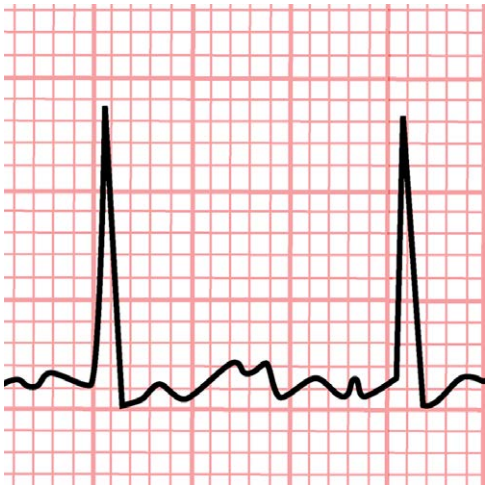
Inflammatory Responses to Surgery and Postoperative Atrial Fibrillation

Sergey Karamnov, M.D., Jochen D. Muehlschlegel, M.D., M.M.Sc., M.B.A.

Postoperative atrial fibrillation is one of the most common complications after thoracic noncardiac surgery. Despite contemporary prevention strategies, the rate of this complication can be as high as 40% in high-risk patients. Certain patient characteristics, including hypertension, obesity, smoking, male sex, and Caucasian ancestry, are known risk factors. Emerging evidence suggests that postoperative atrial fibrillation is not a transient benign phenomenon but rather an ominous postoperative complication associated with increased risk of thromboembolism, stroke, and mortality. Excessive inflammation associated with both tissue and extracellular free radical oxygen–mediated injury resulting from operative insult is thought to be an important contributing factor in postoperative atrial fibrillation pathophysiology. Anti-inflammatory strategies have been investigated for postoperative atrial fibrillation prophylaxis and demonstrated variable success.



"…postoperative atrial fibrillation is not a transient benign phenomenon but rather an ominous postoperative complication associated with increased risk of thromboembolism, stroke, and mortality."

In this issue of Anesthesiology, Amar *et al.*[1] studied the effect of *N*-acetylcysteine, a known antioxidant and free radical scavenger, as a prophylactic measure for postoperative atrial fibrillation after thoracic noncardiac surgery. The authors conducted a double-blind trial to compare amiodarone and the combination of amiodarone and *N*-acetylcysteine on the incidence of postoperative atrial fibrillation and postoperative stroke. They also examined postsurgery samples for serum markers indicative of systemic inflammation. No statistically significant differences were uncovered between the two patient groups in rates of postoperative atrial fibrillation or postoperative stroke or in the serum markers of ongoing inflammation. The study has been stopped in the interim analysis due to futility.

What could be a potential reason for no demonstrated benefits? The concept of atrial fibrillation being mediated by free radicals generated in the inflammatory milieu has not been clearly demonstrated in thoracic noncardiac surgery patients; therefore, *N*-acetylcysteine may not be an effective medication for these patients. An anti-inflammatory approach to postoperative atrial fibrillation is not a novel idea. A wide variety of medications with documented anti-inflammatory properties have been investigated for postoperative atrial fibrillation prophylaxis. Steroid and nonsteroid anti-inflammatory agents, ω-3 polyunsaturated fatty acids, inhibitors of the renin–angiotensin system, statins, and immunosuppressants demonstrated some success in human trials and animal models.[2] However, side effect–related considerations and a lack of strong reproducible benefits resulted in limited applications of anti-inflammatory agents in clinical practice. In fact, anti-inflammatory agents are not included in the most recent postoperative atrial fibrillation prophylaxis guidelines[3] and practice advisories[4] for cardiac and thoracic noncardiac patients.

Moreover, anti-inflammatory strategies *per se* may not be the ideal therapeutic direction to pursue. Inflammation entails way more than simply insult-triggered free radical

Image: J. P. Rathmell.

This editorial accompanies the article on p. 916.

Accepted for publication March 30, 2022.

Sergey Karamnov, M.D.: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Jochen D. Muehlschlegel M.D., M.M.Sc., M.B.A.: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

 Anesthesiology 2022; 136:877–9. DOI: 10.1097/ALN.0000000000004233

<zdoi;. DOI: 10.1097/ALN.0000000000004233>

formation and subsequent tissue damage. In fact, an acute inflammatory response is a host-protective, actively regulated, and, most importantly, normally self-regulating self-limiting process *in vivo*. Specifically, the onset of acute inflammation triggers production of signal molecules, such as specialized proresolving lipid mediators. Specialized proresolving lipid mediator networks serve as a link between mechanisms governing the onset and resolution of inflammation, resulting in insult mitigation, tissue healing, and restoration of homeostasis.[5] In contrast, uncontrolled inflammation and specialized proresolving lipid mediator production dysregulation may lead to excessive tissue damage, chronic inflammation, and deterred recovery as demonstrated in human and animal models.[6,7]

An anti-inflammatory approach for postoperative atrial fibrillation seems like a plausible strategy for postoperative atrial fibrillation prophylaxis. The documented association between postoperative atrial fibrillation and elevated serum concentrations of interleukin-6 and C-reactive protein, as well as higher postoperative leukocyte counts, suggests that inflammation may play an important role in the natural history of postoperative atrial fibrillation. This is further supported by the association between inflammatory conditions of the heart, such as myocarditis and pericarditis, and common atrial fibrillation. Exacerbated arrhythmogenicity of cardiac myocytes by elevated concentration of inflammatory markers due to the stresses of surgery is the likely mechanism of postoperative atrial fibrillation in susceptible patients.

More specifically, in thoracic noncardiac surgery, operative insult–related inflammation is triggered by a variety of different pathways related to one-lung ventilation, which is commonly exercised to facilitate the approach. First, ventilator-induced lung injury is a recognized complication after one-lung ventilation. The ventilated lung is subjected to oxidative stress and hyperemia-related capillary shear stress. Volutrauma due to increased, nonphysiologic tidal volumes and loss of the normal functional residual capacity further exacerbate lung injury.[8] Second, surgical insult itself results in additional mechanical tissue damage and subsequent local inflammation. Third, atelectasis in the nonventilated lung leads to hypoxic pulmonary vasoconstriction and local tissue ischemia. Lung reexpansion and oxygen reentry at the conclusion of one-lung ventilation result in reactive vasodilation and reperfusion. The resulting dissemination of inflammatory markers and oxygen free radicals generated by pulmonary parenchyma, one of the largest natural reservoirs of inflammatory cells, accelerates the systemic effects in target organs. Further work is needed to understand whether these mechanical insults during thoracic surgery are modifiable risk factors that can be attenuated with anti-inflammatory medications or whether they will require other therapeutic strategies, such as changes in ventilatory management.

So why did anti-inflammatory approaches demonstrate success after cardiac but not noncardiac thoracic surgery? Some key differences in cardiac and thoracic noncardiac surgeries may play a role. First, cardiopulmonary bypass utilized during cardiac surgery and the related inflammatory response have been implicated in the pathogenesis of postoperative atrial fibrillation in cardiac surgery patients. Systemic inflammation triggered by cardiopulmonary bypass and massive release of proinflammatory markers is thought to alter cardiac myocyte conduction. The degree of inflammatory response due to cardiopulmonary bypass likely supersedes the one due to one-lung ventilation during noncardiac surgery. In fact, the inflammation pathophysiology of nonventilated lungs applies to both lungs during cardiac surgery with cardiopulmonary bypass. The importance of an anti-inflammatory approach in cardiac surgical patients was recently addressed by Gaudino *et al.*[9] In this study, prophylactic intraoperative decompressive pericardiotomy to offset postoperative inflammation and swelling resulted in a lower incidence of postoperative atrial fibrillation. This study underscores the value of nonpharmacologic approaches to postoperative atrial fibrillation prevention and the value of multimodal therapy. Second, mechanical surgical insult to the myocardium triggers local inflammatory effects in the conduction system itself, contributing to increased incidence of postoperative atrial fibrillation after cardiac surgery. In contrast, postoperative atrial fibrillation after thoracic noncardiac surgery is thought to be triggered by a variety of different factors, such as dysregulation of the autonomic nervous system, age-exacerbated fibrosis, acute atrial stretch, and local pericarditis.[3] Much less is known about the role of local *versus* systemic tissue inflammation in the pathogenesis of postoperative atrial fibrillation after noncardiac thoracic surgery.[10] This may explain, at least in part, the scarce success of anti-inflammatory strategies for postoperative atrial fibrillation prevention in these patients. Similarly, despite the well documented effect of *N*-acetylcysteine on proinflammatory cytokines and oxygen free radicals on ischemia–reperfusion injury, as well as some success in cardiac surgery patients, the utility in postoperative atrial fibrillation prevention in thoracic noncardiac surgery patients may be limited.

In conclusion, the work of Amar *et al.*[1] demonstrates the feasibility and safety of *N*-acetylcysteine administration in this patient population. However, the study, which was stopped early at the interim analysis because of futility, discovered no additional benefit for the prevention of postoperative atrial fibrillation and its complications when compared to a conventional approach. Nevertheless, the emerging evidence of the long-term negative implications of postoperative atrial fibrillation that is further magnified by the unacceptably high rate of this complication calls for novel prophylactic strategies. The restoration of normal inflammatory pathways could be one of the potential therapeutic approaches for postoperative atrial fibrillation. Future

investigations can be directed at further elucidating the role of inflammation in the pathophysiology and pathogenesis of postoperative atrial fibrillation after thoracic noncardiac surgery to determine therapeutic targets.

Research Support

Supported by National Institutes of Health (Bethesda, Maryland) grant No. R01HL149998 (to Dr. Muehlschlegel).

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Muehlschlegel: jmuehlschlegel@bwh.harvard.edu

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