patients. In a large study conducted by Walkey et al. [21], which retrospectively analyzed data from over 60,000 patients admitted for sepsis, the investigators found an overall incidence of AF during sepsis of 25.5%. This number rose to 31.6% when considering only the ICU population.

To date, there have been relatively few published prospective investigations regarding the incidence of AF in septic shock patients, although there is more available information about the general topic of AF in septic patients. Seguin et al. [29] found AF developed in 24 patients (5.3%) of 460 patients admitted to the surgical intensive care unit and followed prospectively during a 6-month period. They reported that 29.2% (7 of 23 patients) of septic shock patients developed AF.

They concluded the presence of shock (especially septic shock) appeared to be an independent risk factor of AF in their cohort. It has to be recognized, however, that the operative definition of septic shock used at that time, the one proposed by Bone et al. [30], has since been substantially modified.

Steinberg et al. [28] published recently a one-year observational prospective study of 27 septic shock patients. Their aim was to evaluate the incidence of AF, and the mortality rate of patients with AF versus patients that maintained sinus rhythm. Nine (33%) patients developed AF during the first 72 hours. At admission and at 72 hours, SOFA was statistically higher in the patients with AF ($p = 0.012$ and $p = 0.002$, respectively).

In a single-center study, Meierhenrich et al. [31] prospectively studied all patients with NOAF and all patients suffering from septic shock in ICU during a 13 month period. Patients with preexisting chronic AF were excluded from their analysis. They found 23 out of the 50 patients with septic shock (46%) developed NOAF, compared to an overall incidence (septic and non-septic patients taken into account) of NOAF of 7.8% (49/629). The same aforementioned limitation in septic shock definition applies to this data.

Guenancia et al. [26] conducted a single-center prospective, observational study on patients with septic shock, and they found an incidence of new-onset AF of 44% (29 of 66 patients). Noteworthy, a 34% of new-onset AF would not be diagnosed without Holter ECG monitoring (silent AF).

More recently—and using an updated definition of septic shock—Rabie et al. [32] prospectively studied 100 septic shock patients, one of the largest series ever published. All patients were continuously monitored by three/five-lead monitor with arrhythmia detection algorithms, alarms, and Holter recording capabilities throughout the ICU stay. The investigators found the development of NOAF in 29 (29%), of which 22 (75,8%) patients had a single occurrence and 7 (24,2%) had recurrent AF during their ICU stay.

5. Prognosis

Whether NOAF acts as a surrogate marker for increased illness severity and subsequently poor prognosis in sepsis or whether it directly contributes to mortality and poor outcomes is not entirely clear. As stated before, the sepsis state can trigger AF mainly because of the combined mechanisms of inflammation, surge in catecholamines, and direct and indirect myocardial injury, and the poor prognosis noted whenever AF develop in critically ill patients may be the consequence of the presence of these factors.

In a retrospective analysis, Walkey et al. [33] found that patients with NOAF during a hospitalization for sepsis showed a higher five-year risk of hospitalization for heart failure (11.2% vs. 8.2%; HR, 1.25; 95% CI, 1.16–1.34), ischemic stroke (5.3% vs. 4.7%; HR, 1.22; 95% CI, 1.15–1.47), and death (74.8% vs. 72.1%; HR, 1.04; 95% CI, 1.01–1.07) than patients who did not develop NOAF.

Specific prospective data regarding the prognosis of NOAF in septic shock patients is also sparse. In a small series of 27 septic shock patients followed prospectively for one year, Steinberg et al. [28] reported that mortality was higher in AF patients (66%) than in patients in sinus ryhtm (11%) ($p = 0.006$). Age, rhythm and noradrenaline dosage were univariate predictors of total mortality. In the aforementioned study of Meierhenrich et al. [31], mortality in septic shock patients with NOAF was 44% compared with 22% in septic shock patients with maintained sinus rhythm ($p = 0.14$). The average length of ICU stay was shown to be increased in patients with NOAF (30 versus 17 days, $p = 0.017$). Failure to achieve sinus rhythm

restoration was associated with greater ICU mortality (71.4% vs. 21.4%, p = 0.015). After two years, the investigators observed a statistically nonsignificant increase in mortality in septic shock patients with NOAF (p = 0.075).

In a larger prospective series, Rabie et al. [32] found that mortality in patients with single AF attacks were not statistically higher than non-AF patients (p = 0.143). However, recurrent attacks of AF had significantly higher mortality than non-AF or single AF attack (p < 0.05). Recurrent AF was associated with increased length of UCI stay (21.6 ± 7.2 vs. 12.9 ± 7.3 days, p = 0.004).

6. Management

When considering use of antiarrhythmic drugs or applying cardioversion in septic patients with atrial fibrillation and hemodynamic instability, causative factors must in parallel be addressed and corrected when feasible [34]. Since diastolic dysfunction is highly prevalent in ICU patients and is also an independent predictor of mortality [35], both excessive or insufficient fluid resuscitation should be avoided. For example, the so-called Early Goal Directed Therapy has shown marginal benefit [36] while heightening the risk of fluid overload and the overuse of betaadrenergic stimulant drugs to achieve central venous saturation above 65%. The resulting high cardiac output constitutes an arrhythmogenic setting. Interestingly, ceasing beta-stimulation and administering low-dose betablockers with concomitant preload correction has led to a dramatic decrease in mortality [37]. While the use of vasopressors in septic shock is recommended in early septic shock, preload assessment and timely administration of vasopressin can assist in diminishing the requirement of catecholaminergic drugs and consequently lower the risk of arrhythmia. Suboptimal volume replacement, on the other hand, carries the risk of higher sympathetic tone and consequent down-to regulation of adrenergic receptors which in turns leads to requirement of greater doses of vasopressor drugs. Hence, both conditions, namely fluid overload and hypovolaemia, are triggering factors for developing arrhythmias.

Electrolyte disturbances, which are commonplace in ICU patients, should be likewise identified and promptly corrected. Hypokalemia and hyperkalemia triggers supraventricular and ventricular arrhythmias. If the potassium level does not respond to adequate supplementation, magnesium levels must be assessed and corrected, since severe hypomagnesemia prevents the potassium level being corrected. It has been shown that septic patients tend to have lower serum magnesium levels when compared to nonseptic patients [38, 39]. Hypophosphatemia is associated with decreased myocardial contractility and a higher incidence of arrhythmia [40], and the correction of phosphorus level has been shown to prevent it [41]. Hypocalcemia may also be associated with arrhythmias [42, 43], although the data in septic patients is scarce.

Right ventricular dysfunction may cause acute cor pulmonale and supraventricular arrhythmias [44]. Instituting aggressive modalities of mechanical ventilation in septic patients with acute distress respiratory syndrome as an attempt to recruit consolidated lungs may trigger an increase in right ventricular afterload, with the consequent development of NOAF. Gradual opening of the consolidated lungs in a prone position [45] guided by periodic chest ultrasound and echocardiographic assessment may prevent the onset of supraventricular arrhythmias.

Guidelines for management of AF [46] do not usually apply readily to critically ill patients, since NOAF in patients treated on an ICU differs from AF in patients in the community in terms of causes of rhythm disturbance [47], and appropriate management [48].

6.1 Electrical therapy

Synchronized direct current cardioversion (SDCC) should be employed for patients with hemodynamic instability related to the arrhythmia, even though the probability of remaining in sinus rhythm may be low. In critically ill patients, SDCC has been investigated in few studies. The reported efficacy is generally low, ranging from 26.9% and 35.1% [49, 50]. Mayr et al. reported successful electrical cardioversion at one hour after the attempt in 13/37 (35.1%) ICU patients with NOAF. After 24 hours, six of these 37 patients (13.5%) remained in sinus rhythm. An additional study evaluating the efficacy of SDCC reported sinus rhythm restoration for at least 24 hours in 7/26 (26.9%) patients. Of note, 18 of these patients had received amiodarone prior to or during electrical cardioversion [49].

In septic shock patients with NOAF, there is lack of data on effectiveness. In a small series [28], SDCC was attempted in five patients due to hemodynamic instability. In three patients, the procedure was not effective, whereas, in one patient, sinus rhythm was restored. However, AF recurred shortly afterwards; and in one case, a stable sinus rhythm was obtained. The effectiveness of electrical therapy may be improved by concomitant antiarrhythmic medication. When electrically cardioverting 24% of septic shock patients on amiodarone and 36% on propafenone, the overall rate of sinus rhythm maintenance was significant (74% and 89%, respectively) [51]. After an initially successful cardioversion, failure to remain in sinus rhythm may signal a poor prognosis.

6.2 Antiarrhythmic pharmacological therapy

6.2.1 Amiodarone

Amiodarone is a Vaughan-Williams class III antiarrhythmic drug that is frequently used to treat atrial fibrillation, both in community and ICU settings. It is currently approved for cardioversion of atrial fibrillation (Class I, level of evidence A) [52]. It is a highly lipophilic compound with a long half life, and it is eliminated by hepatic metabolism and not by dialysis [53]. Being one of the few antiarrhythmic drugs that does not affect significantly the left ventricular ejection fraction (LVEF), its use is however limited by the occasional occurrence of systemic hypotension and because of its relatively highly toxic profile, including thyroid, lung and liver dysfunction among other detrimental effects (eg, corneal microdeposits, skin discoloration and neuropathies).

Amiodarone success in terms of rhythm control in sepsis patients varies widely, from 30% [54] to 95% [55], although rates of sustained sinus rhythm after cardioversion are substantially lower. Comparative observational studies in ICU septic patients have shown that amiodarone achieved lower rates of rhythm control than beta-blockers, magnesium and calcium channel blockers [51, 54, 56].

Specific data on amiodarone effectiveness in septic shock patients is scant. Balik et al. [51] showed in a recent study on septic shock and supraventricular arrhythmias (AF being the most frequent encountered) that amiodarone was the drug of choice in 76% of patients, likely due to the hemodynamic instability of patients in septic shock on vasoactive agents. Restoration to sinus rhythm was achieved in 74% patients while 23.7% of them required additional electrical cardioversion. The median total dose of amiodarone was 3.0 (1.8–4.6) g, given by infusion over 4 (2–6) days with a median of 1.4 (0.9–1.8) g during the first day. Due to its limited efficacy to cardiovert and to maintain sinus rhythm (74%), the patients with a persisting arrhythmia were often switched to propafenone. Interestingly, in this study, successfully cardioverted patients (with either amiodarone, propafenone or

metoprolol) or those having chronic AF demonstrated not significantly lower ICU and 28-day, and 12-month mortalities compared to patients remaining in an acute onset arrhythmia.

In a retrospective review of adult medical or surgical ICU patients with septic shock and NOAF that received amiodarone (n = 239), Betthauser et al. [57] found that exposure to more than or equal to 2700 mg of amiodarone was positively correlated with longer ICU length of stay. The same investigators found that compared to non-septic shock patients, septic shock patients did not show significant difference in hemodynamic deterioration within 72 hours of intravenous amiodarone administration. Of 105 patients surviving hospital discharge, 29% continued receiving oral amiodarone at discharge.

6.2.2 Propafenone

Propafenone is a Vaughan-Williams class IC antiarrhythmic drug with some (but clinically limited) beta-blocking activity as a result of a structural similarity to beta-adrenoceptor antagonists [58]. Propafenone is currently approved and used frequently for cardioversion of atrial fibrillation (Class I, level of evidence A) [52]. However, since CAST (the Cardiac Arrhythmia Suppression Trial) [59] revealed that class IC antiarrhythmic drugs flecainide and encainide could increase the mortality risk when administered to patients with ventricular arrhythmias and coronary artery disease with significant left ventricular systolic dysfunction, current guidelines have restricted the recommendation of this class of drugs (including propafenone) to patients with NOAF who do not have structural heart disease [52].

The aforementioned study by Balik et al. [51], suggests that propafenone could be a drug of choice in septic shock patients with normal to moderately reduced LVEF. Propafenone was used in septic shock patients with NOAF as a primary antiarrhythmic in 17.5% of patients, but this figure rises to 33% if one takes into account the patients who were not able to cardiovert and maintain a sinus rhythm on amiodarone and then received propafenone. The observed cardioversion success rate was 86.1% at 24 h, although 35.5% needed additional SDCC to restore sinus rhythm. The success of cardioversion was significantly higher with propafenone than with amiodarone and almost the same as metoprolol (93%). The average propafenone dose was 670 (460–700) mg/day. Compared with amiodarone, propafenone use did not result in significantly lower ICU and 28-day mortalities, but was associated with a 12-month mortality benefit, although patients in propafenone group tended to have better LVFE at baseline and lower dose of vasopressor drugs (e.g., norepinephrine), likely reflecting more severe compromise of septic shock in the amiodarone group [34].

6.2.3 Beta-adrenergic blockers

Current guidelines recommend beta-blockers as first-choice drugs to control heart rate in AF patients with LVEF >40% (class I, level of evidence B) [52].

Autonomic dysfunction in septic shock may be accompanied by extreme tachycardia and high cardiac output. Tachycardia increases cardiac workload and myocardial oxygen consumption. In addition, shortening of diastolic relaxation time and impairment of diastolic function further affect coronary perfusion, contributing to a lower ischemic threshold. Although norepinephrine is the current recommended mainstay of treatment for sepsis-related hypotension, excessive adrenergic stress has multiple adverse effects including direct myocardial damage (e.g., takotsubo or stress cardiomyopathy and tachyarrhythmias), insulin resistance, thrombogenicity, immunosuppression, and enhanced bacterial growth [60].

Taken together, these mechanisms contribute to worsening of septic myocardial dysfunction and increased mortality [61].

The use of beta-adrenergic blockers has been proposed to mitigate the persistent sympathetic stimulation in septic shock patients, and this mechanism may in part be responsible of the observed improvement in prognosis. The production of cytokines may also be reduced with the consequent improvement in the metabolic dysregulation by means of reducing protein catabolism and by inhibiting gluconeogenesis [62]. On the other hand, using beta-blockers in septic shock patients is not without risks. Many patients with septic shock are already being treated with vasopressor and inotropic drugs, and treating them with beta-blockers can exacerbate hypotension and bradycardia promoting further hemodynamic instability [63].

In order to reduce the unnecessary load of catecholamines and the stimulation of their receptors, an easily titratable beta-blocker (e.g. esmolol or landiolol), may be safe in those patients who require vasopressor drugs in parallel for low systemic vascular resistance and hypotension. In an open-label, randomized single-center study (n = 154) by Morelli et al. [64], septic shock patients were assigned to receive a continuous infusion of esmolol titrated to maintain heart rate between 80/min and 94/min versus standard treatment. It was not specified how many of those patients had atrial fibrillation, so its main interest in this discussion relates to its tolerability, since traditionally it has been feared that betablockage in septic patients could result in hemodynamic deterioration. Nonetheless, the mean arterial pressure was maintained despite a marked reduction in norepinephrine requirements in the esmolol group. Also, stroke volume, systemic vascular resistance, and left ventricular stroke work indices were increased in the esmolol group. Noteworthy, it was shown that 28-day mortality was 49.4% in the esmolol group vs. 80.5% in the control group (adjusted hazard ratio, 0.39; 95% CI, 0.26 to 0.59; $p < 0.001$). These findings suggest that lowering of heart rate by esmolol allows better ventricular filling during diastole, hence improving stroke volume and thereby improving the efficiency of myocardial work and oxygen consumption.

Metoprolol is also well tolerated in septic shock patients with supraventricular arrhythmias. In septic shock patients with NOAF treated with intravenous metoprolol, Balik et al. [51] found that sinus rhythm was achieved in 92.3% patients with no additional electrical cardioversion. The median length of treatment was 5 (2–9) days, while the median intravenous metoprolol dose was 84 (48–120) mg/day.

A relatively new beta-blocker with high selectivity for beta1 receptors and a half-life of only 4 minutes, landiolol, has also been shown to be well tolerated in the critically ill for its limited negative inotropic effect and limited impact on blood pressure, as different Japanese teams of investigators have reported [65–67]. The use of low doses (5–10 mcg/kg/min) of landiolol is usually sufficient for the cardioversion of AF compared to controls. In sinus tachycardia, landiolol may prevent the occurrence of arrhythmias using an even lower dose (3–5 mcg/kg/min). In a multicenter, open-label, randomized controlled trial at 54 hospitals in Japan, in which 76 patients with sepsis or septic shock received intravenous landiolol and 75 patients were assigned to the control group, Kakihana et al. [68] found that Landiolol resulted in significantly more patients with sepsis-related tachyarrhythmia (55% vs. 33%, $p = 0.031$) achieving a heart rate of 60–94 bpm at 24 h and significantly reduced the incidence of new-onset arrhythmia. The investigators report that landiolol was also well tolerated, but should be used under appropriate monitoring of blood pressure and heart rate owing to the risk of hypotension in patients with sepsis and septic shock.

Balik et al. [34], based on studies on tachycardic patients with septic shock requiring catecholamine administration suggest the benefit of slowing heart rate by approximately 20%, but also warn that lowering heart rate below 100 per minute

by means of betablockage may result in a cardiac output inadequate to meet the systemic oxygen demands in septic shock. Appropriately powered, randomized, controlled multicenter trials are required to further clarify the role of beta-blockers in septic shock patients with NOAF.

6.2.4 Digoxin

Digoxin and other cardiac glycosides have been long used to treat patients with heart failure and cardiac arrhythmias, atrial fibrillation among the latter. However, in the last couple of decades, various clinical trials have resulted in limiting the role of digoxin in the management of atrial fibrillation [52]. Digoxin acts at a cellular level by inhibiting the sodium-potassium pump, increasing the calcium availability to the contractile apparatus. This results in an increase in cardiac contractility and slowing of cardiac conduction through the atrioventricular node [69].

There is paucity of data regarding the use of digoxin in septic shock patients with NOAF. In a retrospective cohort study of ICU patients (n = 38,159) by Quian et al. [70], the investigators found an incidence of NOAF rounding 9%. After adjusting for multiple variables, they found that in patients with NOAF the use of digoxin was associated with an increased risk of 90-day mortality (hazard ratio 1.23, 95% CI 1.10–1.39, $p < 0.001$), although the proportion of sepsis patients in this population was not specified.

6.2.5 Anticoagulation therapy

While many clinical trials have shown that warfarin therapy reduces the risk of thromboembolic complications in patients with AF, it has not been unequivocally proved that oral anticoagulants provide similar benefits in critically ill septic patients with AF without carrying a significant bleeding risk. So, a common dilemma arises when deciding which septic patients with AF should receive anticoagulation therapy [71]. Walkey et al. [72] studied the practice patterns of anticoagulation in 38,582 septic patients with AF. They found that more than a third (35.3%) of the patients were anticoagulated with intravenous heparin or subcutaneous enoxaparin, while the rest of the patients did not receive anticoagulants. In those who did, significant bleeding was more frequently observed (8.6% vs. 7,2%, RR 1.21). Interestingly, there was no significant difference in the risk of ischemic stroke between anticoagulated and non-anticoagulated patients (1.4% vs. 1.3%, RR 0.94, CI 0.78–1.12). Furthermore, there was no difference in the risk of ischemic stroke between patients with preexistent AF and those with NOAF (RR, 1,12).

In a retrospective observational study to assess the incidence of stroke and anticoagulation-related complications (e.g., bleeding, heparin-induced thrombocytopenia) in AF patients with severe sepsis (n = 115), Darwish et al. [71] found no statistically significant difference in survival rates during their hospitalization (66.2% [53/80] in the non-anticoagulated group versus 74.3% (26/35) in the anticoagulated group, P = 0.392). There were no reports of strokes in either arm of the study, but this finding is at least in part explained by the small number of patients and the short period of time used for assessment. Up to date, prospective, comparative robust evidence for anticoagulation in septic shock patients is lacking.

6.2.6 Corticosteroid therapy

Due to its anti-inflammatory properties, low-dose hydrocortisone has been frequently used to achieve shock reversal and better outcomes in patients with septic shock [73]. However, after extensive review of the available evidence, the

Surviving Sepsis Campaign's guidelines restricted the use hydrocortisone in shock septic patients only when fluid resuscitation and vasopressor drugs failed to restore hemodynamic stability [74]. In a recent multicenter, prospective nonrandomized observational study in 261 septic shock patients, Launey et al. [75], a atrial fibrillation developed in 33 (24%) and 24 (19%) of no-hydrocortisone patients and hydrocortisone patients, respectively. In the weighted sample, the proportion of patients who developed AF was 28.8% in the nohydrocortisone group and 16.8% in the hydrocortisone group (difference: 11.9%; 95% confidence interval: 23.4% to 0.5%; $p = 0.04$), noting that patients who received hydrocortisone were more severely ill than those who did not receive hydrocortisone. Investigators conclude that low-dose hydrocortisone was associated with a lower risk of developing AF during the acute phase, although serious risk of bias due to missing covariates in the propensity score matching has to be taken into account.

7. Conclusions

AF during septic shock has been insufficiently studied. This has led to relevant uncertainties regarding its etiology, pathophysiology and appropriate management. Risk factors for chronic AF and NOAF frequently differ, and the unique pathophysiology of NOAF remains to be fully elucidated. Despite of a high probability of successful cardioversion achieved by pharmacological or electrical means, these treatment modalities have shown modest efficacy in affecting the medium and long-term prognosis of septic shock patients with AF. The benefits of anticoagulation in shock septic patients with AF have not been firmly established, while the risk of bleeding is increased in septic patients. Evidence-based guidelines and even expert consensus documents on the subject of NOAF management are lacking. Properly designed multicenter, prospective randomized trials are needed to clarify these questions.

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