Atrial fibrillation substrate development before, during and after cardiac surgery

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Editorial

Atrial fibrillation substrate development before, during and after cardiac surgery: Who is to blame for late post-operative atrial fibrillation?

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Postoperative atrial fibrillation (POAF) is defined as new-onset atrial fibrillation (AF) occurring immediately after cardiac or non-cardiac surgery. POAF is a common complication after cardiac surgeries, occurring in 20–50% of patients [1,2]. POAF is usually asymptomatic and self-terminating with peak incidence 2–4 days after interventions [1]. However, POAF predisposes to adverse acute outcomes including hemodynamic instability, prolonged hospitalization, larger healthcare costs and higher in-hospital mortality [1,3]. In addition, accumulating data suggest that patients with POAF suffer from higher risks of recurrent AF, stroke and long-term mortality [3,4]. As such, POAF is a growing clinical concern but its basic mechanisms and therapeutic implications remain poorly understood.

The current conceptual framework for POAF is based on the interaction between transient surgery-related triggers and proarrhythmic atrial substrates produced by pre−/intra-operative remodeling [2,5]. In patients without a history of prevalent AF, the pre-existing atrial substrate is insufficient to elicit AF, but in the presence of surgery-related triggers, including activation of the sympathetic nervous system and inflammation, POAF may clinically manifest (Fig. 1). In agreement, proarrhythmic pre-existing structural remodeling, primarily in the left atrium (LA), has been observed in atrial samples of patients with subsequent POAF [2,6]. By contrast, reentry-promoting ionic remodeling appears to be absent and the atrial effective refractory period is largely unaffected in patients subsequently developing POAF. However, these patients exhibit pre-existing calcium-handling abnormalities [7,8] and upregulation of the NLRP3-inflammasome, potentially predisposing to stronger proarrhythmic responses to post-operative inflammation [8].

In this issue of the *International Journal of Cardiology*, Van Schie et al. [9] provide novel *in vivo* data supporting the presence of a pre-operative vulnerable functional substrate in patients that subsequently develop POAF. In this study, 263 patients with complete 5-year follow-up or persistent AF after cardiac surgery were included. Systematic epicardial high-resolution mapping was performed for every patient before extracorporal circulation in order to analyze the pre-operative electrophysiological characteristics in the LA, right atrium (RA), pulmonary vein area (PVA) and Bachmann's bundle (BB). Of these 263 patients, 82 patients (31%) developed early POAF (E-POAF; occurring ≤5 days after intervention), and 15 of these patients (6% of the total population) developed both E-POAF and late POAF (L-POAF, occurring >5 days after surgery). Patients who developed POAF had significantly lower conduction velocity, lower voltage, higher prevalence of conduction block and larger low-voltage areas compared with those who remained in sinus rhythm. The pre-existing atrial substrates were more severe in patients with L-POAF compared to those developing E-POAF only. Of note, electrophysiological differences were primarily present at BB, followed by LA and RA, without differences in PVA, suggesting significant spatial heterogeneity of the pre-existing atrial substrates.

These functional measurements elegantly support the notion that POAF is the product of the interaction between pre-existing proarrhythmic substrates and transient triggers, and raise a number of interesting questions. Firstly, the pathophysiological factors underlying the pre-existent substrate remain unclear. The previously reported fibrosis in patients developing POAF [2,6] likely contributes to the observed LA conduction abnormalities [9], but divergent data exist on RA structural remodeling [2,6] and no data are available from other regions due to limitations in human atrial tissue availability. Interestingly, calcium-handling abnormalities have been implicated in atrial conduction abnormalities in the setting of catecholaminergic polymorphic ventricular tachycardia [10], suggesting that the calcium-handling abnormalities present in patients that subsequently develop POAF [7,8] might also contribute to the observed conduction abnormalities [9,11]. Secondly, the clinical factors contributing to the

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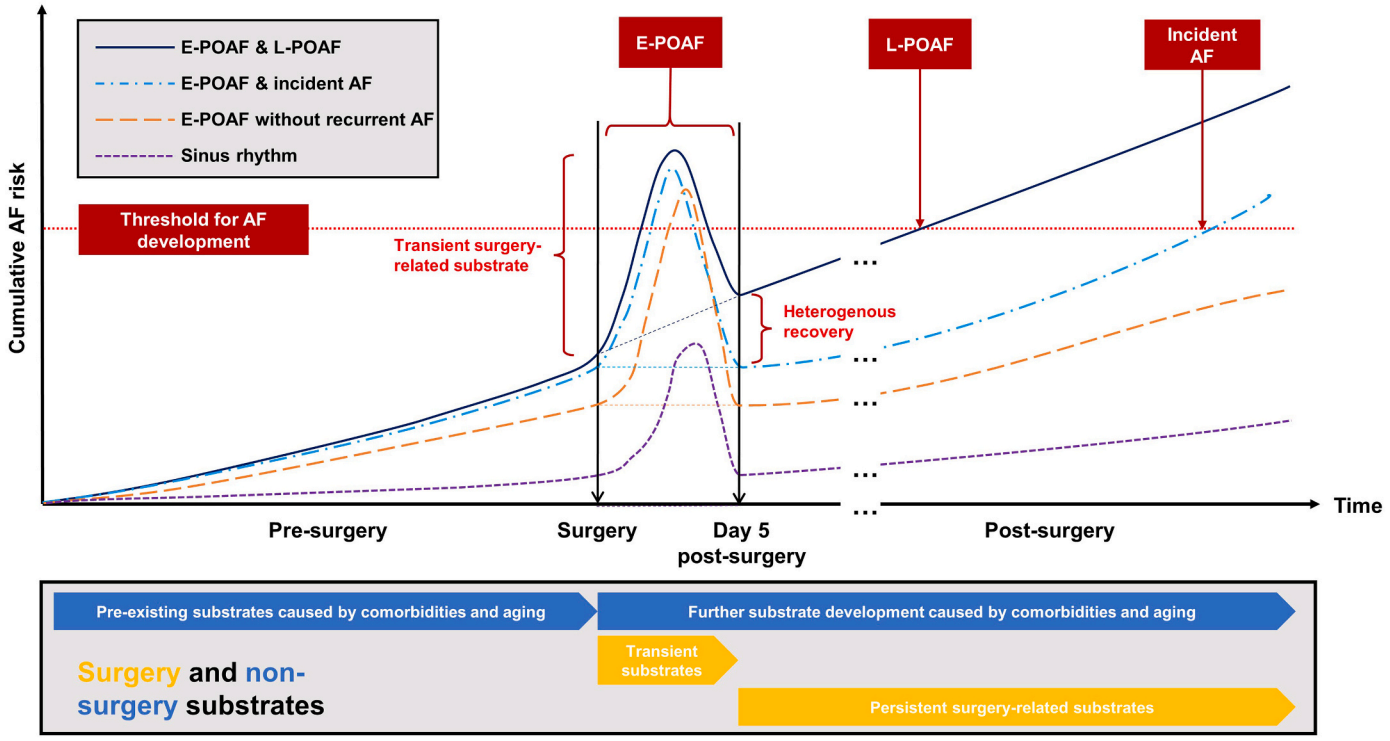

Fig. 1. Timeline and sources of substrate evolution for the development of atrial fibrillation (AF) before, during and after cardiac surgery. Early post-operative AF (E-POAF) requires a pre-existing vulnerable substrate resulting from aging and comorbidities and a transient surgery-related exacerbation. Substrate recovery after surgery is heterogeneous and an incomplete recovery may produce a persistent surgery-related substrate that predisposed to late POAF (L-POAF). Alternatively, even with a completely transient surgery-related substrate, incident AF may occur as a result of substrate progression due to aging and prolonged presence of comorbidities.

proarrhythmic substrate are largely unknown. Patients developing POAF commonly have more comorbidities and are typically older than those who do not [2]. In agreement, age was the only independent factor associated with POAF in multivariable analysis in the study by Van Schie et al. [9], suggesting that the observed conduction abnormalities may be age dependent. However, whether this is due to age-dependent remodeling, or due to a longer timeframe for comorbidity-related remodeling in older individuals is unknown. Although this is a large cohort of patients for such extensive high-density cardiac mapping before surgery, more studies with larger sample size will be needed to validate electrophysiological differences between E-POAF and L-POAF and assess the role of individual comorbidities. Ideally, this should be combined with continuous monitoring to avoid missing potential cases of L-POAF [12].

Perhaps the most intriguing aspect of the study by Van Schie et al. [9] is the nature of L-POAF. In particular, almost half of L-POAF episodes occurred >2 year after the surgery and one can question whether the occurrence of such AF episodes is actually influenced by the preceding surgery. Conceptually, there are two types of patients: those in whom the surgery-related risk is transient, who may develop new-onset AF post-surgery because of progression of the pre-existing substrate, and those in whom there is a persistent effect of the surgery on the substrate that contributes to late AF occurrences (Fig. 1). The difference between the two patterns of AF recurrence may be highly clinical-relevant. For example, additional preventive management or treatment may be needed post-surgery to reduce atrial substrates and flatten the AF-risk curve for patients who would not recover fully and go on to develop L-POAF. Conversely, patients with a fully transient post-operative substrate may benefit more from general risk-factor management to prevent substrate progression and incident AF. Distinguishing these different patient subgroups will be challenging due to limited options for direct measurement of atrial substrates after termination of E-POAF or during the peri-operative period. Van Schie et al. [9] provide arguments for both components: All L-POAF episodes occurred in patients with E-POAF, suggesting that the surgery could have a strong (and potentially lasting) effect on the vulnerable substrate. On the other hand, patients with L-POAF also had more pre-existing remodeling, suggesting that their substrate might already be much closer to the threshold for developing AF, independent of surgery-related triggers. Systematic invasive cardiac mapping in all future patients to assess the extent of the vulnerable substrate is clearly not feasible. However, a better understanding of the type of remodeling, as provided by the current study, may suggest novel, non-invasive biomarkers to characterize the pre-operative substrate in an individual patient. The latter should be molecularly validated in atrial samples from patients undergoing open-heart surgery and subsequently develop POAF.

Taken together, the interesting work by Van Schie et al. [9] strongly supports the notion that POAF is not a separate disease entity, but, like all forms of AF, depends on a pre-existing substrate and acute triggers. This concept has potential implications for the treatment of these patients and suggests that further refinement of the term L-POAF may be needed. The study furthermore provides novel insight into the characteristics of the pre-existing substrate as well as its spatial heterogeneity. Undoubtedly, these insights cover just the tip of the iceberg of POAF pathophysiology. A deeper understanding is expected to significantly improve the management of POAF.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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