

The Role of Atrial Fibrillation Catheter Ablation in Patients with Congestive Heart Failure: “Burning” for a Cure

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Abstract

Atrial Fibrillation (AF) and congestive heart failure (CHF) often co-exist. Catheter ablation is increasingly used to cure AF related to CHF. Clinical evidence supports the feasibility of catheter ablation as a treatment option in drug refractory AF patients with CHF. Investigators have reported an improvement in ejection fraction, quality of life, and functional capacity

Introduction

The interaction between atrial fibrillation (AF) and congestive heart failure (CHF) is complex. There are many issues surrounding the pathophysiology, epidemiology, and treatment which are still debated. Nevertheless, the pernicious impact of the interplay between AF and CHF in terms of morbidity and mortality in patients’ lives is irrefutable. At present, patients with AF and coexistent CHF have several rate versus rhythm control options available to them which use pharmacologic and non-pharmacologic treatments. Rhythm strategies include antiarrhythmic medications, maze procedure, catheter ablation for AF, and implantable atrial defibrillator. Rate strategies include drugs and atrioventricular junctional ablation (AVA) with permanent pacemaker. Antiarrhythmic drugs are often ineffective and have adverse effects. While surgical maze is very effective, it is technically complex and invasive. Pacing and atrial defibrillation can be somewhat effective;

however, there are disadvantages such as warfarin therapy and implantation of a pacemaker. Consequently, catheter ablation is increasingly being performed. In a direct comparison, pulmonary vein isolation (PVI) was shown to be superior to AVA with biventricular device (BI-V).¹

This review article will address the emerging role of catheter ablation in the treatment of AF in patients with coexistent CHF.

The AF and CHF Cardiovascular Epidemics:

AF affects 2.3 million individuals and accounts for over 350,000 U.S. hospitalizations annually.² Two thirds of patients with AF are over the age of 65.³ Having CHF increases the risk of AF 4.5 fold in males and 5.9 fold in females.⁴ CHF affects over 5 million North Americans and accounts for over 995,000 U.S. hospitalizations annually. The prevalence of AF directly increases with New York Heart Association Class

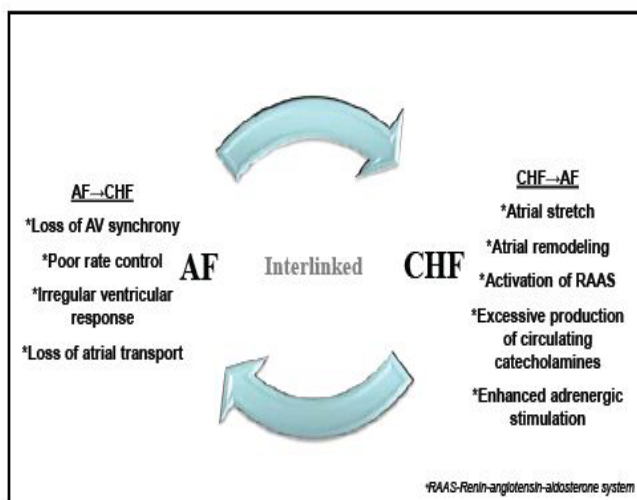
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Association (NYHA) severity. Ten to 26% of patients have AF with NYHA Class II-III and 30-50% patients have AF with NYHA Class IV.⁵⁻⁹

AF as a Predictor of Worse Outcomes in Patients with CHF:

At present, there is no consensus as to whether the presence of AF is an independent predictor for mortality in patients with CHF. In the Vasodilator Heart Failure Trial (V-HeFT), the presence of AF in patients with mild to moderate CHF was not associated with worse outcome.¹⁰ Conversely, in the larger Studies of Left Ventricular Dysfunction (SOLVD) trial, AF was an independent predictor for all-cause mortality, the combined endpoint of death, and hospitalization for heart failure.¹¹ In the Carvedilol or Metoprolol European Trial (COMET) having AF significantly increased the risk for death and heart failure hospitalization. However, after adjusting for confounding factors, AF was found not to be an independent risk factor for mortality.¹² Middlekauf et al. and Correll et al. reported that the presence of AF in patients with CHF was associated with increased mortality. Additionally, in patients with mild to moderate CHF, AF seemed to be a stronger predictor of negative outcome compared with patients with severe heart failure. The findings from most of these studies suggest that having AF is an independent risk factor for mortality in congestive heart failure.

Figure 1: Schema depicting the integration of CHF and AF. A list of factors contribution to the exacerbation of AF and CHF



Moreover, in terms of mortality, the effect of AF is inversely proportional to the severity of CHF.^{13,14,15}

The Interplay between CHF and AF:

The causative relationship between the AF and CHF has not been fully elucidated. Their co-existence can be partially explained by shared risk factors such as age, hypertension, diabetes, obesity, valvular, ischemic and nonischemic structural heart disease. These conditions cause myocardial cellular and extracellular alterations and electrophysiological and neurohormonal changes which interplay to create an environment that predisposes the heart to CHF and AF. Tachycardia, increased cardiac filling pressures, irregular heart rate, loss in atrial transport, and atrioventricular desynchrony are all traits inherent to AF which can impair ventricular function and worsen CHF (Figure 1)¹⁵

CHF, through a series of physiological processes, can cause AF or sustained AF. Sustained AF can result in electrical and structural remodeling of the left atrium. This environment promotes arrhythmogenesis which in turn exacerbates CHF (Figure 2). Whether AF causes CHF or CHF causes AF is still debated.¹⁵

The Electrophysiology of the Pulmonary Veins:

In 1998, Haissaguerre et al. observed that paroxysmal AF was focal in origin and was initiated by triggers in the pulmonary veins. These triggers could successfully be ablated with radiofrequency energy (16). The anatomical substrate of these triggers is the pulmonary vein fascicles.¹⁷ These fascicles are muscular sleeves which extend from the left atrium in a longitudinal and circular manner. The fascicles have patent electrical properties that allow rapid firing which is conducive to the initiation and propagation of AF.^{18,19} Because of the risk of PV stenosis, ablation techniques do not target the triggers within the vein, but rather electrically isolate the pulmonary veins by ablating all of the fascicles (Figure 3).

Catheter Ablation for Atrial Fibrillation:

There have been several advances in the field of catheter ablation of atrial fibrillation in the last 10 years. Catheter ablation has evolved from an experimental therapy to one that is routinely performed in experienced centers worldwide. Preliminary results from the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial suggest that catheter ablation is superior to drug therapy. Freedom from recurrence of symptomatic AF was significantly higher in the ablation group (65% vs. 41%; HR=0.42; 95% CI, 0.19-0.95). This exciting finding validates the benefits of catheter ablation result and may result in more procedures being performed annually and making catheter ablation a mainstay of AF treatment.²⁰

Comparing Different Techniques:

Currently, there is no single accepted dogma on catheter ablation. Catheter ablation strategies can be divided into isolation of the pulmonary veins alone and pulmonary vein isolation with additional lesion sets. Most electrophysiologists create adjunctive lesions particularly in patients with non-paroxysmal AF; however, which sites and how to identify where to place these lesion sets are still debated.

Figure 2: Diagram of the relationship between CHF and the pathophysiology of atrial remodeling. A list of factors which contribute to atrial electrical and structural remodeling (gray shaded).

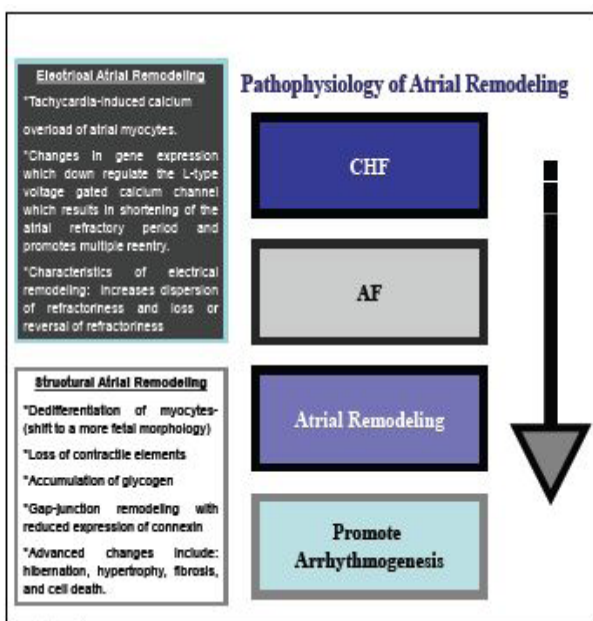
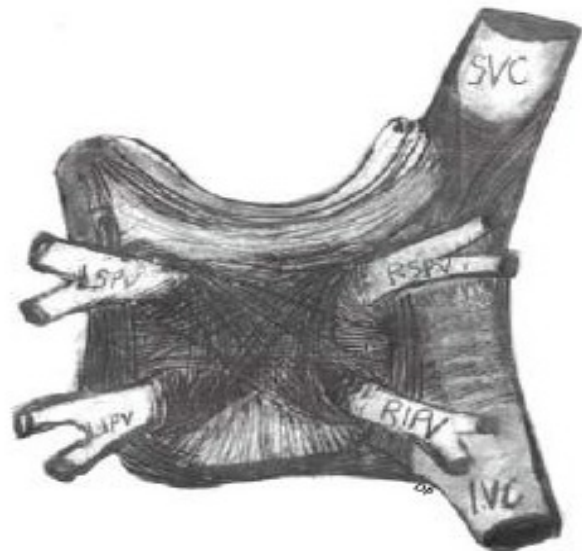


Figure 3: Sketch of the anatomy of the left atrium, pulmonary veins, and muscular fascicles (modified from 52). IVC- Inferior Vena Cava; SVC-Superior Vena Cava; RSPV-Right Superior Pulmonary Vein; RIPV-Right Inferior Pulmonary Vein; LSPV-Left Superior Pulmonary Vein; LIPV-Left Inferior Pulmonary Vein. Drawing recreated by Dimpi Patel.



Pulmonary Vein Ablation Alone:

Pulmonary veins/antrum ablation is performed segmentally, guided by a circular mapping catheter or by a continuous circumferential ablation lines which are created to surround the right or left pulmonary veins.^{21, 22} The creation of the circumferential ablation/isolation line is guided by 3D electroanatomical mapping, fluoroscopy, or by intracardiac echocardiography.^{23, 24, 25, 26} Circumferential ablation targets ipsilateral pulmonary veins separately or both ipsilateral pulmonary veins together. The procedural endpoints are amplitude reduction within the targeted area, elimination or dissociation of the pulmonary vein potentials recorded from the circular mapping catheters, and/or exit block from the pulmonary veins.²⁷ At 6-month follow-up, 54% of patients who had circumferential pulmonary vein ablation and 82% of patients who had segmental PVI remained free of arrhythmia.²⁸

Pulmonary Vein Ablation with Additional Lesion Sets:

TPVI is a cornerstone of most ablation procedures; however, if a focal trigger is identified outside the pulmonary veins it should be targeted

during the procedure (Figure 4 and 5). Non-PV atrial triggers have been found in the posterior wall of the left atrium, the superior vena cava, the fossa ovalis, the coronary sinus, the ligament of Marshall behind the Eustachian ridge, crista terminalis, and adjacent to the AV valve annuli. An isoproterenol challenge (up to 20: $\mu\text{g}/\text{min}$) can be used to find non-PV triggers.²⁹⁻³³

CFAE (complex fractionated electrical electrograms) are electrograms with highly fractionated potentials or with a very short cycle length (≥ 120 ms) which can be targeted during ablation. It has been suggested that CFAEs represent substrate areas that perpetuate AF. The primary end-points are elimination of CFAEs areas, conversion of AF to sinus rhythm, and/or an inability to induce AF. In patients with paroxysmal AF, the procedural endpoint is noninducibility of AF. In patients with persistent AF, the endpoint is termination of AF. If atrial flutter or atrial tachycardia ensues after elimination of the CFAE areas, the atrial arrhythmias are mapped and ablated.^{34,35, 36, 37b} At the one year follow-up, 91% patients were free of arrhythmia and symptoms (34).

A tailored AF ablation approach targets specific drivers of AF without excess anatomical ablation. An electrogram based approach is used in-

stead of a standardized lesion set. The pulmonary veins are isolated first if a rapid electrical activity is found. If AF persists, complex electrograms in the left atrium, coronary sinus, and superior vena cava are ablated. In patients with paroxysmal AF, the endpoint is noninducibility of AF with isoproterenol challenge. At 11 \pm 4 month follow-up, 77% of patients were free from AF and/or atrial flutter without the use of antiarrhythmic drugs.³⁸

In patients with longstanding persistent AF, a step-wise approach is reported to be successful. The pulmonary veins are electrically isolated guided by a circular mapping catheter. If AF has not terminated, a roof line is made. If AF continues, the coronary sinus and complex left atrium activities are targeted. If AF persists and there is perimitral macroreentry, mitral isthmus ablation is performed. If the AF cannot be resolved, an optional ablation of the right atrial/SVC can be done.

If AF is not terminated at that point, the patient is either electrically or pharmacologically cardioverted. The endpoint of ablation is restoration of sinus rhythm, which normally occurs via one or more atrial tachycardia intermediates (Figure 6). At 1 year, after multiple procedures and with antiarrhythmic drugs when needed, 95% of LSPAF patients had freedom from arrhythmia.^{39,40,41}

Figure 4 and 5: 3-D electroanatomical reconstruction of the left atrium in patients with paroxysmal AF and LSPAF

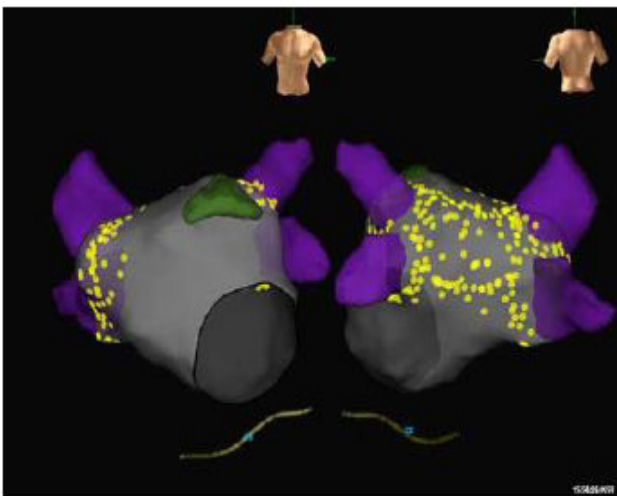


Figure 4

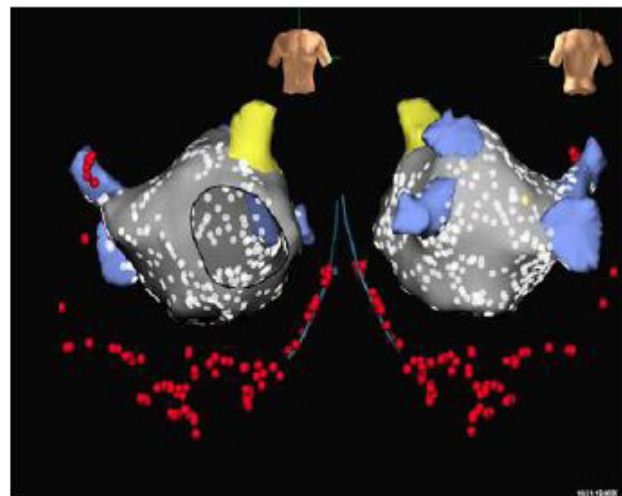


Figure 5

Performing Catheter Ablation in Patients with CHF:

PVI is an intricate procedure. Success is variable based on operator experience. Currently, the majority of the cases are performed in patients with normal systolic function. However, since there is an ever expanding population of patients with CHF and concomitant AF, more ablations are being performed in patients with depressed ejection fraction (EF)

Obstacles of Catheter Ablation in Patients with CHF

PVI in patients with CHF has its own unique set of obstacles. Patients with lower EFs tend to have larger pulmonary vein ostia and left atria, and consequently larger areas need to be ablated. Moreover, patients with left atrial dysfunction tend to have atrial remodeling, which could result in thickening of the areas that are targeted for ablation. CHF patients often have more complex atrial substrates. Therefore, ablation protocols need to include targeting non-pulmonary vein triggers and to completely isolate the posterior wall. The prevalence of non-PV triggers range from 30%

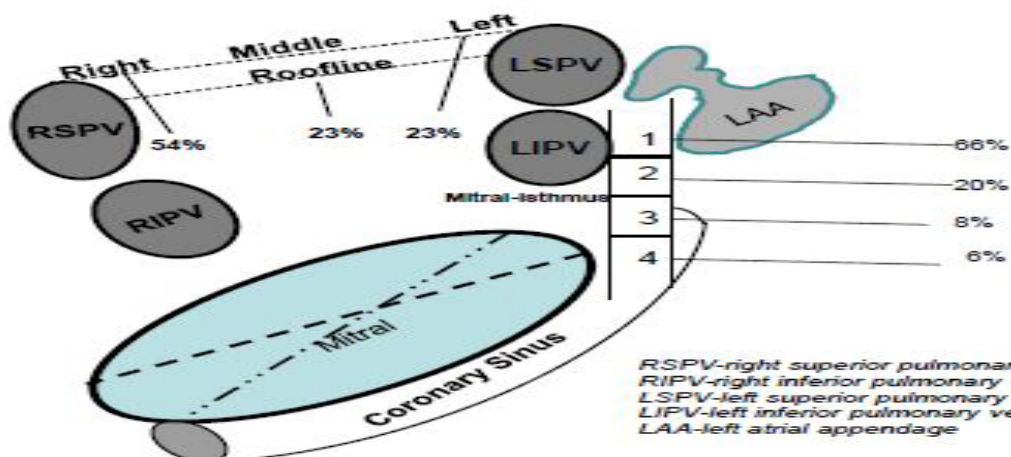
to more than 50% in patients with non-PAF.⁴²

Irrigated catheters are efficacious in this population because they are able to accurately deliver energy. On the other hand, externally irrigated catheters require a large infusion of saline during a procedure and CHF symptoms may be seen or exacerbated. Therefore, CHF patients should be carefully monitored and have aggressive postoperative management with diuretics. Patel et al. reported that despite routine administration of diuretics, 4% of patients experience fluid retention requiring rehospitalization after ablation with an open irrigation catheter. Most rehospitalized patients were obese males with chronic atrial fibrillation.⁴³

Postoperative Management:

Postoperative management varies depending on center protocol and physician's discretion. However, it is recommended that warfarin should be administered for at least two months following an AF ablation procedure. Whether to use warfarin longer than two months following ablation should be based on the patient's risk fac-

Figure 6: From the Bordeaux experience: Schema of gaps in recovered left atrial lines. Most conduction gaps were predominantly located close to the pulmonary veins where catheter stability is often difficult to achieve



The mitral isthmus is divided into 4 regions: 1) High—at the junction of the left inferior pulmonary veins and the left atrial appendage. 2) Middle—at the central part of the mitral isthmus. 3) Low—at the endocardial aspect of the mitral annulus, and 4) Epicardial—at the epicardial. The majority (66%) of conduction gaps in the ML were located in the upper segment (close to the junction between the left inferior pulmonary vein and the left atrial appendage) and the middle part of the line (20%). Only 6% of patients showed a gap at an epicardial location. Recurrences of electrical conduction within the roof line were mainly (54%) observed close to the right superior pulmonary vein and, less frequently, close to the left superior pulmonary vein or in the middle segment. Shorter radiofrequency durations are required for reablation of recovered linear lesions. Conduction times around complete left atrium lines are significantly longer in patients with persistent/permanent AF as compared to patients with paroxysmal AF (41).

tors for stroke and not on the presence or type of AF. Cessation of warfarin therapy after ablation is generally not recommended in patients who have a CHADS score ≥ 2 . Considering this recommendation and the common risk factors associated with CHF, many CHF patients are kept on warfarin indefinitely after catheter ablation.

Suppressive antiarrhythmic drugs are often used during the first one to three months after ablation. Most electrophysiologists use drugs that have been used unsuccessfully prior to ablation

Patients should be seen in follow-up at a minimum of three months following the ablation procedure and every six months henceforth for at least two years. ECGs should be obtained at all follow-up visits. Patients complaining of palpitations should be evaluated with an event monitor. The most effective way to monitor frequent asymptomatic recurrences is to use a 1 to 7 day Holter monitor.

There is no set protocol for imaging studies to screen for PV stenosis following ablation. Ideally, most patients should have computed tomography at baseline and at 3 months after ablation to assess for pulmonary vein stenosis.

Early recurrences of AF and/or atrial tachycardia are often seen in the first two to three months after AF ablation. Recurrences of AF during this blanking period are not considered procedure failure. Therefore, repeat ablation procedures should be postponed for at least three months following the first procedure (44).

Complications of Catheter Ablation:

Pulmonary vein stenosis, atrioesophageal fistula, pericardialeffusion,cardiactamponade,hematoma, and cerebrovascular accident are all possible complications of PVI. There are no differences in the rates of complications in patients who underwent PVI with CHF compared to those without CHF.^{44,45}

Clinical Evidence Supporting the Feasibility of Pulmonary Vein Isolation as a Treatment Strategy in Patients with CHF

Several studies have assessed the feasibility of pulmonary vein isolation in a CHF population (Table 1). Hsu et al. compared 58 patients with CHF to 58 case controlled patients without CHF that underwent catheter ablation. CHF patients had an EF below 45% and \geq NYHA class II. Fifty percent of patients with CHF and 47% of patients in the control group underwent a second procedure.

One year after the final procedure, 78% of patients with CHF and 84% of the controls were free of AF ($P=0.34$). EF increased by an average 21%, left ventricular end-diastolic and end-systolic diameters decreased respectively by 7 and 9mm in the CHF group. Catheter ablation in this study involved PVI with one or more linear lesions, which include a roof line between the left and right superior pulmonary veins and a mitral isthmus line between the mitral annulus and left inferior pulmonary vein.⁴⁶

Chen et al. studied 377 patients. Ninety-four patients had EF $<40\%$ versus 286 EF = 40%. All patients had symptomatic AF refractory to antiarrhythmic drugs and were rate controlled.

Table 1

Studies of patients with low ejection fractions undergoing atrial fibrillation ablation

	Number of patients	EF Pre-ablation (%)	LA (cm)	EF Post-ablation (%)	AF Free (%)
Hsu (23)	58	35	5	56	69
Chen (22)	94	36	4.7	41	73
Tondo (24)	40	33	4.8	47	62
Gentlesk (25)+	67	42	-	56	86
Khan (1)	41	27	4.9	35	88
Bortone(26)*	6	25	-	54	100

+Freedom from AF reported with some patients on antiarrhythmics

*5 out of 6 patients had redo procedures. 1 patient had an post procedural EF of 30. It is not included in the mean

PVAI with cavotri- cuspid isthmus line was performed. At 14 months, 73% of the low EF groups were AF free compared to 87% of the normal EF group (p-value 0.03). Twenty-one of the patients with LV systolic dysfunction underwent repeat PVI. The overall cure rate in patients with LV systolic dysfunction after a second procedure was 96%. Nineteen of the study group had repeat procedures. The overall cure rate in the study group was 94%. The study group had a non-significant increase in EF of 4.6% and significant improvement in quality of life. Complication rates were low with a 1% PV risk of PV stenosis.⁴⁵

Unlike Hsu et al., more patients in Chen et al. had improvement in EF; however, this finding can be attributed to the smaller number of non-paroxysmal AF patients in the study by Chen et al. The requirement for rate control in the study by Chen et al. may have limited the number of patients with tachycardia-mediated cardiomyopathy.^{45,46} Tondo et al. prospectively compared 40 patients with EFs of <40% to 65 patients with EFs =40%. A hybrid ablation procedure which included electro-anatomical mapping-guided PVAI, a mitral isthmus line, and in most patients, ablation of the cavotricuspid isthmus was performed. Eighty-seven percent of patients with impaired EF were arrhythmia free and had improvement in EF from 33±2% to 47±3% at 14±2 months. Ninety-two percent of patients with normal EF were in sinus rhythm at the end of the follow up period with or without antiarrhythmic drugs. Exercise capacity, symptoms, and quality of life scores improved significantly.⁴⁷

Gentlesk et al. studied 67 patients with a mean EF of 42±9 compared to 299 with normal EF. Ablation consisted of proximal isolation of the pulmonary veins and non-pulmonary vein triggers. EF was assessed at 24 hours after ablation and then again at 6 months. At the end of the follow up period, 86% of the left ventricular dysfunction group was arrhythmia free compared to 87% of the control group. However, more repeat procedures were required in patients with left ventricular dysfunction (1.6±0.8 vs. 1.3±0.6; P<or=0.05). In the lower EF group, EF increased from 42±9% to 56±8% (P<0.001) after ablation. These results imply that depressed EF is reversible with successful catheter ablation in many CHF patients with AF induced ventricular cardiomyopathy.⁴⁸

The Pulmonary Vein Antrum Isolation (PVAI) versus AV node Ablation with Bi-Ventricular (BI-V) Pacing for treatment of Atrial Fibrillation in Patients with Congestive Heart Failure (PABA-CHF) was a multicenter, randomized study that compared PVAI to AVA with BI-V in patients with a low EF and symptomatic AF. Forty-one patients underwent PVAI with a mean EF of 27±8 and 40 patients underwent AVA with a mean EF of 29±7. All patients had drug refractory AF and NYHA class II or III.¹

Khan et al. found that the composite primary endpoint favored the PVAI group because they had greater improvement in the quality of life questionnaire at 6 months (60 vs. 82 in the AVA group; P<0.0001), a longer 6-minute-walk-distance (340m vs. 297m; P<0.001), and a higher ejection fraction (35% vs. 28%; P<0.001). There were eight repeat procedures for recurrent AF (in four patients) and atrial flutter or atrial tachycardia (in four other patients) in the PVAI group. At 6 months, 88% of the PVAI group and 71% of the AVA group were free of AF without antiarrhythmic drugs.¹

In the PVAI group, 2 patients had pulmonary vein stenosis, 1 had pericardial effusion, and 1 had pulmonary edema. In the AVA group, 1 had a lead displacement and the other had a pneumothorax.¹

Bortone et al. studied six subjects with an EF of 25.8±7.3% who had drug refractory LSPAF. Five patients had dilated cardiomyopathy and 1 patient had ischemic cardiomyopathy. Patients had NYHA III-IV. All patients underwent stepwise ablation. All patients with dilated cardiomyopathy had significant improvement in NYHA class and EF. In the patient with the ischemic cardiomyopathy, NYHA class improved but not the EF. Four out of 5 patients in the dilated cardiomyopathy group and the ischemic cardiomyopathy group had redo procedures. Sinus rhythm was maintained in all patients. EF and NYHA improved in the dilated cardiomyopathy group (54±4.4%, NYHA I-II) thus, precluding the need for an implantable cardioverter defibrillator (ICD). EF remained at 30% in the patient with ischemic cardiomyopathy, thus an ICD was implanted. While this study was extremely small, it demonstrated that even more severe patients can benefit from catheter ablation.⁴⁹

The results from these studies stalwartly suggest the benefits of restoring and maintaining sinus rhythm with catheter ablation in patients with CHF. Moreover, these studies suggest that repeat procedures in this population are very effective.

Conclusion: Burning for a Cure for CHF coexistent AF

CHF and AF are noxious to patient well-being, overall quality of life and health care cost. Perhaps the continual advances in ablation technology and the broadening indications for treatment may reduce the deleterious effect of CHF and AF.

Fairly recently, advances have been made that focus on enabling inexperienced operators to perform the procedure safely and effectively. Three-dimensional electroanatomical imaging has been integrated with other imaging modalities such as CT and MRI, allowing for better visualization of the left atrial anatomy. Electroanatomical mapping has been particularly beneficial in patients with CHF since extensive ablation and navigation in this anatomy can be difficult.

Robotic technology has emerged as a powerful device for mapping and ablating AF. There are two robotic systems that are being used for catheter ablation: Stereotaxis remote magnetic navigation and Hansen Sensei robotic catheter system. Early clinical experiences with these devices are promising. Robotically guided mapping and ablation may improve both the ease and outcome of complex AF ablations. At present, there are no reported clinical trials focusing on the efficacy of robotic systems in CHF populations.^{50,51}

Presently, catheter ablation for AF in CHF patients is considered second line therapy. Nonetheless, as experience grows in this population and more favorable evidence continues to mount, this will change. In our opinion, it is possible that in the future, catheter ablation may become the treatment of choice in most patients with AF and concomitant CHF; henceforth, "burning" could incinerate the AF with CHF epidemic.

References

1. Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin

DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Ravielle A, Haïssaguerre M, Natale A. PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med.* 2008;359:1778-85.

2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946-52

3. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation.* 2003;108:711-716.

4. American Heart Association. Heart disease and stroke statistics-2004 update. Dallas (Tex): American Heart Association;2003

5. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* 1998;82:2N-9N.

6. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation.* 2003;107:2920-5.

7. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA.* 1994;271:840-844. American Heart Association. Heart disease and stroke statistics-2004 update.

8. Tsutsui H. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. *Am J Cardiol.* 2001;88:530-533.

9. Redfield MM. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA.* 2003;289:194-202.

10. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: the V-HeFT Studies: the V-HeFT VA Cooperative Studies Group. *Circulation.* 1993; 87 (suppl): VI-102.

11. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials: Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol.* 1998; 32: 695-703.

12. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J.* 2005; 26: 1303

13. Middlekauff HR, Stevenson WG, Stevenson LW. Prognos-

- tic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. *Circulation*.1991; 84: 40–48.
14. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail*. 2007; 9: 258–265.
 15. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart-failure: treatment considerations for a dual epidemic. *Circulation*. 2009 May 12;119(18):2516-25.
 16. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659-66.
 17. Ho SY, Cabrera JA, Tran VH, Farré J, Anderson RH, Sánchez-Quintana D. Architecture of the pulmonary veins: relevance to radiofrequency ablation. *Heart*. 2001; 86:265-70.
 18. Jaïs P, Hocini M, Macle L, Choi KJ, Deisenhofer I, Weerasooriya R et al. Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation. *Circulation*. 2002;106:2479-85.
 19. Tada H, Ozaydin M, Oral H, Knight BP, Chugh A, Scharf C et al. Characteristics of rapid rhythms recorded within pulmonary veins during atrial fibrillation. *Pacing Clin Electrophysiol*. 2003; 26:1342-7.
 20. <http://www.theheart.org/article/1057265.do>.
 21. Haïssaguerre M, Shah DC, Jais P, Hocini M, Yamane T, Deisenhofer I, Chauvin M, Garrigue S, Clémenty J. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation* 2000;102:2463-2465.
 22. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. *Circulation* 2000;102:2619-2628.
 23. Ouyang F, Bansch D, Ernst S, Schaumann A, Hachiya H, Chen M, Chun J, Falk P, Khanedani A, Antz M, et al. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. *Circulation* 2004;110:2090-2096.
 24. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *JACC*. 2003;42:185–97.
 25. Takahashi A, Iesaka Y, Takahashi Y, Takahashi R, Kobayashi K, Takagi K, Kuboyama O, Nishimori T, Takei H, Amemiya H, et al. Electrical connections between pulmonary veins: implication for ostial ablation of pulmonary veins in patients with paroxysmal atrial fibrillation. *Circulation* 2002;105:2998- 3003
 26. Marrouche NF, Martin DO, Wazni O, Gillinov AM, Klein A, Bhargava M, Saad E, Bash D, Yamada H, Jaber W, et al. Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: impact on outcome and complications. *Circulation* 2003;107:2710-2716.
 27. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabro MP, Mazzone P, et al. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001;104:2539-2544.
 28. Karch MR, Zrenner B, Deisenhofer I, Schreieck J, Ndrepepa G, Dong J, Lamprecht K, Barthel P, Luciani E, Schomig A, et al. Freedom from atrial tachyarrhythmias after catheter ablation of atrial fibrillation: a randomized comparison between 2 current ablation strategies. *Circulation* 2005;111:2875-2880.
 29. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. *Circulation* 1999;100:1879-1886
 30. Lee SH, Tai CT, Hsieh MH, Tsao HM, Lin YJ, Chang SL, Huang JL, Lee KT, Chen YJ, Cheng JJ, et al. Predictors of nonpulmonary vein ectopic beats initiating paroxysmal atrial fibrillation: implication for catheter ablation. *J Am Coll Cardiol* 2005;46:1054-1059.
 31. Lin D. Provocability of atrial fibrillation triggers during pulmonary vein isolation in patients with infrequent AF. *Heart Rhythm* 2004;1 (Suppl):S231.
 32. Shah D, Haïssaguerre M, Jais P, Hocini M. Nonpulmonary vein foci: do they exist? *Pacing Clin Electrophysiol* 2003;26(7Pt 2):1631-1635.
 33. Lin WS, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, Huang JL, Yu WC, Yang SP, Ding YA, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. *Circulation* 2003;107:3176-3183.
 34. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;43:2044-2053
 35. Scherlag BJ, Nakagawa H, Jackman WM, Yamanashi WS, Patterson E, Po S, Lazzara R. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. *J Interv Card Electrophysiol* 2005;13 Suppl 1:37-42.
 36. Jais P, Haïssaguerre M, Shah DC, Chouairi S, Clémenty J. Regional disparities of endocardial atrial activation in paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 1996;19(11Pt 2):1998-2003.
 37. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. *Circulation* 1997;95:1231-1241
 38. Oral H, Chugh A, Good E, Sankaran S, Reich SS, Igic P,

- Elmouchi D, Tschopp D, Crawford T, Dey S, et al. A tailored approach to catheter ablation of paroxysmal atrial fibrillation. *Circulation* 2006;113:1824-1831.
39. Haissaguerre M, Sanders P, Hocini M, Takahashi Y, Rotter M, Sacher F, Rostock T, Hsu LF, Bordachar P, Reuter S, et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. *J Cardiovasc Electrophysiol* 2005;16:1125-1137.
40. Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, et al. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *Cardiovasc Electrophysiol* 2005;16:1138-1147.
41. Rostock T, O'Neill MD, Sanders P, Rotter M, Jais P, Hocini M, Takahashi Y, Sacher F, Jönsson A, Hsu LF, Clémenty J, Haissaguerre M. Characterization of conduction recovery across left atrial linear lesions in patients with paroxysmal and persistent atrial fibrillation. *JCE*. 2006;17:1106-11.
42. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, Bassouni M, Cummings J, Wang Y, Lewis WR, Diaz A, Horton RP, Beheiry S, Hongo R, Gallinhouse GJ, Zagrodzky JD, Bailey SM, Al-Ahmad A, Wang P, Schweikert RA, Natale A. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm*. 2010;7:167-72.
43. Patel D, Sanchez J, Horton R, Venkatraman P, Shaheen M, Di Biase L, Natale A. The Prevalence of Patients Having Fluid Retention Resulting in Rehospitalization when an Open Irrigation Catheter is Used For Pulmonary Vein Isolation. *Boston HRS* 2009.
44. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ; Heart Rhythm Society; European Heart Rhythm Association; European Cardiac Arrhythmia Society; American College of Cardiology; American Heart Association; Society of Thoracic Surgeons. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. 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) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace*. 2007 Jun;9(6):335-79.
45. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J, Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *JACC*. 2004;43:1004-9.
46. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Scavée C, Bordachar P, Clémenty J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373-83.
47. Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A, Fagundes RL, Picchio E, Laurenzi F, Piazza V, Bisceglia I. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. *Pacing Clin Electrophysiol*. 2006;29:962-70.
48. Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, Callans D, Marchlinski FE. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *JCE*. 2007; 18 :9-14
49. Bortone A, Boveda S, Pasquie JL, Pujadas-Berthault P, Marijon E, Appetiti A, Albenque JP. Sinus rhythm restoration by catheter ablation in patients with long-lasting atrial fibrillation and congestive heart failure: impact of the left ventricular ejection fraction improvement on the implantable cardioverter defibrillator insertion indication. *Europace*. 2009; 11: 18-23.
50. Di Biase L, Fahmy TS, Patel D, Bai R, Civello K, Wazni OM, Kanj M, Elayi CS, Ching CK, Khan M, Popova L, Schweikert RA, Cummings JE, Burkhardt JD, Martin DO, Bhargava M, Dresing T, Saliba W, Arruda M, Natale A. Remote magnetic navigation: human experience in pulmonary vein ablation. *JACC*. 2007; 50:868-74.
51. Saliba W, Reddy VY, Wazni O, Cummings JE, Burkhardt JD, Haissaguerre M, Kautzner J, Peichl P, Neuzil P, Schibgilla V, Noelker G, Brachmann J, Di Biase L, Barrett C, Jais P, Natale A. Atrial fibrillation ablation using a robotic catheter remote control system: initial human experience and long-term follow-up results. *JACC*. 2008;51:2407-11.
52. Nathan H, Eliakim M. The junction between the left atrium and the pulmonary veins. An anatomic study of human hearts. *Circulation*. 1966;34:412-22.
53. Patel D, Natale A, Di Biase L, Burkhardt JD, Wang Y, Sanchez JE, Horton RP, Khan M. Catheter ablation for atrial fibrillation: a promising therapy for congestive heart failure. *Expert Rev Cardiovasc Ther*. 2009;7:779-87.