[3] Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137:352–60.
[4] Dougherty AH, Nacarelli GV, Gray EI, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol 1984;54:778–82.
[5] Saufer R, Wohlgelernter D, Vita NA, et al. Intact systolic left ventricular function in clinical congestive heart failure. Am J Cardiol 1985;55:1032–6.
[6] Grossman W. Diastolic dysfunction in congestive heart failure. N Engl J Med 1991;325:1557–64.
[7] Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Ann Intern Med 1992;117:502–10.
[8] Vansan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565–74.
[9] Kinney EL, Wright RJD. Survival in patients with heart failure and normal basal systolic wall motion. Angiology 1989;40:1025–9.
[10] Cohn JN, Jonhson G. Heart failure with normal ejection fraction. The V-Heft Study. Veterans Administration Cooperative Study Group. Circulation 1990;81:III48–53.
[11] Ghali JK, Kadakia S, Bhatt A, Cooper R, Liao Y. Survival of heart failure patients with preserved versus impaired systolic function: the prognostic implication of blood pressure. Am Heart J 1992;123:993–7.
[12] Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure in elderly patients with normal versus abnormal left ventricular systolic function associated with coronary artery disease. Am J Cardiol 1990;66: 1257–9.
[13] Taffet GE, Teasdale TA, Bleyer AJ, Kutka NJ, Luchi RJ. Survival of elderly men with congestive heart failure. Age Ageing 1992;21:49–55.
[14] McDermott MM, Feinglass J, Lee PI, et al. Systolic function, readmission rates and survival among consecutively hospitalized patients with congestive heart failure. Am Heart J 1997;14:728–36.
[15] Pernenkil R, Vinson JM, Shah AS, Beckham V, Wittenberg C, Rich MN. Course and prognosis in patients > or = 70 years of age with congestive heart failure and normal versus abnormal left ventricle ejection fraction. Am J Cardiol 1997;79:216–9.
[16] Senni M, Tribouillowy C, Rodenheffer R, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.
[17] Vasan RS, Larson M, Benjamin E, Evans J, Reis C, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
[18] Senni M, Redfield M. Heart failure with preserved systolic function. A different natural history? J Am Coll Cardiol 2001;38:1277–82.
[19] Gottdiener JS, Arnold A, Aurigemma G, et al. Predictors of congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol 2000;35:1628–37.
[20] Aurigemma G, Gottdiener JS, Shemansky L, Gardin J. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly. J Am Coll Cardiol 2001;37:1042–8.
[21] How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. Eur Heart J 1998;19:990–1003.
[22] Remme W, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Task Force Report. European Society of Cardiology. Eur Heart J 2001;22:1527–60.
[23] Vasan RS, Levy D. Defining diastolic heart failure. A call for standardized diagnostic criteria. Circulation 2000;101:2118–21.
[24] Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult.
[25] Zile MR, Brutsaert MD. New concepts in diastolic dysfunction and diastolic heart failure: Part I. Diagnosis, prognosis and measurements of diastolic function. Circulation 2002;105:1387–15139.
[26] Zile MR, Brutsaert MD. New concepts in diastolic dysfunction and diastolic heart failure: Part II. Causal mechanism and treatment. Circulation 2002;105:1503–8.
[27] Jensen J, Hedin L, Widell C, Agnhom P, Andersson B, Fu M. Characteristics of heart failure in the elderly — a hospital cohort registry-based study. Int J Cardiol 2008;125:191–6.
[28] Peltier M, Houpe D, Cohen-Solal A, Béguin M, Levy F, Tribouilloy C. Treatment practices in heart failure with preserved left ventricular ejection fraction: a prospective observational study. Int J Cardiol Jun 12 2007;118(3):363–9.

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Atrial fibrillation (mechanistic view point)

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Atrial fibrillation (AF) is characterised by multiple excitation wavelets that propagate around the atrial myocardium [1,2]. Multi-electrode mapping systems have made studying atrial activation pattern feasible, particularly during open heart surgery and percutaneous intervention techniques

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[3–7]. This has shown the pulmonary venous orifices as the most frequent source of AF foci, which may also be detected in other venous-atrial connections [8,9]. Pulmonary venous ablation of AF circutes has significantly altered clinical practice and resulted in better outcome for AF patients [8,10–13].

1. Atrial structural changes in AF

AF results from a complex interaction between various initiating triggers and development of abnormal atrial tissue substrate [13]. Although AF is commonly caused by organic mitral valve disease [14] or functional left ventricular disease [15,16], the resulting raised left atrial pressure seems to be the common underlying disturbed pathophysiology [16,17]. Chronically raised left atrial pressure causes increased wall stress and hence perpetual cavity dilatation [18]. As is the case with the ventricle in cardiomyopathy, cavity dilatation is associated with different degrees of mid-wall fibrosis [19]. This has been histologically confirmed in the atrial wall in AF [19]. The replacement of atrial muscle mass by fibrous tissue [20] has significant implications on the activation time relations of the left atrium. Atrial fibrosis prolongs left atrial depolarisation time, disrupts the cell coupling at gap junction and causes glycogen granules accumulation [21]. The end result of atrial wall fibrosis is cavity remodelling and arrhythmia [22]. We have previously shown that patients prone to atrial arrhythmia demonstrate significantly reversed electromechanical timing between the two atria, with the left atrial electromechanical delay shorter than the right atrium [23].

2. Neural and chemical changes in AF

Normal atrial electrical function is maintained by a balance between sympathetic and parasympathetic driving systems [24]. Evidence exists which demonstrates significant lack of normal autonomic neural balance in patients with chronic AF [24]. When it occurs, AF is associated with altered ion channel function [21] and progressive shortening of atrial refractory periods [25] and hence the established vicious circle ‘atrial fibrillation begets atrial fibrillation’ [26]. Even within the same atrium AF is also associated with increased dispersion of refractoriness between different atrial segments [27]. Finally, evidence for genetic predisposition to AF exists, suggesting that ACE D allele modulates angiotensin II levels and hence contributes to cardiac remodelling and development of AF [28].

Despite the available wealth of knowledge about atrial function in chronic AF, paroxysmal AF in patients with structurally normal or even abnormal heart is less well understood [29]. Such patients may have a labile trigger-predominant mechanism e.g. fluctuating atrial pressure secondary to raised left ventricular end-diastolic pressure, compared to those with permanent AF who have a substrate predominant mechanism [13,27]. Little is known about the mechanism behind paroxysmal AF in such patients and hence the ideal recommendations for its management [30]. Although paroxysmal AF could be heart rate related in some patients, it is not the case in the majority; hence the extreme difficulty in devising a policy for uniform management [13,27]. Few issues need thorough investigation in such patients.

1) Is paroxysmal AF an early warning before patients develop chronic AF? The answer to this question is mainly ‘No’ since patients may develop chronic AF with a completely normal left atrial size, a commonly seen picture in the elderly. However, in some patients paroxysmal AF may be a warning sign, either reflecting progressive mitral valve disease (stenosis or regurgitation) or left ventricular disease, irrespective of its aetiology. Progressive calcium deposition in the epicardial layer of the myocardium may also affect the conduction system and hence eventual development of AF, particularly in the elderly.
2) Frequent paroxysms of AF and lack of optimum contractile atrial function may hypothetically itself cause atrial cavity dilatation, particularly in the presence of an underlying substrate for raised atrial pressure. In this case management should be directed towards the primary underlying problem as well as aggressive control of the episodes of fibrillation.
3) Another potential mechanism behind paroxysmal AF in patients with coronary artery disease is atrial ischaemia. This mechanism is similar in essence to ventricular arrhythmia that reflects myocardial ischaemia.
4) On the other hand, chronic AF may be a desirable development in some clinical conditions. Patients with severe left ventricular disease and raised end-diastolic pressure have very little blood pumped into the ventricle during atrial systole; most of it is reversed back into the pulmonary veins and hence pulmonary venous congestion and breathlessness develop. AF in these patients avoids such pulmonary venous insufficiency and may partially improve symptoms. The same mechanism applies to patients with atrial flutter, particularly with ventricular disease, who improve symptomatically with electric conversion to atrial fibrillation. Thus, paroxysmal AF in these patients should also preferentially be converted into chronic atrial fibrillation to ensure stability.
5) Patients with paroxysmal AF and normal heart may have disturbed atrial wall stability by increased extra-atrial pressure e.g. rapid intrathoracic fluid collection. Thorough investigation of such patients by echocardiography and CT scanning should guide towards optimum management and avoid potentially risky anti-arrhythmic medications.

In summary, atrial fibrillation, whether chronic or paroxysmal, is a complex disease with multifactorial causes. Although predictors of its occurrence are important, i.e. atrial size, detailed assessment of the underlying aetiology is the only determinant of its optimum management.

References

[1] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn 1962;140:183–8.

[2] Moe GK, Abildskov JA. Atrial fibrillation as a self sustaining arrhythmia independent of focal discharge. Am Heart J 1959;58:59–70.
[3] Cox JL, Canavan TE, Schuessler RB, et al. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiological mapping and description of the electrophysiological basis of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg 1991;101:406–26.
[4] Konings KT, Kirchof, Smeets JR, et al. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994;89: 1665–80.
[5] Harada A, Sasaki K, Fukushima T, et al. Atrial activation during chronic atrial fibrillation in patients with isolated mitral valve disease. Ann Thorac Surg 1996;61:104–11.
[6] Holm M, Johansson R, Brandt J, Luhrs C, Olsson SB. Epicardial right atrial free wall mapping in chronic atrial fibrillation: documentation of repetitive activation with a focal spread — a hitherto unrecognized phenomenon in man. Eur Heart J 1997;18:290–310.
[7] Schilling RJ, Kadish AH, Peters NS, Goldberger J, Davies DW. Endocardial mapping of atrial fibrillation in the human right atrium using a non-contact catheter. Eur Heart J 2000;21:550–64.
[8] Jais P, Haissaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95:572–6.
[9] Shah D, Haissaguerre M, Jais P, et al. Nonpulmonary vein foci: do they exist? Pacing Clin Electrophysiol 2003;26:1631–5.
[10] Prystowsky EN, Benson Jr DW, Fuster V, et al. Management of patients with atrial fibrillation. A statement for healthcare professionals. From the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. Circulation 1996;93:1262–77.
[11] Haissaguerre M, Jais P, Shah DC, et al. Electrophysiological breakthroughs from left atrium to the pulmonary veins. Circulation 2000;102: 2463–5.
[12] Oral H, Pappone C, Chung A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N Engl J Med 2006;354: 934–41.
[13] Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary. Eur Heart J 2006;27:1979–2030.
[14] Bailey GW, Braniff BA, Hancock EW, et al. Relation of left atrial pathology to atrial fibrillation in mitral valvular disease. Ann Intern Med 1968;69:13–20.
[15] Tsang TS, Gersh BJ, Appleton CP, et al. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. J Am Coll Cardiol 2002;40: 1636–44.
[16] Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994;89:724–36.
[17] Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Risks for atrial fibrillation and congestive heart failure in patients >65 years of age with abnormal left ventricular diastolic relaxation. J Am Coll Cardiol 2004;93.
[18] Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 1995;92:835–41.
[19] Mary-Rabine L, Albert L, Pham TD, et al. The relationship of human atrial cellular electrophysiology to clinical function and ultastructure. Circ Res 1983;52:188–99.
[20] Aime-Sempe C, Folliguet T, Rucker-Martin C, et al. Myocardial cell death in fibrillating and dilated human right atria. J Am Coll Cardiol 1999;34:1577–86.
[21] Polontchouk L, Haefliger JA, Ebelt B, et al. Effects of chronic atrial fibrillation on gap junction distribution in human and rat atria. J Am Coll Cardiol 2001;38:883–91.
[22] Sanflippo AJ, Abscal VM, Sheehan M, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation 1990;82:792–7.
[23] Li W, Sarubbi B, Sutton R, Somerville J, Gibson D, Henein MY. Atrial and ventricular electromechanical function in 1-ventricle hearts: influence of atrial flutter and Fontan procedure. J Am Soc Echocardiogr 2001;14:186–93.
[24] Maisel WH. Autonomic modulation preceding the onset of atrial fibrillation. J Am Coll Cardiol 2003;42:1269–70.
[25] Misier AR, Opthof T, van Hemel NM, et al. Increased dispersion of "refractoriness" in patients with idiopathic paroxysmal atrial fibrillation. J Am Coll Cardiol 1992;19:1531–5.
[26] Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in wake chronically instrumented goats. Circulation 1995;92:1954–68.
[27] Peters NS, Schilling RJ, Kanagaratnam P, Markides V. Atrial fibrillation: strategies to control, combat, and cure. Lancet 2002;359:593–603.
[28] Otway R, Vandenberg JI, Guo G, et al. Stretch-sensitive KCNQ1 mutation A link between genetic and environmental factors in the pathogenesis of atrial fibrillation? J Am Coll Cardiol 2007;49: 578–86.
[29] Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The college of French Cardiologist. Circulation 1999;99: 3028–35.
[30] Page RL, Wilkinson WE, Claire WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation 1994;89:224–7.

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