Review Article

Arrhythmias in the Elderly: Modern Management

Nikolaos Fragakis, George Katsaris

2nd Cardiac Department, G. Papanikolaou General Hospital, Thessaloniki, Greece

Address:
Nikolaos Fragakis

42 Kromnis St.,
55131 Thessaloniki
Greece
e-mail:
nfrag@panafonet.gr

Cardiac rhythm disturbances are seen frequently in elderly people, even those without a history of cardiac or other diseases, as a result of the degenerative changes to which the ageing heart is subjected.[1] However, most cardiac arrhythmias in the elderly are the consequence of hypertension or coronary artery disease. Problems of the cardiovascular system that are related to ageing, such as vascular stiffness, a reduced β-adrenergic cardiovascular response, an increased dependency on the atrial contribution to left ventricular diastolic filling, and a greater likelihood of coronary artery disease, are all factors that exacerbate the symptoms and worsen the prognosis when arrhythmias appear. In the elderly, arrhythmias are a significant cause of falls, physical disability, and frequent hospital admissions.[2] Recent developments in the treatment of both supraventricular and ventricular arrhythmias can also find important application in elderly patients.

Bradyarrhythmias
Pacing in the elderly

Sinus node dysfunction and disturbances of the atrioventricular conduction system are common causes of bradycardia in the elderly. Permanent pacing is the treatment of choice when the bradycardia is accompanied by symptoms. The mean age for pacemaker implantation is 74 years, while 70% of patients who need pacemaker replacement are over 70 years old.[3] Also, the percentage of aged patients (≥80 years) who receive a permanent pacemaker, according to a recent retrospective study,[4] has shown a notable increase in recent years, from 18% in the nineteen seventies to 32% in the nineteen nineties.

Sick sinus syndrome

This syndrome is manifested through a variety of symptoms (dizziness, fatigue, syncopal or pre-syncopal episodes) and arrhythmias, such as sinus bradycardia (<40 beats/min), sinus pauses (>3 seconds), and episodes of tachycardia-bradycardia. The mean age at which it occurs is 65 years.[5] Ageing leads to a progressive loss of P cells, which are the main pacemaker cells of the sinus node.[6] Histological preparations from patients with sick sinus syndrome show a varying degree of fibrosis and deposition of fatty tissue in the sinus node, although the degree of fibrosis is not related to the severity of sinus node dysfunction.[6,7] Among the causes of secondary sick sinus syndrome are conditions that appear frequently in elderly individuals, such as hypothyroidism, infiltrative diseases (amyloidosis, etc.), inflammatory disorders (pericarditis, collagen diseases), coronary artery disease, malignancies, and kidney and liver dysfunction. The elderly also show a significant predisposition to sinus node dysfunction after taking either purely cardiological medication (β-blockers, calcium inhibitors, cardiac glucosides, antiarrhythmics) or drugs of other cat-

Table 1. Indications for pacing in sick sinus syndrome.

Class I	1. Proven symptomatic bradycardia, including frequent sinus pauses. In certain patients the bradycardia may be iatrogenic because of the taking of drugs that are considered irreplaceable. 2. Symptomatic chronotropic insufficiency.
Class IIa	1. Bradycardia (<40 beats/min) and presence of symptoms without a proven correlation between them. 2. Unexplained syncope in patients where severe sinus node dysfunction is revealed later, either spontaneously or during electrophysiological study.
Class IIb	Minimally symptomatic patients with slow rate (<40 beats/min) in an alert state.
Class III	Asymptomatic patients, or when symptoms are not the result of bradycardia.

egories (simetidine, amitriptiline, phenodiazines, lithium).

Symptomatic sinus node dysfunction is an absolute indication for pacing (Class I). Table 1 shows the indications for pacing in sick sinus syndrome, according to the guidelines of the American College of Cardiology.[8]

The choice of the most appropriate pacing mode (AAIR, DDDR, VVIR) rests on an analysis of the findings of large prospective, randomised studies.[9-13] That these included elderly people can be seen from the mean age of their patient populations (Table 2). Overall, those studies did not show any superiority of atrioventricular over ventricular pacing, as regards survival and stroke prevention. In contrast, physiological pacing was associated with a significant reduction in the incidence of atrial fibrillation and with an improvement in the quality of life. The only study to show an improvement in survival was carried out in Denmark,[9] and this was probably due to the use of exclusively atrial pacing (AAI), thus avoiding the harmful effects of ventricular pacing. The choice of AAI(R) mode in patients with sinus node disease is indicated in cases of symptomatic bradycardia, provided that there are no conduction disturbances at the level of the atrioventricular node. When an atrioventricular pacemaker is chosen, it should be programmed in such a way as to avoid ventricular pacing as far as possible (long atrioventricular delay). According to recent studies, this allows the best preservation of left ventricular fractional shortening and reduces left atrial dilatation.[14,15]

Disturbances of atrioventricular conduction

The atrioventricular node is the first part of the atrioventricular conduction system to be affected by the ageing process. A prolonged PR interval and first degree atrioventricular block are common findings in the elderly (~8%), while second and third degree block are seen more rarely (~1%).[16,17] Histological studies of patients who developed complete atrioventricular block have shown increased deposition of collagen fibres within and around the atrioventricular node and the His-Purkinje system.[18] Also, the process of programmed cell death (apoptosis) is likely to play a role in the appearance of atrioventricular block during ageing.[19]

Idiopathic fibrosis of the His bundle branches occurs in Lev's and Lenègre's diseases.[20,21] In the former case, there is a progressive loss of myocytes in the proximal section of the branches, which may ultimately lead to an interruption of stimulus conduction at a level between the His bundle and the branches. This process usually starts during the fourth decade of life, commencing with the appearance of left bundle branch block and being completed after 20-30 years. Lenègre's disease is characterised by a stronger, diffuse degenerative process that affects the peripheral parts of the branches.

Table 3 shows the indications for pacing in various types of atrioventricular block.[22] First degree block is generally considered to be a Class III indication for pacing. In certain patients, however, who have a particularly prolonged PR interval (>300 ms) and exhibit symptoms similar to those of pacemaker syndrome, it is an indication for a permanent atrioventricular pacemaker (Class IIa). Appearance of the Wenckebach phenomenon in elderly patients is likely to mask disease of the conduction system, rather than being due to increased parasympathetic tone as in young people, and should thus be monitored carefully.

Large, prospective, randomised trials have not shown any superiority of atrioventricular pacing over simple atrial pacing in patients with atrioventricular block (Table 4).[12,23] The recently published UK-PACE trial, which compared VVI(R) and DDD pacing in 2021 patients aged >70 years, found no difference in overall mortality or cardiovascular events over three to five years' follow up.

New indications for pacemaker implantation

Many of the new indications for pacemaker implantation concern elderly and aged patients. Pacemaker

Table 2. Effect of pacing mode on various clinical parameters according to the results of large, randomised studies.

Study	N	Mean age (yrs)	Cause	Follow up (yrs)	Pacing mode	Mortality	HF	AF	Stroke	QL
MOST[13]	2010	74	SSS	2.7	VVIR vs. DDDR	↔	↑	↑	↔	→
Andersen et al[9]	225	76	SSS	5.5	VVI vs. AAI	↑	↑	↑	↑	
CTOPP[12]	2568	73	SSS or AVB	3	VVI(R) vs. DDD(R) or AAI(R)	↔	↔	↑	↔	
PASE[10]	407	76	SSS or AVB	2.5	VVIR vs. DDDR	↔	↔	↑	↔	↓*
Mattioli et al[11]	210	77	SSS or AVB	2	VVI(R) vs. DDD(R) or AAI(R)			↑*	↑*	
UKPACE[23]	2021	80	AVB	4.6	VVI(R) vs. DDD	↔	↔	↔	↑	

AF – atrial fibrillation; AVB – atrioventricular block; HF – heart failure; QL – quality of life; SSS – sick sinus syndrome.

* in patients with SSS

Table 3. Indications for pacing in atrioventricular block

Asymptomatic	Indication
1st degree	Pacing not indicated
2nd degree	Pacing not indicated in type I with narrow QRS Electrophysiological study in type I with wide QRS Pacing in type II
3rd degree	Pacing
Symptomatic	Pacing regardless of type

(Modified from reference 22.)

implantation is particularly useful in patients with carotid sinus hypersensitivity. In this syndrome, coronary sinus massage induces symptomatic bradycardia with pauses longer than three seconds and/or a drop in blood pressure >50 mmHg. From 25% to 40% of elderly patients with syncope or unexplained falls exhibit carotid sinus hypersensitivity.[24] The SAFE-PACE randomised trial, which included patients with a history of falls and a pathological response to carotid sinus massage, showed that the control group were four times more likely to experience a recurrence of symptoms than were those in the group who were treated with atrioventricular pacing.[25]

Atrial pacing from two different sites (bifocal, biatrial), or from different sites in the interatrial septum, has been suggested recently as an alternative method for preventing relapse in patients with paroxysmal or persistent atrial fibrillation.[26,27] Inhomogeneous and delayed intra-atrial and inter-atrial conduction predispose to the development of atrial fibrillation. Simultaneous atrial pacing from two different sites or from the interatrial septum might restore the homogeneity of atrial depolarisation and thus modify the substrate on which atrial fibrillation develops. However, the initially encouraging results from the application of this technique for the prevention of atrial fibrillation were not confirmed by later randomised trials.[28]

Various pacing algorithms for the prevention of atrial fibrillation have been incorporated in modern atrioventricular pacing devices, aiming at the prevention of conditions that usually introduce episodes of paroxysmal atrial fibrillation, such as atrial extrasystoles, bradycardia, etc. Four basic types of algorithm have been developed: Dynamic sinus overdrive (pace conditioning, rate smoothing); reaction to atrial premature complexes (PAC) (post-PAC response, PAC suppression); reaction to restoration of sinus rhythm (post atrial fibrillation response); and prevention of inappropriate rate decrease after exercise (post-exercise response). Studies that evaluated the efficacy of the prevention algorithms showed a reduction of symptoms and total atrial fibrillation burden only in selected patients, without solving the problem of determining in advance which groups of patients would be likely to benefit from the algorithms.[29,30]

To conclude, pacing for the prevention of atrial

Table 4. Recommendations of the American College of Chest Physicians for stroke prevention in atrial fibrillation.[35]

Risk factors	Recommended treatment
Any high risk factor or >1 medium risk factor	Warfarin
1 medium risk factor	Aspirin or warfarin
No high or medium risk factor	Aspirin

High risk factors: Previous stroke, hypertension, reduced left ventricular function, age >75 years, mitral valve stenosis, prosthetic valve.

Medium risk factors: Age 65-75 years, diabetes, coronary artery disease.

fibrillation nowadays only has a place in cases where there are already other indications for pacing.

Tachyarrythmias

Supraventricular tachycardias

The most common supraventricular tachyarrhythmia in the elderly is atrial fibrillation (~ 10% in those aged >75 years). With the exception of atrial fibrillation and flutter, the remaining supraventricular tachycardias do not adversely affect the patient's prognosis.

Atrial fibrillation

This common arrhythmia is an independent risk factor for cardiac and overall mortality.[31] In addition, it increases the risk of heart failure and embolic events, while having a negative effect on the quality of life and the mental function of elderly individuals. The Rotterdam study showed that both Alzheimer's disease and senility were more common in patients with atrial fibrillation.[32,33]

The strategies of atrial fibrillation management include the prevention of thromboembolic episodes through administration of antiplatelet or anticoagulant agents, and control of the arrhythmia, either by restoring and maintaining sinus rhythm (rhythm control strategy) or simply by controlling the heart rate (rate control strategy).

A meta-analysis of five randomised trials that compared aspirin with warfarin in the primary prevention of stroke showed that warfarin reduced the risk by 36% compared to aspirin.[34] The current recommendations of the American College of Chest Physicians are summarised in table 4.[35] The data concerning anticoagulant treatment in patients aged >80 years are equivocal, so in these patients anticoagulant treatment should only be given when there are no contraindications and following careful risk stratification. In the very elderly the tendency is to aim at an international normalised ratio close to 2.0 and not exceeding 2.5, although this guideline is not based on randomised studies. In spite of its efficacy, coumarin therapy has many inherent problems, especially in elderly patients, and attempts are being made to find alternative medications. Ximelagatran is a new direct thrombin inhibitor that is taken orally and is rapidly converted into melagatran, its active form, after absorption. Data from clinical trials (SPORTIF III, V) have confirmed that ximelagatran is not inferior to warfarin in the prevention of embolic episodes, while it is associated with fewer total episodes

of major or minor haemorrhage. However, optimism must be tempered by the need for monitoring of liver function, at least during the first six months of treatment, given that administration of the drug has been related with triple the normal increase in transaminase in 6% of patients. Findings are awaited from studies with longer follow up so that more certain conclusions may be drawn.[36]

The AFFIRM trial[37] was designed to compare the two strategies (rhythm control versus rate control) in more than 4000 patients with atrial fibrillation, mean age 70 ± 9 years, and an elevated risk of stroke or death. The study showed that the rate control strategy in combination with anticoagulation medication was at least as good as rhythm control, over a mean follow up period of 3.5 years. Analysis of subgroups showed that the rhythm control strategy was associated with a greater risk of death in elderly patients (>65 years), probably because of the greater risk of proarrhythmia.

The rate control strategy is therefore a clearly acceptable approach in elderly patients. The drugs of choice are β-blockers, calcium channel blockers (diltiazem, verapamil) and digitalis, or a combination thereof. The role of digitalis in the elderly depends on the characteristics of the patient. In those who are not active, or who have heart failure, monotherapy with digitalis is an acceptable choice. In contrast, in elderly patients who are very active the addition of β-blockers or calcium inhibitors is usually necessary. The reduced glomerular perfusion in elderly people, even those with normal creatinine levels, is a factor that must be taken into account when digitalis is administered.[38]

When patients continue to experience severe symptoms in spite of taking rate control medication, and those symptoms are attributable to atrial fibrillation, then the clinical physician must re-evaluate the option of cardioversion and maintenance of sinus rhythm via antiarrhythmic drugs and/or invasive method (pacing, ablation). Class Ia (quinidine, disopyramide) and Ic (propafenone, flecainide) antiarrhythmics should be used with great caution in the elderly, because of the frequent presence of coronary artery disease. Amiodarone, on the other hand, appears to be the safest and most effective antiarrhythmic drug for the restoration and in particular the maintenance of sinus rhythm.[38]

Apart from pacing, ablation is an alternative therapeutic method for the treatment of atrial fibrillation. Ablation for atrial fibrillation aims at either the control of heart rate, via ablation or modification of the atrioventricular node, or ablation of the foci that trig-

ger the arrhythmia (pulmonary vein ablation) in combination with modification of the atrial substrate.

Atrioventricular nodal ablation and implantation of a permanent pacemaker

This is the therapeutic choice in the case of symptomatic patients with atrial fibrillation whose ventricular response cannot be controlled satisfactorily by medication, or where the use of drugs causes unacceptable side effects. The technique involves the application of radiofrequency current in the region of the compact atrioventricular node, resulting in the induction of complete atrioventricular block. The method is considered to be simple, safe, and almost one hundred percent successful. Control of the heart rate is achieved by implanting a permanent pacemaker, of a type that depends on the form of atrial fibrillation. Various studies have shown that atrioventricular nodal ablation is particularly effective in controlling symptoms and improving exercise tolerance, while it also appears to improve ejection fraction, especially in patients with heart failure.[39,40] Biventricular pacing has recently been proposed for the latter category of patients, as a means of avoiding the deleterious consequences to the myocardium arising from pacing at the right ventricular apex.[41] The PAVE study showed that implantation of a biventricular pacemaker in patients undergoing atrioventricular nodal ablation for atrial fibrillation results in a significant improvement in both ejection fraction and exercise tolerance, in comparison with right ventricular apical pacing. This improvement applies mainly to patients with compromised left ventricular systolic function (ejection fraction ≤45%) who are in NYHA functional classes II-III.[41]

Modification of the atrioventricular node

Modification of the atrioventricular node has been proposed as a way of avoiding the need for permanent pacing. This involves ablation of the slow bundle, while leaving the fibres of the anterior bundle intact.[42] However, the method suffers from serious drawbacks, namely a high incidence of unwanted complete atrioventricular block (up to 36%) and a relatively frequent recurrence of symptoms, because of an increase in ventricular rate, a few months after ablation.

Pulmonary vein ablation

Recent years have seen a recognition of the importance of the pulmonary veins as a main source of ectopic

beats that can trigger paroxysmal atrial fibrillation.[43] Rapidly depolarising ectopic foci within and around the pulmonary veins produce short salvoes of focal depolarisations, triggering episodes of atrial fibrillation that then become self-sustaining. In contrast, persistent atrial fibrillation is usually sustained by an atrial substrate that is capable of maintaining multiple re-entry circuits. The main aim of ablation in atrial fibrillation is the isolation of the pulmonary veins from the atria, thus blocking the conduction of the ectopic beats from the pulmonary veins to the left atrium and preventing the onset of the arrhythmia. Various approaches have been developed aimed at the electrical isolation of the pulmonary veins. The anatomical approach is based on the creation of a continuous line that surrounds and completely encloses the veins, at a distance of >5 mm from their ostia.[44] The use of non-fluoroscopic systems for the three-dimensional imaging of the left atrium (Carto, Ensite NavX, Ensite Array) allows more accurate catheter guidance during the creation of these circumferential lesions at the appropriate location. Pulmonary vein isolation in combination with ablation of the atrial substrate seems to be an important goal of ablation strategy in cases with persistent or chronic atrial fibrillation. Linear ablation lesions in the mitral isthmus and the roof of the left atrium, joining the two superior pulmonary veins, increase the success rate, mainly in forms of persistent atrial fibrillation.[45] Complications of the method (~5%) include atrial tachycardia, thromboembolic episodes, pulmonary vein stenosis, tamponade, phrenic nerve paralysis, atrial-oesophageal fistula, and more rarely, death, while the relapse rate is significant (~30%). According to some reports, patients who suffered stroke after ablation for atrial fibrillation were older than 60 years and had a history of transient ischaemic episodes;[46] thus, special attention should be paid to the administration of anticoagulant medication during the procedure in this group of patients. The method has a generally satisfactory success rate when applied mainly in young patients with idiopathic atrial fibrillation. In contrast, experience from elderly patients, whose atrial fibrillation depends more on the substrate and less on the triggering mechanism, is limited and is insufficient to justify the widespread application of the method in these patients.

Atrial flutter

This is a rather common arrhythmia in the elderly. Typical atrial flutter is due to a re-entrant macrocircuit

and can be treated by ablation of the slow conduction zone represented by the inferior vena cava-tricuspid annulus isthmus.[47] The success rate of ablation for typical atrial flutter reaches 85%, with a relapse rate of 10%.

Paroxysmal supraventricular tachycardias

These include atrioventricular nodal re-entrant tachycardia, which is the most common paroxysmal supraventricular tachycardia, atrioventricular reciprocating tachycardia, and certain atrial tachycardias. According to an epidemiological study, the incidence of paroxysmal supraventricular tachycardia is greater in patients aged >65 years than in younger individuals.[48] Wolff-Parkinson-White syndrome, which usually appears in younger age groups and tends to diminish later, also shows a small increase in the elderly. This is attributed to the fact that calcification of the atrioventricular conduction system impedes conduction of the stimulus, thus facilitating orthodromic conduction via the bypass tract.[49]

The choice of ablation for the treatment of paroxysmal supraventricular tachycardia in the elderly has increased dramatically in recent years. Even though the data come from small series, it appears that the success rate of the method does not differ from that in younger individuals. The small increase in the complication rate is attributed to other coexistent diseases. However, it should also be kept in mind that the taking of medication often entails an increased risk of proarrhythmia in the elderly, and so ablation is likely to be the best solution.[50,51]

Ventricular tachycardias

These are tachyarrhythmias with a very high risk of sudden cardiac death, especially when they occur in the presence of underlying heart disease, such as coronary artery disease or heart failure. The antiarrhythmic drugs that have traditionally been used for the treatment of ventricular tachycardias have narrow therapeutic limits and an increased risk of proarrhythmia in elderly patients. The advent of implantable automatic defibrillators added a new dimension to the treatment of these urgent arrhythmic conditions. Secondary studies of prevention (in patients with a history of ventricular arrhythmias or cardiac arrest) showed that implantable defibrillators reduce overall mortality by 25-30% in comparison with antiarrhythmic drugs (chiefly amiodarone).[52-54] A similar decrease was seen in primary studies involving patients with left ventricular dysfunction, with or without a history of myocardial infarction (MADIT I & II, MUSTT, SCD-HeFT).[55,56] With developments in technology that allow these devices to be deployed intravenously, their small size and multiple programming options, implantable defibrillators have become an attractive therapeutic alternative in elderly patients.

Despite these encouraging data, reservations have been expressed because patients of this age group have been inadequately represented in large trials. Patients aged >80 years are usually excluded from studies, but in general the mean age does not exceed 65 years. Furthermore, in patients of advanced age the survival benefit from an implantable defibrillator is likely to be limited by other, non-cardiac causes of death. A retrospective study comparing 74 patients with ages ≥75 years with 695 younger patients showed that, although there was no difference between the groups in the number of appropriate shocks, the overall mortality in the aged patients was triple that in the younger group.[57] The MADIT II trial, however, showed that defibrillator implantation in a group of patients aged ≥75 years was associated with a greater reduction in overall mortality (>45%) than was seen in younger patients (34%).[58] Additionally, a recent prospective study found that the efficacy and safety of defibrillator implantation did not differ between patients aged 70-79 years and those aged over 80.[59]

Conclusions

As the ageing population grows in size, the number of elderly patients with arrhythmiological problems will increase too. The problems associated with the use of antiarrhythmic drugs in patients of advanced age have led to a steady increase in the proportion of patients who are treated using invasive methods. Already, elderly patients make up the vast majority of those who undergo pacemaker implantation. New indications for the implantation of pacing devices for the treatment of atrial fibrillation, an arrhythmia that is particularly common in the aged, have been tested in recent years, so far with equivocal results. Pulmonary vein ablation could be the solution in certain categories of patients with atrial fibrillation, although so far large series are lacking, especially in the case of elderly patients. Ablation for other types of paroxysmal supraventricular tachycardia has an equally high success rate as in younger patients, with no extra risk of complications. Finally, implantable defibrillator devices,

despite the lack of prospective studies that include a large number of elderly patients, appear to be the indicated method of treatment for malignant ventricular tachycardias, especially in the presence of coronary artery disease.

References

1. Manolio TA, Furberg CD, Rautaharju PM, et al: Cardiac arrhythmias on 24-hr ambulatory electrocardiography in older women and men: The Cardiovascular Health Study. J Am Coll Cardiol 1994; 23: 916-925.

2. O'Mahony D, Foote C: Prospective evaluation of unexplained syncope, dizziness, and falls among community-dwelling elderly adults. J Gerontol 1998; 53: M435-M440.

3. Lamas GA, Lee K, Sweeney M, et al: The Mode Selection Trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. Am Heart J 2000; 140: 541-551.

4. Schmidt B, Brunner M, Olschewski M, et al: Pacemaker therapy in very elderly patients: Long term survival and prognostic parameters. Am Heart J 2003; 146 (5): 908-913.

5. Rodriguez RD, Schocken DD: Update on sick sinus syndrome, a disorder of aging. Geriatrics 1990; 45: 26-36.

6. Shiraishi I, Takamatsu T, Minamikawa T, et al: Quantitative histological analysis of the human sinoatrial node during growth and aging. Circulation 1992; 85: 2176-2184.

7. Bharati S, Lev M: The pathologic changes in the conduction system beyond the age of 90. Am Heart J 1992; 124: 486-496.

8. Gregoratos G, Abrams G, Epstein AE, et al: Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: The American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2002; 106: 2145-2161.

9. Andersen HR, Nielsen JC, Thomsen PEB, et al: Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick sinus syndrome. Lancet 1997; 350: 1210-1216.

10. Lamas GA, Orav EJ, Stambler BS, et al, for the Pacemaker Selection in the Elderly Investigators: Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. N Engl J Med 1998; 338: 1097-1104.

11. Mattioli AV, Vivoli D, Mattioli G: Influence of pacing modalities on the incidence of atrial fibrillation in patients without prior atrial fibrillation: a prospective study. Eur Heart J 1998; 19: 282-286.

12. Connolly SJ, Kerr CR, Gent M, et al: Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular cause: Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000; 342: 1385-1391.

13. Lamas GA, Lee KL, Sweeny MO, et al: Mode selection trial in sinus-node dysfunction: ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; 346: 1854-1862.

14. Nielsen JC, Kristensen L, Andersen HR, et al: A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome. J Am Coll Cardiol 2003; 42: 614-623.

15. Wilkoff BL, Cook JR, Epstein AE, et al: Dual-chamber pacing or ventricular backup pacing in patients with an implantable de-fibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002; 288: 3115-3123.

16. Mymin D, Mathewson FAL, Tate RB, et al: The natural history of first-degree atrioventricular block. N Engl J Med 1986; 315: 1183-1186.

17. Frishman WH, Heiman K, Karpenos A, et al: Twenty-four hour ambulatory electrocardiography in elderly subjects: Prevalence of various arrhythmias and prognostic implications (report from the Bronx longitudinal study). Am Heart J 1996; 132: 297-302.

18. Titus JL, Edwards JE: Pathology of the aging heart, in Chesler E (ed.): Clinical Cardiology in the Elderly, 2nd ed. Futura Publishing Company, Inc. Armonk, NY, 1999.

19. James TN: Normal and abnormal consequences of apoptosis in the human heart. From postnatal morphogenesis to paroxysmal arrhythmias. Circulation 1994; 90: 556-573.

20. Lev M: The pathology of complete atrioventricular block. Prog Cardiovasc Dis 1964; 6: 317-326.

21. Lenègre J: Etiology of bilateral bundle branch fibrosis in relation to complete heart block. Prog Cardiovasc Dis 1964; 6: 409-444.

22. Kusumoto F, Phillips R, Goldshlager N, et al: Pacing therapy in the elderly. Am J Geriatr Cardiol 2002; 11: 305-316.

23. Toff WD, Camm AJ, Skehan JD: Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med 2005; 353: 145-155.

24. Huang SK, Ezri MD, Hauser RG, et al: Carotid sinus hypersensitivity in patients with unexplained syncope: clinical, electrophysiologic, and long term follow-up observations. Am Heart J 1988; 116: 989-996.

25. Kenny RA, Richardson DA, Steen NI, et al: Carotid sinus syndrome: a modifiable risk factor for no accidental falls in older adults (SAFE-PACE). J Am Coll Cardiol 2001; 38: 1491-1496.

26. Saksena S, Prakash A, Hill M, et al: Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 1996; 28: 687-694.

27. Daubert C, Mabo PH, Berder V, et al: Atrial tachyarrhythmias associated with high degree interatrial conduction block: prevention by permanent atrial resynchronisation. Eur JCPE 1994; 4: 35-44.

28. Saksena S, Prakash A, Ziegler P, et al: Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. J Am Coll Cardiol 2002; 40: 1140-1150.

29. Israel C, Hohnloser S: Pacing to prevent atrial fibrillation. J Cardiovasc Electrophysiol 2003; 14: S20-S26.

30. Mitchell ARJ, Sulke N: How do atrial pacing algorithms prevent atrial arrhythmias? Europace 2004; 6: 351-362.

31. Benjamin EJ, Wolf PA, D'Agostino RB, et al: Impact of atrial fibrillation on the risk of death. Circulation 1998; 98: 946-952.

32. Sabatini T, Frisoni GB, Barbisoni P, et al: Atrial fibrillation and cognitive disorders in older people. J Am Geriatr Soc 2000; 48: 387-390.

33. Ott A, Breteler MMB, deBruyne MC, et al: Atrial fibrillation and dementia in a population-based study: The Rotterdam Study. Stroke 1997; 28: 316-321.

34. Go AS, Hylek EM, Philipps KA, 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: 2370-2375.

35. lbers GW, Dalen JE, Laupacis A, et al: Antithrombotic therapy in atrial fibrillation. Chest 2001, Suppl 1: 194-206.

36. Olsson SB: Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003; 362: 1691-1698.

37. Wyse DG, Waldo AL, DiMarco JP, et al: A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825-1833.

38. Falk R: Ventricular rate control in the elderly: Is Digoxin enough? Am J Geriatr Cardiol 2002; 11: 353-356.

39. Brignole M, Gianfranchi L, Menozzi C, et al: Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. Circulation 1997; 96: 2617-2624.

40. Rodriguez LM, Smeets JLRM, Xie B, et al: Improvement in left ventricular function by ablation of atrioventricular nodal conduction in selected patients with lone atrial fibrillation. Am J Cardiol 1993;72:1137-1141.

41. Doshi R, Daoud E, Fellows C, et al: Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (The PAVE Study). J Cardiovasc Electrophysiol 2005; 16: 1160-1165.

42. Feld GK, Fleck RP, Fujimura O, et al: Control of rapid ventricular response by radiofrequency catheter modification of the atrioventricular node in patients with medically refractory atrial fibrillation. Circulation 1994; 90: 2299-2307.

43. Haissaguerre M, Jais P, Shah DC, et al: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339: 659-666.

44. Pappone C, Nabar: S, Oreto G, et al: Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 2000; 102: 2619-2628.

45. Verma A, Wazni OM, Marrouche NF, et al: Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol 2005; 45: 285-292.

46. Kok LC, Maggrum JM, Haines DE, et al: Cerebrovascular complication associated with pulmonary vein ablation. J Cardiovasc Electrophysiol 2002; 13: 764-767.

47. Poty H, Saoudi N, Nair M, et al: Radiofrequency catheter ablation of atrial flutter: further insights into the various types of isthmus block: application to ablation during sinus rhythm. Circulation 1995; 92: 430-435.

48. Orejarena L, Vidaillet H, DeStefano F, et al: Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol 1998; 31: 150-157.

49. Fan W, Peter CT, Gang ES, et al: Age-related changes in the clinical and electrophysiologic characteristics of patients with Wolf-Parkinson-White syndrome-comparative study between young and elderly patients. Am Heart J 1991; 122: 741-747.

50. Smith P, Vidaillet H, Sharma P, et al: Catheter ablation in the elderly in the United States: Use in the medicare population from 1991 to 1998. Pacing Clin Electrophysiol 2001; 24: 66-69.

51. Zado E, Callans D, Gottlieb C, et al: Efficacy and safety of catheter ablation in octogenarians. J Am Coll Cardiol 2000; 35: 458-462.

52. The Antiarrhythmic versus Implantable Defibrillators (AVID) Investigators: A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337: 1576-1583.

53. Connolly SJ, Gent M, Roberts RS, et al: Canadian Implantable Defibrillator Study (CIDS). A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000; 101: 1297-1302.

54. Kuck KH, Cappato R, Siebels J, et al: Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest. The Cardiac Arrest Study Hamburg (CASH). Circulation 2000; 102: 748-754.

55. Buxton AE, Lee KL, Fisher JD, et al, for the Multicenter Unsustained Tachycardia Trial Investigators: A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999: 341: 1882-1890.

56. Moss AJ, Zareba W, Hall WJ, et al: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877-883.

57. Panotopoulos P, Axtell K, Anderson A, et al: Efficacy of the implantable cardioverter-defibrillator in the elderly. J Am Coll Cardiol 1997; 29: 556-560.

58. Huang DT, Sesselberg H, Salam T, et al: Survival benefits associated with defibrillator implant in elderly patients enrolled in MADIT II. Circulation 2003; 108 (Suppl IV): IV-386, abstract 1790.

59. Noseworthy P, Lashevsky I, Dorian P, et al: Feasibility of implantable cardioverter defibrillator use in elderly patients: A case series of octogenarians. Pacing Clin Electrophysiol 2004; 27: 373-378.