Atrial ^{18}F-FDG uptake is related to permanent atrial fibrillation: Will substrate-based patient selection improve outcome?

Hein J. Verberne, MD, PhD[a]

[a] Department of Radiology and Nuclear Medicine, F2-238, Amsterdam UMC, Location AMC, University of Amsterdam, Amsterdam, The Netherlands

Received Sep 24, 2018; accepted Sep 25, 2018
doi:10.1007/s12350-018-01480-3

See related article, pp. 1501–1512

The prevalence of atrial fibrillation (AF) in the developed world is currently estimated at approximately 1.5% to 2% of the general population. The average age of patients with AF rises steadily and averages now between 75 and 85 years. AF is associated with a five-fold risk of stroke and a three-fold incidence of congestive heart failure, and higher mortality. AF patients are also often hospitalized. In addition to its impact on individual patients, AF has a major socioeconomic impact. Furthermore, based on projected estimates of increased AF, incidence over the coming decades will most likely worsen both individual patient burden and impact on socioeconomics.

Worldwide approximately 20.9 million men and 12.6 million women were diagnosed with AF in 2010. In developed countries higher incidence and prevalence are reported.[1,2] It is estimated that one in four middle-aged adults in Europe and the US will develop AF.[3–5] Furthermore it is estimated that by 2030, there will be 14 to 17 million AF patients in the European Union. Important to realize is that this equals to approximately 120,000 to 215,000 newly diagnosed AF patients per year.[2,6,7] AF prevalence is higher in the elderly [1] and in patients with conditions associated with AF (e.g., hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease (CKD)).[7–13] Better detection of silent AF,[14–16] in combination with increasing age and increasing prevalence of conditions predisposing to AF, explains the expected increase in AF prevalence.[17]

AF is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men.[18–20] Anticoagulation therapy diminishes death due to stroke in AF patients. However, even if AF patients are treated according to the latest evidence, death due to heart failure and sudden death remain common.[21] AF is also related to increased morbidity of diseases such as heart failure and stroke.[20,22,23] For example, approximately 25% of patients with an ischaemic stroke have AF either diagnosed before, during, or after the initial event.[14,24,25] White matter lesions in the brain, cognitive impairment,[26–28] decreased quality of life,[29,30] and depressed mood [31] are common in AF patients, and between 10% and 40% of AF patients are hospitalized each year.[21,32,33]

Based on clinical presentation, duration, and spontaneous termination of AF episodes, five types of AF are traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF.[34] As the most recent ESC guidelines on AF point out, it is important to realize that these AF classifications patterns do not correspond well to the AF burden measured by long-term ECG monitoring.[35] Even less is known about the response to therapy in patients with long-standing persistent AF or long-standing paroxysmal AF. Despite these inaccuracies, the distinction between paroxysmal and persistent AF has been used in many trials.

Treatment of patients with AF is aimed at hemodynamic stability, reduction of cardiovascular risk, prevention of stroke, improvement of symptoms and preservation of LV function.[36] Fortunately a number of valuable treatment options have been developed in

Reprint requests: Hein J. Verberne, MD, PhD, Department of Radiology and Nuclear Medicine, F2-238, Amsterdam UMC, Location AMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; *h.j.verberne@amc.uva.nl*
J Nucl Cardiol 2020;27:1517–20.
1071-3581/$34.00

recent years that help to achieve these treatment goals. However, they are not perfect and do not always solve the clinical problem.

In recent years, complete pulmonary vein ablation has arisen as an option to control rhythm in AF patients both with paroxysmal as with persistent AF. However, the rhythm outcome after catheter ablation of AF is difficult to predict in individual patients.[37–40] Multiple variables have been identified as risk factors for recurrence after catheter ablation of AF, but their predictive power is weak. Therefore, the most recent ESC guideline advocates that the decision for catheter ablation should be based on a shared decision-making process.[34]

Apart from the risk of recurrence of AF after catheter ablation, it is important to realize that these interventions are associated with complications. Although the systematic registration of these complications is in need of improvement, the reported incidence of severe complications ranges between 5% and 7% with 2% to 3% of patients experiencing life-threatening complications.[41–44]

Of interest is that the addition of ganglionated plexi (GP) ablation to pulmonary vein isolation further improves AF-free survival in both patients with paroxysmal and persistent AF. Despite this improved patient outcome, the combined ablation still results in approximately 25% and 50% recurrence of AF in paroxysmal and persistent AF, respectively.[45,46] These studies support the autonomic hypothesis for AF. In addition, it seems that GP activity is most important in the early stages of AF, while its importance may diminish with progression of the disease to more advance stages and the development of atrial remodeling and fibrosis. This nicely shows that a better understanding of the pathophysiology of AF leads to more targeted treatment plans (personalized medicine) and may result in better patient outcome.

One of the conclusions that can be drawn from these observations is that the success of AF ablation procedures depends on the elimination of substrate. Therefore, improved patient selection may improve outcome, i.e., only those patients with substrate most eligible to improve after a specific intervention should undergo these interventions. Therefore, an understanding of the pathophysiology related to AF initiation and progression is essential.

AF is very likely a multifactorial process (e.g., changes in the cardiac autonomic nervous system) where different factors interact resulting in either the incidence of AF or sustaining already existing AF. Amongst others, the initiation and persistence of AF is associated with inflammation. In patients with AF inflammation has been observed in cardiac tissue, epicardial adipose tissue (EAT), hematopoietic tissue, and the systemic circulation. Although the trigger for inflammation in AF is unknown (also most likely multifactorial), inflammation most likely induces electrophysiological and structural changes in the atria eventually leading to AF. On the other hand, AF by itself results in an inflammatory response, and elevated inflammatory markers have been shown in patients with long-standing AF. It is therefore not remarkable that some reports in the literature showed increased uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), as a marker of inflammation, in the atria of AF patients.

In this issue of Journal of Nuclear Cardiology, there is a study by Xie et al. reporting on factors that are associated with increased ^{18}F-FDG uptake in the atria or atrial appendage (AA).[47] In total, 48 AF patients were retrospectively identified. All patients with permanent AF showed increased atrial ^{18}F-FDG uptake, primarily localized in the right atrium. Multivariate logistic regression analyses identified that female gender, persistent AF, and ^{18}F-FDG uptake in EAT were independent predictors of increased atrial ^{18}F-FDG uptake. In addition, ^{18}F-FDG uptake in EAT was linearly correlated with the activity of the atrium and AA. The authors conclude that this finding might suggest a link between the inflammatory activity in EAT and atria in AF, pointing to the possibility that a local inflammatory burden in the EAT may lead to localized atrial inflammation.

There are some obvious limitations to this study that are adequately addressed (i.e., uniform patient preparation, low carbohydrate diet and impact on atrial ^{18}F-FDG uptake, atrial ^{18}F-FDG uptake in patients without AF). The main interest of this study lies in the fact that atrial ^{18}F-FDG uptake as a surrogate marker of inflammation is related to patients with permanent AF. It is tempting to speculate on the possible role of atrial ^{18}F-FDG uptake in the selection of patients for specific therapies. As especially patients with permanent AF tend to respond poorer to catheter ablation of the pulmonary veins, this finding may open ways to more targeted intervention studies using atrial ^{18}F-FDG uptake as tool to guide these interventions. However, for this daydream to become reality, a lot of effort needs to be put in harmonization and standardization of the imaging protocols including patient preparation.

Disclosure

Author have nothing to disclose.

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. Circulation 2014;129:837-47.

2. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol 2013;112:1142-7.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.
4. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: The Rotterdam study. Eur Heart J 2006;27:949-53.
5. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. Circulation 2004;110:1042-6.
6. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, 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.
7. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol 2014;6:213-20.
8. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. Int J Cardiol 2013;167:1807-24.
9. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: Insight from the real-life global survey evaluating patients with atrial fibrillation international registry. Cir Arrhythm Electrophysiol 2012;5:632-9.
10. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. Am J Cardiol 1998;82:2n-9n.
11. McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. Circulation 2012;126:e143-6.
12. Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of atrial fibrillation in developing countries. Int J Cardiol 2013;167:2412-20.
13. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: The RE-LY Atrial Fibrillation Registry. Circulation 2014;129:1568-76.
14. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: A systematic review and meta-analysis. Stroke 2014;45:520-6.
15. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Eng J Med 2014;370:2478-86.
16. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. Circulation 2003;107:2920-5.
17. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: A cohort study. Lancet 2015;386:154-62.
18. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: A Swedish nationwide long-term case-control study. Eur Heart J 2013;34:1061-7.
19. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998;98:946-52.
20. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-Year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359-64.
21. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: An individual-patient data meta-analysis. Lancet 2014;384:2235-43.
22. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476-84.
23. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke 1991;22:983-8.
24. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, et al. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: A prospective multicenter cohort study. Stroke 2013;44:3357-64.
25. Henriksson KM, Farahmand B, Asberg S, Edvardsson N, Terent A. Comparison of cardiovascular risk factors and survival in patients with ischemic or hemorrhagic stroke. Int J Stroke 2012;7:276-81.
26. Ball J, Carrington MJ, Stewart S. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: A forgotten component of clinical management? Heart 2013;99:542-7.
27. Knecht S, Oelschlager C, Duning T, Lohmann H, Albers J, Stehling C, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J 2008;29:2125-32.
28. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study: The Rotterdam Study. Stroke 1997;28:316-21.
29. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: Results of the ONTARGET and TRANSCEND studies. CMAJ 2012;184:E329-36.
30. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: A systematic review. Am J Med 2006;119:e1-19.
31. von Eisenhart Rothe A, Hutt F, Baumert J, Breithardt G, Goette A, Kirchhof P, et al. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: A longitudinal analysis—data from the German Competence Network on Atrial Fibrillation. Europace 2015;17:1354-62.
32. Kirchhof P, Schmalowsky J, Pittrow D, Rosin L, Kirch W, Wegscheider K, et al. Management of patients with atrial fibrillation by primary-care physicians in Germany: 1-Year results of the ATRIUM registry. Clin Cardiol 2014;37:277-84.
33. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J 2014;167:e2.
34. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.

35. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: Insights from 1,195 patients continuously monitored with implantable devices. J Am Coll Cardiol 2014;63:2840-8.
36. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, et al. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. Europace 2013;15:1540-56.
37. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: Two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol 2009;2:349-61.
38. Ganesan AN, Nandal S, Luker J, Pathak RK, Mahajan R, Twomey D, et al. Catheter ablation of atrial fibrillation in patients with concomitant left ventricular impairment: A systematic review of efficacy and effect on ejection fraction. Heart Lung Circ 2015;24:270-80.
39. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, et al. Long-term outcomes of catheter ablation of atrial fibrillation: A systematic review and meta-analysis. J Am Heart Assoc 2013;2:e004549.
40. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: The DECAAF study. JAMA 2014;311:498-506.
41. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:32-8.
42. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K, et al. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: Still cause for concern? J Cardiovasc Electrophysiol 2009;20:1014-9.
43. Deneke T, Jais P, Scaglione M, Schmitt R, Di Biase L, Christopoulos G, et al. Silent cerebral events/lesions related to atrial fibrillation ablation: A clinical review. J Cardiovasc Electrophysiol 2015;26:455-63.
44. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, et al. Complications of catheter ablation of atrial fibrillation: A systematic review. Circ Arrhythm Electrophysiol 2013;6:1082-8.
45. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: A randomized clinical trial. J Am Coll Cardiol 2013;62:2318-25.
46. Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Shirokova N, Karaskov A, et al. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: A randomized comparison. Heart Rhythm 2013;10:1280-6.
47. Xie B, Chen BX, Wu JY, Liu X, Yang MF. Factors relevant to atrial ^{18}F-fluorodeoxyglucose uptake in atrial fibrillation. J Nucl Cardiol 2018. https://doi.org/10.1007/s12350-018-1387-4.