



EDITORIAL COMMENT

Oxidative stress and atrial fibrillation – association or causation?

Stress oxidativo e fibrilhação auricular – associação ou causa?

Francisco Moscoso Costa^{a,b,c,*}, Fu Siong Ng^d

^a Department of Cardiology, Santa Cruz Hospital, Portugal

^b Heart Rhythm Center, Hospital da Luz Lisboa, Portugal

^c Department of Cardiology, Hospital da Luz Setubal, Portugal

^d National Heart & Lung Institute, Imperial College London, United Kingdom

Available online 9 January 2021

Atrial fibrillation (AF) is the commonest arrhythmia, with >8 million people in the European Union estimated to have AF in 2010.¹ AF increases mortality at least 1.5-fold, is responsible for an increase in embolic strokes, and can also cause a range of debilitating symptoms. At present, treatments for AF, especially persistent AF, have limited success. Catheter ablation, which is a key treatment for AF, has a ceiling of success of approximately 50% in persistent AF. A possible reason for the lack of success in treating persistent AF may be that current antiarrhythmic medications and ablation strategies do not adequately target the underlying mechanisms of AF and its pathophysiology.²

The pathophysiology of AF is complex. The pulmonary veins are important triggers for AF, and a number of electrophysiological (e.g. reduced IK1 and ICa-L currents) and anatomical (branching fibers with limited lateral coupling and abrupt fiber orientation change) features predispose the pulmonary veins to ectopy.³ This has led to electrical isolation of the pulmonary veins being the cornerstone of AF ablation. However, the triggers are only part of the story, and remodeling of the atrial substrate is equally, if not

more, important. The atrial substrate undergoes a series of adverse remodeling changes, including upregulation of potassium channels leading to a reduction in action potential duration, increased fibrosis and a reduction in gap junction coupling. These abnormalities of conduction and refractoriness all promote re-entry, and thus the maintenance of AF.

An often neglected aspect of AF pathophysiology is the potential role played by inflammation and oxidative stress in creating the electrical and structural remodeling that predisposes to AF. Inflammatory markers have been shown to be increased in patients with AF. Furthermore, in chronic inflammatory conditions such as rheumatoid arthritis, there are approximately 1.5- and 2.0-fold increases in atrial arrhythmias and sudden cardiac death, respectively.⁴ This is because inflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor alpha, increase fibrosis by causing cardiac fibroblasts to proliferate, promoting differentiation to myofibroblasts, and increasing collagen deposition. They also modulate the activity of a number of ion currents, for example reducing the transient outward current (Ito) and both components of the delayed rectifier potassium current (IKs and IKr) to reduce refractoriness,⁵ all of which combine to promote arrhythmogenesis.

Oxidative stress, which is increased in inflammation, is also thought to play an important role in AF.⁶ Increased reactive oxygen species (ROS), more specifically, increased nicotinamide adenine dinucleotide phosphate oxidase (NOX)

DOI of original article: <https://doi.org/10.1016/j.repc.2020.05.011>

* Corresponding author.

E-mail address: fmoscocosta@gmail.com (F. Moscoso Costa).

<https://doi.org/10.1016/j.repc.2020.12.007>

0870-2551/© 2020 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



and endothelial nitric oxide synthase activity, have been demonstrated in patients with AF.⁷ Increased NOX can promote fibrosis through stimulation of transforming growth factor beta, which then increases atrial arrhythmogenesis. Furthermore, ROS signaling has also been shown to modulate both ion channel function and calcium-induced calcium release, both directly and via second messenger systems. However, despite evidence linking oxidative stress with AF, antioxidant therapy has not been shown to reduce AF in clinical trials. This may be because existing antioxidant therapies are not sufficiently targeting the key oxidative stress pathways. Another possible reason is that increased oxidative stress is merely associated with AF, and is a general marker for atrial myopathy, but does not play a key role in AF pathogenesis.

In this issue of the *Journal*, Tascanov et al.⁸ investigate the relationship between total oxidative status (TOS), DNA damage and paroxysmal AF (PAF). The authors compared a series of 56 patients with paroxysmal AF to healthy controls and reported higher high-sensitivity C-reactive protein, TOS and 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in the PAF group. Furthermore, they propose that TOS and DNA damage can be used to detect patients at higher risk of AF.

Elevated TOS levels have been related to AF in patients admitted for ST-elevation myocardial infarction⁹ and patients referred for coronary artery bypass graft surgery.¹⁰ Also, blood 8-OHdG levels (indicating DNA damage) levels have been related to progression from paroxysmal to persistent AF and have been proposed as a biomarker for AF staging and recurrence after cardioversion and pulmonary vein isolation.¹¹

Tascanov et al.'s findings add to this body of evidence by relating TOS and DNA damage in a general population with PAF, but they do not go on to clarify a potential causal relationship. Whether oxidative stress (OS) causes AF, AF increases OS, or they are independent markers of atrial cardiomyopathy, remains to be answered.¹²

The authors propose using TOS and DNA damage to identify patients at higher risk for AF. Current strategies to mitigate the consequences of AF focus on early diagnosis and treatment and, to achieve this, opportunistic and systematic screening for AF is recommended for patients at higher thromboembolic risk, mostly defined by age over 65 years and other clinical variables.¹³ In the future, if TOS, DNA damage or other biomarkers prove to be effective in better stratifying and identifying individuals at highest risk of AF to target screening, they could add value to the current approach. Better identifying a population at high risk of developing AF would help not only to improve screening efforts but also to select patients who could benefit from more aggressive risk factor management. Nevertheless, any potential change to the current benchmark needs not only to prove cost-effectiveness but to be widely available in clinical practice.

Finally, current AF treatment relies mostly on stroke prevention, rate and rhythm control. Further insight into the pathogenesis of AF may also unveil novel treatment options that could help delay or ideally suppress AF progression. Future research should focus on the translation of

our basic understanding of the role of oxidative stress in AF pathophysiology into more focused preventive strategies and more effective treatment options, and for this, the possible causative relation between oxidative stress and atrial fibrillation still needs to be clarified.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–51.
2. Ng FS, Handa BS, Li X, et al. Toward mechanism-directed electrophenotype-based treatments for atrial fibrillation. *Front Physiol*. 2020;11:987. PMID: 33013435; PMCID: PMC7493660.
3. Nattel S, Heijman J, Zhou L, et al. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. *Circ Res*. 2020;127:51–72. Epub 2020 Jun 18 PMID: 32717172; PMCID: PMC7398486.
4. Lazzarini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. *Eur Heart J*. 2017;38:1717–27. PMID: 27252448.
5. Patel KHK, Jones TN, Sattler S, et al. Proarrhythmic electrophysiological and structural remodeling in rheumatoid arthritis. *Am J Physiol Heart Circ Physiol*. 2020;319:H1008–20. Epub 2020 Sep 18 PMID: 32946265.
6. Samman Tahhan A, Sandesara PB, Hayek SS, et al. Association between oxidative stress and atrial fibrillation. *Heart Rhythm*. 2017;14:1849–55. Epub 2017 Jul 27 PMID: 28757307; PMCID: PMC5817893.
7. Woods CE, Olgin J. Atrial fibrillation therapy now and in the future: drugs, biologicals, and ablation. *Circ Res*. 2014;114:1532–46. PMID: 24763469; PMCID: PMC4169264.
8. Tascanov MB, Tanriverdi Z, Gungoren F, et al. Relationships among paroxysmal atrial fibrillation, total oxidate status and DNA damage. *Rev Port Cardiol*. 2021;40.
9. Bas HA, Aksoy F, Icli A, et al. The association of plasma oxidative status and inflammation with the development of atrial fibrillation in patients presenting with ST elevation myocardial infarction. *Scand J Clin Lab Invest*. 2017;77:77–82. Epub 2016 Dec 1.
10. Oktay V, Baydar O, Yaşar Sinan Ü, 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.
11. Li OJ, Zhang OD, Kennedy S, et al. Brundel blood-based 8-hydroxy-2'-deoxyguanosine level: a potential diagnostic biomarker for atrial fibrillation. *Heart Rhythm* 2020. 2020, <http://dx.doi.org/10.1016/j.hrthm.2020.09.017>.
12. Kennedy S, Ramos Bianca J, Brundel JM. DNA damage, an innocent bystander in atrial fibrillation and other cardiovascular diseases? *Front Cardiovasc Med*. 2020;7:67, eCollection 2020.
13. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2020;00:1125.