IJC Heart & Vasculature 32 (2021) 100693

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Commentary

Surgery-related cardiac stress: A susceptibility test of late atrial fibrillation recurrence?

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Atrial fibrillation (AF) is a highly prevalent arrhythmia, with substantial associated morbidity and mortality. Contemporary therapeutic approaches have many limitations, including limited efficacy and significant adverse-effect potential for antiarrhythmic drugs [1], risk of bleeding complications with anticoagulants [2], and recurrences and potential complications for AF-ablation [3]. The complexity and progressive nature of the arrhythmic substrate is a major problem limiting long-term successes [4]. AF is also increasingly considered as the consequence of a progressive atrial cardiomyopathy [5,6], with a better understanding of the mechanisms underlying AF-promoting progressive atrial cardiomyopathy being expected to improve both our understanding and ability to develop novel therapeutic approaches.

AF is a frequent complication after both cardiac and non-cardiac surgeries. Post-operative atrial fibrillation (POAF), defined by the documentation of new-onset AF within 96 h after surgery, occurs in approximately 30–50% of patients after cardiac surgery, 10–30% after non-cardiothoracic surgery and in 5–10% after vascular or large colorectal surgery [7]. Moreover, recurrence of AF following non-cardiac surgery is a common but rarely detected complication [8]. Many episodes of POAF are self-terminating and some are asymptomatic. Although POAF was considered as a benign and transient condition with limited long-term clinical significance, there is accumulating evidence that POAF is clearly associated with higher risk of stroke, bleeding, hemodynamic instability, prolonged hospitalization and death compared with non-postoperative AF patients [7]. Most important, a large registry by Butt et al. showed that new-onset POAF following non-cardiac surgery was associated with a long-term risk of thromboembolism similar to common clinical AF [9]. In addition, in a recent meta-analysis of 28 studies assessing adverse outcomes associated with POAF following non-cardiac surgery, the associated risk of stroke after POAF seemed to be even higher after non-thoracic compared with thoracic surgery [10]. These data demonstrate that some patients are susceptible for POAF after both cardiothoracic and non-cardiothoracic surgery likely because they have a silent arrhythmogenic atrial substrate before surgery that is unmasked by perioperative related triggering events. This notion has important clinical implications because it suggests that patients susceptible for POAF already have some sort of atrial cardiomyopathy, which is expected to promote future AF recurrences ultimately leading to the evolution of common clinical AF. The presence of silent atrial cardiomyopathy also likely explains the increased rate of AF patients during COVID-19 pandemic. Patients with newly diagnosed AF may have a pre-existing substrate for AF and the acute COVID-19 infection may provide the trigger for AF initiation [11].

POAF has been associated with a five- to twelve-fold risk of recurrent AF in the next years following cardiac surgery, while the long-term risk of AF recurrence after non-cardiac surgery is poorly defined [7]. Of note, the Framingham Heart Study found a higher AF-recurrence rate in patients with POAF after non-cardiothoracic compared to cardiothoracic surgery (64% vs 47%) [12], which may be due to differences in severity of pre-existing atrial cardiomyopathy, which creates a vulnerable substrate for AF, which is unmasked by surgery-induced triggers. In agreement, we recently identified molecular evidence for the presence of a pre-existing subclinical atrial cardiomyopathy that predisposes POAF-patients to AF development. Pre-existing Ca^{2+}-handling abnormalities and activation of NLRP3-inflammasome/CaMKII signaling are evident in atrial cardiomyocytes from patients who subsequently develop POAF [13]. Despite the presence of abnormalities in patients destined to manifest POAF, none of these patients had manifested clinical AF, indicating that these abnormalities were insufficient in themselves to generate AF. It appears that the pre-existing atrial cardiomyopathy determines which atria will cross the AF threshold, initiating POAF, when acted upon by post-operative triggers. In particular, post-operative inflammation can exacerbate pre-existing atrial abnormalities, promoting the formation of delayed afterdepolarizations that can lead to POAF. Combined these findings provide a novel unifying paradigm that

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https://doi.org/10.1016/j.ijcha.2020.100693

POAF patients share a common atrial cardiomyopathy with patients with common forms of AF, predisposing POAF-patients to both POAF caused by transient surgery-induced inflammation (explaining the usually self-limited nature of POAF) and to long-term AF (explaining the predilection for recurrence) [13]. Clearly, much more work is needed to detect and precisely define the nature of this silent atrial cardiomyopathy and its causal and mechanistic contribution to new-onset POAF and its late recurrences.

A number of risk scores were developed to predict POAF, albeit with limited applicability [14]. Their limited predictive value might reflect the fact that the risk factors and the associated atrial cardiomyopathy are itself insufficient to cause POAF in the absence of appropriate triggers. Therefore, the surgery-induced stress likely identifies a subset of patients with propensity to develop clinical AF providing some sort of "susceptibility test" for long-term recurrence of AF [15]. Interestingly, in our previous study [13], no differences between patients with POAF and postoperative sinus rhythm were noted for sex, body-mass index, comorbidities and echocardiographic parameters including left atrial diameter, degree of valvular regurgitation, and left-ventricular ejection fraction. The only difference was older age and renal function, which suggests that these two factors could play an important role in the evolution of the pro-arrhythmic atrial substrate. Interestingly, the NLRP3 inflammasome, which appears a key player in the development of the arrhythmic substrate for POAF, is hyperactive in aged individuals [16], and its attenuation prevents adverse cardiac remodelling in a rat model of chronic kidney disease [17], which further highlights the importance of the NLRP3 system for the development of an AF-promoting substrate. A better understanding of the mechanisms of intra- and postoperative transient AF triggers interacting with pre-existing atrial substrate might lead to the identification of new therapeutic targets for POAF prevention and its late recurrences.

Funding sources

The authors research is supported by grants from the National Institutes of Health (R01HL136389, R01HL131517 and R01HL089598 to D.D.), the German Research Foundation (DFG, Do 769/4-1 to D.D.), and the European Union (H2020, MAESTRIA to D.D.).

Declaration of Competing Interest

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

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