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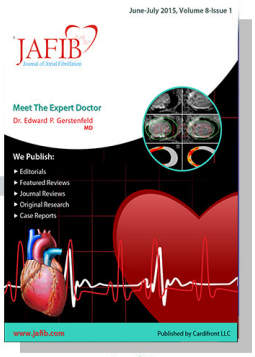

Lone AF: is There a Rationale?

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Abstract

Although atrial fibrillation (AF) development has been demonstrated to be associated with underlying cardiovascular conditions such as hypertension, valvular heart disease or diabetes mellitus; in a subset of relatively younger patients, no cardiopulmonary disease diagnosis can be established. AF patients younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease are defined as lone AF patients. Despite the decrease in lone AF prevalence due to advances in understanding of AF pathogenesis, there are still issues yet to be resolved. Future studies are needed to demonstrate the cost- effectiveness of the routine use of more advanced diagnostic tools, such as non- invasive assessment of endothelial function, autoimmune markers or genetic screening and whether they would have clinical implications on treatment of lone AF.

This review focuses on the suggested mechanisms in lone AF initiation and maintenance.

Introduction

Although atrial fibrillation (AF) development has been demonstrated to be associated with underlying cardiovascular conditions such as hypertension, valvular heart disease or diabetes mellitus; in a subset of relatively younger patients, no cardiopulmonary disease diagnosis can be established. AF patients <60 years without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus are defined as lone AF patients.[1] This term was first introduced by Evans and Swann in 1954.[2] Due to advances in understanding of AF pathogenesis, prevalence of lone AF has decreased in a significant way from 30% to 5%.[3,4]

A recent survey[5] has reported that AF patients without conventional cardiovascular risk factors were not further evaluated for other possible risk factors for development of AF. Results of the survey, which was conducted in thirty-two European centers, all members of the EHRA electrophysiology research network, has shown that assessment for sleep apnea, obesity, and intensive sports activity in lone AF was performed at 27 (84%) centres.[5] According to the survey,[5] number of centers where exercise testing, coronary angiography and a computed tomography were performed were 8 (25%), 2 (6%), and 1 (3%), respectively. The work-up typically included screening for known risk factors but not genetic testing.[5] 10 (31%) centers did perform genetic testing only when there was a family history of AF.[5] Therefore, some of the patients diagnosed with "lone AF" are actually under-evaluated.

Key Words:
Lone Atrial Fibrillation, Definition, Pathogenesis, Treatment.

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Atrial Structural and Functional Changes

Atrial fibrosis has been regarded as the hallmark of the structural changes in the atria in AF patients.[6,7] Atrial fibrosis was found to be prominent in the tissue samples of patients with history of AF when compared to those without.[8] Extent of fibrosis was found to be comparable in patients with paroxysmal vs. persistent AF, or in lone AF patients vs. those with AF accompanied with mitral valve disease.[9,10]

Atrial fibrosis was previously demonstrated with electroanatomic voltage mapping in clinical electrophysiological studies. Stiles et al.[11] have shown that even after maintenance of sinus rhythm for 10 days, lone AF patients had biatrial low voltage values when compared to control patients without AF. More recently, studies have focused on quantification and grading of atrial fibrosis with delayed-enhancement magnetic resonance imaging (DE- MRI).[12-14] These studies, on the other hand, have shown that there was no profound difference in the degree of atrial remodeling between lone AF patients and those with AF and an accompanying cardiopulmonary disease, and that the extent of atrial remodeling poorly correlated with AF duration, even in lone AF patients.[12,13,15,16]

Rather than just a pathologic finding on atrial specimens, atrial fibrosis has therefore led to a novel definition of the disease. The term "fibrotic atrial cardiomyopathy (FACMP)", which was originally proposed by Kottkamp et al.[17], is being used to describe a specific, primary form of biatrial pathology, characterized by extensive fibrosis as the substrate underlying atrial arrhythmias and thromboembolism.

According to this hypothesis, multifactorial insults to the atrium may contribute to the development of an atrial cardiomyopathy, and subsequently to the "symptom" of AF.[18] Therefore, lone AF has been proposed to be actually one of the arrhythmic manifestations of a structural atrial disease defined as FACMP.[19] The utility of screening patients for a FACMP has been highlighted by several studies examining the substrate of lone AF.[16] Indeed, Han et al. have stated that they had adopted the approach of using DE-MRI to diagnose true lone AF in patients who were younger than 60 years, lacked comorbidities, and had < 10% LA fibrosis.[18]

In addition, isolated atrial myocardial perfusion abnormalities and coronary flow reserve impairment indicative of microvascular dysfunction have been reported in patients with lone AF.[7,20]

Autoimmune Biomarkers

Emerging evidence has suggested that autoimmunity may contribute to the development of AF.[21] Although the association between AF and several autoantibodies, including the anti-myosin heavy chain autoantibody,[22] anti-M2-muscarinic receptor autoantibody (anti-M2-R),[23] anti-B1-adrenergic receptor autoantibody (anti-B1-R)[24] and the anti-heat shock protein autoantibody[25] have been demonstrated, data on the relationship between autoimmunity and lone AF is limited. A recent study[26] has reported that anti- M2-R and anti-B1-R levels were significantly elevated in lone AF patients when compared to age- and gender- matched control subjects. Autoantibody levels were also found to be correlated with the left atrial diameter and hs- CRP levels.[26]

Exact pathophysiological mechanisms underlying this relationship have not been fully elucidated yet. Hong et al.[27] have demonstrated that anti-M2-R positive rabbits had longer intra-atrial activation times, shorter atrial effective refractory periods and significantly increased atrial arrhythmogenicity compared to control rabbits possibly due to activation of acetylcholine-gated potassium channel IKACh.[27] Anti-M2-R levels in paroxysmal lone AF patients were found to be strongly correlated with the extent of LA fibrosis in another study, suggesting that severe LA fibrosis may be speculated to be the underlying mechanism for the role of anti-M2-R in the development and maintenance of lone AF in humans.[14] As for anti-B1-R, it has been suggested to promote the passage of calcium through L-type calcium channels by increasing production of cAMP and protein kinase A,[28,29] which is followed by myocyte destruction, fibrotic repair and electrical instability of the heart,[30] causing atrial inflammation and maintenance of AF.[31]

Genetic Factors

Heritability of AF has been evaluated in several studies.[32,33] However, although successful linkage studies in AF have been reported, the majority of studies have relied on the candidate gene approach in small families followed by functional studies of identified putative mutations.[34,35]

A family history of lone AF has been found to expose individuals to a 3.5-fold greater risk of developing arrhythmia.[36] Mutations and polymorphisms in genes coding ion channels involved in cardiac repolarization[35,37] and connexins[38,39] in the atria have been found to be associated with the development of lone AF.

Coronary Artery Disease

Weijs et al.[40] have reported that actually insidious coronary artery disease may be present in AF patients with no documented cardiovascular disease. Coronary computed tomographic examination showed that half of the patients had concealed and sometimes advanced coronary artery disease while patients were evaluated for AF.[40] Therefore, asymptomatic coronary artery disease may be suggested as a factor in pathogenesis of lone AF.

Subclinical Atherosclerosis and Endothelial Eysfunction

Increased intima-media thickness, which is an established indicator of subclinical atherosclerosis, has been shown to predispose to AF.[41] Chen et al.[42] have demonstrated that increased carotid intima- media thickness and arterial stiffness were associated with lone AF. Another study has also reported impaired endothelial function in patients with lone AF compared to control subjects reflected with lower FMD.[43]

Variations in Autonomic System Abnormalities

Although both sympathetic and parasympathetic components play a role in AF, the cholinergic component appears to be important for spontaneous initiation of AF. In the experimental setting, electrical stimulation of the left atrial ganglionic plexi or the autonomic nerve endings with retrograde activation of the ganglia has been shown to induce spontaneous firing from pulmonary veins followed by AF.[44] Lone AF patients more frequently have paroxysmal AF in the setting of increased vagal tone, especially during sleep.[45]

Vigorous Physical Activity

Several studies have demonstrated that long-lasting endurance sport practice was associated with an increase in the risk of lone AF.[46-48] Molina et al.[49] have reported that marathon running and the practice of >1500 lifetime hours of sport have been associated with a higher risk of lone AF when compared with sedentary men. Accompanying left atrial dilatation or increased vagal tone have been suggested to contribute to the pathogenesis.[49] However exact electrophysiological mechanisms underlying this association have not been elucidated fully yet.

Social Characteristics

The type of personality (type A behavior), anger, hostility and acute life stress have been shown to be associated with[50] and predictive of[51] incident AF. Excessive sympathetic activity has been proposed to mediate these effects. Increased circulating catecholamines in acute life stress[52] and the observation that beta-adrenergic blockade prevents the arrhythmogenic effects of acute life stress[53,54] support this hypothesis. Same changes may also apply in the pathogenesis of lone AF.

Alcohol and Other Stimulants

A 'holiday heart syndrome' of paroxysmal AF after occasional excessive alcohol intake was described over 30 years ago.[55] Alcohol is known to have a direct toxic effect on cardiomyocytes and cause a hyperadrenergic state with impaired vagal tone.[55]

Several case-control studies have found relatively similar odds of AF among abstainers and moderate drinkers, but significantly higher odds of AF among heavier drinkers,[56,57] a finding confirmed in a prospective analysis of the Copenhagen City Heart Study.[58] Another study has reported higher risks of AF associated with the 3 highest quintiles of alcohol intake, when compared with the lowest quintile, but only among men.[59] Similarly, heavy alcohol consumption may also have a role in lone AF pathogenesis.

Caffeine consumption and nicotine have also been associated with AF.[60]

Air Pollution

Air pollution has been suggested to predispose to AF. A study has shown that an interquartile increase in NO_2 was associated with an increase in the percentage of time in atrial fibrillation of 4.39% among those ≤ 50 years old, and 7.1% among males.[61] Link et al.[62]

had suggested the influence of air pollutants on new- onset atrial fibrillation, with a 26% increase in the risk of arrhythmic incidence for each 6-μg/m^3 increase in particulate matter aerodynamic diameter. Underlying mechanisms include endothelial dysfunction secondary to direct translocation; pulmonary oxidative stress and inflammation; alterations in the autonomic nervous system and secondary repolarization abnormalities.[63] Further studies are needed to identify the link between air pollution and lone AF, since study population in forementioned previous studies had co- morbidities.

Anatomic Abnormalities

Tran et al.[64] have reported an association of AF with pectus excavatum. Pectus excavatum is known to result in right atrial and right ventricular compression with potential effects on stroke volume and heart rhythm.[65] They have reported that patients with lone AF were significantly more likely to have mild, moderate, or severe pectus excavatum as defined by the pectus severity index compared to those with non- lone AF and controls.[64]

Unclarified Points

Some clinicians consider an isolated left atrial enlargement as a sign of heart disease which excludes the diagnosis of lone AF.[5] Same also applies for left ventricular diastolic dysfunction.[5] However, there is still no consensus on the definition for the extent of these echocardiographic abnormalities.

Treatment of Lone AF

Anti-arrhythmic medications are not well studied in lone AF patient population in randomized controlled trials. However, inferences can be made from studies that mainly included paroxysmal AF patients, suggesting that anti-arrhythmic medications are useful in maintenance of sinus rhythm and probably improve quality of life in lone atrial fibrillation.[66] PV isolation may be combined with linear lesions in the left atrium; ablation of non- PV triggers, complex fractionated atrial electrograms or ganglionated plexi and focal impulse and rotor modulation.[67-69] Surgical treatment of AF using the Cox–Maze procedure has not been accepted due to its complexity.[70] Surgical AF ablation has been reported to be indicated in symptomatic AF patients who prefer a surgical approach; who have failed one or more attempts at catheter ablation or who have contraindications for catheter ablation.[67]

Some authors have suggested that treatment should be personalized based on LA structural remodeling quantified by the degree of LA fibrosis determined with DE- MRI. Akoum et al.[13] have previously suggested that PV isolation strategy was effective for patients in Utah stages I and II. Furthermore, they have reported a low success rate of ablation for Utah stages III and IV. Extent of fibrosis detected on DE- MRI pre- procedurally has been shown to be a predictor of AF ablation success in lone AF patients.[71]

Prognosis

A study with a 12-year follow-up, including 346 newly diagnosed lone AF patients, has shown that these patients had a favorable prognosis as long as they had truly 'lone' arrhythmia.[72] However, with aging and/or the occurrence of cardiovascular comorbidities, the risk of AF-related complications, including thromboembolism and heart failure have been shown to increase.[72] Furthermore, also when compared to healthy control subjects, patients diagnosed with lone AF developed cardiovascular disease more often, at younger age and with a more severe disease profile.[73]

In the original description of lone AF, the authors had emphasized that there was no increase in the left atrial size during follow-up, but this assessment was done using chest radiography.[2] More recently, it has been shown that lone AF patients with increased left atrial volume (>32 ml/m^2), either at diagnosis or during the follow-up, subsequently experienced adverse cardiovascular events including stroke.[74]

Therefore, although lone AF occurs in relatively younger patients with no documented cardiopulmonary disease, long follow- up studies have demonstrated that half of lone AF patients develop cardiovascular disease over time.[73,74]

Conclusion

Lone AF patients should regularly undergo a clinical follow-up dedicated to the primary prevention of cardiovascular disease and AF-related complications.

Future studies are needed to demonstrate the cost- effectiveness of the routine use of more advanced diagnostic tools, such as non-invasive assessment of endothelial function, autoimmune markers and genetic screening and whether they would have clinical implications on treatment.

References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice G. 2014 aha/acc/hrs guideline for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. J Am Coll Cardiol 2014;64:e1-76.
2. Evans W, Swann P. Lone auricular fibrillation. Br Heart J 1954;16:189-194.
3. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M. Lone atrial fibrillation: Does it exist? J Am Coll Cardiol 2014;63:1715-1723.
4. Gallagher MM, Camm J. Classification of atrial fibrillation. Am J Cardiol 1998;82:18N-28N.
5. Pison L, Hocini M, Potpara TS, Todd D, Chen J, Blomstrom-Lundqvist C, Scientific Initiative Committee EHRA. Work-up and management of lone atrial fibrillation: Results of the european heart rhythm association survey. Europace 2014;16:1521-1523.
6. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230-246.
7. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997;96:1180-1184.
8. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. Structural correlate of atrial fibrillation in human patients. Cardiovasc Res 2002;54:361-379.
9. Boldt A, Wetzel U, Lauschke J, Weigl J, Gummert J, Hindricks G, Kottkamp H, Dhein S. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. Heart 2004;90:400-405.
10. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. J Am Coll Cardiol 2011;58:2225-2232.
11. Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH, Dimitri H, Roberts-Thomson KC, Wilson L, De Sciscio P, Young GD, Sanders P. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: Characterizing the "second factor". J Am Coll Cardiol 2009;53:1182-1191.
12. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, Blauer JJ, Rao SN, DiBella EV, Segerson NM, Daccarett M, Windfelder J, McGann CJ, Parker D, MacLeod RS, Marrouche NF. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in

patients with atrial fibrillation. Circulation 2009;119:1758-1767.
13. Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally S, Badger T, Burgon N, Haslam T, Kholmovski E, Macleod R, Marrouche N. Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: A de-mri guided approach. J Cardiovasc Electrophysiol 2011;22:16-22.
14. Gurses KM, Yalcin MU, Kocyigit D, Kesikli SA, Canpolat U, Yorgun H, Sahiner ML, Kaya EB, Hazirolan T, Ozer N, Oto MA, Guc D, Aytemir K. M2-muscarinic acetylcholine receptor autoantibody levels predict left atrial fibrosis severity in paroxysmal lone atrial fibrillation patients undergoing cryoablation. Europace 2015;17:239-246.
15. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Sparks PB, Morton JB, Kalman JM. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. J Cardiovasc Electrophysiol 2012;23:232-238.
16. Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS, Badger CT, McGann CJ, Akoum N, Kholmovski E, Macleod RS, Marrouche NF. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced mri: Implications for disease progression and response to catheter ablation. Heart Rhythm 2010;7:1475-1481.
17. Kottkamp H. Fibrotic atrial cardiomyopathy: A specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, av node disease, and thromboembolic complications. J Cardiovasc Electrophysiol 2012;23:797-799.
18. Han FT, Akoum N, Marrouche N. Value of magnetic resonance imaging in guiding atrial fibrillation management. Can J Cardiol 2013;29:1194-1202.
19. Kottkamp H. Human atrial fibrillation substrate: Towards a specific fibrotic atrial cardiomyopathy. Eur Heart J 2013;34:2731-2738.
20. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. J Am Coll Cardiol 2008;51:2053-2057.
21. Baba A, Fu M. Autoantibodies in atrial fibrillation: Actor, biomaker or bystander? Autoimmunity 2008;41:470-472.
22. Maixent JM, Paganelli F, Scaglione J, Levy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 1998;9:612-617.
23. Zou C, Zhang Z, Zhao W, Li G, Ma G, Yang X, Zhang J, Zhang L. Predictive value of pre-procedural autoantibodies against m2-muscarinic acetylcholine receptor for recurrence of atrial fibrillation one year after radiofrequency catheter ablation. J Transl Med 2013;11:7.
24. Novikova DS, Bekbosynova MS, Antidze T, Loladze NV, Domogatskii SP, Golitsyn SP, Nasonov EL, Denisova IA, Tonevitskii SP. Autoantibodies against beta(1)-adrenoreceptors in patients with cardiac rhythm disorders. Prevalence and possible role in development of arrhythmia. Kardiologiia 2004;44:17-22.
25. Mandal K, Jahangiri M, Mukhin M, Poloniecki J, Camm AJ, Xu Q. Association of anti-heat shock protein 65 antibodies with development of postoperative atrial fibrillation. Circulation 2004;110:2588-2590.
26. Yalcin MU, Gurses KM, Kocyigit D, Kesikli SA, Ates AH, Evranos B, Yorgun H, Sahiner ML, Kaya EB, Oto MA, Guc D, Ozer N, Aytemir K. Elevated m2-muscarinic and beta1-adrenergic receptor autoantibody levels are associated with paroxysmal atrial fibrillation. Clin Res Cardiol 2015;104:226-233.
27. Hong CM, Zheng QS, Liu XT, Shang FJ, Wang HT, Jiang WR. Effects of autoantibodies against m2 muscarinic acetylcholine receptors on rabbit atria in vivo. Cardiology 2009;112:180-187.
28. Chiale PA, Rosenbaum MB, Elizari MV, Hjalmarson A, Magnusson Y, Wallukat G, Hoebeke J. High prevalence of antibodies against beta 1- and beta 2-adrenoceptors in patients with primary electrical cardiac abnormalities. J Am Coll Cardiol 1995;26:864-869.
29. Chiale PA, Garro HA, Schmidberg J, Sanchez RA, Acunzo RS, Lago M, Levy G, Levin M. Inappropriate sinus tachycardia may be related to an immunologic disorder involving cardiac beta andrenergic receptors. Heart Rhythm 2006;3:1182-1186.
30. Brisinda D, Sorbo AR, Venuti A, Ruggieri MP, Manna R, Fenici P, Wallukat G, Hoebeke J, Frustaci A, Fenici R. Anti-beta-adrenoceptors autoimmunity causing 'idiopathic' arrhythmias and cardiomyopathy. Circ J 2012;76:1345-1353.
31. Molina CE, Leroy J, Richter W, Xie M, Scheitrum C, Lee IO, Maack C, Rucker-Martin C, Donzeau-Gouge P, Verde I, Llach A, Hove-Madsen L, Conti M, Vandecasteele G, Fischmeister R. Cyclic adenosine monophosphate phosphodiesterase type 4 protects against atrial arrhythmias. J Am Coll Cardiol 2012;59:2182-2190.
32. Fox CS, Parise H, D'Agostino RB, Sr., Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA 2004;291:2851-2855.
33. Christophersen IE, Ravn LS, Budtz-Joergensen E, Skytthe A, Haunsoe S, Svendsen JH, Christensen K. Familial aggregation of atrial fibrillation: A study in danish twins. Circ Arrhythm Electrophysiol 2009;2:378-383.
34. Koopmann TT, Bezzina CR. Genetics of lone atrial fibrillation. Europace 2010;12:1351-1352.
35. Roberts JD, Gollob MH. Impact of genetic discoveries on the classification of lone atrial fibrillation. J Am Coll Cardiol 2010;55:705-712.
36. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, Wohlfahrt J, Melbye M. Familial aggregation of lone atrial fibrillation in young persons. J Am Coll Cardiol 2012;60:917-921.
37. Watanabe H, Darbar D, Kaiser DW, Jiramongkolchai K, Chopra S, Donahue BS, Kannankeril PJ, Roden DM. Mutations in sodium channel beta1- and beta2-subunits associated with atrial fibrillation. Circ Arrhythm Electrophysiol 2009;2:268-275.
38. Chaldoupi SM, Loh P, Hauer RN, de Bakker JM, van Rijen HV. The role of connexin40 in atrial fibrillation. Cardiovasc Res 2009;84:15-23.
39. Gollob MH, Jones DL, Krahn AD, Danis L, Gong XQ, Shao Q, Liu X, Veinot JP, Tang AS, Stewart AF, Tesson F, Klein GJ, Yee R, Skanes AC, Guiraudon GM, Ebihara L, Bai D. Somatic mutations in the connexin 40 gene (gja5) in atrial fibrillation. New Engl J Med 2006;354:2677-2688.
40. Weijs B, Pisters R, Haest RJ, Kragten JA, Joosen IA, Versteylen M, Timmermans CC, Pison L, Blaauw Y, Hofstra L, Nieuwlaat R, Wildberger J, Crijns HJ. Patients originally diagnosed with idiopathic atrial fibrillation more often suffer from insidious coronary artery disease compared to healthy sinus rhythm controls. Heart Rhythm 2012;9:1923-1929.
41. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation 2007;115:459-467.
42. Chen LY, Foo DC, Wong RC, Seow SC, Gong L, Benditt DG, Ling LH. Increased carotid intima-media thickness and arterial stiffness are associated with lone atrial fibrillation. Int J Cardiol 2013;168:3132-3134.
43. Polovina M, Potpara T, Giga V, Stepanovic J, Ostojic M. Impaired endothelial function in lone atrial fibrillation. Vojnosanit Pregl 2013;70:908-914.
44. Zhou J, Scherlag BJ, Edwards J, Jackman WM, Lazzara R, Po SS. Gradients of atrial refractoriness and inducibility of atrial fibrillation due to stimulation of ganglionated plexi. J Cardiovasc Electrophysiol 2007;18:83-90.
45. Huang JL, Wen ZC, Lee WL, Chang MS, Chen SA. Changes of autonomic tone before the onset of paroxysmal atrial fibrillation. Int J Cardiol 1998;66:275-283.
46. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: Case-control study. BMJ 1998;316:1784-1785.
47. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, Pare C, Azqueta M, Sanz G. Long-lasting sport practice and lone atrial fibrillation. Eur Heart J

2002;23:477-482.
48. Elosua R, Arquer A, Mont L, Sambola A, Molina L, Garcia-Moran E, Brugada J, Marrugat J. Sport practice and the risk of lone atrial fibrillation: A case-control study. Int J Cardiol 2006;108:332-337.
49. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C, Elosua R. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: A follow-up study. Europace 2008;10:618-623.
50. Mattioli AV, Bonatti S, Zennaro M, Mattioli G. The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation. Europace 2005;7:211-220.
51. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB, Sr., Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the framingham offspring study. Circulation 2004;109:1267-1271.
52. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192-2217.
53. Brodsky MA, Sato DA, Iseri LT, Wolff LJ, Allen BJ. Ventricular tachyarrhythmia associated with psychological stress. The role of the sympathetic nervous system. JAMA 1987;257:2064-2067.
54. Verrier RL, Hagestad EL, Lown B. Delayed myocardial ischemia induced by anger. Circulation 1987;75:249-254.
55. Potpara TS, Lip GY. Lone atrial fibrillation: What is known and what is to come. Int J Clin Pract 2011;65:446-457.
56. Djousse L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, Massaro JM, D'Agostino RB, Wolf PA, Ellison RC. Long-term alcohol consumption and the risk of atrial fibrillation in the framingham study. Am J Cardiol 2004;93:710-713.
57. Rich EC, Siebold C, Campion B. Alcohol-related acute atrial fibrillation. A case-control study and review of 40 patients. Arch Intern Med 1985;145:830-833.
58. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: The copenhagen city heart study. Circulation 2005;112:1736-1742.
59. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: A cohort study. Arch Intern Med 2004;164:1993-1998.
60. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: Causes of 'not-so-lone atrial fibrillation'. Europace 2008;10:668-673.
61. Cakmak S, Kauri L, Shutt R, Liu L, Green MS, Mulholland M, Stieb D, Dales R. The association between ambient air quality and cardiac rate and rhythm in ambulatory subjects. Environ Int 2014;73:365-371.
62. Link MS, Luttmann-Gibson H, Schwartz J, Mittleman MA, Wessler B, Gold DR, Dockery DW, Laden F. Acute exposure to air pollution triggers atrial fibrillation. J Am Coll Cardiol 2013;62:816-825.
63. Watkins A, Danilewitz M, Kusha M, Masse S, Urch B, Quadros K, Spears D, Farid T, Nanthakumar K. Air pollution and arrhythmic risk: The smog is yet to clear. Can J Cardiol 2013;29:734-741.
64. Tran NT, Larry Klein J, Paul Mounsey J, Chung EH, Schwartz JD, Pursell I, Gehi AK. Lone atrial fibrillation is associated with pectus excavatum. Heart Rhythm 2013;10:1263-1269.
65. Oezcan S, Attenhofer Jost CH, Pfyffer M, Kellenberger C, Jenni R, Binggeli C, Faeh-Gunz A, Seifert B, Scharf C, Kretschmar O, Valsangiacomo Buechel ER. Pectus excavatum: Echocardiography and cardiac mri reveal frequent pericardial effusion and right-sided heart anomalies. Eur Heart J Cardiovasc Imaging 2012;13:673-679.
66. Kumareswaran R, Dorian P. Utility of anti-arrhythmic medications in 'lone atrial fibrillation'. Curr Pharm Design 2015;21:573-579.
67. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D, Heart Rhythm Society Task Force on C, Surgical Ablation of Atrial F. 2012 hrs/ehra/ecas expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the heart rhythm society (hrs) task force on catheter and surgical ablation of atrial fibrillation. Developed in partnership with the european heart rhythm association (ehra), a registered branch of the european society of cardiology (esc) and the european cardiac arrhythmia society (ecas); and in collaboration with the american college of cardiology (acc), american heart association (aha), the asia pacific heart rhythm society (aphrs), and the society of thoracic surgeons (sts). Endorsed by the governing bodies of the american college of cardiology foundation, the american heart association, the european cardiac arrhythmia society, the european heart rhythm association, the society of thoracic surgeons, the asia pacific heart rhythm society, and the heart rhythm society. Heart Rhythm 2012;9:632-696 e621.
68. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: Confirm (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. J Am Coll Cardiol 2012;60:628-636.
69. Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: On-treatment analysis of the confirm trial (conventional ablation for af with or without focal impulse and rotor modulation). J Am Coll Cardiol 2013;62:138-147.
70. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Guidelines-CPG ESCCfP, Document R. 2012 focused update of the esc guidelines for the management of atrial fibrillation: An update of the 2010 esc guidelines for the management of atrial fibrillation--developed with the special contribution of the european heart rhythm association. Europace 2012;14:1385-1413.
71. Canpolat U, Oto A, Hazirolan T, Sunman H, Yorgun H, Sahiner L, Kaya EB, Aytemir K. A prospective de-mri study evaluating the role of tgf-beta1 in left atrial fibrosis and implications for outcomes of cryoballoon-based catheter ablation: New insights into primary fibrotic atriocardiomyopathy. J Cardiovasc Electrophysiol 2015;26:251-259.
72. Potpara TS, Stankovic GR, Beleslin BD, Polovina MM, Marinkovic JM, Ostojic MC, Lip GY. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: Implications of arrhythmia progression on prognosis: The belgrade atrial fibrillation study. Chest 2012;141:339-347.
73. Weijs B, de Vos CB, Tieleman RG, Peeters FE, Limantoro I, Kroon AA, Cheriex EC, Pisters R, Crijns HJ. The occurrence of cardiovascular disease during 5-year follow-up in patients with idiopathic atrial fibrillation. Europace 2013;15:18-23.
74. Osranek M, Bursi F, Bailey KR, Grossardt BR, Brown RD, Jr., Kopecky SL, Tsang TS, Seward JB. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: Three-decade follow-up. Eur Heart J 2005;26:2556-2561.