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Left ventricular systolic dysfunction by itself does not influence outcome of atrial fibrillation ablation

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Aims The objective of the study was to analyse the influence of left ventricular (LV) ejection fraction (EF) on the outcomes of atrial fibrillation (AF) ablation after a first procedure. Pre-procedural predictors of recurrences after AF ablation can be useful for patient information and selection of candidates. The independent influence of LV systolic dysfunction on recurrence rate has not been studied.

Methods and results A case–control study (1:1) was conducted with a total of 72 patients: 36 cases (depressed LVEF) and 36 controls (normal LVEF). Patients were matched by left atrial diameter (LAD), the presence of arterial hypertension, and other variables that might influence the results (age, gender and paroxysmal vs. persistent AF). There were no statistical differences in the variables used to perform the matching. Patients with depressed LVEF had higher LV end diastolic diameter (55.6 ± 6.2 vs. 52.4 ± 5.5, $P = 0.03$), higher LV end systolic diameter (40.3 ± 6.9 vs. 32.6 ± 4.3, $P < 0.001$), lower LVEF (41.4 ± 8.0 vs. 63.1 ± 5.5, $P < 0.001$) and were more likely to have structural heart disease. After a mean follow-up of 16 ± 13 months, survival analysis for AF recurrences showed no differences between patients with depressed vs. normal LVEF (50.0 vs. 55.6%, log rank = 0.82). Cox regression analysis revealed LAD to be the only variable correlated to recurrence [OR 1.11 (1.01–1.22), $P = 0.03$]. Analysis at 6 months showed a significant increase in LVEF (43.23 ± 7.61 to 51.12 ± 13.53%, $P = 0.01$) for the case group.

Conclusion LV systolic dysfunction by itself is not a predictor of outcome after AF ablation. LAD independently correlates with outcome in patients with low or normal LVEF.

Keywords Atrial fibrillation • Radiofrequency ablation • Heart failure

Introduction

The establishment of catheter ablation treatment of 'lone' paroxysmal and persistent atrial fibrillation (AF) using radiofrequency (RF) ablation led to attempts to expand this treatment strategy to heart failure (HF) populations with AF as the logical next step.[1,2] However, reported success rates for RF ablation in HF patients are clearly inferior to those in patients without structural heart disease.[3,4] The reasons for this relative failure are unclear.

Published pre-procedural predictors of AF recurrence after RF ablation include left atrial (LA) size, type and duration of AF and age.[5–9] Of these, the most powerful and independent predictor is LA size. As HF patients usually have LA dilatation concomitant with left ventricular (LV) dysfunction, this could readily explain the observed decrease in RF efficacy. On the other hand, it is also possible that HF patients suffer from a condition that leads to a different mode of AF (through fibrosis or other disease of the LA), less responsive to pulmonary vein (PV) ablation.

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To evaluate these possibilities, this study used pre-procedural predictors of success to match patients with diminished left ventricular ejection fraction (LVEF) undergoing circumferential PV ablation (CPVA) to patients with normal LVEF and compared RF ablation outcomes for the two groups.

Methods

Patient population

A case–control study (1:1) was conducted with a total of 72 patients, 36 consecutive cases (depressed LVEF, defined as $<50\%$[10]) and 36 controls (normal LVEF), retrospectively selected from our database. During the period studied, 2003–2007, all ablations for depressed ejection fraction (EF) cases were performed by the same two experienced operators. Cardiac dimensions and EF were evaluated by one full-time specialized physician, using 2-D transthoracic echocardiography in a dedicated echo lab. If the patient was in AF during data acquisition, the mean value of five consecutive beats was calculated, minimizing the effect of the varying heart rate. Cases were matched to controls by left atrial diameter (LAD), presence of arterial hypertension (AHT), age, sex, and type of AF (paroxysmal vs. non-paroxysmal). All patients were referred for percutaneous catheter ablation of symptomatic AF after having failed treatment with at least two antiarrhythmic drugs. Patients on oral anticoagulation stopped medication 3 days prior to the procedure and low-molecular-weight heparin was administered until the day before ablation. Patients underwent transoesophageal echocardiography and cardiac magnetic resonance (or computed tomography scan) prior to the ablation. Clinical characteristics are shown in *Table 1*.

Circumferential pulmonary vein ablation procedure

Catheters were introduced percutaneously through the femoral vein and, after verifying the absence of a patent foramen ovale, a transseptal puncture was performed to access the LA. After transseptal access, a bolus of intravenous heparin (5000 IU) was administered, with additional bolus to maintain an activated clotting time $\geq$200 s in the first 18 patients and $\geq$250 s in the rest. The ablation procedure was performed under deep sedation, using the CPVA technique previously described[5,11] for both cases and controls. An electroanatomic mapping system (CARTO, Biosense-Webster or NavX, St Jude Medical) generated a three-dimensional map to support the creation and validation of RF lesions during ablation. A thermocouple-equipped 8 mm or irrigated tip catheter (Navistar, Biosense-Webster or Therapy Cool Path, St Jude Medical) was used, with target temperatures of 55°C at 50 W maximum output and 45°C at 40 W maximum output, respectively.

The ablation scheme consisted of continuous RF lesions to encircle the left- and right-sided PV antrums, plus two ablation lines connecting contralateral PV-encircling lesions through the LA roof and the inferior aspect of the LA posterior wall, respectively. The end point of the procedure was the absence or dissociation of local electrograms inside the surrounded regions. In addition, mitral isthmus ablation was anatomically performed by creating a RF line from the infero-lateral aspect of the lateral PV circle to the mitral annulus.

Follow-up

Follow-up was performed on an ambulatory basis, with scheduled clinical controls including ECG and Holter examinations at 3, 6, and 12 months. A repeat echo with the same acquisition method was performed in all patients at 6 months after the AF ablation. At 3 months follow-up (the end of the initial blanking period), antiarrhythmic drugs were discontinued if possible. A successful outcome was defined as freedom from any episode of AF or atrial flutter lasting more than 30 s after this initial 3-month blanking period, including asymptomatic recurrence as evidenced by Holter examinations. Outcome was analysed after a single procedure. Survival and regression analysis did not include data from any additional procedures patients may have required.

Statistical analysis

All continuous data are expressed as mean $\pm$ standard deviation (SD) and were compared by Student's *t*-test. Categorical values are expressed as frequency or percentage and were compared using the χ^2 or Fisher's exact test. Survival analysis was performed using the log-rank test. Individual determinants of outcome were analysed using univariable Cox regression analysis, after which two multivariable Cox proportional-hazards models were developed. In the first model, all variables associated with a *P*-value $\leq$0.2 on univariable analysis were evaluated using backward stepwise logistic regression ($P < 0.1$ for entry and $P > 0.05$ for removal). The second model entered five variables with established clinical relevance: age, presence of hypertension, type of AF, LAD, and EF. All variables in this model were entered in

Table 1 Clinical characteristics of the patient population

	Patients with normal LVEF ($n = 36$)	Patients with low LVEF ($n = 36$)	*P*-value
Age (years)	51.32 $\pm$ 9.89	51.72 $\pm$ 10.49	0.87
Male gender	34 (94.4)	32 (88.9)	0.67
Paroxysmal	15 (41.7)	14 (38.9)	1.0
AHT	19 (52.8)	19 (52.8)	1.0
Ischemic/idiopathic/hypertensive/valvular	N/A	9/18/5/4	N/A
Duration of AF (months)	78.12 $\pm$ 99.90	43.96 $\pm$ 48.08	0.14
LVEDD (mm)	52.41 $\pm$ 5.05	55.63 $\pm$ 6.21	0.03
LVESD (mm)	32.64 $\pm$ 4.28	40.29 $\pm$ 6.95	$<$0.001
LAD (mm)	42.81 $\pm$ 5.43	42.61 $\pm$ 6.00	0.89
EF (%)	63.14 $\pm$ 5.47	41.36 $\pm$ 8.02	$<$0.001

AHT, Arterial hypertension; AF, Atrial fibrillation; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LAD, Left atrial diameter; EF, Ejection fraction; mm, millimetres.
Continuous variables listed $\pm$ standard deviation. Discontinuous variables listed with (percentage).

one step. Serial measurements were compared using repeated ANOVA measures. An alpha level of 0.05 was defined as the threshold for rejecting the null hypothesis. All statistical analyses were performed using SPSS software version 16.0 and software from the R project for statistical computing (http://www.r-project.org).

Results

Patient population

There were no differences in the variables used to perform matching between cases and controls (*Table 1*). In the depressed LVEF group, higher LV end diastolic diameter (55.6 ± 6.2 vs. 52.4 ± 5.5 mm, $P = 0.03$), higher LV end systolic diameter (40.3 ± 6.9 vs. 32.6 ± 4.3 mm, $P < 0.001$) and lower LVEF (41.3 ± 8.0 vs. 63.1 ± 5.5%, $P < 0.001$) were observed. Procedure times and RF time did not differ significantly between normal and low LVEF groups (133.1 ± 41.9 vs. 140.4 ± 47.6 min and 2015 ± 842 vs. 1929 ± 1017 s, respectively, $P =$ NS for both comparisons). In the control group, 16/36 (44%) patients were taking amiodarone before ablation, vs. 20/36 (55%) patients in the case group ($P = 0.4$).

Outcomes and predictors of success after AF ablation

The mean number of procedures for the entire population was 1.4 ± 0.6, without differences between the two groups (1.38 for cases vs. 1.36 for controls, $P = 0.89$). After a mean follow-up of 16 ± 13 months (range 6–59 months), there were no differences between the normal and depressed LVEF groups in the arrhythmia-free survival curves (*Figure 1*).

After a first AF ablation procedure, 38/72 patients (52.8%) were free of AF. Of 34 treatment failures, 26 redo procedures were performed in 21 patients. In this group, success was ultimately achieved in 12/21 patients (57.1%), bringing the total population of patients free from AF to 50/72 (69.4%) (*Table 2*).

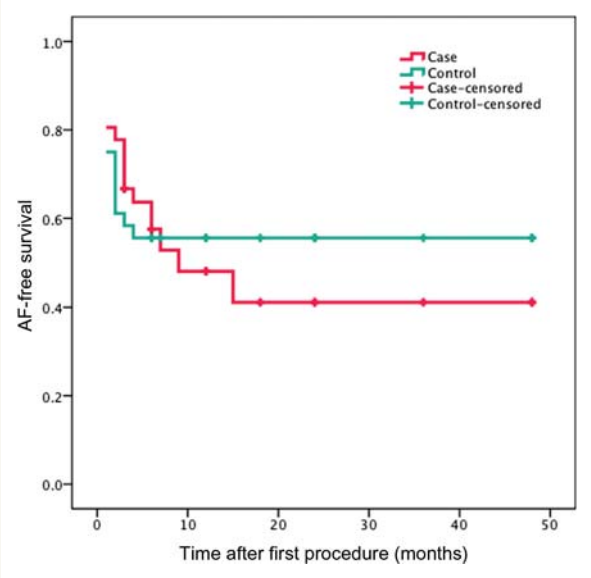

Figure 1 Kaplan–Meier curves (P Log rank test = 0.82).

Table 2 Clinical outcomes after AF ablation

	Patients with normal LVEF ($n = 36$)	Patients with low LVEF ($n = 36$)	P-value
Follow-up (months)	16.8 ± 13.7	14.1 ± 13.7	0.45
Success first procedure	20 (55.6)	18 (50.0)	0.81
Success second procedure	5/10 (50.0)	7/11 (63.6)	0.67
Total cure	25 (69.4)	25 (69.4)	1.00

LVEF, Left ventricular ejection fraction.
Continuous variables listed ± standard deviation. Discontinuous variables listed with (percentage).

Table 3 lists all pre-procedural parameters that were compared for successful and failed ablations. Univariable analysis found no differences between groups in age, sex, clinical type of AF, and presence of AHT or structural heart disease. Dichotomization of normal and depressed LVEF also failed to predict successful CPVA outcome ($P = 0.83$). In contrast, LAD clearly differed between patients with or without recurrences (*Table 3*): mean LAD was 40.9 ± 5.5 mm in the successful group and 44.7 ± 5.3 mm in the failed ablation group ($P < 0.01$). Cox regression analysis of both models confirmed that LAD was the only significant and independent predictor of a successful outcome after CPVA [Model 1: OR 1.11 (1.03–1.20), $P < 0.01$; Model 2: OR 1.12 (1.04–1.20), $P < 0.01$)] (*Table 2*).

Evolution of systolic function

After 6 months follow-up of the low EF group, repeat echo showed a significant increase in EF, from 43.23 ± 7.61 to 51.12 ± 13.53% ($P = 0.01$). There was no significant interaction between the outcome of the procedure and the change in EF ($P = 0.75$, *Figure 2*), although a trend could be observed toward a somewhat less consistent improvement in the failed ablation group. In the group with sinus rhythm after 6 months, mean EF rose from 42.14 to 56.54% ($P < 0.001$) whereas the increase in the recurrent AF group was 44.64–48.21% ($P = 0.28$).

The evolution of systolic function was also analysed by type of structural heart disease. In the case of ischemic heart disease, the mean EF increased from 42.14 ± 3.53 to 55.00 ± 13.56 ($n = 9$, $P = 0.05$). In the case of idiopathic dilated cardiomyopathy, the mean EF improved from 42.64 ± 8.91 to 52.07 ± 11.93 ($n = 18$, $P < 0.01$). Finally, grouping all the non-idiopathic dilated cardiomyopathy patients, the EF increased from 44.31 ± 4.29 to 52.38 ± 12.35 ($n = 18$, $P = 0.05$).

Complications

There was no difference ($P = 0.61$) in procedure-related complications (*Table 4*). In the case group, one transient coronary vasospasm was observed. In the control group, two peripheral vascular haematomas and one transient ischemic attack were observed. All complications were treated conservatively and recovered completely.

Table 3 Cox regression analysis of pre-procedural characteristics

	Univariable		Multivariable Model 1		Multivariable Model 2	
	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Age	0.99 (0.96–1.02)	0.55			0.98 (0.93–1.02)	0.28
Gender	3.8 (0.52–27.88)	0.19		0.42		
Paroxysmal vs. persistent	0.55 (0.27–1.14)	0.11		0.23	0.68 (0.31–1.48)	0.33
Duration of AF	1.00 (0.99–1.00)	0.37				
AHT	1.12 (0.57–2.21)	0.73			1.19 (0.50–2.84)	0.69
RF time	1.00 (1.00–1.00)	0.59				
LVESD	1.00 (0.95–1.05)	0.92				
LVEDD	1.01 (0.96–1.07)	0.64				
LAD	1.10 (1.03–1.16)	0.004	1.10 (1.03–1.16)	0.004	1.09 (1.02–1.16)	0.009
EF	0.99 (0.97–1.02)	0.65		0.78	0.99 (0.97–1.02)	0.83

HR, Hazard ratio; AF, Atrial fibrillation; AHT, Arterial hypertension, RF, Radiofrequency, LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter, LAD, Left atrial diameter, EF, Ejection fraction.

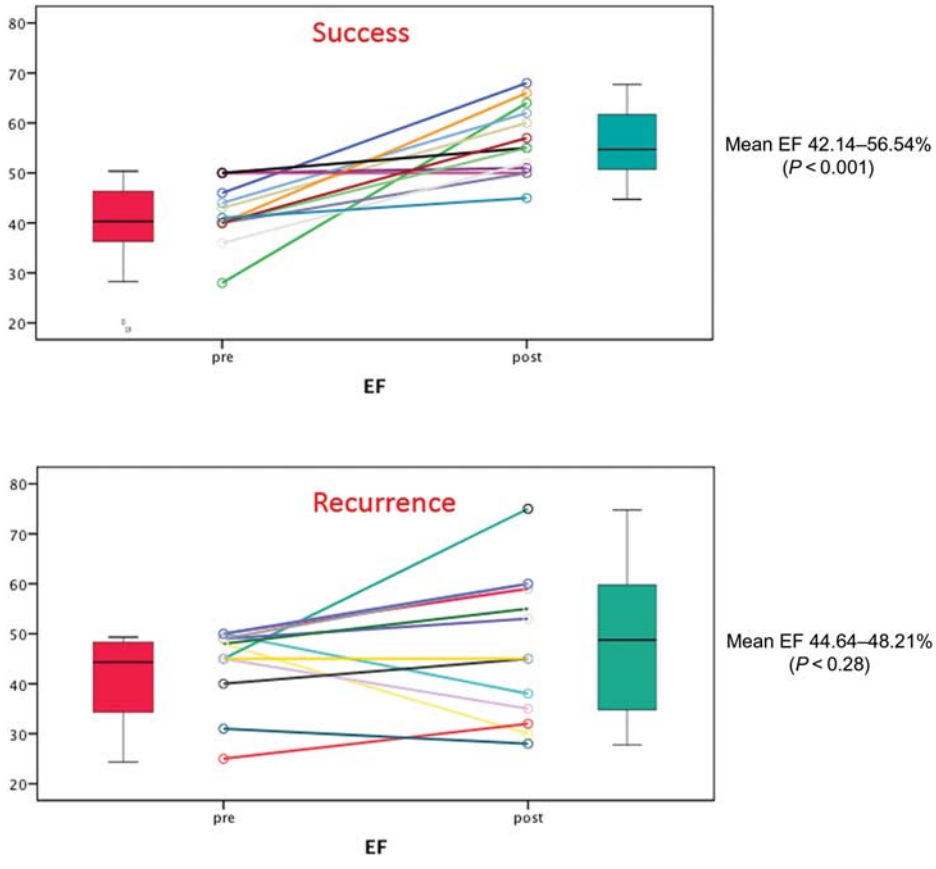

Figure 2 Changes in left ventricular ejection fraction (EF) after atrial fibrillation ablation (Post), as compared with left ventricular ejection fraction prior to the procedure (Pre) for each individual patient, and a comparison of the means.

Table 4 Complications

	Patients with normal LVEF ($n = 36$)	Patients with low LVEF ($n = 36$)	*P*-value
Complications	3	1	0.61
Transient coronary vasospasm		1	
Peripheral vascular pathology	2		
TIA	1		

LVEF, Left ventricular ejection fraction; TIA, Transient ischemic attack.

Discussion

AF and HF are two disease entities that share a remarkable bond, inducing, sustaining, and aggravating each other.[12–14] Although irregular and non-physiological ventricular rates in AF are detrimental to ventricular function, a poor ventricular contractile state itself leads to structural and electrical atrial remodelling, increasing the probability of developing AF. Both conditions might be seen as part of a vicious circle in advanced HF. Much attention is therefore drawn to the treatment of AF in HF patients, both because they represent a vastly larger population than the 'lone AF' group and because there is at least a theoretical hope that by treating AF some of the HF pathophysiology might also be treated.

Although earlier studies such as RACE and AFFIRM failed to show a benefit of rhythm control strategies, and the recent AF-CHF trial confirmed these results for a low EF population, these trials were focused on pharmacological treatment.[15–17] Strategies such as catheter ablation of AF might offer the benefits of rhythm control in HF without the drawbacks of most pharmaceutical regimens. Therefore, AF ablation has been well studied in patients with low EF.[3,4,18–20] The only large series of these trials ($n = 660$) reports a clearly inferior ablation efficacy in low EF, whereas the smaller series document a non-significant trend.[3] However, the reason for any lower ablation efficacy is unclear.

Predictors of outcome

In the current study, we used a case–control matching design to establish whether or not LV dysfunction itself independently contributes to AF ablation failure or success. Considering the random wavelet theories of AF maintenance, a parameter correlating in some way with the amount of fibrosis in the LA, such as LA dilatation, would seem an attractive candidate for predicting procedural success. In addition, recent publications studying populations with more chronic forms of AF suggest that two types of treatment strategies can be considered: Isolating the PVs to eliminate ectopy-based triggering of AF from focal sources, seems to offer greater success in patients without advanced LA disease; the alternative, which is currently under intense evaluation for AF patients suspected of having a large amount of atrial fibrosis, would be an approach focused on eliminating the substrate maintaining AF.[21–23] Following this line of reasoning, the presence of a low EF in a patient with a somewhat healthy LA should not impair CPVA efficacy. Results from this study clearly indicate that indeed LAD independently predicts procedural success after CPVA, and that a low EF by itself does not negatively impact outcome.

Evolution of EF after ablation

In light of the aforementioned relationship between AF and HF, a degree of improvement in LV function might be anticipated after successful restoration of sinus rhythm. Studies in patients with HF presumably due to sustained tachycardia (as seen in uncontrolled AF) do indeed establish the potential to reverse systolic dysfunction after control of ventricular rate, whether through regularization of rhythm or blocking of atrioventricular conduction.[4,18,19,24–26] Similarly, case reports have documented the existence of the entity dubbed tachycardiomyopathy in disease states such as altered ventricular activation due to extreme incidence of ventricular premature beats.[27,28] Interestingly, the present results not only support a favourable EF evolution after successful abolishment of AF, but also show EF evolution, similar in direction although smaller in magnitude, in patients where CPVA had failed. One possible explanation for this outcome is the strict definition of recurrence as any AF episode during follow-up; a lesser AF burden might positively influence EF evolution. On the other hand, conversion to another type of atrial arrhythmia with a slower ventricular rate might also have favourably impacted EF evolution in this group.

The improvement in LVEF may be considered a manifestation of tachycardiomyopathy in the present patient cohort, where lower mean ventricular rates during sinus rhythm may contribute to the overall positive evolution of EF. In addition, the presence of only moderate LV end diastolic enlargement with depressed EF may be interpreted as an argument in favour of tachycardiomyopathy. In most cases, no objective criterion for pre-procedural identification of isolated tachycardiomyopathy is available in low EF patients. Therefore, we were not able to analyse the specific contribution of this phenomenon to the overall outcome. However, the LVEF improvement is very encouraging, showing that the vast majority of patients with AF and LV systolic dysfunction have at least some degree of tachycardiomyopathy. Indeed, LVEF improvement was observed even in patients with ischemic heart disease and did not differ from that of idiopathic LV dysfunction patients. This result warrants further investigation with a larger cohort of patients.

Limitations

The most important limitation of the study is the small sample size, although it is statistically large enough to support the two main findings: that a low EF by itself does not significantly influence the results of the procedure and that the strongest pre-procedural predictor of AF ablation outcome is the atrial disease state, as estimated by the presence of atrial dilatation, even in the presence of HF.

Another potential limitation is that EF was evaluated during AF before the procedure in some patients in persistent AF and during sinus rhythm afterwards if the procedure was successful.

Conclusion

CPVA is feasible and safe in patients with low EF. Success rates after a first procedure are not inferior to those for patients with normal systolic function. Therefore, a low EF by itself does not preclude a successful outcome. Rather, LAD is the strongest factor predicting maintenance of sinus rhythm after AF ablation. In addition, EF has the potential to increase after CPVA, which seems to hold true both for successful and failed ablations, suggesting that the end point might be the 'AF burden' reduction rather than 'absence of any AF episode'. Tachycardiomyopathy might be present in varying degrees in most AF patients with low EF.

Conflict of interest: T.D.P. has received an unrestricted clinical research grant from the Cardiovascular Centre, OLV Hospital, Aalst, Belgium, and is a consultant for Biotronik. J.B. and L.M. have given lectures and courses, and are consultants for St. Jude Medical and Biosense Webster. A.B. has given lectures and courses for St. Jude Medical and Biosense Webster.

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