respond to physiological emotional arousal, and increase their pacemaker function.[11] The concept is to have the electronic pacemaker provide a bridge to biological pacing therapeutics, until there is more solid evidence for the safety and efficacy of this revolutionary novel approach.

Whether the end result of the application of all these preliminary data will be a clinically applicable biological pacemaker remains to be proven. Although proof of concept has been demonstrated, there is still a long way to go and many obstacles to overcome before its safe and reliable clinical application. First, one needs to identify the ideal candidate pacemaker cells, and second to make headway in fine-tuning the behavior of these pacemaking cells, while finally monitoring and controlling the interactions between the pacemaker and host myocardium. Thus, there is still need for development of new technologies and more testing in the animal laboratory to enhance our understanding of mechanisms that control gene expression and cell coupling until the biological pacemaker becomes a feasible and realistic project. Meanwhile, electronic pacemaker systems have proven their value, while they are still rapidly evolving and for now remain the main and only player in the field.

As the inventor himself, Dr Michael Rosen,[12] has put it, in order to "see biological pacemaking in our lifetime", the following are needed: "For virus or stem cell, we need evidence that it is superior to the electronic pacemaker in terms of adaptability to the body's physiology and duration of effectiveness; evidence regarding long-term incidence of inflammation, infection, rejection, neoplasia; evidence for/against long-term proarrhythmic potential; localization at site of implantation vs migration to other sites; other toxicity; optimization of delivery systems". "For stem cell (embryonic, mesenchymal), we need evidence regarding persistence of the administered cell type vs differentiation into other cell types; in the latter event, evidence regarding persistence of pacemaker function (current and coupling)".

REFERENCES

1. Rosen MR, Brink PR, Cohen IS, Robinson RB. Genes, stem cells and biological pacemakers. *Cardiovasc Res* 2004; 64: 12– 23.
2. Rosen MR, Brink PR, Cohen IS, Robinson RB. Cardiac pacing: from biological to electronic …to biological? *Circ Arrhythmia Electrophysiol* 2008;1:54-61.
3. Rosen MR, Brink PR, Cohen IS, Robinson RB. Biological pacemakers based on *If*. *Med Bio Eng Comput* 2007; 45:157–166.
4. Potapova I, Plotnikov A, Lu Z, et al. Human mesenchymal stem cells as a gene delivery system to create cardiac pacemakers. *Circ Res* 2004;94:952-959.
5. http://gtp.autm.net/technology/view/11063
6. Plotnikov AN, Shlapakova I, Szabolcs MJ. Xenografted adult human mesenchymal stem cells provide a platform for sustained biological pacemaker function in canine heart. *Circulation* 2007;116:706-713.
7. Cingolani E, Yee K, Shehata M, Chugh SS, Marban E, Cho HC. Biological pacemaker created by percutaneous gene delivery via venous catheters in a porcine model of complete heart block. *Heart Rhythm* 2012; Epub 2012 Apr 20.
8. Plotnikov AN, Sosunov EA, Qu J, et al. Biological pacemaker implanted in canine left bundle branch provides ventricular escape rhythms that have physiologically acceptable rates. *Circulation* 2004;109:506-512.
9. Plotnikov AN, Bucchi A, Shlapakova I, et al. HCN212-channel biological pacemakers manifesting ventricular tachyarrhythmias are responsive to treatment with If blockade. *Heart Rhythm* 2008; 5: 282–288.
10. Bucchi A, Plotnikov AN, Shlapakova I. Wild-type and mutant HCN channels in a tandem biological-electronic cardiac pacemaker. *Circulation* 2006;114:992-999.
11. Shlapakova IN, Bearing B, Lau DH, et al. Biological pacemakers in canines exhibit positive chronotropic response to emotional arousal. *Heart Rhythm* 2010; 7:1835-1840.
12. Rosen RM. Biological pacemaking: In our lifetime? *Heart Rhythm* 2005; 2: 418-428.

Long-Term Results of Atrial Fibrillation Ablation

Sokratis Pastromas, MD

Department of Cardiology, Evagelismos Hospital, Athens, Greece

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population, affecting about 0.4% of the general population. Its prevalence increases with age reaching 15% in adults over 70 years of age.[1] During the past decade, as techniques and technologies have improved, catheter ablation of AF has become a standard and effective therapy for patients with symptomatic and drug-refractory AF. The improved three-dimensional electroanatomic mapping systems and the induction in the clinical practice of other ablation techniques, such as cryoablation, have contributed to the worldwide increase of the number of ablation procedures. Catheter ablation seems to be superior to antiarrhythmic drug therapy (ADT) which is also associated with potential toxic or proarrhythmic effects after long term use. The recently presented data from RAAFT 2 study, showed that 55% of the patients who had randomized to AF ablation had had a recurrence compared to 72%, of those who had received ADT after 2 years follow up.[2] For the first time, the 2012 updated guidelines from the

European Society of Cardiology, recommend catheter ablation as the first line therapy in selected patients with paroxysmal AF alternative to ADT (class IIa, level B).[3] The main target of the AF catheter ablation is the circumferential electrical isolation of the pulmonary veins (PVs) ostium or antrum. In some patients suffering from persistent AF, a more aggressive strategy is adopted, including left atrial substrate modification with linear ablation or rarely with lesions in other anatomical structures as right atrium, superior or inferior vena cava, fossa ovalis, left atrial appendage and coronary sinus or the ligament of Marshall.[3]

Success rates for AF ablation depend on a large number of factors. Of great importance, are the type of AF (paroxysmal, persistent, or long-standing persistent AF), the presence or absence of comorbidities, such as uncontrolled hypertension, obesity and sleep apnea, the definition of success, and the duration of follow-up.[3] The fact is that the single procedure results for AF catheter ablation, are a bit disappointing as a large number of patients, about 20% - 40%, present with early or late recurrences of AF.[4] These episodes are common, during the first 2 or 3 months after the ablation procedure and most studies have reported that the main problem is the electrical reconduction of the previously isolated PVs. The short term use of ADT, after AF ablation during the first three months after the procedure, seems to reduce the incidence of the early recurrence episodes, but not the late recurrence after the 6 months.[3] Sorgente et al suggested that after 6 years of follow up in patients with mainly persistent AF resistant to ADT, 41% of them underwent a second ablation procedure. Only 23% after the first procedure were free of AF after 6 years of follow up in contrast to 39% after the last procedure. Moreover, multivariate regression analysis showed that the only clinical factor that affected the possibility of recurrence, was the presence of non paroxysmal AF.[5] Similar results were obtained by 5 years follow up in patients after AF ablation, to whom late recurrence rate was associated independently to the presence of persistent AF and diabetes mellitus.[6] Thus, the most predictive factor for the late recurrence, seems to be the presence of persistent AF. Older patients with cardiomyopathy, ischemic or dilatative, diabetes mellitus and large atrium, are more prone to recurrences. The redo ablation procedures, always target to the circumferential re-isolation of the PVs or to new arrhytmogenic foci outside the PVs.

Most of the published studies about the AF ablation efficacy, presented data from short term follow up in less than 12 months. The outcomes of catheter ablation were better compared to ADT in the majority of these randomized trials. During one year follow up of 198 patients with paroxysmal AF enrolled in the APAF study, 93% of them who underwent catheter ablation were free of symptoms compared to 35% who received ADT.[7] Similarly, one year data from the A4 study showed that 89% of patients had no recurrence after catheter ablation compared to 23% enrolled in the ADT group.[8] Moreover, a meta-analysis of four randomized trials revealed the superiority of the ablation compared to ADT (75.7% vs. 18.8%, $P<0.001$).[9]

Data in the literature is not so much as regards the long term results of AF catheter ablation and mostly are derived from single center as well as multicenter studies involving patients with paroxysmal and persistent AF. Table 1 presents the most important studies published the last years.[6,10-16] Patients in the majority of the trials didn't receive long-term ADT and they mostly underwent more than one procedure. Gaita et al[10] enrolled 204 patients with either paroxysmal or persistent/permanent AF and they reported that PV isolation plus linear left atrial ablation without ADT is superior to the PV isolation after the first and second procedure in maintaining sinus rhythm at 3 years follow up. Pulmonary vein isolation has better long term outcomes in patients with paroxysmal AF. One hundred patients who underwent AF ablation were followed up for 39±10 months after their last procedure. The mean time to AF recurrence was 6 ± 10 months. After a single procedure, sinus rhythm was maintained at long-term follow-up in 49% patients without ADT. With a repeat procedure 57% of the patients had stable sinus rhythm without ADT and 82% with ADT.[17]

In the study of Wokhlu et al[12] factors associated independently to very late recurrence after 6 years, were the persistent AF and the wide area circumferential PV isolation. In this study left atrial diameter >45 mm was also associated independently with recurrence in patients with paroxysmal AF. Recently, Chao et al[16] reported that $CHADS_2$ score ≥3 was also an independent predictor in patients with non paroxysmal AF of recurrences. Patients who undergo a second ablation procedure have better long term success rates, than after the first ablation. Data from the group of Haissaguerre shows, that after 5 years of follow up in 100 patients arrhythmia – free rates after a single catheter ablation procedure were 40%, 37%, and 29% at 1, 2, and 5 years, respectively, with most recurrences over the first 6 months.[15] On the contrary, for the same follow up periods the rates following the redo – ablations, were 87%, 81%, and 63%, respectively.[15] As far as the patients with left ventricular systolic dysfunction are concerned, they have not participated in the majority of these clinical studies. However, a recent meta-analysis suggested that AF ablation improves left

ventricular systolic function by 11%, but patients with coronary heart disease benefit less compared to others.[18] We will have more specific results, from two on going multicenter trials (CASTLE-AF and AMICA) which evaluating the benefit of AF catheter ablation in patients with heart failure. Moreover, we have to notice, that there is not enough data about the long term efficacy of AF cryoablation. The only prospective randomized study in this field is the STOP-AF trial that enrolled 245 patients, with 163 randomized to cryoballoon treatment and 82 patients randomized to ADT [279]. After a mean follow-up of 9 months, 69.9% of patients treated with cryoballoon ablation, were free from AF compared with 7.3% of patients on antiarrhythmic drug therapy. Nineteen percent of the patients required a repeat procedure and 12% remained on ADT.[19]

The incidence of stroke episodes after AF ablation, is a very important parameter for the monitoring of these patients. A multicenter study enrolled 3,355 patients of whom 2,692 discontinued oral anticoagulation therapy (OAT) 3 to 6 months after ablation and 663 remained on OAT after this period. Follow up period was more than 2 years and 0.07% of the first group patients versus 0.045% of the second one had an ischemic stroke.[20] The incidence of the stroke seems to be higher, during the first two weeks after the procedure (0.9%) and lower later (0.1% for every year). The incidence after the discontinuation of the OAT 3 months after the ablation did not differ significantly between the patients without risk factors and those with ≥1 risk factor. [21]

The fact is that catheter ablation has become an important and widely used treatment modality for patients with symptomatic AF. The target remains the PV isolation or the left atrium modification using mostly radiofrequency energy with the support of the electroanatomical mapping systems. Patients may require more than one procedure and this can improve the success rate to around 50% to 70%. Of course the hope is to avoid the repetition of the procedures and this could maybe happen in the near future, with the evolution of the technology. Moreover, we are waiting the results from the CABANA trial which is expected to be completed in 2015 and about 3,000 patients will be enrolled, comparing the efficacy of the ablation versus ADT during a follow up period of 5 years.

REFERENCES

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. *N Engl J Med* 1982;306:1018-1022
2. Heart Rhythm 2012: www.hrsonline.org/Sessions/Scientific Program/upload/2012LBCT_Friday.pdf
3. Calkins H, Kuck KH, Cappato R, et al. 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. *J Interv Card Electrophysiol* 2012;33:171-257.
4. Kobza R, Hindricks G, Tanner H, et al. Late recurrent arrhythmias after ablation of atrial fibrillation: Incidence, mechanisms, and treatment. *Heart Rhythm* 2004;1:676–683.
5. Sorgente A, Tung P, Wylie J, Josephson ME. Six year follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. *Am J Cardiol* 2012;109: 1179-1186.
6. Wokhlu A, Hodge DO, Monahan KH, et al. Long-term outcome of atrial fibrillation ablation: impact and predictors of very late recurrence. *J Cardiovasc Electrophysiol* 2010;21:1071-1078.
7. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: The APAF Study. *J Am Coll Cardiol* 2006; 48:2340–2347.
8. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: The A4 study. *Circulation* 2008;118:2498–2505.
9. Noheria A, Kumar A, Wylie JV Jr, Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. *Arch Intern Med* 2008; 168:581-586.
10. Gaita F, Caponi D, Scaglione M, et al. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2008;1:269-75.
11. Katritsis D, Wood MA, Giazitzoglou E, Shepard RK, Kourlaba G, Ellenbogen KA. Long-term follow-up after radiofrequency catheter ablation for atrial fibrillation. *Europace* 2008;10:419-424.
12. Bhargava M, Di Biase L, Mohanty P, et al. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm* 2009;6:1403-1412.
13. Tzou WS, Marchlinski FE, Zado ES, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3:237-42.
14. Ouyang F, Tilz R, Chun J, Schmidt B, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation* 2010;122: 2368-2377.
15. Weerasooriya, R., Khairy, P., Litalien, J., et al. Catheter ablation for atrial fibrillation: Are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011;57:160–166.
16. Chao TF, Tsao HM, Lin YJ, et al. Clinical outcome of catheter ablation in patients with nonparoxysmal atrial fibrillation: results of 3-year follow-up. *Circ Arrhythm Electrophysiol* 2012;5:514-520.

17. Medi C, Sparks PB, Morton JB, Kistler PM, et al. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. *J Cardiovasc Electrophysiol* 2011;22:137-141.
18. Dagres N, Varounis C, Gaspar T, et al. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail* 2011;17:964-970.
19. Packer D. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front Stop-AF Clinical Trial. Presented at the ACC 59th Annual Meeting, Atlanta, March 14–16, 2010
20. Themistoclakis S, Corrado A, Marchlinski FE, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;55:735-743
21. Oral H, Chugh A, Ozaydin M, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. *Circulation* 2006;114:759-65.

Table 1. **Most Important Studies for Long-term Results of AF Catheter Ablation**

Study	***No. of patients***	***AAD***	***Ablation strategy***	***FU***	***Success rate***	
Gaita F et al[10]	204 pts(PAF & persAF/permAF)	no	PVI or PVI+ LL	3 years	*PAF*	
					PVI: 1st 29%, 2nd 62%	PVI+LL: 1st 53%, 2nd 85%
					persAF/permAF	
					PVI: 1st 19%, 2nd 39%	PVI+LL: 1st 41%, 2nd 75%
Katritsis et al[11]	39 pts (14 pts 1 abl., 19 pts 2 abl. & 6 pts 3 abl.) PAF	33 pts Amio- for 6 weeks after abl.	PVI	42.2±6 months	21.4% for 1 abl, 52.6% for 2 abl. & 66.7% for 3 abl.	
Bhargava et al[12]	1404 pts(728 PAF, 676 NPAF)	pts without redo-ablation	PVI & SVC guided by ICE	57±17 months	PAF: 1st 77.6%, 2nd 92.4% (without ADT)	NPAF: 1st 67.2%, 2nd 84% (without ADT)
Wokhlu et al[6]	774 pts (55% PAF, 45% persAF)	yes	PVI (38%), WACA (62%)	3.0±1.9 years	PAF: 71%, pers AF: 61%. Recurrence from 1 to 2.5 years increased by 20% in persAF vs. 12% in PAF.	
Tzou et al[13]	239 pts (85% PAF & persAF), 123 were free from AF 1 year after one abl. procedure	no	PVI & non PV triggers	5.9±1.5 years	AF free were 85% at 3 yrs and 71% at 5yrs, 7% per year recurrence rate after the 1st year	
Ouyang et al[14]	161 pts with PAF	3 months after ablation	PVI	median 4.6 years	75 pts were in SR after the 1st ablation, 66 pts 2nd ablation, 12 pts 3rd abl. 79.5% of the pts had SR during FU (median 1 procedure)	
Weerasoo riya et al[15]	100 pts (64% PAF)	Discontinued after 1 month with stable SR	PVI + CTI + LL (persAF)	5 years	AF free were 40%, 37%, and 29% at 1, 2, and 5 years (median 2 procedures per patient)	
Chao et al[16]	88 pts with NPAF	no	PVI + LL + CFAE + nonPVI foci	mean 36.8 months	71.6% had recurrence , 47.7% after the 2nd ablation & 51.1% after the 3rd ablation were free of recurrence	

AAD = antiarrhythmic drug (therapy); abl = ablation; AF = atrial fibrillation; CFAE: complex fractionated atrial electrograms; CTI = cavo-tricuspid isthmus; FU = follow-up; ICE = intracardiac echocardiography; LL = left linear; NPAF = non paroxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation, persAF = persistent atrial fibrillation; pts = patients; PV = pulmonary veins; PVI = pulmonary vein isolation; SR = sinus rhythm; SVC = superior vena cava; WACA = wide antrum circumferential ablation