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Pulmonary Vein Isolation for the Treatment of Atrial Fibrillation in Patients With Impaired Systolic Function

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OBJECTIVES We aimed to determine the safety and efficacy of pulmonary vein isolation (PVI) in atrial fibrillation (AF) patients with impaired left ventricular (LV) systolic function.

BACKGROUND To date, PVI has been performed primarily in patients with normal LV function. Yet, many AF patients have impaired LV systolic function. The outcomes of PVI in patients with impaired LV systolic function are unknown.

METHODS We included 377 consecutive patients undergoing PVI between December 2000 and January 2003. Ninety-four patients had impaired LV function (ejection fraction [EF] <40%), and they comprised the study group. The control group was the remaining 283 patients who had a normal EF. End points included AF recurrence and changes in EF and quality of life (QoL).

RESULTS Mean EF was 36% in our study group, compared with 54% in controls. After initial PVI, 73% of patients with impaired EF and 87% of patients with normal EF were free of AF recurrence at 14 ± 6 months ($p = 0.03$). In the study group, there was a nonsignificant increase in EF of 4.6% and significant improvement in QoL. Complication rates were low and included a 1% risk of pulmonary vein stenosis.

CONCLUSIONS Although the AF recurrence rate after initial PVI in impaired EF patients was higher than in normal EF subjects, nearly three-fourths of patients with impaired EF remained AF-free. Although our sample size was nonrandomized, our results suggest PVI may be a feasible therapeutic option in AF patients with impaired EF. Randomized studies with more patients and longer follow-up are warranted. (J Am Coll Cardiol 2004;43:1004–9) © 2004 by the American College of Cardiology Foundation

Pulmonary vein isolation (PVI) has become a valid treatment option for patients with atrial fibrillation (AF) (1–6). A variety of PVI approaches using different ablation technologies have been reported (3,4,7–9). The vast majority of PVI procedures have been performed in patients with preserved left ventricular (LV) systolic function (1,2,6,10,11).

See page 1010

However, a significant percentage of patients with AF have impaired ejection fraction (EF). In one study of 163 patients with refractory AF referred for atrioventricular node ablation, 39% had LV systolic dysfunction (12). The combination of AF and structural heart disease has been thought to be associated with a different substrate that could result in a higher risk of procedural complications.

Clinically, AF and heart failure are intertwined, for each can result in the other (13–15). Atrial fibrillation is generally accepted to be a cause of tachycardia-induced cardiomyopathy. Conversely, heart failure is a powerful predictor of the development of AF. After 38-year follow-up of subjects from the Framingham study, heart failure was associated with approximately a fivefold increase in the risk of developing AF (16). In further analysis from the Framingham study, Wang et al. (17) recently showed that patients with heart failure who develop AF, as well as AF patients who develop heart failure, have increased mortality. Finally, the risk of both AF and heart failure increases with age (18). To date, the clinical outcomes of PVI in AF patients with impaired systolic function are largely unknown. The objective of this study was to assess the safety and efficacy of PVI in AF patients with impaired LV systolic function.

METHODS

Patient population. Between December 2000 and January 2003, 377 consecutive patients were referred to our laboratories for AF ablation. Selection criteria for AF ablation included: 1) symptomatic AF; 2) refractoriness to antiarrhythmic drug therapy; and 3) no indication for open-heart surgery. No patient with a low EF was turned down.

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Abbreviations and Acronyms

AF = atrial fibrillation
CHF = congestive heart failure
EF = ejection fraction
ICE = intracardiac echocardiogram
LV = left ventricular/ventricle
NYHA = New York Heart Association
PV = pulmonary vein
PVI = pulmonary vein isolation
QoL = quality of life
SF-36 = 36-Item Short-Form Health Survey

All patients signed a written, informed consent approved by the institutional Ethics Committee. Amiodarone was discontinued for five to six months before ablation, and other anti-arrhythmic drugs were discontinued five half-lives before ablation. All patients underwent transthoracic echocardiography before undergoing the procedure. Immediately before the procedure, transesophageal echocardiography was also performed in all study patients. Of these 377 patients, 94 had impaired LV systolic function, defined as EF <40%, and they comprised the study group. The remaining 283 patients had normal LV systolic function and served as the control group. This was a retrospective case series of AF patients undergoing PVI.

Pulmonary vein isolation. Angiogram-guided mapping and isolation of the pulmonary veins (PVs) were applied in the first 56 of our study patients, as previously described (3). In the remaining 321 patients, intracardiac echocardiogram (ICE)-guided mapping and ablation of the PV ostia were performed using a 10F, 64-element, phased-array ultrasound imaging catheter (Biosense, Diamond Bar, California) and a decapolar Lasso catheter (AcuNav, Acuson, Mountain View, California).

Radiofrequency energy was delivered using the cooled-tip ablation catheter (EP Technologies, Sunnyvale, California) in all study patients. Ablation lesions were delivered in front of the tube-like portion of the PVs. In the first 163 patients, a 35°C target temperature was chosen for radiofrequency energy delivery through the cooled-tip catheter. At each site, energy was delivered for 45 s. In the remaining 214 patients, energy delivery was titrated up under ICE guidance while monitoring for microbubble formation (19–21). Two types of microbubble patterns were seen with ICE. The type 1 pattern, which reflected early tissue overheating, consisted of scattered microbubbles. When the type 1 microbubble pattern was seen, energy was titrated down by 5-W decrements until the type 1 pattern subsided. The type 2 pattern represented an impending impedance rise and consisted of brisk generation of microbubbles. The goal was to avoid type 2 microbubbles and to discontinue radiofrequency energy delivery if type 2 microbubbles were observed.

The goal of PVI was to abolish all PV potentials, as measured by the circular mapping catheter. Nineteen patients with normal LV function and four patients with impaired LV function underwent cavotricuspid isthmus ablation for isthmus-dependent flutter at 13 ± 7 months before the PVI procedure. In addition, 28 patients (10%) in the normal LV function group and seven patients (7%) in the impaired LV function group underwent isthmus ablation during the PVI procedure for concomitant typical atrial

Table 1. Patient Demographics

	Patients With Normal LV Function (n = 283)	Patients With Impaired LV Function (n = 94)	p Value
Women	22% (61)	20% (19)	0.1
Age (yrs)	55 ± 11	57 ± 8	0.9
LA size (cm)	4.5 ± 0.3	4.7 ± 0.8	0.06
Ischemic, hypertensive, or idiopathic heart disease*	22% (62)	91% (86)	0.02
Valvular heart disease*	13% (36)	16% (15)	0.1
Mean EF (%)	54 ± 3%	36 ± 8%	0.02
NYHA			
Class I	95% (268)	None	0.001
Class II	5% (15)	30% (28)	0.009
Class III	None	68% (64)	0.005
Class IV	None	2% (2)	0.01
Duration of AF (yrs)	5 ± 4	6 ± 2	0.7
Type of AF			
Paroxysmal	55% (155)	43% (39)	0.8
Persistent	12% (35)	13% (13)	0.9
Permanent	32% (93)	43% (42)	0.8
Number of anti-arrhythmic drugs tried before PVI	3 ± 1	2 ± 1	0.5

*Note that a small number of patients were counted in both categories, as they had both ischemic/hypertensive/idiopathic heart disease, as well as valvular heart disease. Data are presented as the percentage (n) of patients or mean value ± SD.

AF = atrial fibrillation; EF = ejection fraction; LA = left atrial; LV = left ventricular; NYHA = New York Heart Association; PVI = pulmonary vein isolation.

flutter. Four patients in the normal LV function group underwent ablation of non-PV foci during a second procedure. No linear lines from the PV to the mitral annulus were made in our study population.

Follow-up and end points. Recurrence of AF, LV systolic function, quality of life (QoL), and complication rates were compared between the control and study groups. Recurrence of AF was assessed by a loop recorder one month after ablation; 24-h Holter monitoring at 3, 6, and 12 months; and 12-lead electrocardiography at 2, 3, 6, and 12 months. Monthly telephone interviews were conducted with patients. Additional monitoring with the loop recorder or Holter monitor was considered in the presence of symptoms. Interrogation of implanted devices was also used to confirm the recurrence of arrhythmias. Any episode of AF identified on the Holter monitor, loop recorder, or electrocardiogram (ECG), regardless of the duration and including asymptomatic AF, was considered a recurrence. Left ventricular systolic function was compared by echocardiography before PVI and approximately six months after PVI. Using the Medical Outcomes Survey 36-Item Short-Form Health Survey (SF-36), we assessed patients both before and after the procedure with respect to several indexes of QoL (22–24). Spiral computed tomography was performed at 10 to 12 weeks after ablation to assess for PV stenosis.

Statistical analysis. Continuous variables are expressed as the mean ± SD. Analysis of variance was used to compare mean values between the study and control groups, and the unpaired *t* test was used to compare proportions between the two groups. Categorical variables were compared by chi-square analysis. Changes in QoL before and after ablation within the same group were compared using the paired *t* test. Kaplan-Meier analysis with the log-rank test was used to determine cumulative AF-free survival. Cox multivariate regression analysis was done to assess variables predicting the recurrence of AF.

RESULTS

Patient demographics are shown in Table 1. Approximately 80% of subjects were male, and the mean age was 55 years. Of the 94 patients in the study group, LV systolic dysfunction was predominantly due to ischemic heart disease (n = 73), valvular heart disease (n = 15), idiopathic cardiomyopathy (n = 4), and hypertensive heart disease (n = 2).

Patients with impaired LV function had a mean EF of 36 ± 8%, whereas patients with normal LV function had a mean EF of 54 ± 3% (p = 0.002). The two groups differed significantly with respect to their New York Heart Association (NYHA) functional class: 68% of patients with impaired LV function were in class III, 30% in class II, and 2% in class IV. In contrast, 95% of patients with normal LV function were in class I. The two groups did not differ significantly with respect to other clinical characteristics, including the duration and type of AF, although there was a nonsignificant trend toward a larger left atrial size in patients with impaired LV function. Thirty (32%) of 94 patients with impaired LV function had an implantable cardioverter-defibrillator, and 9 patients (10%) had a pacemaker.

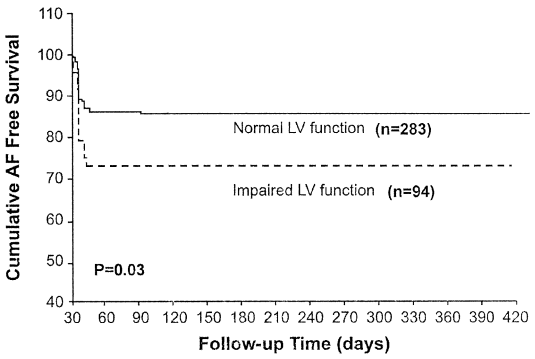

Figure 1. Kaplan-Meier analysis of our subjects. Freedom from atrial fibrillation (AF) after pulmonary vein isolation in patients with normal **(solid line)** and impaired **(dashed line)** left ventricular (LV) function ($p < 0.04$).

Recurrence of AF/atrial flutter. After a mean follow-up of 14 ± 5 months, the recurrence of AF was lower in patients with normal LV function than in patients with impaired LV function (13% vs. 27%; p = 0.03) (Fig. 1, Table 2) . The patients who remained free of AF did not require anti-arrhythmic drug therapy. Four patients with normal LV function experienced occurrence of left atrial flutter after PVI, one of whom was successfully treated with isolation of the recovered right upper and right lower PV ostia. The remaining three patients with normal LV function who developed atrial flutter are controlled in normal sinus rhythm with anti-arrhythmic drugs.

Of the patients with LV dysfunction experiencing recurrence, three had their AF completely suppressed with drugs that were previously ineffective, one experienced less frequent and shorter episodes of AF, and one appeared unaffected by the procedure. One patient with depressed LV function experienced occurrence of left atrial flutter, which was controlled with anti-arrhythmic medications. Twenty-one of the patients with LV systolic dysfunction underwent repeat PVI and were cured. Thus, the overall cure rate in patients with LV systolic dysfunction, after a second procedure in 21 of 94 patients, was 96%. On multivariate analysis, age, gender, duration of AF, number of anti-arrhythmic drugs, and left atrial size did not predict the recurrence of AF; only LVEF and PV ostial size were predictors of recurrence of AF.

Pulmonary vein ostia size. From ICE measurements, patients with impaired LV systolic function had significantly larger PV ostia (average of all four veins = 2.2 cm), as compared with patients with normal LV systolic function (average of all four veins = 1.4 cm) ($p < 0.05$) (Table 3).

Left ventricular function and QoL after PVI. Figure 2 illustrates the individual changes in LVEF in patients with impaired LV systolic function before PVI, as compared with six months after PVI. Overall, LVEF increased nonsignificantly from 36.4% before PVI to 41.0% after PVI. Fifty-six

Table 2. Follow-Up Results

	Patients With Normal LV Function (n = 283)	Patients With Impaired LV Function (n = 94)	p Value
Follow-up (months)	15 ± 8	14 ± 6	0.1
Recurrence	13% (36)	27% (25)	0.03
Controlled on AAD	6% (17)	3% (3)	0.1
Successful second PVI	7% (19)	22% (21)	0.05
Total cure off AAD (including second procedure)	94% (266)	96% (90)	0.2

Data are presented as the percentage (n) of patients or mean value ± SD.
AAD = anti-arrhythmic drugs; other abbreviations as in Table 1.

of the 94 patients experienced an improvement of LVEF after PVI, and in these 56 patients, the mean increase in LVEF was 7.2 ± 3%. Of the remaining 38 patients, 31 had no change in LVEF after PVI, and three patients showed a minimal decline. No correlation existed between improvement of LVEF and type of structural heart disease, age, type or duration of AF, or left atrial size.

Forty-three patients in the LV dysfunction group and 150 patients in the normal LV function group completed the SF-36 questionnaire before and six months after PVI. The patients' QoL was significantly improved by PVI (Table 4). Six months after the procedure, patients with impaired LV function reported an improvement in several areas, including general health, energy, physical functioning, and emotional well-being. In patients with preserved LV function, QoL measures improved as well.

Complications. Table 5 illustrates the complication rates. Periprocedural stroke occurred in 3 (1%) of 283 patients with normal LV function and 2 (2%) of 94 patients with impaired LV function (p = 0.08). In one patient with impaired LV function, the first procedure was terminated prematurely due to pulmonary edema. A second procedure was subsequently performed in this patient and resulted in a cure of the patient's AF. Severe PV stenosis, defined as >70% narrowing on the computed tomographic scan three months after PVI, was found in 1 (1.1%) of 94 patients with impaired LV dysfunction and 5 (1.7%) of 283 patients with normal LV function.

DISCUSSION

Primary findings. Our results suggest that PVI appears to be safe and effective in patients with impaired LV systolic function. Previously reported success rates for PVI in AF have generally been for patients with normal LV function, with AF-free rates at five to 36 months ranging from 62% to 86% (1,2,6,10,11). Although the AF recurrence rate at approximately one year was significantly higher in our patients with impaired systolic function than in patients with normal LV function (27% vs. 13%, p = 0.04), our 73% success rate after initial PVI in patients with impaired LV function is well within the range of success rates cited in the literature for patients with normal LV systolic function. Thus, our experience indicates that patients with AF and impaired LV systolic function could be considered for PVI.

Improvement in LV function after PVI. Overall, the LVEF in our study group of patients improved nonsignificantly by 5%, from 36% before ablation to 41% after ablation. However, 60% of our study group showed an increase in LVEF after PVI, and in these responders, the average increase in LVEF was 7%. Previous studies have reported LVEF to improve in patients with systolic dysfunction after treatment of AF. In 10 patients with AF and severe LV dysfunction initially thought to be due to idiopathic dilated cardiomyopathy, rate control or successful restoration of sinus rhythm appeared to result in an increase in median LVEF from 25% to 52% (25). Other studies have shown that in AF patients with systolic dysfunction undergoing atrioventricular node ablation, the EF increases in approximately one-quarter of them (12,26,27). Although the nonsignificant trend toward improvement in LVEF observed in our patients appears to be consistent with previous studies, the small sample size limits our conclusions. Our demonstrated increase in LVEF may not have

Table 3. Pulmonary Vein Ostia Size

	Patients With Normal LV Function (n = 283)	Patients With Impaired LV Function (n = 94)	p Value
Right upper PV (cm)	1.5 ± 0.5	2.3 ± 0.3	<0.05
Right lower PV (cm)	1.4 ± 0.2	2.1 ± 0.2	<0.05
Left upper PV (cm)	1.5 ± 0.3	2.2 ± 0.3	<0.05
Left lower PV (cm)	1.3 ± 0.2	2.3 ± 0.3	<0.05

Data are presented as the mean value ± SD.
LV = left ventricular; PV = pulmonary vein.

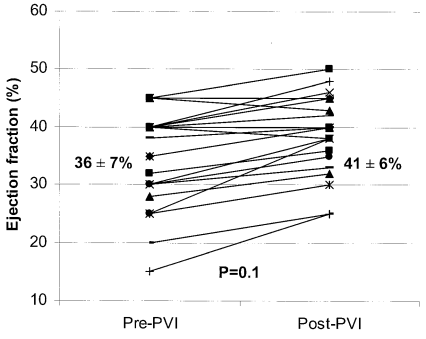

Figure 2. Changes in left ventricular ejection fraction before versus after pulmonary vein isolation (PVI) for each individual patient with impaired ejection fraction.

Table 4. Changes in Quality of Life Before Versus After Pulmonary Vein Isolation

	Physical Functioning	Role Limitation Due to Physical Health	Role Limitation Due to Physical Problem	Energy and Fatigue	Emotional Well-Being	Social Functioning	Pain	General Health
Before PVI (normal LVEF)	28.7	8.3	22.2	25.2	39.7	44.2	68.9	48.5
After PVI (normal LVEF)	96.8*	70.8*	65.2*	65.2*	76*	93.2*	97.2*	78.9*
Before PVI (impaired LVEF)	28.7	8.3	22.2	25.2	39.7	44.2	68.9	48.5
After PVI (impaired LVEF)	90.8*	65.8*	62.2*	61.2*	72*	93.2*	95.2*	76.9*

*$p < 0.05$ versus before PVI.
LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.

been as dramatic as in previous studies, as our patients were already reasonably well rate-controlled before PVI. In previous reports, some of the increase in LVEF from treatment of AF is likely due to achievement of adequate rate control (12).

Quality of life. Previous studies have reported improvements in QoL after PVI for AF (6,7). Our patients reported an improvement in QoL after PVI for AF, consistent with results from previous studies. Gerstenfeld et al. (7) described 71 patients undergoing attempted PV ablation for AF. Thirty-two percent underwent mapping but no ablation because of insufficient or multifocal ectopy, whereas the remaining 68% underwent attempted ablation. Of the subgroup that underwent ablation, only 33% were found at 60 ± 33 weeks to be free of AF recurrences. The authors prospectively assessed QoL before and after ablation. The group that underwent mapping only did not demonstrate any improvement in QoL. However, the group that had long-term successful ablation had improvement in all six QoL measures, and the group that had AF recurrence still had QoL improvement in four of the six measures. More recently, Pappone et al. (6) described the results from a controlled, nonrandomized trial of PVI and reported that patients undergoing PVI had significant improvement in QoL, reaching normative levels, based on the SF-36 score, whereas patients in the medical therapy group had no change in QoL. Our results suggest that the benefits of PVI with respect to QoL may extend to include patients with impaired LV systolic function.

Timing of PV ablation. Recent data suggest that congestive heart failure (CHF)-induced atrial fibrosis may be irreversible. Shinagawa et al. (15) induced CHF in 14 dogs by rapid ventricular pacing. They subsequently measured the duration of burst-induced AF, as well as the degree of atrial fibrosis, at the end of a five-week recovery period. They found that reversal of CHF resulted in a decreased duration of AF and normalization of atrial function. However, the CHF-induced atrial fibrosis was not reversible during this period. Their results imply that for patients with AF and LV dysfunction, atrial fibrosis occurs and may be irreversible, thus suggesting that systolic dysfunction, as well as AF, should be aggressively and expeditiously treated.

Technical challenges of PVI. Pulmonary vein isolation and ablation are technically more challenging in patients with an impaired LV, as these patients have elevated filling pressures and larger PV ostia. This results in a larger area that potentially needs to be ablated. In addition, patients with LV dysfunction may have hypertrophy of the atrial muscle, which could result in thickening of the areas targeted for ablation. It is important to recognize that the high success rates in our series may reflect isolation of all PVs and the use of ICE to facilitate PVI.

Ablation was performed using a cooled-tip ablation catheter. Different catheter types might result in better results. Our group has found that the cooled-tip ablation catheter produced slightly better results than the conventional 4-mm-tip ablation catheters, although not as successful as 8-mm-tip ablation catheters (3). Further prospective studies are required to determine the optimal catheter tip in the subset of patients with impaired LV systolic function and enlarged PV ostia.

Whether the recurrence of AF reflects the presence of non-PV foci remains unanswered. In our experience, the majority of patients returning for a repeat procedure showed recovery of conduction in one or more of the PVs ablated.

Study limitations. This study was a retrospective case series of patients who underwent PVI. Randomized trials would strengthen the validity of the findings, as would a larger sample size and longer-term follow-up. There could potentially be bias in measurement of LVEF due to the lack of blinding. However, echocardiography staff uninvolved with the PVI procedure interpreted the serial echocardiograms, so bias is unlikely in ascertaining pre- and postprocedural EFs. A placebo effect could have contributed to the improvement in the QoL measures, because each patient served as his or her own control, with QoL scores before and

Table 5. Complications

	Patients With Normal LV Function (n = 283)	Patients With Impaired LV Function (n = 94)	p Value
CVA	1% (3)	2% (2)	0.7
Tamponade	<1% (2)	None	0.8
Pulmonary edema leading to procedure termination	None	1% (1)	0.8
Severe PV stenosis	1.7% (5)	1% (1)	0.08

Data are presented as the percentage (n) of patients.
CVA = cerebrovascular accident; LV = left ventricular; PV = pulmonary vein.

after PVI being compared. However, the fact that the AF recurrence rate was low and EF tended to increase suggests that the improvement in the patients' sense of well-being was due to physiologic reasons.

Conclusions. We report our experience with PVI in AF patients with impaired LVEF. Although the AF-free rate of 73% after initial PVI in impaired EF subjects was lower than that observed in normal LV function patients, this result compares favorably with previous series on PVI. We also observed a significant improvement in QoL in patients with impaired LV function and a nonsignificant trend toward improvement in LV systolic function after PVI. Our results, although limited by the small sample size, suggest that PVI appears to be a safe and effective therapeutic option for AF patients with impaired LV systolic function. Randomized trials with larger numbers of patients and longer follow-up are necessary to confirm our preliminary findings.

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