Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality

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Electronic appendixes are available online.

Objectives: In studying cardiac surgical patients undergoing atrial fibrillation ablation with bipolar radiofrequency, we sought to (1) quantify the time-related prevalence of atrial fibrillation postoperatively and identify its risk factors and (2) determine time-related ablation failure and its risk factors.

Methods: From November 2001 to January 2004, 513 patients underwent atrial fibrillation ablation (bipolar radiofrequency alone or with cryotherapy) and other cardiac operations. Rhythm documented on 3495 postoperative electrocardiograms was used to estimate the prevalence of and risk factors for atrial fibrillation across time. Ablation failure was defined as occurrence of atrial fibrillation any time beyond 6 months after operation.

Results: Prevalence of postoperative atrial fibrillation peaked at about 1 month, decreased to 13% at 6 months, and gradually increased thereafter. Risk factors associated with increased prevalence varied by time period and included older age ($P = .004$) for early occurrence, lesion set in permanent atrial fibrillation ($P = .02$) for late occurrence, and larger left atrial diameter ($P = .02$) and permanent atrial fibrillation ($P < .0001$) for occurrence across the entire time span. Freedom from ablation failure was 72% at 12 months. Risk factors for ablation failure included lesion set in permanent atrial fibrillation ($P = .001$), longer duration of atrial fibrillation ($P = .01$), and larger left atrial diameter ($P = .03$).

Conclusions: Bipolar radiofrequency enables extension of ablation to most cardiac surgical patients with atrial fibrillation. Recurrence is influenced by the type and duration of atrial fibrillation, choice of lesion set in permanent atrial fibrillation, and left atrial size. Early operation, careful choice of lesion set, and left atrial reduction might enhance results.

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Atrial fibrillation (AF) is common in patients presenting for cardiac surgery and, if left untreated, is associated with reduced survival and increased risk of stroke. Successful intraoperative ablation of AF improves outcomes,¹⁻³ but until recently, surgeons were unlikely to combine ablation and other cardiac operations. This is because although the Cox maze III procedure eliminates AF in 70% to 90% of patients, it is complex and increases operative time.³⁻⁵

Recently, there has been great interest in direct surgical ablation of AF, fueled by technologic advances and demonstration that the pulmonary veins and left atrium are the primary sites of drivers of AF.⁶⁻¹² Ablation technologies, such as bipolar radiofrequency (RF), enable surgeons to isolate the pulmonary veins and create linear left atrial lesions rapidly and safely.⁶⁻¹¹ However, results of these new procedures require scrutiny. The objectives of this study of cardiac surgical patients undergoing AF ablation with bipolar RF were to (1) quantify the time-related prevalence of AF after operation and identify its risk factors and (2) determine time-related ablation failure and its risk factors.

TABLE 1. Patient characteristics

Characteristic	n*	No.	%
Demographic	513		
Male		298	58
Age (y), mean $\pm$ SD		67 $\pm$ 12	
Cardiac			
NYHA functional class	513		
I		93	18
II		293	57
III		111	22
IV		16	3.1
Emergency operation	513	4	0.78
Left main disease†	493	34	6.9
LAD disease†	493	165	33
Circumflex disease†	493	133	27
Right coronary disease†	489	144	29
Previous cardiac operation	513		
0		426	83
1		76	15
2		10	2.0
3		1	0.19
History of myocardial infarction	513	141	27
Mitral valve disease cause	513	354	69
Degenerative‡		211	60
Rheumatic‡		76	21
Ischemic‡		36	10
Endocarditis‡		2	0.56
Functional‡		16	4.5
Radiation‡		2	0.6
Prosthetic valve dysfunction‡		10	2.8
Unspecified‡		1	0.3
Mitral regurgitation grade	512		
0		67	13
1+		70	14
2+		67	13
3+		108	21
4+		200	39
Atrial fibrillation type	513		
Permanent		289	56
Persistent		74	14
Paroxysmal		139	27
Flutter		11	2.1
Duration of atrial fibrillation (mo)	512	3, 24, 108§	
LV end-diastolic diameter (cm)	444	5.1 $\pm$ 0.98	
LV end-systolic diameter (cm)	442	3.5 $\pm$ 1.1	
LA diameter (cm)	427	5.12 $\pm$ 0.90	
Fractional shortening	442	0.32 $\pm$ 0.12	
Ejection fraction (%)	442	58 $\pm$ 18	
Estimated wall stress	442	0.49 $\pm$ 0.17	
Noncardiac			
Hypertension	510	327	64
BUN (mg $\cdot$ dL ⁻¹)	508	22 $\pm$ 11	
Bilirubin (mg $\cdot$ dL ⁻¹)	480	0.5, 0.8, 1.4§	
Hematocrit (%)	501	38 $\pm$ 5	

TABLE 1. continued

Characteristic	n*	No.	%
Preoperative thrombotic events	513		
Syncope		49	9.6
Transient ischemic attack		49	9.6
CVA		48	9.4
Embolus		9	1.8
Intraoperative support			
Aortic clamp time (min)	504	87 $\pm$ 32	
CPB time (min)	512	113 $\pm$ 39	
Procedure	513		
Mitral valve repair		227	44
Mitral valve replacement		127	25
Aortic valve replacement		164	32
Tricuspid valve repair		133	26
CABG		195	38

NYHA, New York Heart Association; LAD, left anterior descending coronary artery; LV, left ventricle; LA, left atrium; BUN, blood urea nitrogen; CVA, cerebrovascular accident; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting. *Data available. †>50%. ‡Percent of patients undergoing mitral valve surgery. §15th, 50th (median), and 85th percentiles.

Materials and Methods

Patients

From November 2001 to January 2004, 513 patients underwent AF ablation with bipolar RF at The Cleveland Clinic Foundation. This represents 25% of the 2079 patients with preoperative AF undergoing cardiac surgery during this time frame and 67% of the 769 patients who had some form of AF ablation. Patients were identified, and preoperative, operative, and postoperative variables were retrieved from the Cardiovascular Information Registry, which has been approved for research by the institutional review board. Mean patient age was 67 $\pm$ 12 years (Table 1). The most common indication for operation was mitral valve disease (69%).

AF was classified as paroxysmal (27%), persistent (14%), or permanent (56%)¹³; 2.1% of patients had atrial flutter as their primary arrhythmia. Median duration of preoperative AF was 24 months (range, 1-612 months). Mean left atrial diameter was 5.1 $\pm$ 0.9 cm. Preoperative treatment of AF consisted of antiarrhythmic medications (n = 147 [29%]), warfarin (n = 215 [42%]), and electrical cardioversion (n = 69 [13%]). Preoperative thromboembolic events included transient ischemic attack (10%), stroke (9%), and other systemic embolism (2%).

AF Ablation

Bipolar RF. All patients underwent AF ablation with the Atricleure (West Chester, Ohio) bipolar RF system. In this system, electrodes reside in the jaws of an atraumatic clamp. Energy delivery is continued until tissue conductance between electrodes decreases and reaches a steady state for 2 seconds, indicating transmural conduction block.^{8,9}

Lesion sets. Ablation was generally performed after cardiac arrest but before the principal operative procedure. Lesion sets varied over time and were performed at the discretion of the surgeon in a nonrandomized fashion (see Electronic Appendix

Figure 1. Schematic representation of left atrial lesion sets created with bipolar RF. *White ovals* represent mitral valve, sets of *4 black ovals* represent pulmonary veins, and *dashed lines* represent sites of ablation. All ablation lesions are created with bipolar RF, except in lesion sets 3 and 4, in which the lesion connecting the left pulmonary vein lesion to the mitral valve annulus is created with cryotherapy.

Figure E1). Four basic lesion sets were used most commonly, and these were termed lesion sets 1, 2, 3, and 4 (Figure 1). In all patients, pulmonary veins were isolated with the bipolar RF clamp.

Left atrial connecting lesions (lesion sets 2, 3, and 4) were created with the bipolar clamp by opening the left atrium and placing one jaw on the endocardium and one on the epicardium. The lesion connecting the left pulmonary veins to the mitral annulus (left atrial isthmus, lesion sets 3 and 4) was created by using cryotherapy (Cooper Surgical, Shelton, Conn). The left atrial appendage was excluded or excised in all patients. Some patients in each group had connecting lesions from the left atrial appendage to the left pulmonary veins. One hundred seventy-five (34%) patients received a cryotherapy lesion on the right atrial isthmus.

There were differences between patients receiving different lesion sets. Compared with those receiving lesion set 1, patients receiving lesion sets 2, 3, and 4 were more likely to have a mitral valve procedure; in addition, those receiving lesion sets 3 and 4 were less likely to have paroxysmal AF. Compared with patients receiving lesion set 1, patients with permanent AF receiving lesion sets 2, 3, and 4 were more likely to have mitral valve disease and left atrial enlargement and less likely to have coronary artery disease (see Electronic Appendixes 1-4).

Follow-up

Postoperative electrocardiograms (ECGs) were used to assess AF. ECGs were performed routinely before discharge and at the discretion of referring physicians during follow-up. Recommended ECG follow-up intervals were 1 month, 3 months, 6 months, 1 year, and annually thereafter. A total of 3495 postoperative ECGs were retrieved. Every patient had at least one record available for analysis (range, 1 day to 25 months). One hundred ninety-five patients had an ECG 6 months or more after operation (Figure 2

Figure 2. Number of patients with ECG follow-up available at and beyond various time points and number of ECGs available for analysis at and beyond these same time points.

and see Electronic Appendix 5, available at www.mosby.com/jtcvs). For purposes of analysis, any one of the following 3 rhythms was considered as postoperative AF: AF, atrial flutter, or a paced rhythm with underlying AF or atrial flutter.

Clinical follow-up for survival, morbid events, and medication history was obtained by using patient visit and systematic telephone or mailed questionnaires at 3, 6, and 12 months. Median clinical follow-up was 7 months, with a total of 317 patient-years available for analysis. Use of class I and III antiarrhythmic drugs and warfarin was recorded at each follow-up. Patients were questioned concerning recurrence of AF; however, only those episodes identified by means of ECG were entered into the analyses.

Analysis and Depiction of Data

Prevalence of and risk factors for AF. Because there is no practical method for continuous heart rhythm assessment, a novel statistical technique was developed to depict the prevalence of AF versus time on the basis of discrete ECG recordings. We attempted to solve multiple challenges simultaneously: repeated ECG recordings for each patient (repeated measures), variable times of recording, censoring by death, and a complex temporal pattern of AF prevalence that likely represented the variable effect of different modulating factors across time. The analytic approach taken was temporal decomposition, using several simple additive components (early, constant, and late in this instance) into which separate streams of modulating variables were incorporated for simultaneous analysis. The mathematic models used were derived from those previously used over the last 20 years for decomposition of time-to-event data.¹⁴ Longitudinal binary logistic regression analysis for repeated measurements (PROC NLMIXED, SAS, Inc, Cary, NC) was used to resolve the number of time components and to estimate the shaping parameters of each.

Multivariable analysis was performed in the odds domain to identify risk factors for each component (see Electronic Appendix 6, available at www.mosby.com/jtcvs). Because of the limited ability of PROC NLMIXED to explore multivariable relations, we screened

Figure 3. Temporal pattern of AF after ablation on the basis of postoperative ECGs. The solid line represents point estimates enclosed within 68% bootstrap CLs.

variables using ordinary multivariable logistic regression analysis (PROC LOGISTIC, SAS) with a liberal retention criterion ($P \leq .15$). Candidate risk factors identified were entered at once into PROC NLMIXED and then eliminated one by one until all variables remaining had a P value of .1 or less.

Ablation failure and risk factors. Ablation failure was defined as any occurrence of AF or atrial flutter 6 months or more after ablation. Therefore, to be at risk of ablation failure, patients had to have an ECG obtained in this timeframe. Patients were considered to have ablation failure even if late AF was transient. Data were considered interval censored, with the event assumed to occur between the time of an ECG showing AF and the immediately preceding ECG not showing AF.

To identify risk factors for ablation failure,¹⁴ a parametric model was used to resolve a number of instantaneous risks of the interval-censored event (hazard function) and to estimate shaping parameters. (For additional details, see <http://www.clevelandclinic.org/heartcenter/hazard>.) Variable selection was by bootstrap bagging^{15,16} using a retention criterion of P less than .05 and considering variables appearing in 50% or more models as reliably significant at this level.

Presentation

Predicted percentages of prevalence of AF and freedom-from-event curves are accompanied by asymmetric 68% confidence limits (CLs) comparable to ± 1 SE.

Results

In Hospital

There were no ablation device-related complications. Hospital morbidity included stroke in 8 (2%) patients, transient ischemic attack in 4 (1%), and reoperation for bleeding in 25 (5%). Strokes were judged to be related to the patient's underlying disease (atherosclerosis or calcified valvular heart disease requiring extensive debridement). There were 10 hospital deaths (2%; CL, 1.3%-2.8%).

TABLE 2. Incremental risk factors for higher prevalence of atrial fibrillation

Risk factor	Estimate $\pm$ SE	P value
Overall		
Preoperative permanent AF vs paroxysmal	0.89 ± 0.20	$<.0001$
Preoperative persistent AF vs paroxysmal	0.080 ± 0.27	.8
Greater ventricular wall stress*	-0.67 ± 0.16	$<.0001$
Larger left atrial diameter†	-1.2 ± 0.51	.02
Thinner septum‡	1.1 ± 0.57	.06
Early phase		
Older age§	-1.5 ± 0.52	.004
Greater aortic valve regurgitation	0.21 ± 0.082	.01
Lesion set 2 vs 1	0.46 ± 0.27	.09
Lesion sets 3 or 4 vs 1	0.19 ± 0.23	.4
Constant phase		
None		
Late phase		
Lesion set 2 and permanent AF	0.54 ± 0.23	.02

AF, Atrial fibrillation. *(1/relative wall thickness), inverse transformation. †(5/left atrial diameter), inverse transformation. ‡(1/septal thickness), inverse transformation. §(70/age), inverse transformation.

Heart Rhythm

Prevalence of AF and its risk factors. A curve demonstrating the time-related predicted prevalence of AF or atrial flutter after operation is depicted in Figure 3. Early prevalence of AF peaked at 38% (CL, 35%-41%) at 2 weeks. By 6 months, the prevalence decreased to 13% (CL, 12%-15%), gradually increasing thereafter to 16% (CL, 13%-19%) at 1 year. At 6 months, 26% of patients were taking antiarrhythmic medications (see Figure E2), and 50% were taking warfarin (see Figure E3).

Temporal decomposition of AF prevalence yielded 3 time phases (see Figure E4), and multivariable analysis identified different factors modulating each (Table 2). Because the number of ECGs collected for patients receiving lesion set 4 was low after 6 months, lesion sets 3 and 4 were combined as one set for all analyses.

Preoperative permanent AF (Figure 4, A) and larger left atrial diameter (see Figure E5) were associated with increased prevalence of AF. All lesion sets achieved similar results with paroxysmal AF (Figure 4, C), but lesion set 2 was associated with increased prevalence of AF in patients with permanent AF (Figure 4, C).

Ablation failure. One hundred ninety-five patients had ECGs obtained 6 or more months after ablation and were therefore at risk for ablation failure (see the "Materials and Methods" section). Ablation failure occurred in 53 patients; mode of failure was AF in 41 and atrial flutter in 12. Freedom from ablation failure were 72% at 12 months and 66% at 18 months (Figure 5). Risk factors for ablation

Figure 4. Nomograms from the multivariable equation (Table 2) demonstrating effects of factors on prevalence of AF. **A**, Type of AF. **B**, Lesion set in paroxysmal AF. There is no difference between lesions sets. **C**, Lesion set in permanent AF. Note that 1+ refers to both lesion set 1 and miscellaneous additional lesions, generally to the left atrial appendage. Results with lesion set 2 are inferior.

Figure 5. Freedom from ablation failure. The solid line represents parametric estimate enclosed within dashed 68% CLs. Numbers in parentheses represent patients remaining at risk. The horizontal scale begins at 6 months postoperatively because patients are not at risk for ablation failure until that time.

failure included longer duration of preoperative AF, larger left atrial diameter, and use of lesion set 2 in patients with permanent AF (Table 3 and see Figure E6).

Discussion

Key Findings

This report documents early results with application of bipolar RF to facilitate AF ablation in cardiac surgical patients. Key findings are that (1) the prevalence of AF peaks early after surgical intervention and then decreases to 16% at 1 year, (2) freedom from ablation failure is 72% at 12 months, and (3) recurrence of AF is influenced by the type and duration of AF, the choice of lesion set in permanent AF, and left atrial size.

AF in Cardiac Surgical Patients

The rationale for restoring sinus rhythm in patients presenting for cardiac surgery includes (1) improving survival, (2)

TABLE 3. Risk factors for ablation failure

Risk factor	Estimate $\pm$ SE	P value	R (%) [*]
Lesion set 2 and permanent AF	1.1 $\pm$ 0.33	.001	92
Longer duration of preoperative AF [†]	0.29 $\pm$ 0.12	.01	70
Larger left atrial diameter [‡]	-2.1 $\pm$ 0.97	.03	49
Greater wall stress [§]	1.3 $\pm$ 0.62	.03	43

AF, Atrial fibrillation. ^{*}Reliability: percentage of occurrences in bootstrap models. [†]Ln(duration of AF + 1), logarithmic transformation. [‡](5/left atrial diameter), inverse transformation. [§](Relative wall thickness)², squared transformation.

reducing risk of stroke and other systemic embolism, (3) eliminating need for anticoagulation, (4) reducing symptoms associated with tachycardia, and (5) improving cardiac output.¹⁻³ Because most of these patients do not revert to sinus rhythm with treatment of their primary cardiac lesion (with the possible exception of AF of short duration), we took an aggressive approach to ablation.¹⁷

Although the Cox maze III procedure restores sinus rhythm or an atrioventricular paced rhythm in 75% to 95% of patients undergoing concomitant cardiac surgery,¹⁻⁵ it has not been widely performed. Recently, there has been great interest in treating AF surgically, which is attributable to increased understanding of its pathogenesis and development of new ablation technologies. In most patients, triggers and substrates for AF are located in the left atrium and pulmonary veins,¹² and therefore ablation is now focused on these areas. Alternative energy sources enable rapid creation of lines of conduction block without the laborious cutting and sewing of the Cox maze III procedure. Reported ablation success ranges from 60% to 95% using a variety of different energy sources and lesion sets in various types of patients.^{6,7,10,11} However, there are few data identifying patient- and procedure-related risk factors for ablation failure, and no valid statistical technique to assess results.⁷

Prevalence of AF, Ablation Failure, and Risk Factors

In the current study, bipolar RF was the predominant modality used to create left atrial lesions; cryotherapy was used to create lesions on the right and left atrial isthmuses in some patients. Four basic left atrial lesion sets were used. This variability in lesion sets, coupled with varying patient characteristics and types and durations of AF, facilitated identification of risk factors for return of AF and ablation failure.

Risk factors for AF prevalence and ablation failure were both patient and procedure related. Longer duration of AF, permanent AF, and larger left atrial diameter increased either the prevalence of AF, the risk of ablation failure, or both. In fact, these characteristics tended to occur together in the same patients. Others have demonstrated increased risk of ablation failure when these factors were present.¹⁸⁻²² These findings suggest that it is unlikely that “one size fits all” in ablating AF²³; rather, a tailored approach is indicated.

Procedural risk factors were related to choice of lesion set. In patients with paroxysmal and persistent AF, all lesion sets produced equivalent results. Each lesion set included pulmonary vein isolation, suggesting that drivers of AF in these patients might reside in the pulmonary veins. In contrast, choice of lesion set affected results in patients with permanent AF. Those who received lesion sets 2, 3, and 4 tended to have mitral valve disease and left atrial enlargement (see Electronic Appendix 4 available at www.mosby.com/jtcvs).

Lesion set 2, which does not include a lesion to the mitral annulus, produced inferior results in these patients compared with lesion sets 3 and 4. It has been suggested that failure to ablate the left atrial isthmus jeopardizes success.^{24,25} Our results support this concept in patients with mitral valve disease. As in previous reports, addition of right atrial lesions (eg, isthmus lesions) did not affect results.²⁶

Others have reported that lesion set affects results. Gaynor and colleagues²⁷ found that the Cox maze III procedure was more effective than the Cox maze I and II. Data from catheter-based procedures in patients with paroxysmal AF suggest that the more left atrial area isolated, the better the freedom from AF.²⁸⁻³⁰

Limitations

This series contains early follow-up of a large cohort of patients undergoing intraoperative RF ablation with or without cryotherapy. ECGs used for analysis were obtained routinely in the hospital but opportunistically after hospital discharge. Although only 195 patients had ECGs beyond 6 months after operation, there are a sufficient number for analysis. Patients having late ECGs might be selected because they had symptomatic AF, leading to overestimation of the prevalence of AF and ablation failure. Alternatively, asymptomatic AF episodes without ECG verification might have been missed, leading to underestimation of events.³¹ Although periodic Holter monitoring and event recorders would have provided more data for analysis, these methodologies might still fail to capture all AF episodes. Limitations in the ability to document heart rhythm continuously over time led us to develop novel statistical methods that we believe provide accurate estimates of AF prevalence. Although not perfect, this method represents an important improvement over analyses relying on rhythm at last follow-up or patient self-reporting.

Results of AF ablation were assessed and presented in 2 related but different fashions. We estimated the prevalence of AF to depict the predicted prevalence of AF in the population at any given time after ablation. In such a depiction, a given patient might have AF on one ECG and sinus rhythm on the next, unlike in a time-to-event analysis. We also estimated freedom from ablation failure, with ablation failure defined as any recurrence of AF beyond 6 months after operation. Although this definition is stringent, it is appropriate.

The analyses of prevalence of AF and ablation failure do not take into account antiarrhythmic medications that patients might have been taking. The prevalence of antiarrhythmic medication use is depicted separately. Although we recommend discontinuing antiarrhythmic agents 3 months after ablation, continued use is at the discretion of referring cardiologists, which hampered our ability to report the prevalence of AF and freedom from ablation failure off medications.

We did not assess lesion integrity using pacing or other methods; it is therefore possible that operator error or other factors might have resulted in some patients receiving incomplete lesions, which might have contributed to ablation failures.

Clinical Inferences

AF is common early but is transient after intraoperative ablation. Early operation after the development of AF and left atrial size reduction in those with enlarged left atria might improve results. In patients with paroxysmal and persistent AF, simple pulmonary vein isolation might be adequate. In patients with permanent AF, we recommend the left atrial lesion set of the Cox maze III procedure. A prospective randomized clinical trial with longer follow-up is necessary to test these strategies.

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Discussion

Dr Donald B. Doty (Salt Lake City, Utah). Dr Gillinov and his associates have provided us with information on a large series of patients, 513, having ablation procedures with bipolar RF for the treatment of AF during slightly more than a 2-year period. It is a retrospective study and is subject to all of the problems associated

with such studies. One, there was no protocol or agreement as to the lesion pattern in these patients. Choice was by surgeon discretion, and the lesion pattern changed and evolved over time. The patients were classified according to established American Heart Association and American College of Cardiology criteria: paroxysmal, meaning easily or spontaneously converted to normal sinus rhythm; persistent, probably can be converted; and permanent, cannot be converted. But the lesion pattern choice was apparently not consistently applied by category of patient.

The title of the article implies that bipolar RF energy was the energy used to create left atrial ablation lesions, but the data show that patients having lesion patterns 3 and 4 had the left atrial isthmus lesion created by means of cryothermia and that one third of the patients had right atrial inferior isthmus ablation lesions created by means of cryothermia, presumably to prevent postoperative atrial flutter.

Data have been analyzed by using complex statistical methods in an attempt to compensate for events occurring over time and in which they used analysis of ECGs obtained nearly randomly in the postoperative period. Terms such as *longitudinal binary logistic regression analysis* and *bootstrap bagging* are used. Now Gene Blackstone has explained this to me on frequent occasions, making nearly perfect logical sense, and I accept these methods knowing Gene Blackstone is correct, although I confess I really do not understand them very well, and I am not even going to ask Marc to try to explain them to us.

Dr Gillinov. But I am ready to explain them.

Dr Doty. Well, you do not have to. We accept them. And I think the authors have done a very good job of making some sense out of some difficult data, nearly 3500 ECGs. Let me give you what my interpretation of these data is based on reading the article and hearing what is presented, which quite accurately matches the article. Except for the connecting lesion, lesion patterns 1 and 2 are the same. These are patients who had in common pulmonary vein isolation lesions, and they worked well with the paroxysmal or persistent types of AF, in which one would expect trigger points in the pulmonary veins to initiate the arrhythmia. Lesion pattern 2 added the connecting lesion, but this was not enough when it came to permanent forms, and it has biased the data because the patients who had lesion pattern 2 were heavily weighed with patients with mitral valve disease, whereas the patients with lesion pattern 1 were not, and therefore one would expect the data to come out that way because the substrate for patients receiving lesion pattern 2 implies a much more complex pathogenesis of the AF than trigger points in the left pulmonary veins.

Now lesion patterns 3 and 4 are also the same, having in common pulmonary vein isolation and left atrial isthmus lesions, except that lesion pattern 4 has a double connecting lesion, which, by the way, leads to a portion of the left atrial posterior wall isolated from any electrical depolarization. And this appears to be a more effective lesion pattern when the left atrium is abnormal, such as in mitral valve disease. We do not know from the data, and we have not heard anything presented, what the effect of right atrial isthmus lesions, which were done by means of cryothermia in about one third of these patients, might be, and I would say that the conclusion of the authors, proposed effect of left atrial reduction, is purely speculative

because there are no data in this presentation or the article on which you can base that conclusion.

The first question is as follows: What is the added cost of using 2 energy sources for this operation? Second, what is the role of the right atrial isthmus ablation in the treatment of AF? Three, should pulmonary vein isolation lesions be restricted to patients having paroxysmal forms or perhaps persistent forms of AF? And finally, what is the currently recommended lesion pattern for permanent forms of AF?

Dr Gillinov. Thank you, Dr Doty, for all of your comments. I think the preamble to your questions hits on something that can be used as the strength of this presentation. It is incredibly heterogeneous. There were 10 surgeons handling many different types of patients with different lesion sets in different approaches. At first glance that might produce just chaos, but on the other hand, if you have enough patients and enough follow-up, it allows you to discern patterns that relate to both the sort of patients and the lesions created, and you can get the beginnings of some answers, and therefore the heterogeneity was useful.

Regarding the cost of the 2 energy sources? Well, it is higher than we would like, but we used the older reusable cryo system, so that is a sunk cost from 15 years ago. It does not cost us anything additional to use the Cooper Surgical or Frigtronics system once we have already purchased it, and therefore we are paying for only one disposable ablation unit per case. There are people who create the isthmus lesion with RF. We have not because of fear of injury to the circumflex artery, although I am not sure that has been reported.

What about the right atrial isthmus lesion? We analyzed that to determine whether its presence or absence is a risk factor for failure. In our experience the answer is that no, it has no effect, and therefore we create one now only in someone who has a history of flutter.

Should pulmonary vein isolation be restricted to patients with paroxysmal AF? Not entirely. Pulmonary vein isolation is now our lesion set of choice with excision of the appendage in the paroxysmal patient. However, in patients who are very ill and who undergo a complex operation in which we do not want to spend even the additional 10 minutes to open the atrium and create connecting lesions, we will just do the pulmonary veins, and about 40% or 50% of those might have some success. On the other hand, if a patient has permanent AF and there is no specific contraindication or difficulty to opening the atrium and making connecting lesions, then our lesion set of choice in the left atrium looks like a maze procedure.

Dr Vaughn Starnes (*Los Angeles, Calif*). It is not only a very heterogeneous group of surgeons but also a heterogeneous population of patients.

My question pertains to the mitral valve repair itself. Did the repair and durability of that repair affect in any way the results of your AF; that is, if you had some residual mitral regurgitation or regurgitation developed, did it affect your outcome?

Dr Gillinov. I do not know whether recurrent mitral regurgitation influences the results; it very well might. Because recurrent mitral regurgitation and return of AF are both time-related outcomes of the surgical procedure, analysis of their relationship is statistically challenging.

Electronic Appendix 1. Patient characteristics according to lesion set: categoric variables

Characteristic	Lesion set				P value
	1, n = 194 (38%), No. (%)	2, n = 96 (19%), No. (%)	3/4, n = 183 (36%), No. (%)	Other, n = 40 (8%), No. (%)	
Demographic					
Male	122 (63)	54 (56)	94 (51)	28 (70)	.05
Cardiac comorbidity					
NYHA functional class					.4
I	30 (15)	18 (19)	38 (21)	7 (18)	
II	106 (55)	51 (53)	109 (60)	27 (68)	
III	50 (26)	23 (24)	32 (17)	6 (15)	
IV	8 (4)	4 (4)	4 (2)	0 (0)	
Emergency operation	4 (2)	0 (0)	0 (0)	0 (0)	.08
Left main disease*	21 (11)	7 (7)	4 (2)	2 (5)	.007
LAD disease*	82 (45)	30 (32)	38 (21)	15 (39)	<.0001
Circumflex disease*	65 (35)	23 (24)	34 (19)	11 (29)	.006
Right coronary disease*	75 (41)	25 (27)	34 (19)	10 (26)	<.0001
Previous cardiac operation					.5
0	160 (82)	78 (81)	156 (85)	32 (80)	
1	28 (14)	16 (17)	24 (13)	8 (20)	
2	6 (3)	1 (1)	3 (1.6)	0 (0)	
3	0 (0)	1 (1)	0 (0)	0 (0)	
Previous myocardial infarction	74 (38)	22 (23)	32 (17)	13 (32)	<.0001
Mitral valve disease cause	90 (46)	74 (77)	152 (83)	38 (95)	
Degenerative†	44 (49)	47 (64)	99 (65)	21 (55)	.07
Rheumatic†	19 (21)	17 (23)	34 (22)	6 (16)	.8
Ischemic†	17 (19)	7 (9)	5 (3)	7 (18)	.0004
Endocarditis†	0 (0)	1 (1)	1 (0.66)	0 (0)	.7
Functional†	4 (4)	1 (1.3)	10 (5)	1 (3)	.3
Radiation†	1 (1)	0 (0)	1 (0.7)	0 (0)	.8
Prosthetic valve dysfunction†	5 (6)	1 (1.3)	1 (0.7)	3 (8)	.03
Unspecified†	0 (0)	0 (0)	1 (0.7)	0 (0)	.7
Mitral regurgitation grade					<.0001
0	38 (20)	13 (14)	15 (8)	1 (2.5)	
1+	38 (20)	14 (15)	17 (9)	1 (2.5)	
2+	33 (17)	9 (9)	19 (10)	6 (15)	
3+	31 (16)	23 (24)	46 (25)	8 (20)	
4+	53 (27)	37 (38)	86 (47)	24 (60)	
Atrial fibrillation type					
Permanent	101 (52)	45 (47)	121 (66)	22 (55)	.007
Persistent	25 (13)	13 (14)	29 (16)	7 (18)	.8
Paroxysmal	65 (34)	35 (36)	29 (16)	10 (25)	.0002
Flutter	3 (1.6)	3 (3)	4 (2)	1 (2.5)	.9
Noncardiac comorbidity					
Hypertension	131 (68)	62 (65)	110 (61)	24 (60)	.5
Preoperative thromboembolic event					
Syncope	22 (11)	9 (9)	15 (8)	3 (8)	.7
Transient ischemic attack	20 (10)	7 (7)	17 (9)	5 (12)	.8
Cerebrovascular accident	24 (12)	6 (6)	16 (9)	2 (5)	.2
Embolus	3 (1.6)	1 (1)	5 (3)	0 (0)	.6
Procedure					
Mitral valve repair	54 (28)	46 (48)	103 (56)	24 (60)	<.0001
Mitral valve replacement	36 (19)	28 (29)	49 (27)	14 (35)	.05
Aortic valve replacement	76 (39)	35 (36)	46 (25)	7 (18)	.004
Tricuspid valve repair	50 (26)	23 (24)	52 (28)	8 (20)	.7
Isolated CABG	31 (16)	4 (4)	3 (2)	1 (2)	<.0001
Any CABG	92 (47)	35 (36)	50 (27)	18 (45)	.0007

Electronic Appendix 1. continued

Characteristic	Lesion set				P value
	1, n = 194 (38%), No. (%)	2, n = 96 (19%), No. (%)	3/4, n = 183 (36%), No. (%)	Other, n = 40 (8%), No. (%)	
Lesion					
Right atrial lesion	9 (5)	8 (8)	141 (77)	17 (42)	<.0001

NYHA, New York Heart Association; LAD, left anterior descending coronary artery; CABG, Coronary artery bypass grafting. * $>50\%$. †Percentage of patients undergoing mitral valve surgery.

Electronic Appendix 2. Patient characteristics according to lesion set: continuous variables*

Characteristic	Lesion set				P value†
	1	2	3/4	Other	
Demographic					
Age (y)	68 ± 12	67 ± 12	67 ± 11	64 ± 13	.08
Cardiac comorbidity					
Duration of AF (mo)‡	3, 24, 84	3, 31, 100	4, 36, 120	2, 13, 60	.006
LV end-diastolic diameter (cm)	5.1 ± 1.1	5 ± 0.95	5.1 ± 0.87	5.4 ± 0.88	.1
LV end-systolic diameter (cm)	3.7 ± 1.4	3.3 ± 0.92	3.4 ± 0.88	3.8 ± 1.0	.09
Left atrial diameter (cm)	5 ± 0.77	5 ± 0.78	5.3 ± 1.0	5.5 ± 0.88	.0005
Fractional shortening	0.30 ± 0.14	0.33 ± 0.11	0.35 ± 0.11	0.30 ± 0.11	.008
Ejection fraction (%)	54 ± 22	59 ± 17	62 ± 15	56 ± 16	.01
Estimated wall stress	0.51 ± 0.17	0.51 ± 0.21	0.47 ± 0.13	0.45 ± 0.13	.03
Noncardiac comorbidity					
BUN (mg · dL ⁻¹)	23 ± 13	22 ± 9	21 ± 8	21 ± 8	>.9
Bilirubin (mg · dL ⁻¹)‡	0.5, 0.8, 1.4	0.5, 0.8, 1.3	0.5, 0.8, 1.4	0.45, 1.0, 1.5	.6
Hematocrit (%)	38 ± 6	38 ± 6	38 ± 5	38 ± 5	.8
Intraoperative support					
Aortic clamp time (min)	81 ± 31	92 ± 34	90 ± 32	89 ± 25	.006
CPB time (min)	112 ± 40	115 ± 40	113 ± 37	116 ± 33	.5

AF, Atrial fibrillation; LV, left ventricular; BUN, blood urea nitrogen; CPB, cardiopulmonary bypass. *Mean ± SD unless otherwise noted. †Wilcoxon rank-sum nonparametric test. ‡Median, 15th, and 85th percentiles.

Electronic Appendix 3. Factors associated with lesion sets

Factor	Estimate $\pm$ SE	P value
Lesion set 2 vs lesion set 1		
Date of operation	-32 ± 13	.01
Date of operation*	390 ± 155	.01
Fewer with RCA system disease	-0.66 ± 0.31	.03
Higher ejection fraction†	1.6 ± 0.48	.0006
Longer aortic clamp time	0.015 ± 0.005	.002
More with a mitral procedure	1.2 ± 0.33	.0002
Lesion set 3 vs lesion set 1		
Higher ejection fraction†	1.9 ± 0.57	.0009
Fewer with paroxysmal AF	-1.3 ± 0.37	.0007
Fewer with RCA system disease	-0.89 ± 0.33	.006
Longer aortic clamp time	0.016 ± 0.0053	.004
Longer duration of AF‡	0.31 ± 0.11	.006
Fewer with heart failure	-0.93 ± 0.33	.004
More with a mitral procedure	1.5 ± 0.37	<.0001
Fewer with diabetes	-1.2 ± 0.51	.02
Lesion set 4 vs lesion set 1		
Date of operation	29 ± 10	.002
Date of operation*	-333 ± 116	.004
Fewer with paroxysmal AF	-1.4 ± 0.42	.0005
Higher ejection fraction†	1.5 ± 0.50	.003
Fewer with RCA system disease	-1.5 ± 0.36	<.0001
Smaller septum§	2.9 ± 1.0	.004
Longer aortic clamp time	0.020 ± 0.0057	.0003
Fewer with aortic valve stenosis	-1.3 ± 0.45	.003
More with a mitral procedure	1.2 ± 0.39	.003

RCA, Right coronary artery; AF, atrial fibrillation. *Ln(interval from date of operation to 1/1/1991), logarithmic transformation. †Ln(ejection fraction), logarithmic transformation. ‡Ln(duration of AF), logarithmic transformation. §Ln(relative wall thickness + 5), logarithmic transformation.

Electronic Appendix 4. Patient characteristics within permanent AF group

Characteristic	Lesion set			P value
	1, n = 101 (38%), No. (%)	2, n = 45 (17%), No. (%)	3/4, n = 121 (45%), No. (%)	
Demographic				
Age (y), mean $\pm$ SD	71 $\pm$ 11	70 $\pm$ 9	69 $\pm$ 10	.3
Cardiac comorbidity				
Left main disease*	14 (15)	5 (11)	4 (3)	.01
LAD disease*	48 (51)	16 (37)	28 (24)	.0002
Circumflex disease*	39 (41)	14 (32)	26 (22)	.01
Right coronary disease*	45 (48)	15 (35)	26 (22)	.0004
Previous myocardial infarction	46 (46)	11 (24)	24 (20)	.0001
Mitral valve disease cause				
Rheumatic	13 (13)	12 (27)	25 (21)	.1
Degenerative	24 (24)	22 (49)	66 (55)	<.0001
Mitral valve regurgitation grade				.004
0+	21 (21)	9 (20)	11 (9)	
1+	21 (21)	6 (13)	12 (10)	
2+	21 (21)	5 (11)	16 (13)	
3+	15 (15)	8 (18)	27 (22)	
4+	23 (23)	17 (38)	55 (45)	
Ejection fraction (%), mean $\pm$ SD	50 $\pm$ 20	58 $\pm$ 14	62 $\pm$ 16	.002
Left atrial diameter (cm)†	4.2, 5.2, 6.0	4.4, 5.0, 5.9	4.7, 5.5, 6.6	.01
>6 cm	13 (16)	4 (12)	31 (30)	.03
Fractional shortening†	0.12, 0.26, 0.42	0.22, 0.30, 0.45	0.23, 0.34, 0.47	.001
Procedure				
Mitral valve repair	26 (26)	15 (33)	64 (53)	.0001
Mitral valve replacement	22 (22)	19 (42)	37 (31)	.04
CABG	56 (55)	20 (44)	34 (28)	.0002
Lesion				
Right atrial	8 (8)	6 (13)	96 (79)	<.0001

LAD, Left anterior descending coronary artery; CABG, coronary artery bypass grafting. * $\geq$ 50%. †Median, 15th, and 85th percentiles.

Electronic Appendix 5. Distribution of electrocardiographic records over time

Time (mo)	0	1	3	6	9	12
Overall						
No. of patients	513	313	253	195	120	72
No. of ECGs	3495	1070	694	401	219	113
Lesion set 1						
No. of patients	194	115	91	69	47	26
No. of ECGs	1278	414	270	167	91	46
Lesion set 2						
No. of patients	96	74	61	49	21	13
No. of ECGs	676	233	150	80	39	15
Lesion set 3						
No. of patients	96	72	67	51	35	24
No. of ECGs	805	300	207	113	66	39
Lesion set 4						
No. of patients	87	34	17	14	10	5
No. of ECGs	496	67	30	20	13	6
Other lesions						
No. of patients	40	18	17	12	7	4
No. of ECGs	240	56	37	21	10	7

ECG, Electrocardiogram.

Electronic Appendix 6. Variables used in the analyses

Preoperative

Demographic	Age (y), sex, weight (kg), height (cm), body surface area (m^2), body mass index ($\text{kg} \cdot \text{m}^{-2}$)
Symptoms	New York Heart Association functional class (I-IV), emergency operation
Left ventricular function	Ejection fraction (%), end-diastolic diameter (cm), end-systolic diameter (cm), fractional shortening, mass (g), mass index ($\text{g} \cdot \text{m}^{-2}$), end-diastolic volume (mL), end-systolic volume (mL), end-diastolic volume index ($\text{mL} \cdot \text{m}^{-2}$), end-systolic volume index ($\text{mL} \cdot \text{m}^{-2}$), posterior wall thickness (cm), estimated wall stress
Right ventricular function	Estimated systolic pressure
Atrial size	LA diameter (cm), LA volume (mL), LA volume index ($\text{mL} \cdot \text{m}^{-2}$)
Mitral valve pathology	Mitral regurgitation
Mitral valve disease cause	Ischemic, rheumatic, degenerative
Other valve pathology	Aortic valve regurgitation, tricuspid valve regurgitation
Cardiac comorbidity	Complete heart block–pacer, ventricular arrhythmia, number of previous cardiac operations
Noncardiac comorbidity	Insulin-treated diabetes, non–insulin-treated diabetes, treated diabetes, history of peripheral vascular disease, history of smoking, carotid disease, chronic obstructive pulmonary disease, hypertension, renal disease, creatinine ($\text{mg} \cdot \text{dL}^{-1}$), blood urea nitrogen ($\text{mg} \cdot \text{dL}^{-1}$), bilirubin ($\text{mg} \cdot \text{dL}^{-1}$), hematocrit (%)
Coronary anatomy	Maximum % stenosis in: left main trunk, left anterior descending coronary artery system, right coronary artery system, left circumflex coronary artery system
Experience	Date of operation (years since January 1, 2001)
Atrial fibrillation types	Permanent, persistent, paroxysmal, duration of atrial fibrillation (mo)
Thromboembolic events	Transient ischemic attack, cerebrovascular accident

Intraoperative

Procedure	Internal thoracic artery graft used, coronary artery bypass grafting, tricuspid valve repair, MV repair, MV replacement, MV bioprosthetic replacement, aortic valve replacement
Lesion sets	Lesion set 1, lesion set 2, lesion set 3, lesion set 4, connection to mitral annulus, connection between inferior pulmonary veins, connection between superior pulmonary veins, connection to left atrial appendage, right atrial lesion
Source	Cryotherapy
Support	Aortic clamp time (min), cardiopulmonary bypass time (min)

LA, Left atrium; MV, mitral valve.

Electronic Appendix Figure E1. Use of various lesion sets (1-4) across the study period.

Electronic Appendix Figure E2. Prevalence of class I and III antiarrhythmic agent use after ablation. The horizontal axis begins at 3 months, marking the first systematic follow-up of patients. *Filled circles* represent observed prevalences, but only approximate the data because of multiple follow-up inquiries per patient. The *solid curve* represents the prevalence estimate from the logistic mixed model, and *dashed lines* represent 68% confidence limits.

Electronic Appendix Figure E3. Prevalence of warfarin use after ablation. Format is as for Electronic Appendix Figure E2.

Electronic Appendix Figure E4. Decomposition of temporal pattern of atrial fibrillation (AF) after ablation, based on postoperative electrocardiograms, demonstrating 3 phases of prevalence: an early peaking phase, a constant phase, and a late rising phase.

Electronic Appendix Figure E5. Nomogram from the multivariable equation ([Table 2](#)) demonstrating the effect of 2 left atrial diameters.

Electronic Appendix Figure E6. Effect of (1) lesion set, (2) type of atrial fibrillation (AF), and (3) duration of AF (along horizontal axis) on estimated 1-year freedom from ablation failure (vertical axis) based on multivariable analysis (see [Table 3](#)). *Dashed lines* enclose 68% confidence limits.