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When Rhythm Changes Cause the Blues: New-Onset Atrial Fibrillation during Sepsis

During the past decade, atrial fibrillation (AF) has become increasingly recognized as a complication of sepsis (1–4). Multiple physiological changes during sepsis (1, 5, 6) interact to generate an atrial substrate vulnerable to AF, resulting in more than a sixfold (2) greater risk for developing AF during sepsis compared with other reasons for hospitalization. Only postoperative patients have similarly high risks for development of new-onset AF (7). However, evidence-based guidelines support interventions to prevent postoperative AF (8), whereas few approaches have been developed to guide the prevention or management of AF in the context of sepsis.

If development of AF results in worse sepsis outcomes, then prevention of AF during sepsis represents a logical clinical goal. Administrative claims data suggest that patients who develop AF during sepsis generally do not have a high burden of cardiovascular comorbidities associated with risk of "conventional" AF (9), but nearly one-half of patients with new-onset AF during sepsis experience recurrent AF after hospital discharge (10). Thus, prevention of AF during sepsis may avoid entrainment of the arrhythmogenic pathways that lead to chronic AF and its complications in patients who otherwise might have been at low risk for development of AF. Further evidence supporting a role for AF in contributing to poor sepsis outcomes generally comes from studies that used administrative claims data (2), but characterization of the clinical course of sepsis using claims data is limited. Whether AF is merely an epiphenomenon of acute sepsis severity without a role for modifying outcomes, or can directly worsen sepsis, has thus far been unclear (11).

The study by Klein Klouwenberg and colleagues in this issue of the *Journal* (pp. 205–211) attempts to address two barriers to the study of clinical implications of new-onset AF during sepsis (12). First, few studies have evaluated the changing severity of illness at the time of AF onset. If sepsis worsened immediately before AF onset, then studies might spuriously attribute poor sepsis outcomes to AF, rather than preceding physiological deterioration. Second, studies have not been designed to prevent AF during sepsis and assess for associations between AF avoidance and mortality reduction. Trials seeking to prevent AF during sepsis would be most feasible if enriched through enrollment of patients at high risk for developing AF, but the incidence and risk factors for AF during sepsis might have been incompletely characterized in previous studies using claims data (9).

Klein Klouwenberg and colleagues (12) used daily, prospective, detailed electronic medical record data collected from 1,782 adult intensive care unit (ICU) patients to characterize patients with sepsis and new-onset AF at two centers in the Netherlands. New-onset AF was found to occur among 23% of patients with sepsis, which was a twofold higher incidence than previous estimates from claims data (9), with increasing rates as sepsis severity increased (40% of patients with septic shock had an episode of new-onset AF). Not surprisingly, initial episodes of AF resulted in significantly increased heart rates and lower mean arterial pressures. Nearly all patients received treatment directed at rate or rhythm control after the initial episode of AF, most commonly amiodarone. Despite treatment, most patients had recurrence of AF. Findings of altered hemodynamics immediately after AF onset support the hypothesis that AF may contribute to poor outcomes during sepsis, potentially through lower cardiac output, decreased organ perfusion, and increased risk of organ dysfunction.

In addition to physiological decompensation and treatment changes, new-onset AF during sepsis was associated with increased ICU mortality. Specifically, development of AF during sepsis was associated with a twofold increased risk of cumulative ICU mortality and a 50% increased daily risk of dying in the ICU. Cumulative mortality risks were greater than daily risks due to the fact that AF was also associated with increased ICU length of stay. Importantly, the authors adjusted not only for baseline sepsis severity, but also for changing disease severity immediately before AF onset, and did not find different results. These findings provide further support for the hypothesis that AF does not result from clinical deterioration, but rather, induces deterioration.

To promote follow-up studies that evaluate interventions to prevent AF during sepsis, the authors derived and validated a risk

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score for AF. Similar to previous studies that used claims data, many of the cardiovascular comorbid characteristics generally associated with increased risk for development of AF in the community were not associated with risk for AF during sepsis (9). Clinical factors associated with AF onset included older age, obesity, immunocompromised state, acute organ failures, serum potassium (a U-shaped relationship), higher oxygen requirements, inflammation (high C-reactive protein or leukocytosis), and fewer days since ICU admission. The risk model performed well in discriminating patients who did and did not develop AF and was well calibrated in a contemporary validation cohort. The authors offer a helpful online tool to calculate patients' risks for developing AF during sepsis. Strengths of the risk score include a parsimonious model with good predictive ability and few missing variables used in the construction of the score.

Unlike previous studies, the authors used statistical models that accounted for the "immortal time bias" that exists in patients before AF onset; patients who developed AF during sepsis had to be alive to develop AF, whereas patients without AF could have died before AF. Immortal time bias would falsely reduce the observed mortality risks associated with AF. In addition, the authors used appropriate statistical models that accounted for the competing risks of discharge from the ICU and analyses that accounted for potential changes in disease severity before AF onset. The authors are to be congratulated for their detailed data collection and robust analytic approaches, which reduced the likelihood that the observed association between AF and death was due to other factors.

Some limitations should be considered in any evaluation of observational research, such as potentially unmeasured confounding variables and misclassified data. The prospective data collection used in the current study may attenuate, but not prevent, some of these issues. Other limitations to note include a lack of racial diversity in the Dutch cohort. European ancestry is strongly associated with AF susceptibility (2, 9, 13), a factor that may influence estimates of AF incidence, risk factors, and generalizability of study results to other populations. As recommended by the authors, the risk score should be validated in additional cohorts.

The study by Klein Klouwenberg and colleagues (12) expands upon previous retrospective or claims data-based studies with a robust, prospective analysis of AF during sepsis. We now have a greater understanding that new-onset AF during sepsis represents a common, and potentially modifiable, risk factor for poor outcomes during and long after sepsis. However, Klein Klouwenberg and colleagues not only present a problem, but also show a potential way forward for future research. Although validation in other cohorts is needed, we will soon be able to use predictive models like those constructed by Klein Klouwenberg and colleagues to identify and study patients at highest risk for development of AF during sepsis. We now look forward to randomized trials that can assess different strategies for AF prevention in these high-risk patients, which can potentially discover novel avenues to meaningfully improve outcomes for many patients with sepsis. ■

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