Late outcomes after the Cox maze IV procedure for atrial fibrillation

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ABSTRACT

Objective: The Cox maze IV procedure (CMPIV) has been established as the gold standard for surgical ablation; however, late outcomes using current consensus definitions of treatment failure have not been well described. To compare to reported outcomes of catheter-based ablation, we report our institutional outcomes of patients who underwent a left-sided or biatrial CMPIV at 5 years of follow-up.

Methods: Between January 2002 and September 2014, data were collected prospectively on 576 patients with AF who underwent a CMPIV (n = 532) or left-sided CMPIV (n = 44). Perioperative variables and long-term freedom from AF, with and without AADs, were compared in multiple subgroups.

Results: Follow-up at any time point was 89%. At 5 years, overall freedom from AF was 93 of 119 (78%), and freedom from AF off AADs was 77 of 177 (66%). No differences were found in freedom from AF, with or without AADs, at 1, 2, 3, 4, and 5 years for patients with paroxysmal AF (n = 204) versus with persistent/longstanding persistent AF (n = 305), or for those who underwent standalone versus a concomitant CMP. Duration of preoperative AF and hospital length of stay were the best predictors of failure at 5 years.

Conclusions: The outcomes of the CMPIV remain good at late follow-up. The type of preoperative AF or the addition of a concomitant procedure did not affect late success. The results of the CMPIV remain superior to those reported for catheter ablation and other forms of surgical AF ablation, especially for patients with persistent or longstanding AF. (J Thorac Cardiovasc Surg 2015;150:1168-78)

Freedom from atrial tachyarrhythmias was equivalent in those with paroxysmal versus nonparoxysmal atrial fibrillation.

Central Message

At 5 years, sinus rhythm was restored in most patients after a CMPIV, regardless of AF type. The duration of AF predicted failure.

Perspective

The CMPIV remains the most successful surgical treatment for AF, even in patients with non-paroxysmal AF, and regardless of the complexity of the concomitant procedures. Pre-operative AF duration predicted failure at 5 years and suggests the need for earlier intervention.

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Supplemental material is available online.

The first effective surgical treatment for atrial fibrillation (AF), now formally known as the Cox maze procedure (CMP), was introduced by James Cox, MD, in 1987.¹ On

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the basis of extensive clinical experience and ongoing animal investigations at our institution, substantial revisions of the original “cut-and-sew” technique have led to the current, fourth iteration of the procedure. Introduced clinically in 2002, the Cox maze IV procedure (CMPIV) consists of a combination of bipolar radiofrequency and cryothermal ablation lines that replace most of the surgical incisions of its predecessor (Figure 1).^{2,3}

Analysis of early and 1- to 2-year follow-up has demonstrated that the CMPIV provided equivalent rates of freedom from AF and can be performed with shorter cardiopulmonary bypass and crossclamp times, and with less perioperative morbidity, than the traditional “cut-and-sew” CMPIII.^{3,4} Additionally, we have shown that the procedure is equally effective in patients undergoing ablation for lone AF and concomitant cardiac surgery, including coronary artery bypass grafting, mitral valve, and aortic valve procedures.⁵⁻¹⁰

The modifications of the CMPIV have allowed it to be performed through a right minithoracotomy approach,

Abbreviations and Acronyms

AAD	= antiarrhythmia drugs
AF	= atrial fibrillation
ATA	= atrial tachyarrhythmia
CI	= confidence interval
CMP	= Cox maze procedure (III and IV)
OR	= odds ratio
PVD	= peripheral vascular disease

which has further reduced major morbidity, mortality, and hospital stay compared with those who underwent sternotomy while enjoying outcomes with equivalent freedom from AF.¹¹⁻¹³ Finally, the CMPIV has proven to be effective in patients with both paroxysmal and nonparoxysmal (persistent and longstanding persistent) forms of AF, a quality that distinguishes the CMPIV from other less-extensive lesion sets used for catheter and surgical AF ablation.¹⁴⁻¹⁶

Although our results to date establish the CMPIV as the current gold standard for surgical AF ablation, late outcomes of AF freedom using current consensus definitions of treatment failure have yet to be confirmed. Recent reports of long-term (>5-year) outcomes after the CMP have demonstrated good results¹⁷; whereas catheter ablation and pulmonary vein isolation have yielded suboptimal rates of freedom from AF in most patients.^{16,18-23} In this report, we examine our late outcomes of patients undergoing the CMPIV procedure for AF ablation at 5-year follow-up.

METHODS

The Washington University School of Medicine Institutional Review Board approved this study, and written informed consent was obtained from each patient prior to their enrollment. Over 400 demographic and perioperative variables were prospectively entered into the Society for Thoracic Surgery database or a longitudinal database maintained at our institution.

Patient Population

Between January 2002 and December 2014, data were collected prospectively on 576 consecutive patients with AF who underwent a CMPIV (n = 532) or left-sided CMP (n = 44) with or without a concomitant procedure. The operative details of the CMPIV lesion set through a sternotomy or right minithoracotomy have been described previously by our group.^{4,11-12} In 2005, the CMPIV was modified to include a superior connecting lesion, which formed a “box lesion” by completely isolating the entire posterior left atrium (Figure 1).^{2,24} Prior to 2005, patients underwent the original iteration of the CMPIV lesion set, which lacked a superior left atrial bipolar radiofrequency lesion connecting the right and left superior pulmonary veins.³ Of the patients who received a CMPIV, 472 of 532 (89%) had a box lesion, and 40 of 44 (90%) who received a left-sided CMP had a box lesion. Otherwise, patients who underwent a left-sided CMP had a complete CMPIV left atrial lesion set. Preoperative and perioperative variables were retrospectively evaluated and compared.

Follow-up

Freedom from atrial tachyarrhythmias (ATAs) and from antiarrhythmic drugs (AADs) at 1, 2, 3, 4, and 5 years were evaluated by electrocardiogram or prolonged monitoring by either 24-hour Holter monitoring, pacemaker interrogation, or interrogation of implantable loop recorders, as recommended by consensus guidelines.²⁵ Success was defined as freedom from ATAs (AF, atrial flutter, or atrial tachycardia) after a 3-month blanking period, as defined in the expert consensus statements,²⁵ and those with subsequent ablations were deemed permanent failures. Patients were discharged on class I or III AADs and warfarin for at least 2 months, unless contraindicated. The AADs were discontinued after 2 months if the patient was in a normal sinus rhythm; anticoagulation was discontinued at 3 months if prolonged monitoring showed no AF, and no evidence of left atrial stasis was found on echocardiography. Calcium channel blockers and β -blockers were not considered to be AADs.

The average follow-up time was 3.3 ± 4.7 years. At 1, 2, 3, 4, and 5 years after surgery, follow-up was 446 of 534 (84%), 304 of 457 (67%), 223 of 383 (58%), 166 of 300 (55%), and 139 of 241 (58%), respectively. Prolonged continuous monitoring was obtained in 298 of 446 (67%), 201 of 305 (66%), 142 of 224 (63%), 95 of 167 (57%), and 72 of 139 (52%), at 1, 2, 3, 4, and 5 years, respectively.

Freedom From Atrial Tachyarrhythmias and Antiarrhythmia Drugs

Late freedom from ATAs and AADs was compared for those who underwent a box lesion set (512 of 576) versus those who did not (64 of 576). Those who did not undergo a box lesion were excluded from the remainder of analyses. In the patients with a box lesion set (n = 512), long-term freedom from ATAs and AADs, as well as selected preoperative and perioperative variables, were compared for those patients with paroxysmal AF (n = 204) versus those with persistent or longstanding persistent AF (n = 305). Most patients in both the paroxysmal and nonparoxysmal groups underwent concomitant procedures. Of those who underwent concomitant procedures, 206 of 408 (50%) underwent a concomitant mitral valve procedure with or without a tricuspid procedure, whereas 93 of 408 (23%) underwent coronary artery bypass grafting with or without a mitral procedure (Table E1). In addition, late freedom from ATAs and AADs was compared for those who underwent a standalone (n = 146) versus concomitant CMPIV (n = 366).

Statistical Analysis

Continuous variables were expressed as mean $\pm$ SD or as median with range; they were compared using the *t* test for means of normally distributed continuous variables and the Mann-Whitney *U* nonparametric test for skewed distributions. Categorical variables were expressed as frequencies and percentages, with outcomes compared using χ^2 analysis or the Fisher exact test. Twenty preoperative and perioperative variables were evaluated in a univariate analysis, to identify potential predictors of late ATA recurrence or AAD use at 1 and 5 years. Significant covariates on univariate analysis ($P \leq .10$), or covariates deemed clinically relevant based on our experience, were entered into a multivariate binary logistic regression analysis, and receiver operator curves were constructed. All data analyses were performed using Systat 13 software (Systat Software, Inc, Chicago, Ill).

RESULTS**Demographics**

The mean overall age was 64 ± 12 years, and 351 of 576 (61%) of the population were men. Of the overall cohort, 237 of 576 (41%) had paroxysmal AF, and 336 of 576 (58%) had nonparoxysmal AF, with 66 of 336 (20%)

A Right Atrial Lesion Set

B Left Atrial Lesion Set

FIGURE 1. Standard (A) right and (B) left atrial lesion sets utilized for the CMPIV procedure. In the right atrium (A), radiofrequency ablation lines (white lines) extend from the superior to inferior vena cava, and along the right atrial free wall down to the tricuspid valve annulus. In the left atrium (B), all ablation lines are performed with a bipolar radiofrequency clamp, except for an endocardial cryoablation at the mitral annulus and an epicardial cryoablation over the coronary sinus. Full isolation of the posterior left atrium (blue area) by creating a “box lesion” was accomplished by adding a superior connecting lesion (black arrow) joining the right and left circumferential pulmonary vein ablations. The box lesion was added to the CMPIV lesion set in 2005.²⁴ (Figure modified with permission from Weimar and colleagues²).

having persistent and 270 of 336 (80%) having longstanding persistent AF. Demographic data were compared for those with paroxysmal AF versus those with nonparoxysmal AF (Table E2). Compared with the paroxysmal AF group, the nonparoxysmal AF group of patients had a worse substrate of AF, as indicated by longer duration of preoperative AF (6.6 ± 6.8 vs 4.9 ± 7.1 years, $P = .005$), larger left atria (5.3 ± 1.1 vs 5.0 ± 1.1 cm, $P = .006$), and more failed

catheter ablations (95 of 336 [28%] vs 22 of 237 [9%], $P < .001$).

Perioperative Results

Most patients underwent sternotomy in both the paroxysmal AF and nonparoxysmal AF groups (182 of 237 [77%] and 273 of 336 [81%]), respectively, $P = .113$; Table E3, whereas the remaining patients underwent a right minithoracotomy as previously described.¹¹⁻¹³ More patients underwent concomitant procedures in the paroxysmal, compared with the nonparoxysmal AF group (193 of 237 [81%] vs 212 of 336 [63%], $P < .001$; Table E3). As expected, no differences were found between the 2 groups in 30-day mortality, postoperative pacemaker implantations, intensive care unit length of stay, hospital length of stay, or most major complications. The paroxysmal group had a slightly higher rate of postoperative pneumonia (11% vs 7%; $P = .04$). In the nonparoxysmal group, 293 of 305 (96%) underwent a biatrial CMPIV, compared with 178 of 204 (87%) of the paroxysmal group ($P < .001$), whereas all others underwent a left-sided CMPIV.

Freedom From Atrial Tachyarrhythmias and Antiarrhythmia Drugs

In the entire cohort, including both those who did and those who did not undergo box lesion sets ($n = 576$), the overall freedom from ATAs at 1, 2, 3, 4, and 5 years was 411 of 446 (92%), 267 of 304 (88%), 194 of 223 (87%), 135 of 166 (81%), and 102 of 139 (73%). Overall freedom from ATAs and AADs for the entire cohort at 1, 2, 3, 4, and 5 years was 357 of 440 (81%), 231 of 298 (78%), 164 of 213 (77%), 110 of 160 (69%), and 83 of 235 (61%). Freedom from anticoagulation at 1, 2, 3, 4, and 5 years was 286 of 440 (65%), 184 of 296 (62%), 136 of 213 (64%), 92 of 161 (57%), and 76 of 138 (55%), respectively.

Lesion Set

Freedom from ATAs, either with or without taking AADs, was significantly higher in those who underwent box lesion sets, compared with those who did not, at 5 years (93 of 119 [78%] vs 9 of 20 [45%], $P = .005$; and 77 of 117 [66%] vs 6 of 18 [33%], $P = .017$, respectively; Figure 2, A and B). No significant difference was found in freedom from ATAs, either with or without taking AADs, between the biatrial CMPIV lesion set and the left-sided CMPIV lesion set at 5 years (95 of 130 [73%] vs 7 of 9 [78%], $P = .758$, and 78 of 126 [62%] vs 5 of 9 [56%], $P = .705$, respectively). However, the number of left-sided CMPIV patients was small, making ensuring validity of comparisons difficult.

FIGURE 2. Freedom from (A) atrial tachyarrhythmias, and (B) atrial tachyarrhythmias without antiarrhythmia drugs in patients who underwent full posterior left atrial isolation (box lesion) and those who did not.

Paroxysmal Versus Nonparoxysmal Atrial Fibrillation

With those who did not undergo box lesion sets excluded, freedom from ATAs at 1, 2, 3, 4, and 5 years was not significantly different between those with paroxysmal versus nonparoxysmal AF, which were, respectively, at 1 year, 151 of 158 (96%) versus 210 of 230 (91%), $P = .105$; at 2 years, 101 of 109 (93%) versus 140 of 165 (85%), $P = .051$; at 3 years, 79 of 89 (89%) versus 98 of 114 (86%), $P = .554$; at 4 years, 53 of 66 (80%) versus 70 of 82 (85%), $P = .414$; and at 5 years, 40 of 51 (78%) versus 53 of 68 (78%), $P = .97$, respectively; [Figure 3, A](#).

No significant differences were found in freedom from ATAs, without taking AADs, between the paroxysmal and nonparoxysmal AF groups at any time point (1 year: 137 of 156 [88%] vs 187 of 227 [82%], $P = .147$; 2 years: 86 of 106 [81%] vs 126 of 162 [78%], $P = .509$; 3 years: 70 of 86 [81%] vs 84 of 110 [76%], $P = .394$; 4 years: 42 of 51 [69%] vs 59 of 81 [73%], $P = .604$; and 5 years: 33 of 50 [66%] vs 44 of 67 [66%], $P = .97$, respectively; [Figure 3, B](#)). No significant differences were found in freedom from ATAs, with or without taking AADs, at 1, 2, 3, 4, and 5 years between those who underwent stand-alone CMPIV versus concomitant procedures ([Figure 4, A and B](#)).

FIGURE 3. Freedom from (A) atrial tachyarrhythmias and (B) atrial tachyarrhythmias without antiarrhythmia drugs in patients with paroxysmal versus nonparoxysmal atrial fibrillation.

Predictors of Recurrence

Univariate analyses of preoperative and perioperative variables were performed to determine predictors of late ATA recurrence or AAD use at 1 and 5 years. At 1 year, the absence of a box lesion, early ATAs, preoperative pacemaker implantation, and left atrial size were all predictive of recurrence (Table E4). In a multivariable binary logistic regression analysis, a preoperative pacemaker (odds ratio [OR] 2.492, 95% CI (1.351-4.599), $P = .012$), left atrial size (OR 1.285, 95% CI (1.022-1.615), $P = .031$), and absence of a box lesion set (OR 4.556, 95% CI (2.364-8.780), $P < .001$) were predictive of ATA recurrence or AAD use at 1 year.

In the univariate analyses at 5 years, the absence of a box lesion, early ATAs, the duration of preoperative AF, total

intensive care unit time, overall complications, and hospital length of stay were all predictive of failure (Table E4). In the multivariate analysis, the duration of preoperative AF (OR 1.09, 95% CI (1.02-1.16), $P = .008$) and hospital length of stay (OR 1.09, 95% CI (1.01-1.17), $P = .026$) predicted recurrence of ATAs or AAD use at 5 years. The probability of failure increased with increasing duration of preoperative AF (Figure 5).

DISCUSSION

Over the past 3 decades, the CMP has been the most successful surgical treatment for AF.^{4,8,26} In the current study, 5-year outcomes of the newest iteration of the Cox maze procedure, the CMPIV, are reported. The primary finding

FIGURE 4. Freedom from (A) atrial tachyarrhythmias and (B) atrial tachyarrhythmias without antiarrhythmia drugs in patients who underwent stand-alone CMPIV versus CMPIV with a concomitant procedure.

is that the CMPIV provided a high level of freedom from ATAs at late follow-up. Moreover, the CMPIV was equally effective in patients with both paroxysmal and nonparoxysmal AF, and in patients undergoing both stand-alone and concomitant AF ablation procedures. The only predictors of late recurrence were duration of preoperative AF and hospital length of stay.

Our 5-year results were consistent with the good early and midterm results of the CMPIV.^{4,26} In patients receiving a complete lesion set, our 5-year freedom from ATAs was 93 of 119 (78%); freedom from ATAs, without AADs, was 77 of 177 (66%). In the only other study to report late outcomes of the CMPIV, Ad and colleagues¹⁷ demonstrated that 5-year freedom from ATAs was 85%, and freedom from ATAs without AADs was

71% in a group of 120 patients. The higher percentages in their results may be explained by the fact that their study population had a much shorter median duration of preoperative AF (27 months), compared with that in our study cohort (42 months). As we demonstrated in the present study, preoperative AF duration is an important predictor of late failure, and their freedom from ATAs was consistent with our calculated probability curves (Figure 5).

Our results compare favorably to 2 recent multi-institutional trials that both showed 66% freedom from AF, at only the 9 or 12 months' follow-up.^{27,28} However, these studies did not have standardized ablation techniques and included institutions that had variable amounts of experience with surgical ablation.

FIGURE 5. Relationship between preoperative AF duration and the probability of ATA recurrence or AAD use at 5-year follow-up. ATA, Atrial tachyarrhythmia; AAD, antiarrhythmia drug; AF, atrial fibrillation.

The CMPIV results in our series were better than what has been achieved with catheter ablation. In a study²³ of 100 patients with mainly paroxysmal AF who underwent catheter ablation, the arrhythmia-free survival after a single ablation procedure was only 29% at 5 years. Allowing for multiple catheter ablations improved the arrhythmia-free survival, compared with the preceding intervention, to 63% at 5 years, with a median of 2 procedures per patient. Scherr and colleagues²¹ evaluated arrhythmia-free survival at 5 years for patients that underwent catheter ablation for persistent AF, which was most of the patients in our study. In that study, 150 patients underwent catheter ablation, and the 5-year single procedure success was 17%. Several other large studies evaluating 5-year success rates after catheter ablation have equally poor results.^{18,20,22} As a comparison to these studies, our data demonstrated 5-year freedom from ATAs of 78% from a single procedure.

Our results compared favorably to other surgical lesion sets, in particular, pulmonary vein isolation. In a study of 139 patients who underwent minimally invasive surgical pulmonary vein isolation, with up to 5 years of follow-up, freedom from AF, without AADs, was 52%, 28%, and 29% for paroxysmal, persistent, and longstanding persistent AF, respectively.¹⁶ This finding is consistent with those of other studies indicating that surgical pulmonary vein isolation might be more effective in patients with paroxysmal AF than persistent or longstanding persistent AF.^{19,29} In contrast, our data and those from others^{14,17} have demonstrated that the CMPIV is equally effective in all groups of patients at both early and late follow-up. The

consistent efficacy of the CMPIV in nonparoxysmal AF is impressive in light of the worse substrate of AF in this group, as indicated by the longer duration of preoperative AF, increased left atrial size, and a higher number of failed catheter ablations.

The success of the CMPIV in the concomitant setting is of equal importance considering that most surgical ablations in the United States are performed as part of concomitant cardiac procedures.³⁰ Our long-term results are consistent with early and midterm results, both from our institution and others, that have documented high rates of restoration of sinus rhythm with concomitant procedures, including coronary artery bypass, mitral valve surgery, and aortic valve surgery.⁵⁻¹⁰ These data reinforce our belief that the CMPIV should be considered in all patients with AF who are undergoing concomitant cardiac surgery, as long as it can be performed without adding morbidity to the procedure.

This study identified several risk factors for recurrent ATAs by multivariate linear regression models at 1 and 5 years. At 1 year, left atrial size, preoperative pacemaker implantation, and the absence of a box lesion set were predictive of failure, which is consistent with previous studies from our group and others.³¹⁻³⁴ These variables were not predictors of failure at 5 years: In a recent report from Ad and colleagues,¹⁷ predictors of recurrence were left atrial size at 2 years and left atrial size, age, and length of hospital stay at 5 years. These inconsistencies suggest the possibility of different underlying pathophysiologic mechanisms of failure at different time points.

The duration of preoperative AF and the length of hospital stay were both independent predictors of failure at 5 years. Duration of preoperative AF has been shown to predict late recurrence after both catheter and surgical ablation at 5 years in previous studies.^{17,21,35} This finding is likely due to the substrate remodeling that occurs with AF. In patients with long duration of preoperative AF, this remodeling may not be reversible, and the CMP works poorly in this subgroup, particularly in patients with AF for >11 years, for whom success rates at 5-year follow-up were <50%. Hospital length of stay is likely a marker of more underlying comorbidities, which could contribute to late failure.

Limitations

The success rates were reported for both the biatrial CMPIV and the left-sided CMPIV combined. The left-sided CMPIV lesion set was included in the analysis because the success rates were observed to be similar to that of the biatrial CMPIV. However, this group of patients was highly selected. In our center, a left-sided CMPIV was chosen for patients with paroxysmal AF, left atrial size <5.0 cm, and no evidence of right atrial enlargement. In this selected group, late efficacy was good; however, comparisons with

the biatrial CMPIV were not possible because of the limited number of patients available for late follow-up.

This study was retrospective and nonrandomized, which introduced confounding factors that may have affected the results. Incomplete follow-up and not universal continuous cardiac monitoring could have led to overestimation of the freedom results. Additionally, the groups with paroxysmal and nonparoxysmal AF, as well as patients who underwent standalone versus concomitant procedures, were inherently different, making comparisons less than ideal. However, the series included a large number of patients, and the conclusions that the CMPIV works well for all groups is valid and clear. Given that this study was conducted at a single institution, these outcomes may not be obtainable at less-experienced centers.

CONCLUSIONS

The CMPIV remains the most successful surgical treatment for AF, even in patients with nonparoxysmal AF and regardless of the complexity of the concomitant procedures. The duration of preoperative AF predicted failure at 5 years, and suggests the need for earlier intervention. Further follow-up of this patient cohort is needed to determine whether a further decrement in success will occur over time.

Conflict of Interest Statement

RJD receives research grants and educational funding from AtriCure and Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

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Key Words: atrial fibrillation, arrhythmia therapy, ablation

Discussion

Dr Richard Lee (*St. Louis, Mo*). I would like to thank the society for the opportunity to discuss this article. I have 3 questions. I will ask them sequentially. Dr Damiano and colleagues again set the bar for success with a success rate in excess of 90% at 1 year for freedom from AF in this group. In contrast, in a recently randomized prospective study published in the *New England Journal of Medicine*, by Gillinov et al, the success rate was only 63% at 1 year, with no difference between biatrial maze and pulmonary vein isolation alone. CURE-AF and ABLATE-AF, both prospective, multi-institution studies, also had rates that hovered between 65% and 70%. How do you reconcile the difference between your results and the others?

Dr Lancaster. Thank you, Dr Lee, and it is a pleasure to have you review our work. We are a high-volume center for AF ablation, and we have multiple decades of experience with this lesion set. Both the Cox maze III and IV lesion sets were developed at our institution. The results that we present here are similar to those reported by other centers, including Niv Ad's group in Virginia, who just published their 5-year results, as well as the group at Northwestern.

The recent multi-institutional trials that you mention, the CURE-AF trial and Dr Gillinov's recent *New England Journal of Medicine* publication, reported notably worse results than ours, both showing less than 70% freedom from AF for the biatrial maze at only 9 or 12 months of follow-up. I do not have a good explanation

for this discrepancy, other than that these were multi-institutional experiences that may have included centers with variable amounts of experience with surgical ablation. For instance, in the CURE-AF trial, in which we participated, the range in freedom from AF at 9 months of follow-up for the individual participating institutions varied from 33% to 100%. So obviously, there was a large amount of variability in the results at different institutions.

This is a complex lesion set that is dependent on surgeon experience and consistent completion of the full lesion set. We think that it is translatable to the surgical population at large, but even in our center, where both lesion sets were developed, we still have a 20% to 30% rate of treatment failure at long-term follow-up. So there is still room for improvement.

Dr Lee. Although the authors report a benefit of a complete box lesion, it was not an independent predictor of failure at year 5. Please explain why you think it was not, and the potential implications. As you know, the reason why we stopped doing the superior lesion was to increase atrial contractility. In fact, even in the group that did not have a box lesion, about 33% more were free of AF. So essentially, is there any patient that you think might benefit from a "nonbox" lesion to preserve atrial contraction?

Dr Lancaster. The absence of a complete posterior left atrial box lesion (nonbox) was analyzed as a predictor of ATA recurrence, and it was found to be a significant predictor in univariate analysis at both 1 and 5 years of follow-up. In the multivariate analysis, it was only a significant predictor in the 1-year model, not the 5-year model. However, the difference in freedom from ATAs at 5 years in the non-box lesion group was notably inferior (66% freedom without AADs in the box lesion group, and only 33% freedom in the nonbox group). It is likely that if we had a larger number of patients with a non-box lesion set available at late follow-up, this would have been a significant predictor of failure. However, we stopped performing the non-box lesion set in 2005 because of concerns about its efficacy.

At the present time, there is no patient in whom we would consider not performing a box lesion. It is true that the original maze IV lesion set was designed to minimize any compromise to left atrial function that might occur with complete electrical isolation of the posterior left atrium. However, we have demonstrated in magnetic resonance imaging studies that the posterior left atrium actually moves very little during atrial contraction, so any potential compromise that may occur is likely minimal. Additionally, the impact of having a 70% risk of treatment failure with a nonbox lesion, with those patients who fail remaining in a state with AF, without the benefit of atrioventricular

synchrony, would most certainly have a greater effect on impaired cardiac output than any potential compromise to left atrial function.

Dr Lee. For my last question—with the advent of new technology, a myriad of lesion sets have evolved over the past decade or so. When the term “mini maze” was popularized, the authors wisely and vocally directed us to use the term maze only for a complete biatrial lesion set, and to label others as AF procedures.

In this maze series, the authors included a traditional biatrial lesion set, a biatrial lesion set minus the superior lesion, as well as left side-only lesions. So now, in 2015, what should and can we call a maze?

Dr Lancaster. As I said earlier, we now consider the left atrial superior connecting lesion to be an essential component of the CMPIV lesion set. We no longer consider the patients that had a nonbox lesion to accurately represent the CMPIV.

We did in this series include 44 patients who had only a left atrial CMPIV. Their lesion set was identical to the left atrial lesion set of the biatrial CMPIV; however, they did not undergo right atrial ablation. This was, however, a highly selected group of patients who had a left atrial size less than 4 cm, paroxysmal AF, and no evidence of right atrial enlargement or tricuspid valve pathology by echocardiography. We decided to include those patients in this study because there was no significant difference in their late outcomes, compared with the biatrial patients. Having said that, only 9 patients in the left atrial group had follow-up at 5 years, and so we are not able to comment on the broader applicability of a left atrial-only versus biatrial CMPIV.

Our policy is to perform a biatrial CMPIV, as we have indicated in published results multiple times, in most patients, unless it is contraindicated. Going forward, the challenge is to define the mechanisms of AF in the individual patient. With better mechanistic information, it is certain that a left atrial lesion set alone could be appropriate in some patients. Until we have better diagnostic capability, a biatrial lesion set is still our preferred approach.

Dr John Puskas (*New York, NY*). Dr Lancaster—I know that your mentor, Dr Damiano, has done a lot of work in the laboratory and in the operating room documenting transmural lesions for the CMPIV, with different energy sources, for instance, and applying them multiple times, for instance. I wonder if you could tell us how these lesions of the CMPIV were created in this series, and I wonder if Dr Lee could tell us if that is the same way it was done in the other series that you cited that had lower success rates?

Dr Lancaster. In the CMPIV lesion set, as I showed in the illustration, there is a single right atrial incision and a single left atrial incision, and the remainder of the ablation

lesions are made with either a bipolar radiofrequency clamp or cryothermal ablation. The bulk of the lesions are made with the bipolar radiofrequency clamp, and cryoablation in our practice is used for the lesions near the mitral valve and tricuspid valve annuli.

Dr Puskas. And are the radiofrequency clamps applied twice, three times, once? How should we be doing them?

Dr Lancaster. Three applications of the clamp: a central application, and then 1 application on either side. We confirm exit block from the pulmonary veins in every patient.

Dr Puskas. So it is applying the clamp 3 times and confirming block. Is that an explanation, Richard?

Dr Lee. Well, it could be. Obviously the other studies did not necessarily require a block. In addition, ABLATE-AF was almost exactly the same. For CURE-AF, they used a unipolar pen instead of cryoablation for the mitral annular lesion. For the *New England Journal of Medicine* article, a combination of lesions and technologies were used, particularly for the mitral annular lesion. So that might account for some of the variability, but it is still a surprise to be that disparate, especially given the high success rates of pulmonary vein isolation alone reported in some series of paroxysmal patients.

Dr Alexandr Bogachev-Prokophiev (*Novosibirsk, Russia*).

I would like to thank you for these interesting data. You have in your analysis more than 100 patients with a minimally invasive approach. Did you find any differences between the conventional and minimally invasive approach in AF freedom?

Dr Lancaster. We did not do that analysis in this study, but we have previously published results showing that there was no difference in up to 2-year freedom from AF between patients that underwent the CMPIV by either a minimally invasive or a standard sternotomy approach.

Dr Harold Roberts (*Aventura, Fla*).

One short comment and a question. As far as the comment, I think this paper further and again illustrates the fact that it is incumbent for us as surgeons to indefinitely follow our patients after ablation, because the results can and do deteriorate with time.

As far as the question I had, I do not know if this is a chicken-or-egg type scenario, but you had distinctly worse freedom from AF in your patients that were off antiarrhythmics. Was this predominantly because they were off antiarrhythmics, or was it the fact that the cardiologist had just given up?

Dr Lancaster. We reported both overall freedom from ATAs (including patients who are on and off AADs), and freedom from ATAs in patients not taking AADs. In our institutional experience, we have very little control over which patients are taking AADs postoperatively, because many of our

patients are referred from out of town and from long distances and choose to continue follow-up with their local cardiologist. So some patients continue to take or are told to resume taking AADs without our input. This does raise the point about whether or not we should be relying on that 1 outcome, freedom from ATAs without AADs, as the single benchmark for success, because it may not accurately reflect the success of the procedure. Our practice is to also report overall freedom from ATAs, which may be a more relevant measure of procedural success.

Dr James Edgerton (*Dallas, Tex*). I would like to make a comment, if I may. I will echo the statement that was just made about following your patients long term. If you are going to do arrhythmia surgery, you really need to adopt a disease management approach to your care, rather than a proceduralist approach.

But I want to answer something that you said about the lesion creation. In my own personal series, every lesion we put on the atrium, we tested for block, by creating an activation sequence of the atrium. And one of the things we are hindered by, as surgeons, is that we do the lesion, we test it, and we move on, because we have got to keep moving, and we cannot get back to that later; or if you are under cardioplegia, you cannot test it at all.

During our hybrid experience doing hybrids in the same day, I would do my procedure, check my lesions for block; everything was blocked. The electrophysiologist was getting to this 3 hours later, checking my lesions and calling me, and saying, Jimmy, you do not have block.

What we learned from that is that we were getting temporary block from the edema, the crushing nature of the clamp; and we had to move the application of the clamp from 3 to 4 applications up to 7 to 8 applications for every line before we consistently had block when he tested them 3 or 4 hours later.

So that may have significant implications for the earlier studies that were done. Thank you.

Dr Puskas. Were those dry or irrigated clamps, Jimmy?

Dr Edgerton. Well, what you are really talking about is cooling, and that was the AtriCure clamp that cools by a

different mechanism as a pair of electrodes and they alternate electrodes. So in essence, a cooled lesion is what you are looking for.

Dr Puskas. Can you respond to that question?

Dr Lancaster. This may be a theoretical advantage of the hybrid approach, in that the continuity of surgical ablation lesions can be tested in the operating room or electrophysiology laboratory immediately after the procedure. It will be very interesting to see what the significance of this advantage is in improving the long-term outcomes of hybrid procedures. Unfortunately, these data are not available yet.

Dr Takashi Nitta (*Tokyo, Japan*), I have a question about the box lesion versus nonbox lesion, particularly about the reason for the different outcome, because I also did a similar analysis and did not see any difference in AF recurrence between the box lesion and the nonbox lesion.

There would be 2 possibilities for the better results after the box lesion in your data. First, your patients frequently had abnormal activations arising from the posterior left atrium that can be encircled by the box lesion. But according to our mapping data, only 4% of the patients showed that type of abnormal activations from the posterior left atrium.

The other possibility for the different results could be incomplete ablation of the pulmonary vein isolation in the non-box lesion cohort.

What do you think about the reason for the different results?

Dr Lancaster. I might add a third possibility to your suggestions, which is that achieving a full left atrial box lesion not only serves to isolate ectopic AF drivers located in the posterior left atrium, but may also help to reduce the contiguous surface area of the left atrium below the critical mass necessary to perpetuate AF. In other words, it might help block the reentrant conduction of arrhythmias that originate outside of the posterior left atrium, in addition to isolating AF-originating foci located in the posterior left atrium. In an attempt to address some of those questions, we are pursuing our own atrial mapping studies in patients with AF, and it will be interesting to see how many of our patients have origins of AF in the posterior left atrium.

TABLE E1. Concomitant procedures

Procedures in addition to CMP	Number of patients, n (%; of 408)
Mitral valve ± tricuspid	206 (50)
CABG ± mitral	93 (23)
Aortic valve ± CABG	57 (14)
Aortic valve + mitral valve	13 (3)
Other	39 (10)

CMP, Cox-maze procedure; CABG, coronary artery bypass grafting.

TABLE E2. Preoperative demographics

Demographic	Overall* (n = 576)	Paroxysmal AF (n = 237)	Nonparoxysmal AF (n = 336)	P value
Age (y)	64 ± 12	63 ± 12	64 ± 12	.737
Male	351 (61)	133 (56)	217 (65)	.041
Persistent AF	66 (11)	N/A	66 (20)	N/A
Longstanding persistent AF	270 (47)	N/A	270 (80)	N/A
Preoperative duration of AF (y)	5.8 ± 6.9	4.9 ± 7.1	6.6 ± 6.8	.005
Left atrial size (cm)	5.2 ± 1.1	5.0 ± 1.1	5.3 ± 1.1	.006
Failed catheter ablation	117 (20)	22 (9)	95 (28)	<.001
Preoperative pacemaker	73 (13)	30 (13)	43 (13)	.961
NYHA class III or IV	337 (59)	134 (57)	202 (60)	.392
LVEF (%)	54 ± 12	55 ± 12	53 ± 12	.092
PVD	63 (11)	23 (10)	40 (12)	.407
Hypertension	378 (66)	148 (62)	227 (68)	.205
Dyslipidemia	337 (59)	134 (57)	200 (60)	.476
Chronic lung disease (moderate to severe)	31 (5)	9 (4)	22 (7)	.152
Diabetes	108 (19)	45 (19)	63 (19)	.943
Renal failure	21 (4)	10 (3)	11 (3)	.553
Dialysis	4 (1)	1 (0)	3 (1)	.505

Values are n (%), or mean ± SD, unless otherwise indicated. AF, Atrial fibrillation; N/A, not applicable; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease. *Includes 3 patients with large atria but no preoperative AF who underwent ablation at the time of a concomitant procedure.

TABLE E3. Perioperative data

Demographic	Overall* (n = 576)	Paroxysmal AF (n = 237)	Nonparoxysmal AF (n = 336)	P value
Sternotomy†	357 (79)	182 (77)	273 (81)	.194
Concomitant procedure	408 (71)	193 (81)	212 (63)	<.001
CPB time (min)	174 ± 47	182 ± 46	171 ± 48	.004
Crossclamp time (min)	83 ± 35	90 ± 32	78 ± 36	<.001
Box lesion	509 (88)	204 (86)	305 (91)	.079
Early atrial tachyarrhythmias	325 (56)	132 (56)	193 (57)	.678
ICU length of stay (d)	4.7 ± 6.5	5.0 ± 6.1	4.6 ± 6.8	.579
Hospital length of stay (d)	12 ± 10	12 ± 9	12 ± 10	.607
30-d mortality	17 (3)	4 (2)	13 (4)	.142
Postoperative permanent pacemaker	70 (12)	36 (15)	34 (10)	.068
Major complications	90 (16)	42 (18)	48 (14)	.266
Renal failure (dialysis)	25 (4)	12 (5)	13 (4)	.491
Myocardial infarction	1 (0)	0 (0)	1 (0)	.401
Stroke	7 (1)	5 (2)	2 (1)	.104
Mediastinitis	2 (0)	2 (1)	0 (0)	.092
Reoperation for bleeding	25 (4)	12 (5)	13 (4)	.491
Pneumonia	49 (9)	27 (11)	22 (7)	.041
Intra-aortic balloon pump	16 (3)	4 (2)	12 (4)	.178

Values are n (%), or mean ± SD, unless otherwise indicated. AF, Atrial fibrillation; CPB, cardiopulmonary bypass; ICU, intensive care unit. *Includes 3 patients with large atria but no preoperative AF who underwent ablation at the time of a concomitant procedure. †All patients who did not undergo sternotomy underwent right minithoracotomy.

TABLE E4. Variables predicting atrial tachyarrhythmia recurrence by univariate analysis

Variable	P value (at 1 y)	P value (at 5 y)
No box lesion	<.001	.008
Early atrial tachyarrhythmia	.001	.013
Preoperative duration of atrial fibrillation	.568	.010
Left atrial size	.002	.547
Preoperative pacemaker	.003	.070
Overall major complications	1.000	.045
Intensive care unit length of stay	.797	.035
Hospital length of stay	.723	.009