

Reversal of Left Ventricular Dysfunction Following Ablation of Atrial Fibrillation

PHILIP J. GENTLESK, M.D., WILLIAM H. SAUER, M.D., EDWARD P. GERSTENFELD, M.D., DAVID LIN, M.D., SANJAY DIXIT, M.D., ERICA ZADO, PA-C, DAVID CALLANS, M.D., and FRANCIS E. MARCHLINSKI, M.D.

From the Cardiovascular Division, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Ventricular Function After Atrial Fibrillation Ablation. *Background:* Evaluation of ventricular rate control in atrial fibrillation (AF) can be difficult, and the presence of an AF-induced ventricular cardiomyopathy due to intermittent poor rate control or other causes may be underestimated. The outcome with AF ablation in patients with a decreased left ventricular ejection fraction (LVEF) may provide insight into this important clinical issue.

Objective: To determine the effect of pulmonary vein isolation on LVEF in patients with AF and decreased LVEF ($\leq 50\%$).

Methods: Ablation consisted of proximal isolation of arrhythmogenic pulmonary veins (PVs) and elimination of non-PV triggers. LVEF was determined within 24 hours after ablation and again at up to 6 months follow-up. Transtelephonic monitoring was performed routinely for 2–3 weeks prior to ablation, at 6 weeks, and 6 months post and with symptoms following ablation. AF control was defined as freedom from AF or marked ($>90\%$) reduction in AF burden on or off previously ineffective antiarrhythmic medication.

Results: AF ablation was performed in 366 patients and 67 (18%) patients had decreased LV function with a mean LVEF of $42 \pm 9\%$. An average of 3.4 ± 0.9 PVs were isolated. AF control in the depressed LVEF group compared favorably with the normal EF group (86% vs. 87% $P = NS$), although more redo procedures were required (1.6 ± 0.8 vs 1.3 ± 0.6 procedures; $P \leq 0.05$). Only 15 of 67 patients (22%) with decreased LVEF had shown tachycardia (>100 bpm) on repeated preablation ECG recordings during AF. In the decreased LVEF group, the LVEF increased from $42 \pm 9\%$ to $56 \pm 8\%$ ($P < 0.001$) after ablation.

Conclusions: Patients with AF and decreased LVEF undergoing AF ablation have similar success to patients with normal LVEF and have improvement in LVEF after ablation. These results suggest the presence of a reversible AF-induced ventricular cardiomyopathy in many patients with AF and depressed LV function. The presence of under-recognized and reversible cardiomyopathy even when tachycardia is not persistent is important to recognize. (*J Cardiovasc Electrophysiol*, Vol. 18, pp. 9–14, January 2007)

atrial fibrillation, arrhythmia, catheter ablation, cardiomyopathy, congestive, myocardial diseases

Introduction

Most atrial fibrillation (AF) patients with decreased left ventricular ejection fraction (LVEF) in the absence of coronary or severe valvular disease are thought to have an idiopathic cardiomyopathy. However, clinical evaluation of the ventricular rate in AF can be difficult, and the presence of a tachycardia-induced cardiomyopathy may be underestimated when the AF is paroxysmal and the tachycardia response is intermittent.¹

AF-induced ventricular cardiomyopathy can reverse after achievement of rate control,¹ restoration of sinus rhythm,^{1–3} or atrioventricular node ablation and pacemaker placement.^{4–11} An improvement in LVEF is often seen over a period of weeks to months. The improvement in LVEF has also

been demonstrated in patients with paroxysmal AF^{6,9} and AF with a well-controlled ventricular response.¹¹ The improvement in LVEF suggests that usual practices for determining rate control may be suboptimal, although other factors such as loss of atrial transport¹² and R-R interval irregularity¹³ may also contribute to the decreased LV function as well.

The development of catheter ablative techniques for cure of AF may offer potential for improvement in LVEF in patients with AF and dilated cardiomyopathy. Although recent literature demonstrated that pulmonary vein isolation (PVI) is effective in a heterogeneous group of patients with depressed LVEF,¹⁴ outcome data for ablation of AF triggers in patients with nonischemic cardiomyopathy have not been firmly established.

We sought to evaluate the outcome and effect on LV function of AF trigger ablation in patients with AF and left ventricular dysfunction.

Methods

Study Population

Patients referred for AF ablation for drug refractory, symptomatic AF were included. Patients with reduced LVEF ($\leq 50\%$) were compared with patients with normal LVEF.

Address for correspondence: Francis E. Marchlinski, M.D., Cardiac Electrophysiology, 9 Founders Pavilion, 3400 Spruce Street, Philadelphia, PA 19104, USA. Fax: 215-662-2879; E-mail: francis.marchlinski@uphs.upenn.edu

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Data Collection

Prospective data collection included clinical characteristics of patients, observations noted during ablation, and electrophysiologic data. LVEF was measured by transthoracic echocardiography the day after the procedure in sinus rhythm, and at up to 6 month follow-up. All echocardiographic data were obtained from transthoracic 2D echocardiograms interpreted by readers blinded to the study. The left atrial-emptying fraction (LAEF) was calculated using the ratio of measured left atrial volumes during atrial systole and diastole.¹⁵ Transtelephonic monitoring was performed routinely for 2–3 weeks prior to ablation, at 6 weeks, 6 months, and with symptoms following ablation. Patients transmitted recordings twice daily and with symptoms.

AF Ablation

All patients gave written informed consent in accordance with institutional guidelines of the University of Pennsylvania Health System. Antiarrhythmic drug therapy was stopped at least five half-lives. Amiodarone was stopped at least 2 weeks before the procedure. Isolation of arrhythmogenic pulmonary veins (PVs) was performed as previously described.¹⁶ Briefly, patients were brought to the electrophysiology laboratory and decapolar catheters (Irvine Biomedical, Irvine, CA, USA) were placed in the coronary sinus and along the crista terminalis for recording and internal cardioversion. An intracardiac phased-array ultrasound catheter (Acunav, Acuson, Inc., Mountain View, CA, USA) was placed in the right atrium to guide transseptal puncture and assess PV flow. Two transseptal atrial punctures were performed and a cooled-tip catheter (Chilli, Cardiac Pathways Corporation, Sunnyvale, CA, USA) or a 4-mm or 8-mm tip NaviStar mapping/ablation catheter and a Lasso circular mapping catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) were advanced to the left atrium for mapping and ablation. All patients received graded isoproterenol infusion (3, 6, 12, 20 µg/min) followed by cardioversion of burst pacing induced AF on low dose (2–3 µg/min) isoproterenol to elicit spontaneous atrial premature beats and/or AF.

Isolation of arrhythmogenic PVs (PVs demonstrating triggers for AF or reproducible atrial premature depolarizations) was performed. Entry and exit block were confirmed for each PV.¹⁷ After PVI, the isoproterenol infusion protocol was repeated and non-PV triggers of AF were targeted for ablation. In patients with persistent AF and those who returned for a repeat ablation procedure, all PVs were isolated.

Preprocedure Assessment of AF Burden and Ventricular Rate Control

In patients with a decrease in LVEF, the preprocedure transtelephonic monitoring results were reviewed for the presence of frequent or persistent tachycardia (>100 bpm) suggesting poor rate control. Patients with at least 50% of transtelephonic recordings showing AF episodes with tachycardia were considered to demonstrate definite evidence of poor rate control with significant AF burden.

Postprocedure Management

A class 1C drug or sotalol was routinely used. AF occurring in the first month was censored from analysis. All patients were seen routinely at 6–8 weeks after ablation and

then at 3–4 months and every 6 months. If there were no AF occurrences at the initial follow-up appointment, antiarrhythmic drugs were discontinued routinely at 6–8 weeks in patients with paroxysmal AF and at 6 months in patients with persistent AF. If AF recurred after discontinuing antiarrhythmic agents, they were restarted. AF control was defined as freedom from AF or a >90% decrease in the patient's AF burden after a minimum of 3-month follow-up. Freedom from AF was documented by the absence of AF symptoms and at least one 3-week period of transtelephonic ambulatory monitoring with no AF on twice-daily transmission. A 90% decrease in AF burden was rigidly defined. All such patients had to have documented daily episodes of AF prior to the procedure. After the procedure, to demonstrate a >90% reduction in AF burden, patients were not allowed to demonstrate more than one paroxysm lasting >2 minutes during 2–3 weeks of transtelephonic monitoring (recorded at least twice a day) or more than one symptomatic episode of suspected or ECG-documented AF paroxysm during each 1-month follow-up period.

Statistical Analysis

Results are expressed as mean ± standard deviation. Analyses of LVEF change and echocardiographic parameters were made using the Wilcoxon signed ranks test. An independent samples *t*-test was used to evaluate the effect of AF control on the magnitude of LVEF change and to evaluate for significant difference in number of PVI procedures. The Chi-square test was used to compare PVI outcome between normal and low LVEF groups. Statistical analyses were performed using the SPSS (version 12.0), and significance was defined as a two-sided *P* value < 0.05.

Results

There were 366 consecutive patients with paroxysmal (*n* = 299) or persistent (*n* = 67) AF. The baseline clinical characteristics of the study cohort are displayed in Table 1. The mean age was 54 ± 11 years, and 21% of the group was female. Two hundred and ninety-nine patients had normal LV function with a mean EF of 61 ± 6%. Sixty-seven (18%) patients had a decreased LV function with a mean EF of 42 ± 9%

TABLE 1
Baseline Patient Demographics

	Patients With Decreased LVEF (<i>n</i> = 67)	Patients With Normal LVEF (<i>n</i> = 299)
Women (%)	5 (7)	71 (23)
Age (years)	54 ± 9	54 ± 11
Left atrial size (cm)	4.4 ± 0.7	4.4 ± 0.6
Mean LVEF (%)	42 ± 9	61 ± 6
AF duration (years)	5.6 ± 4.9	5.9 ± 5.7
Paroxysmal AF (%)	47 (70)	246 (82)
Persistent AF (%)	20 (30)	53 (18)
Hypertension (%)	21 (31)	133 (44)
Sleep apnea (%)	1 (2)	32 (11)
Coronary artery disease (%)	12 (18)	26 (9)
Valvular artery disease (%)	6 (9)	15 (5)
Mean number of veins isolated	3.4 ± 0.9	3.3 ± 1.0
Mean number of PV isolation procedures	1.6 ± 0.8	1.3 ± 0.5

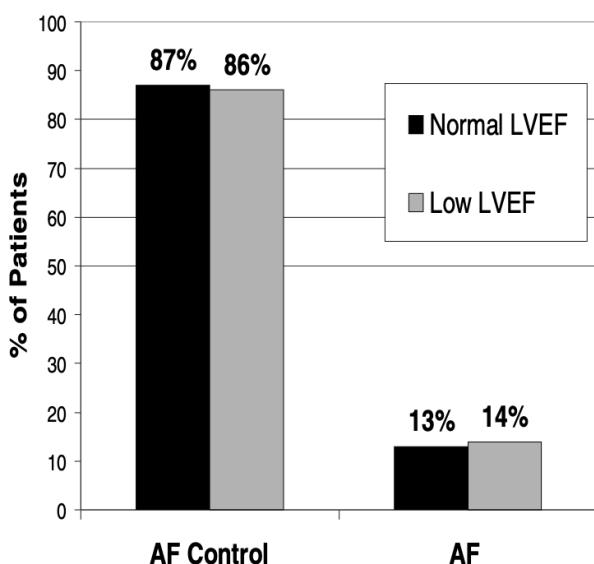


Figure 1. Pulmonary vein isolation outcome based on LV ejection fraction. Comparison of procedural outcome for patients with normal ($>50\%$) and decreased ($<50\%$) left ventricular ejection fraction (LVEF). Outcome in terms of AF recurrence (AF Control versus Recurrent AF) was similar in the two groups ($P = NS$).

(range: 25–50%). The mean number of veins isolated was 3.4 ± 0.9 per patient. The mean number of procedures was 1.4, with 97 (31.4%) of the patients requiring a repeat procedure. Mean follow-up time postablation was 20 ± 9 months.

AF control was achieved in 318 (87%) of the patients, with 206 (57%) patients off antiarrhythmic agents at last follow-up. In the low EF group, coronary artery disease was present in 12 patients and valvular heart disease was present in 6 patients. AF control in the depressed LVEF group compared favorably with that achieved in the group with normal EF group (86% vs. 87% AF control; $P = NS$, Fig. 1), although more repeat procedures were required (1.6 ± 0.8 vs 1.3 ± 0.6 procedures; $P \leq 0.05$). In further comparing the outcome in patients with normal LVEF versus those with low EF after the ablation procedure, complete AF control off antiarrhythmic medications (58% vs 59%), complete AF control on antiarrhythmic medications (21% vs 18%), and control identified by a $>90\%$ reduction in AF burden (10% vs 9%), were also noted to be similar.

Follow-up transthoracic echocardiography in the patients with depressed LVEF demonstrated an improvement in LVEF from $42 \pm 9\%$ to $56 \pm 8\%$ ($P < 0.001$). The EF improvement was significantly greater in the 58 patients with successful AF control (Fig. 2). There was also a significant decrease in left ventricular and left atrial dimensions after ablation in the patients with decreased LVEF (Fig. 3). The mean LAEF one day after ablation in patients with low LVEF was 0.32 ± 0.11 . This compares with an LAEF of 0.54 ± 0.18 in the same patients with follow-up echocardiograms 6 months later ($P < 0.01$ for improvement in LAEF).

Excluding the patients with known coronary artery or valvular disease, there were 50 patients who carried the diagnosis of an “idiopathic” dilated cardiomyopathy. In this group, 36 patients had paroxysmal AF and 14 patients had persistent AF. LVEF increased from $42 \pm 9\%$ preablation to

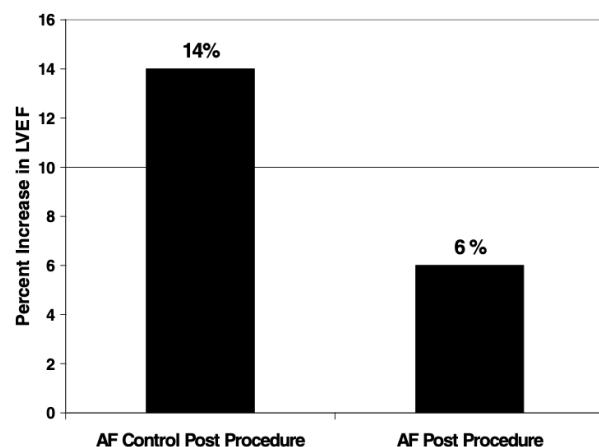


Figure 2. Improvement in LV ejection fraction based on AF control with ablation in patients with low LVEF. Improvement in LVEF was greater in those patients with AF (AF) control after ablation than in those with recurrent AF ($P < 0.01$). Patients with AF control after ablation experienced a 14% mean improvement in LVEF. Even patients with recurrent AF after pulmonary vein isolation still exhibited a 6% mean improvement in LVEF, likely due to a decrease in AF burden compared to preablation.

$57 \pm 7\%$ ($P < 0.001$) postablation. The LVEF increased by $>5\%$ in 41 (82%) patients with normalization of LVEF to $\geq 55\%$ in 36 (72%) patients (Fig. 4).

Preablation ECG monitoring strongly suggested the probable diagnosis of tachycardia-induced ventricular cardiomyopathy in 15 of the 67 (22%) patients with decreased LVEF, including nine patients with persistent and six patients with paroxysmal AF. Ten of the 15 patients had daily ECG documentation of heart rate >100 bpm in persistent or paroxysmal AF, and the remaining five patients demonstrated at least 50% of all transtelephonic transmissions with heart rate >100 bpm in AF. Although an additional 19 patients (28%) had at least one recorded heart rate prior to ablation >100 bpm during AF, the finding was not consistent.

Importantly, of 67 patients with decreased LVEF, drug therapy commonly used in the setting of decreased LVEF

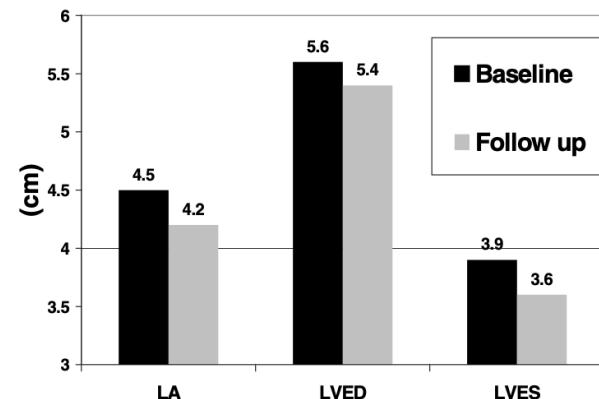


Figure 3. Comparison of echocardiographic measurements at baseline and after 3–6 months follow-up in study population with decreased left ventricular ejection fraction ($n = 67$). There were significant decreases in left atrial (LA), left ventricular end-diastolic (LVED), and left ventricular end-systolic (LVES) diameters ($P < 0.05$ for each measurement).

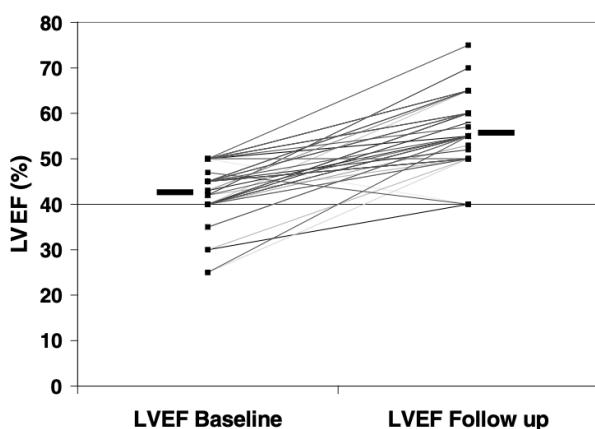


Figure 4. Effect of pulmonary vein isolation on left ventricular ejection fraction (LVEF) in 50 patients without coronary artery or valvular disease and with a preablation diagnosis of idiopathic cardiomyopathy. All but three patients experienced an increase in LVEF with the mean LVEF increasing from $42 \pm 9\%$ to $57 \pm 7\%$, $P < 0.001$.

was similar during pre and postablation. Twenty-three (34%) of the patients were on ACE inhibitors before the ablation procedure and 26 (38%) after the procedure. No patient had a dose increase following the procedure. In addition, 49 (73%) of the patients were on β -blockers pre and 54 (80%) postablation. The five additional patients treated with beta blockers were started on sustained release metoprolol at a dose of ≤ 50 mg/day. Beta blockers were used in 39 of 50 patients (78%) with normalization of LV function and 16 of 17 patients (94%) who failed to demonstrate normalization ($P = 0.27$). ACE inhibitors were used in 18 of 50 patients (36%) with normalization of LV function and 8 of 17 patients (47%) who failed to demonstrate normalization ($P = 0.42$).

Discussion

Our study demonstrates that PVI is effective in patients with depressed LVEF, and is associated with reversal of AF-induced ventricular cardiomyopathy following successful PVI.

Our results of PVI were similar to the reported success rates in studies of patients with primarily normal LV function. In these studies, 62–94% of patients were AF-free at 6–36 months.^{14,16,18–24} Approximately 2–10% of patients had depressed LV function, with no reported difference in outcome between those patients with depressed LVEF and those with normal LVEF.^{22,23,25,26} However, the small numbers of patients with decreased LVEF precluded precise evaluation of outcomes in this population.

Chen and colleagues recently published their experience with PVI in patients with primarily ischemic or valvular cardiomyopathy.¹⁴ Despite the presence of structural heart disease, PVI successfully controlled AF in 73% patients with an initial procedure and another 23% who underwent additional procedures. The AF recurrence rate was significantly higher (27% vs. 13%) after the initial procedure when compared with patients with normal EF. However, after a second procedure, the results were equivalent to that of patients with normal LVEF (96% vs. 94% with $P = 0.02$). We also noted a lower success rate after the initial PVI (63%) in patients with

depressed LVEF that improved to 86% after additional procedures. Likewise, the eventual achievement of AF control was equivalent between the patients with depressed LVEF and the patients with normal LVEF.

We found a significant 12% absolute mean improvement in LVEF after PVI, and over 70% of the patients had normalization of their LVEF to 55% or greater. A notable aspect of the finding is that the baseline LVEF was obtained within 24 hours after the PVI. With both the baseline LVEF and the follow-up LVEF obtained with the patient in sinus rhythm, LVEF improvement cannot be attributed to a change in rhythm. Interestingly, this improvement was seen despite the fact that the most of the patients had paroxysmal AF and that the majority of patients with persistent AF had an apparent controlled ventricular response during preablation clinical evaluation. The improvement in LVEF is similar to that seen in studies examining LVEF after cardioversion or AV-node ablation.^{4–11} In addition, Chen and colleagues found a trend in improvement in EF from 36% to 41% after PVI despite a high incidence of ischemic and valvular cardiomyopathy in their study group.¹⁴ These results, in addition to the present study, suggest the presence of an unrecognized AF-induced ventricular cardiomyopathy in many patients with AF and depressed LV function referred for PVI. Of note, a recent report by Hsu and colleagues documented that even patients with apparent rate control during AF on 48-hour Holter monitor and depressed LV function demonstrate an improvement in function following successful AF ablation.²⁷ These investigators emphasized the possible beneficial role of resynchronized atrial contraction and regularization of ventricular rhythm on LV contractility. In the present study, we found that atrial function improved in those patients with reduced LVEF. This association is in support of the hypothesis that atrial transport function improves LVEF, although does not prove its causality. Improved atrial transport that accompanies restoration of sinus rhythm would be expected to improve cardiac output in patients with low ejection fraction; however, it is unclear whether this phenomenon, per se, would lead to improved LVEF. Because some atrial ablation adversely affects atrial transport, further investigation into its role for improvement in LVEF is warranted with the development of ablation strategies that include extensive left and right atrial ablation.²⁸ Alternatively, regularization of ventricular rhythm, despite an unchanged average ventricular rate, may also lend to the mechanism for improved LVEF with sinus rhythm restoration following PVI. This potential underlying mechanism for this reversal of this arrhythmia-induced ventricular cardiomyopathy may be similar to that observed after suppression²⁹ or ablation³⁰ of frequent ventricular ectopy in patients with normal heart rates.

Of course, if patients have poor rate control, even if intermittent, improvement of ventricular rate with restoration of sinus rhythm would be expected to improve LVEF. We suspect that this phenomenon, in part, is the most likely explanation for our results; however, we cannot definitely prove that heart rate control alone is the mechanism for reversal of cardiomyopathy. Unfortunately, a snapshot assessment of heart rate and AF burden during the brief period prior to ablation may overestimate heart rate control during many months of recurrent AF prior to the evaluation. Regardless of the potential mechanism, we believe that our results suggest that PVI leads to reversal of an under-recognized AF-induced ventricular cardiomyopathy.

Study Limitations

The study results would suggest that the noted improvement in LV function was not dramatic, averaging 14%. However, we feel that the improvement in LVEF observed was clinically significant because the majority of study patients had no other defined reversible etiology for their depressed LVEF and were maintained on a stable medical regimen. Furthermore, the potential for inaccuracies in estimating LV function was minimized with the blinded reading of the echocardiograms and the comparison of echocardiograms obtained in sinus rhythm. Periprocedural administration of medication, including isoproterenol, and the procedure itself, which may involve the administration of large amounts of intravascular volume, may have affected the postprocedure echocardiograms. However, if this effect did occur, there would be equal improvement in LVEF for all patients who underwent the procedure. However, we observed a greater increase in those who achieved AF control compared with those who did not. Therefore, this potential phenomenon cannot explain our results.

Documentation of ventricular rate control in AF was determined primarily from review of patients' electrocardiographic recordings during office visits and twice-daily resting transtelephonic monitor transmissions for 2 weeks prior to undergoing ablation. Although a more rigorous evaluation with more extended and continuous monitoring might find periods of inadequate heart rate control in more patients, these ECG monitoring techniques are often used clinically to assess heart rate control. In addition, the assessment of rate control during the weeks before the ablation procedure does not preclude the possibility of inadequate rate control during the months prior to this assessment. It is certainly possible that inadequate rate control over a more prolonged period may have been responsible for the observed depressed LVEF at the time of the ablation procedure. Sorting out the role of intermittent or prior long-standing tachycardia as the primary cause of reversible AF-induced myopathy should remain an important goal based on our observations.

Conclusions

Patients with AF and decreased LVEF undergoing PVI have eventual success rates similar to patients with normal LVEF. A significant percentage of the patients with AF and depressed LV function demonstrate marked improvement or normalization of LVEF after PVI. These results suggest the presence of an under-recognized AF-induced ventricular cardiomyopathy in many patients with AF and depressed LV function. The presence of this potentially reversible ventricular cardiomyopathy with AF, even when tachycardia is not persistent and rates that are apparently well-controlled, is important to recognize.

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