Osmar Antonio Centurión[1,2]*, Fabiola Rodríguez[2], Karina Scavenius[2], Luis Miño[2] and Orlando Sequeira[2]

[1]Department of Health Sciences's Investigation, Sanatorio Metropolitano, Fernando de la Mora, Paraguay

[2]Cardiology Department, Clinic Hospital, Asunción National University, San Lorenzo, Paraguay

*Corresponding author: Osmar Antonio Centurión, Professor of Medicine, Asuncion National University, Department of Health Sciences's Investigation, Sanatorio Metropolitano, Teniente Ettiene 215 c/ Ruta Mariscal Estigarribia Fernando de la Mora, Paraguay, E-mail: osmarcenturion@hotmail.com

https://www.peertechz.com

Editorial

Postoperative Atrial Fibrillation and its association with the Atrial Substrate and the electrophysiological properties of the Atrial Myocardium

Editorial

Postoperative atrial fibrillation (AF) has a high prevalence, affecting up to 45% of coronary artery bypass graft surgery patients within the first week of the operation [1-4]. Interestingly, asymptomatic AF was reported more likely to occur after the first 4 days following the cardiac surgery. Postoperative AF is associated with increased morbidity and several types of complications. It was associated with increased duration of hospitalization, with high healthcare costs, and has been associated with an increased incidence of stroke, the need for permanent pacemaker placement, and early and late mortality. Several factors were found to be associated with new-onset AF following multivariate analysis, including advanced age, higher Killip class or heart failure, hypotension, higher heart rate, history of hypertension, history of stroke, female gender, increased peak creatinine, and increased Creactive protein levels [5-9]. In addition, AF may adversely affect quality of life and is associated with a higher risk of acute heart failure, and with thromboembolic events. It has recently been demonstrated that early and late postoperative AF have different predictors [9]. Early postoperative AF is the one occurring within the first 5 days after cardiac surgery, and late postoperative AF is the one occurring between the 6 and 30 days after cardiac surgery. Late postoperative AF was associated with conventional risk factors of AF in the general population. However, early AF was associated with low body mass index, high CRP levels, and previous myocardial infarction, higher EuroScore, and higher age [10-13]. Moreover, patients who develop postoperative AF are more likely to have left atrial dilation. This finding may suggest that left atrial size should be considered as a good predictor of postoperative AF [12,13]. As an interesting intraoperative related matter, Bidar et al., have observed that aortic cross-clamp time was a strong predictor of 30-day postoperative AF [9]. They carefully recorded any AF episode within the 30 days after cardiac surgery using an external 1-lead trans-telephonic loop recorder with an auto-trigger for AF. Late postoperative AF was associated with longer aortic cross-clamp times. In addition, this observation suggests that postoperative AF occurs not only during the first postoperative days but also in the weeks thereafter [9]. This fact has implications against the early discontinuation of oral anticoagulation [14].

On the other hand, clinical studies aiming to investigate the pathogenesis of postoperative AF have demonstrated that inflammatory reactions and oxidative stress are the most important factors for its development. Inflammation and active infection promote the release of cytokines and up-regulation of Toll-like receptor-2 expression on monocytes, which may act as a trigger for postoperative AF. The inflammation process induces atrial electrophysiological changes, activates reentry mechanisms and precipitates the development of postoperative AF [15-18].There is a high inflammation state during the intraoperative period due to the extracorporeal circulation, the cardiac ischemia-reperfusion injury, and oxidative stress. In addition, pulmonary infections and cardiac dysfunction during the postoperative period may worsen the inflammatory process. Hence, the inflammatory activity and CRP levels reach its highest value in the first postoperative week [18]. After the first week, surgery induced inflammatory activity decreases, and postoperative risk factors gradually diminish. Therefore, surgery-related metabolic changes and oxidative stress after heart operation induce inflammatory reactions and increase inflammatory capacity which is associated to a higher risk of developing postoperative AF.

Most of the cardiac surgeries in organic heart disease are performed in elder patients. There is a, well documented, rise

in prevalence of atrial AF with advancing age [19-21]. Several electrophysiological and pathological studies have shown that there is clear evidence in the human atrial myocardium of age-related electrical uncoupling of the side-to-side connections between bundles. This is related to the proliferation of extensive collagenous tissue septa in intracellular spaces [22-24]. In pathological studies, it was demonstrated that these age-induced changes include a reduction in the number of myocardial cells within the sinus node, a generalized loss of atrial myocardial fibers, as well as an increase in fibrosis which leads to an apparent loss of myocardial fiber continuity [19-24]. It is so clear to observe that patients with diseased atrial tissue with progressive fibro-degenerative changes may develop abnormal electrophysiological alterations [25-29]. Connective tissue surrounding atrial myocardial cells represents sites where electrical coupling between adjacent cells is altered [19-21]. Therefore, the micro-architecture and anisotropic characteristics may play an important role in reentry by causing inhomogeneous and discontinuous propagation of the impulse in the atrium [21]. These findings suggest that progressive electro-pathological changes within the atria are associated with persistent

AF. Previous studies have investigated the underlying cause responsible for perpetuation of AF. Atrial fibrosis has been suggested to be an important element in the pathophysiology of AF. There is a significant larger amount of atrial fibrosis seen in patients with AF. The degree of fibrotic tissue in AF patients demonstrated heterogeneity and does not always predict the severity of the AF burden. An excessive extracellular matrix leads to uncoupling of cells and may facilitate inhomogeneous conduction, re-entry, and multiple wavelets. During the preoperative evaluation of the patients, MRI can be a helpful diagnostic tool for the determination of degree of fibrosis in AF patients and identification of areas of fibrosis. It was demonstrated that the activation of cellular signaling pathways plays an important role in human atrial structural remodeling, and promotes the proliferation of atrial fibroblasts, leading to atrial fibrosis. In addition, it is involved in apoptosis, inflammation and epithelial mesenchymal transformation [30-35]. The exact mechanism and signal transduction pathway underlying atrial muscle fibrosis is unknown. However, it was reported that the following mechanisms are mainly involved in atrial fibrosis: 1) the renin angiotensin aldosterone system, 2) transforming growth factor-β1 and 3) inflammation and oxidative stress. Transforming growth factor-β1, a key growth factor in fibrosis, can regulate cell proliferation, apoptosis and migration, and extracellular matrix synthesis. It up-regulates the expression of fibronectin and collagen, and its over-expression can lead to the occurrence of atrial fibrosis and AF [32-35].

Considering the relatively high incidence of postoperative AF, it is important to try to identify patients at risk of developing AF after surgery. In this regard, Luo W et al. observed with logistic regression analyses performed in 304 patients that a history of hypertension, left atrium diameter, and EuroSCORE I were independent risk factors for postoperative AF in patients older than 60 years of age [36]. Other studies have identified

the following independent predictors of postoperative AF: high CHA2DS2-VASc, Age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, severe obesity, preoperative β-blocker use, preoperative antiplatelet therapy, renal insufficiency, and preoperative systolic pulmonary arterial pressure [37-39]. Patients with these independent predictors of postoperative AF may constitute a target population to test preventive strategies.

Another helpful diagnostic tool is P-wave duration and dispersion (PWD) which is considered a noninvasive electrocardiographic (ECG) marker for atrial remodeling and predictor for AF [40-43]. PWD reflects disturbances of intra-atrial and inter-atrial conduction, and it is defined as the difference between the wider and the narrower P-wave duration recorded from the 12 ECG leads at a paper speed of 50 mm/s. It has been shown that increased P-wave duration and PWD reflect prolongation of intra-atrial and inter-atrial conduction time and the inhomogeneous atrial propagation of sinus impulses [40-42]. The analysis of the P-wave with the 12 standard surface ECG leads in the stratification of patient suffering from AF is a recognized universal approach. It is well accepted that not only the P-wave duration, but also the P-wave morphology and dispersion have the potential to give information about the anatomical substrate predisposing to AF [41-44]. Extensive clinical evaluation of P-wave dispersion has been performed in the assessment of the risk for atrial fibrillation in patients without organic heart disease, in patients with arterial hypertension, in patients with coronary artery disease, in patients undergoing coronary artery bypass surgery, in patients with congenital heart diseases, as well as in other groups of patients suffering from various cardiac or non-cardiac diseases [45,46]. Consequently, PWD can be helpful in discriminating patients with different kinds of diseases whom are prone to develop paroxysmal AF in the postoperative scenario [47,48].

We have previously found that patients with a predisposition to develop AF have significantly higher incidence of atrial conduction defects, and abnormally prolonged and fractionated atrial endocardial electrograms [25-29]. At the time of the atrial endocardial catheter mapping during sinus rhythm, we have found that an abnormally prolonged and fractionated right atrial electrogram may reflect inhomogeneous local electrical activity related to a delayed and non-uniform anisotropic conduction through diseased atrial muscle, and were closely related to the vulnerability of the atrial muscle in patients with paroxysmal AF [27-29]. Indeed, we demonstrated that the greater the extent of the compromised atrial muscle, the greater the likelihood that paroxysmal AF would develop [27]. Qualitative and quantitative analysis of atrial endocardial electrograms recorded during sinus rhythm should be an important analysis in evaluating local atrial electrophysiological abnormalities, and acquire particular relevance in the study of patients with paroxysmal AF.

In the evaluation of patients with altered P wave morphology and dispersion in the electrocardiogram, it is very important to keep in mind that patients who have a great susceptibility

to develop AF possess abnormally prolonged and fractionated atrial endocardial electrograms, a significantly longer P wave duration, a significantly longer intra–atrial and inter–atrial conduction time of sinus impulses; and a significantly greater sinus node dysfunction and higher incidence of induction of sustained atrial fibrillation. In conclusion, the heterogeneous presentation, development and progression of AF implicate the existence of different pathophysiological processes. In order to improve surgical outcomes is necessary to individualized diagnostic and therapeutic management of the arrhythmogenic substrate underlying AF and minimize the metabolic, oxidative stress and inflammation process during surgery

References

1. Stamboul K, Zeller M, Fauchier L, Gudjoncik A, Buffet P, et al. (2014) Incidence and prognostic significance of silent atrial fibrillation in acute myocardial infarction. Inter J Cardiol 174: 611-617. **Link:** https://goo.gl/KsxXma

2. Echahidi N, Pibarot P, O'Hara G, Mathieu P (2008) Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 51: 793-801. **Link:** https://goo.gl/Rjqzqy

3. Willems S, Weiss C, Meinertz T (1997) Tachyarrhythmias following coronary artery bypass graft surgery: epidemiology, mechanisms, and current therapeutic strategies. Thorac Cardiovasc Surg 45: 232-237. **Link:** https://goo.gl/H35RKy

4. Ommen SR, Odell JA, Stanton MS (1997) Atrial arrhythmias after cardiothoracic surgery. N Engl J Med 336: 1429-1434. **Link:** https://goo.gl/uF94rj

5. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL (1993) Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 56: 539-549. **Link:** https://goo.gl/bVRddG

6. Lapar DJ, Speir AM, Crosby IK, Fonner E Jr, Brown M, et al. (2014) Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg 98: 527-533. **Link:** https://goo.gl/izjnv4

7. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, et al. (2005) Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Am Heart J 149: 657-663. **Link:** https://goo.gl/CC51cn

8. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, et al. (2012) Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 366: 120-129. **Link:** https://goo.gl/pUUH23

9. Bidar E, Maesen B, Nieman F, Verheule S, Schotten U, et al. (2014) A prospective randomized controlled trial on the incidence and predictors of late-phase postoperative atrial fibrillation up to 30 days and the preventive value of biatrial pacing. Heart Rhythm 11: 1156-1162. **Link:** https://goo.gl/iBboVy

10. Nisanoglu V, Erdil N, Aldemir M, Ozgur B, Berat Cihan H, et al. (2007) Atrial fibrillation after coronary artery bypass grafting in elderly patients: incidence and risk factor analysis. Thorac Cardiovasc Surg 55: 32-38. **Link:** https://goo.gl/hSWMYP

11. Hernández-Romero D, Vílchez JA, Lahoz A, Romero-Aniorte AI, Orenes-Piñero E, et al. (2014) High sensitivity troponin T as a biomarker for the development of atrial fibrillation after cardiac surgery. Eur J Cardio Thorac Surg 45: 733-738. **Link:** https://goo.gl/5XHxwJ

12. Dittrich HC, Pearce LA, Asinger RW, McBride R, Webel R, et al. (1999) Left atrial diameter in nonvalvular atrial fibrillation: an echocardiographic study. Am Heart J 137: 494-499. **Link:** https://goo.gl/SQ7QK5

13. Manning WJ, Gelfand EV (2006) Left atrial size and postoperative atrial fibrillation: the volume of evidence suggests it is time to break an old habit. J Am Coll Cardiol 48: 787-789. **Link:** https://goo.gl/xTRtUR

14. El-Chami MF, Kilgo P, Thourani V, Delurgio DB, Guyton RA, et al. (2010) New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. J Am Coll Cardiol 55: 1370-1376. **Link:** https://goo.gl/C6Z6Tn

15. Yadava M, Hughey AB, Crawford TC (2014) Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. Cardiol Clin 32: 627- 636. **Link:** https://goo.gl/DtyRZp

16. Arakawa M, Miyata H, Uchida N, Motomura N, Katayama A, et al. (2015) Postoperative atrial fibrillation after thoracic aortic surgery. Ann Thorac Surg 99: 103-108. **Link:** https://goo.gl/ZBMMXV

17. Aydin U, Yilmaz M, Duzyol C, Ata Y, Turk T, et al. (2015) Efficiency of postoperative statin treatment for preventing new-onset postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting: A prospective randomized study. Anatol J Cardiol 15: 491-495. **Link:** https://goo.gl/VCHJuE

18. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, et al. (2001) C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 104: 2886-2891. **Link:** https://goo.gl/8r4po3

19. Spach, Dober PC, Anderson PA (1989) Multiple regional differences in cellular properties that regulate repolarization and contraction in the right atrium of adult and newborn dogs. Circ Res 65: 1594-1611. **Link:** https://goo.gl/4WuCK3

20. Spach MS, MillerWT, Dolber PC, Kootsey JM, Sommer JR, et al. (1952) The functional role of structural complexities in the propagation of depolarization in the atrium of the dog: cardiac conduction disturbances due to discontinuities of effective axial resistivity. Circ Res 50: 175-191. **Link:** https://goo.gl/9xkSck

21. Spach MS, Dober PC (1986) Relating extracellular potentials and their derivatives to anisotropic propagation at microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res 58: 356-371. **Link:** https://goo.gl/VCKCEB

22. Lev M (1954) Aging changes in the human sinoatrial node. J Geront 9: 1-9. **Link:** https://goo.gl/myAgV2

23. Davies MJ, Pomerance A (1972) Quantitative study of aging changes in the human sinoatrial node and internodal tracts. Br Heart J 34: 150-152. **Link:** https://goo.gl/n7vgRm

24. Hudson REB (1960) The human pacemarker and its pathology. Br Heart J 22: 153-167. **Link:** https://goo.gl/oeccLN

25. Centurión OA, Isomoto S, Shimizu A, Konoe A, Kaibara M, et al. (2003) The effects of aging on atrial endocardial electrograms in patients with paroxysmal atrial fibrillation. Clin Cardiol 26: 435-438. **Link:** https://goo.gl/jgxS3t

26. Centurión OA, Shimizu A, Isomoto S, Konoe A, Kaibara M, et al. (2005) Influence of advancing age on fractionated right atrial endocardial electrograms. Am J Cardiol 96: 239-242. **Link:** https://goo.gl/XdoyHr

27. Centurión OA, Fukatani M, Konoe A, Tanigawa M, Shimizu A, et al. (1992) Different distribution of abnormal endocardial electrograms within the right atrium in patients with sick sinus syndrome. Br Heart J 68: 596-600. **Link:** https://goo.gl/bKd1YV

28. Centurión OA, Isomoto S, Fukatani M, Shimizu A, Konoe A, et al. (1993) Relationship between atrial conduction defects and fractionated atrial endocardial electrograms in patients with sick sinus syndrome. PACE 16: 2022-2033. **Link:** https://goo.gl/556F7T

29. Centurión OA, Shimizu A, Isomoto S, Konoe A, Hirata T, et al. (1994) Repetitive atrial firing and fragmented atrial activity elicited by extrastimuli in the sick sinus syndrome with and without abnormal atrial electrograms. Am J Med Sci 307: 247-254. **Link:** https://goo.gl/J5tFLH

30. Landstrom M (2010) The TAK1-TRAF6 signalling pathway. Int J Biochem Cell Biol 42: 585-589. **Link:** https://goo.gl/s1A9Sc

31. Yamashita M, Fatyol K, Jin C, Wang X, Liu Z, et al. (2008) TRAF6 mediates Smadindependent activation of JNK and p38 by TGF-beta. Mol Cell 31: 918-924. **Link:** https://goo.gl/L2CJ4k

32. Ko WC, Hong CY, Hou SM, Lin CH, Ong ET, et al. (2011) Elevated expression of connective tissue growth factor in human atrial fibrillation and angiotensin IItreated cardiomyocytes. Circ J 75: 1592-1600. **Link:** https://goo.gl/ZTMb4q

33. He X, Gao X, Peng L, Wang S, Zhu Y, et al. (2011) Atrial fibrillation induces myocardial fibrosis through angiotensin II type 1 receptor-specific Arkadiamediated downregulation of Smad7. Circ Res 108: 164-175. **Link:** https://goo.gl/1m7W9q

34. Gu J, Liu X, Wang QX, Tan HW, Guo M, et al. (2012) Angiotensin II increases CTGF expression via MAPKs/TGF-beta1/TRAF6 pathway in atrial fibroblasts. Exp Cell Res 318: 2105-2115. **Link:** https://goo.gl/8cMMWT

35. Zhang D, Chen X, Wang Q, Wu S, Zheng Y, et al. (2017) Role of the MAPKs/TGF?1/TRAF6 signaling pathway in postoperative atrial fibrillation. PLoS ONE 12: e0173759. **Link:** https://goo.gl/6W23R7

36. Luo W, Huaibin W, Wenjun Z, Jie T, Xiaokang O, et al. (2017) Predictors of Postoperative Atrial Fibrillation after Isolated On-Pump Coronary Artery Bypass Grafting in Patients ?60 Years Old. Heart Surg Forum 20: E038-E042. **Link:** https://goo.gl/WWJ3rf

37. Perrier S, Meyer N, Hoang Minh T, Announe T, Bentz J, et al. (2017) Predictors of Atrial Fibrillation After Coronary Artery Bypass Grafting: A Bayesian Analysis. Ann Thorac Surg 103: 92-97. **Link:** https://goo.gl/2RmtqX

38. Kotova S, Wang M, Lothrop K, Grunkemeier G, Merry HE, et al. (2017) CHADS2 Score Predicts Postoperative Atrial Fibrillation in Patients Undergoing Elective Pulmonary Lobectomy. Ann Thorac Surg. 103: 1566-1572. **Link:** https://goo.gl/9mqrUz

39. Jesel L, Barraud J, Lim HS, Marzak H, Messas N, et al. (2017) Early and late atrial arrhythmias after lung transplantation: Incidence, predictive factors and impact on mortality. Circ J 81: 660-667. **Link:** https://goo.gl/2t4Cbv

40. Centurión OA (2009) Clinical implications of the P wave duration and dispersion: Relationship between atrial conduction defects and abnormally prolonged atrial endocardial electrograms. Int J Cardiol 134: 6-8. **Link:** https://goo.gl/z8Aw7g

41. Aytemir K, Ozer N, Atalar E, Sade E, Aksöyek S, et al. (2000) P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 23: 1109-1112. **Link:** https://goo.gl/Gk4rXp

42. Dilaveris PE, Gialafos JE (2001) P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 6: 159-165. **Link:** https://goo.gl/qEM1nr

43. Lazzeroni D, Parati G, Bini M, Piazza P, Ugolotti PT et al. (2016) P-wave dispersion predicts atrial fibrillation following cardiac surgery. Int J Cardiol 203: 131-133. **Link:** https://goo.gl/h3itkj

44. Yoshizawa T, Niwano S, Niwano H, Igarashi T, Fujiishi T, et al. (2014) Prediction of new onset atrial fibrillation through P wave analysis in 12 lead ECG. Int Heart J 55: 422-427. **Link:** https://goo.gl/nnpas4

45. Ertem AG, Erdo_gan M, Keles̨ T, Durmaz T, Bozkurt E (2015) P-wave dispersion and left ventricular diastolic dysfunction in hypertension. Anatol J Cardiol 15: 78-79.

46. Kizilirmak F, Demir GG, Gokdeniz T, Gunes HM, Cakal B, et al. (2016) Changes in electrocardiographic P wave parameters after Cryoballoon ablation and their association with atrial fibrillation recurrence. Ann Noninvasive Electrocardiol 21: 580-587. **Link:** https://goo.gl/4E1Q9M

47. Kawamura M, Scheinman MM, Lee RJ, Badhwar N (2015) Left atrial appendage ligation in patients with atrial fibrillation leads to a decrease in atrial dispersion. J Am Heart Assoc 4: e001581. **Link:** https://goo.gl/a7dLTX

48. Badhwar N, Lakkireddy D, Kawamura M, Han FT, Iyer SK, et al. (2015) Sequential percutaneous LAA ligation and pulmonary vein isolation in patients with persistent AF: initial results of a feasibility study. J Cardiovasc Electrophysiol 26: 608-614. **Link:** https://goo.gl/bwzvBq