## Editorial / *Editöryal Yorum*

# Postoperative atrial fibrillation and oxidative stress

## Ameliyat sonrası atriyum fibrilasyonu ve oksidatif stres

**Dursun Aras, M.D., Özcan Özeke, M.D.**

Department of Cardiology, Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara

Postoperative atrial fibrillation (POAF) is the most common arrhythmia associated with coronary artery bypass graft (CABG) surgery and is an important factor contributing to postoperative morbidity and mortality. While its pathogenesis is multifactorial, increasing evidence supports that inflammation and oxidative stress[1] caused by ischemia-reperfusion during cardiac surgery may play an important role in the pathogenesis of POAF.[2]

In the current issue of the Archives of the Turkish Society of Cardiology, Oktay et al.[3] reported on the role of oxidative stress related with ischemia-reperfusion damage on the pathogenesis of POAF after elective isolated on-pump CABG surgery. In this study, the authors measured the levels of plasma total oxidative status (TOS) after replacement and removal of aortic cross-clamping (ACC) in the jugular vein samples obtained from 118 consecutive patients who underwent isolated on-pump CABG. During the postoperative period, POAF was detected in 31% of the patients (POAF group), and the remaining 69% of patients in sinus rhythm were followed as the control group. Patients in the POAF group were older in age, had a lower hematocrit level and an enlarged left atrium diameter compared to the control group. While differences in the plasma TOS levels taken after replacement and removal of ACC were observed to be statistically significant in the POAF group (13 to 30, p=0.001), this difference was not statistically significant in the control group (14 to 24, p=0.060). Postoperative length of hospital stay (both in intensive care unit and in total hospital stay) was longer in the POAF group compared to the control group. In multivariate logistic regression analysis, aging (odds ratio (OR): 1.050, p=0.030), hematocrit level (OR: 0.718, p=0.025), pump temperature (OR: 1.445, p=0.020), and plasma TOS level (OR: 1.040, 95% confidence interval (CI): 1.020-1.050, p=0.040) were found to be independent predictors of POAF. Based on these observations, the authors proposed that the ischemia-reperfusion damage related with ACC replacement may be an important factor in the pathogenesis of POAF.

The potential role of oxidative stress in the initiation and maintenance of AF is becoming increasingly recognized. A growing body of evidence points toward an important role of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the release and activation of inflammatory markers and the stimulation of pro-fibrotic cascades during ischemia and post-ischemic reperfusion in humans.[1] At least three enzymatic pathways are involved in up-regulating the production of ROS, contributing to structural and functional remodelling in AF, namely myeloperoxidase (MPO), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and "uncoupled" nitric oxide synthase (NOS); over-expression of these enzymes has been detected in the atria in experimental and clinical models of AF.[2] In particular, atrial NADPH oxidase

*Correspondence:* Dr. Dursun Aras. Türkiye Yüksek İhtisas Hastanesi, Kardiyoloji Klinigi, 06100 Ankara, Turkey
Tel: +90 312 - 306 10 00 e-mail: drdaras@gmail.com

has emerged as a potential enzymatic source for ROS production in POAF based on growing evidence from clinical and experimental studies, suggesting that this oxidase system may be a key mediator of atrial oxidative stress, leading to the development of POAF.[4]

The earliest observed change in AF is an abbreviation of the atrial effective refractory period (ERP), and there is a correlation between oxidative stress and atrial ERP shortening.[1] The electrophysiological remodeling is thought to be related to the generation of ROS, RNS and inflammatory factors during the ischemia-reperfusion phase of cardiac surgery. Non-uniform or heterogeneous atrial refractoriness provides the substrate for development of POAF. In particular, the pulmonary veins (PVs) are of major interest as a result of their prominent arrhythmogenic role in AF. The limited mapping studies in patients during open heart surgery and during electrophysiologic studies using endocardial catheter electrodes are most consistent with the concept of a driver, seemingly most often a focus in or near one or more of the PVs, precipitating and maintaining AF.[5] Some studies have indicated that an electrophysiological substrate within the PVs allows reentry due to heterogeneous refractory periods and decremental conduction. However, while the importance of ectopic foci from the PVs for the initiation of POAF is not currently known, the reduced ERP shortens the depolarizing wavelength, promoting reentry, and has been shown to precede the development of POAF,[6] suggesting that these cellular electrophysiologic alterations might contribute to the arrhythmia substrate and might represent targets for preventive therapy. This mechanism is of interest, however, in light of data showing a relationship between left ventricular venting through the PVs and POAF in high-risk patients.[7] It would be useful to discuss whether there was such as a relationship in the current study.

Although POAF can occur at anytime after surgery, it tends to occur within 2-4 days after the procedure, with a peak incidence on postoperative day 2. Recently, Melby et al.[8] reported that POAF occurs in two distinct phases, with different risk factors for each. The first peak in the onset of POAF occurred in the first 3 hours after surgery, which was followed by a sharp decline in incidence over the next 24 hours. The second peak occurred on postoperative day 2. It has been speculated that whereas the first peak may be the result of tissue trauma, which is typically greater with more complex operations having longer cross-clamp times, the second peak may be related with increased inflammation and higher oxidative stress. Redistribution of interstitial fluid into the vascular compartment can cause atrial stretch and predispose to POAF. As these changes usually occur around the second postoperative day, it could also explain the high incidence of POAF during this time.[9] In the current study, only the early TOC status was evaluated; however, further investigation into the mechanisms of POAF with respect to time (1st vs. 2nd phase) is also clearly warranted.

Varying systemic inflammatory response to cardiopulmonary bypass could also explain the delayed onset of AF after surgery. The ACC without the benefits of hypothermic cardioplegia to reduce myocardial oxygen demand promotes atrial ischemia, potentially contributing to AF susceptibility. However, if atrial myocyte alterations resulting from ACC are a mechanism for POAF, AF should be less common after surgery without ACC. On the other hand, the use of beating-heart and off-bypass coronary artery surgery has not eliminated POAF in most studies.[10] In the present study, there was no control group with patients undergoing beating-heart and off-bypass coronary artery surgery. Further, this study used TOS obtained from plasma as a surrogate marker of oxidative stress but not the tissue level, and this can be considered another limitation of the study. It would be useful to also study TOS at the tissue level. Finally, this association between oxidase activity and the development of POAF might not establish a causal relationship between changes in serum TOC and POAF. It is possible that oxidative stress activity is one of the many biochemical changes that occur during the development of POAF and is not the primary causal event.[11] However, these initial observations will hopefully prompt additional studies to further investigate the specific pathways involved in the initiation and perpetuation of POAF.

***Conflict-of-interest issues regarding the authorship or article: None declared.***

## REFERENCES

1. Carnes CA, Chung MK, Nakayama T, Nakayama H, Baliga RS, Piao S, et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. Circ

Res 2001;89:32-8. CrossRef
2. Violi F, Pastori D, Pignatelli P, Loffredo L. Antioxidants for prevention of atrial fibrillation: a potentially useful future therapeutic approach? A review of the literature and meta-analysis. Europace 2014. CrossRef
3. Oktay V, Baydar O, Sinan UY, Koçaş C, Abacı O, Yıldız A, et al. The effect of oxidative stress related with ischemia-reperfusion damage on the pathogenesis of atrial fibrillation developing after coronary artery bypass graft surgery. Turk Kardiyol Dern Ars 2014;42:419-25.
4. Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:68-74. CrossRef
5. Waldo AL. Mechanisms of atrial fibrillation. J Cardiovasc Electrophysiol 2003;14(12 Suppl):267-74. CrossRef
6. Pichlmaier AM, Lang V, Harringer W, Heublein B, Schaldach M, Haverich A. Prediction of the onset of atrial fibrillation after cardiac surgery using the monophasic action potential. Heart 1998;80:467-72.
7. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA 1996;276:300-6. CrossRef
8. Melby SJ PD, Wallace JP, McGiffin DC,George JF Kirklin JK. Postoperative atrial fibrillation occurs in two distinct phases after cardiac surgery. Circulation 2013;128:A12139.
9. Nair SG. Atrial fibrillation after cardiac surgery. Ann Card Anaesth 2010;13:196-205. CrossRef
10. Møller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. Cochrane Database Syst Rev 2012;3:CD007224.
11. Oral H. Post-operative atrial fibrillation and oxidative stress: a novel causal mechanism or another biochemical epiphenomenon? J Am Coll Cardiol 2008;51:75-6. CrossRef