

## Minimally invasive surgical ablation of atrial fibrillation: Six-month results

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**Background:** A minimally invasive surgery for treatment of atrial fibrillation was developed with bilateral pulmonary vein isolation, mapping, and ablation of the ganglionic plexi and excision of the left atrial appendage. A prospective multicenter registry was created to evaluate the outcomes.

**Methods:** The procedure was performed through bilateral minithoracotomies with video assistance. It included bilateral pulmonary vein isolation with bipolar radiofrequency with documentation of conduction block, location of ganglionic plexi by high-frequency stimulation, and appropriate ablation and left atrial appendage exclusion/excision. Clinical follow-up at 6 months included monitoring with electrocardiogram, Holter, event monitor, or pacemaker interrogation.

**Results:** One hundred fourteen patients with 60 (52.6%) paroxysmal, 32 (28.1%) persistent, and 22 (19.3%) long-standing persistent atrial fibrillations were treated. The mean age was  $59.5 \pm 10.6$  years, and 69.3% were men. The mean follow-up period was  $204 \pm 41$  days (median 195). There were 2 (1.8%) operative mortalities. At 6-month follow-up, with long-term monitoring, 52/60 (86.7%) patients with paroxysmal fibrillations were in normal sinus rhythm and 43/60 (71.7%) were both in normal sinus rhythm and off antiarrhythmic drugs. The patients with persistent atrial fibrillation had a lower success rate, with 18/32 (56.3%) being in normal sinus rhythm and 46.9% both in normal sinus rhythm and off antiarrhythmic drugs; for long-standing persistent cases, 11/22 (50%) were in normal sinus rhythm and 7/22 (31.9%) were also off antiarrhythmic drugs.

**Conclusions:** Minimally invasive atrial fibrillation surgery is an effective treatment of paroxysmal atrial fibrillation at 6 months. Continuous event monitoring is necessary to accurately assess treatment results. A more extensive lesion set seems to be required for treatment of persistent atrial fibrillation.

The pathophysiology of atrial fibrillations (AF) involves the interplay between triggers and a changing left atrial substrate. A complex network of interconnecting nerves (the intrinsic cardiac autonomic nervous system) joins the left atrium to the pulmonary veins (PVs). The neurons join in clusters of autonomic ganglia in fat pads overlying the junction of the PVs and the left atrium.<sup>1,2</sup> These clusters are referred to as ganglionated plexi (GP) by Armour and colleagues.<sup>2</sup> In 1987, Fee and associates<sup>3</sup> found that blocking the atrial fat pad ganglia produced chronotropic, inotropic, and dromotropic changes in the atria. Pappone and coworkers<sup>4</sup> showed that long-term success in maintaining sinus rhythm was correlated with the presence of a vagal response during radiofrequency ablation and attenuation of heart rate variability during subsequent follow-up. Elimination of the GP in the canine model prevents inducibility of AF.<sup>5</sup> Additionally, there is clinical evidence for

successful elimination of AF by ablating areas of the autonomic ganglia, suggesting that ganglia play a critical role in the initiation and maintenance of AF.<sup>4,6-9</sup> Scherlag and his colleagues<sup>6</sup> have shown increased efficacy in the elimination of AF by adding GP ablation to PV isolation in humans. Additionally, they have begun to study the elimination of AF by ablation of GP alone without PV electrical isolation.

Based on the above findings, we began performing a standardized procedure for the minimally invasive surgical treatment of AF consisting of bilateral PV antral electrical isolation and targeted autonomic denervation of the left atrium with selective left atrial appendectomy. The feasibility of minimally invasive PV isolation has been previously described.<sup>10-14</sup> This study included 5 centers and their patients.

### PATIENTS AND METHODS

The study was approved by the institutional review board at each participating center and individual consents were obtained. One hundred seventy-one patients underwent bilateral PV antral electrical isolation using a bipolar radiofrequency clamp. A subset of 114 (66.7%) had complete 6-month follow-up data including electrocardiogram (ECG), long-term monitoring, and antiarrhythmic drug usage data. This group included 60 cases of paroxysmal (52.6%), 32 of persistent (28.1%), and 22 of long-standing persistent (19.3%). Patients were grouped using the terminology recommended in "HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation,"<sup>15</sup> in which *paroxysmal* refers to recurrent AF that terminates spontaneously within 7 days; *persistent AF* is AF

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**Abbreviations and Acronyms**

AF	= atrial fibrillations
ECG	= electrocardiogram
GP	= ganglionated plexi
LTM	= long-term monitor
NSR	= normal sinus rhythm
PV	= pulmonary vein

sustained beyond 7 days, or lasting less than 7 days but requiring either pharmacologic or electrical cardioversion; and *long-standing persistent AF* is continuous AF of greater than 1-year duration.

All patients underwent transesophageal echocardiography on the table prior to the procedure, and those who had a prior catheter ablation had a left atrial magnetic resonance imaging or left atrial computed tomography scan to rule out pulmonary vein stenosis. The procedure was accomplished in 2 stages. With the patient in a left lateral decubitus position, the right-sided PVs were approached through a small thoracotomy in the right chest, and the patient then was repositioned and redraped in the right lateral decubitus position to approach the left PVs through a limited left thoracotomy. This thoracotomy, used to introduce instruments, was a 5.0-cm to 6.0-cm incision in the third or fourth intercostal space without rib spreading. Visualization was accomplished with a 5.0-mm 30° endoscope placed in the middle to posterior axillary line in the sixth or seventh intercostal space.

The pericardium was opened widely, 2.0 cm anterior to the phrenic nerve, with great caution to protect the phrenic nerve. Pericardial retraction sutures were brought out through the posterior chest wall to aid in visualization. The PVs were mapped by first sensing in the PV to determine baseline electrical activity. Then ganglionated plexi were located by high-frequency stimulation of 12 V at a cycle length of 50 ms and a pulse width of 1 to 10 ms.<sup>6</sup> The presence of a GP was confirmed if a vagal response (increase in the R-R interval of 50% or greater) occurred. After dissecting around the PVs, a bipolar radiofrequency device was introduced and placed around the PV antrum well up onto the left atrium, as far as possible away from the PV bifurcation. Three to five ablation lines were placed in slightly different positions to ensure electrical isolation. Following this, sensing was repeated on the PVs to confirm entrance block from the left atrium indicating electrical isolation. The ablation was repeated as necessary until block was demonstrated. High-frequency burst pacing was again done in areas where GP were initially identified. If any vagal responses remained, these areas were further locally ablated until the response to high-frequency stimulation was considered negative as defined by no significant increase in the R-to-R interval during stimulation.

A 19-French silastic drain was placed through the scope site, the working port incisions were closed, the wounds dressed, and the patient was then positioned in the right lateral decubitus position to approach the left-sided PVs.

Similar exposure was obtained on the left side. On this side, the pericardium was opened posterior to the phrenic nerve, thus aiding in visualization of the PVs, the ligament of Marshall, and the base of the left atrial appendage. Again, baseline mapping was done on the PVs as well as high-frequency stimulation for localization of GP. Electrical isolation of the left PV antrum was accomplished again with a bipolar radiofrequency clamp after identifying and dividing the ligament of Marshall. Electrical block was again confirmed by sensing for entrance block in the PVs. High-frequency stimulation was repeated to ensure that there were no remaining GP as measured by a vagal response during high-frequency stimulation. The trabeculated portion of the left atrial appendage was then excised or excluded using a stapling device, the pericardium closed, drain placed, and the wounds were closed and dressed. The patient was then awakened, extubated in the operating room, and transferred to the intensive care unit for observational care.

**Rhythm Monitoring**

Rhythm was monitored at the 6-month office visit. At 6 months, all patients had an ECG, and 1 long-term monitor (LTM), either a 14- to 21-day auto-triggered event monitor or 24-hour Holter monitor. Patients with implanted pacemakers had the pacemaker interrogated for recorded episodes of AF. The LTMs sampled the incoming rhythm at 15-second intervals, and if an irregular rhythm was detected, a single 15-second rhythm sample was recorded. Another rhythm sequence was not recorded during that episode. Accordingly, we counted the number of episodes of AF but were unable to determine the duration of episodes over 15 seconds or the true burden of AF. Five patients who displayed AF on the ECG monitoring were not hooked up to a LTM, thus reducing costs when no new information would be provided.

**Data Analysis**

Data were imported into SAS 9.2 for analysis. Categorical variables were compared across categories using chi-square or Fisher exact test, and continuous variables were compared across groups using analysis of variance and Tukey post hoc testing if the differences were statistically significant. All *P* values are 2-tailed tests.

**RESULTS****Demographics**

Patient demographics are presented in Table 1. The age at surgery, ejection fraction, and follow-up period were not different between groups. The patients had a history of long-duration AF with 88.5% (10/113) reporting a history of more than 1 year and a further 6.2% (7/113) reporting 6 to 12 months of AF. Twenty-four (21.1%) had had an unsuccessful previous catheter ablation. In 92.7% of the patients (101/109), the surgeon either amputated or sealed off the left atrial appendage.

The mean length of stay from surgery to discharge was 4.8 ± 1.9 days with a median value of 4.0 days.

**Morbidity and Mortality**

There were 13 complications among the 114 patients (11.4%) undergoing ablation, as listed in Table 2. Two patients died within the 30-day perioperative period: 1 very early in the surgeon's experience from hemorrhage resulting from an avulsed left atrial appendage and 1 from unknown (inconclusive autopsy) cause. The latter patient was sent to recovery after the surgery in normal sinus rhythm (NSR). The patient was responsive and conversing with the nursing staff when he complained of feeling nauseous. The patient went into respiratory arrest, developed bradycardia as he was being intubated, and then was transferred back to the operating room. The patient was reexplored, and at that time, he went into cardiopulmonary arrest, cardiogenic shock, and ventricular fibrillation. After defibrillation, the left ventricle was observed to be hypokinetic. No hemorrhage was found, and the pulmonary veins looked intact. A saphenous vein graft to the left anterior descending coronary artery was carried out, and an intra-aortic balloon pump placed. The patient left the operating room for the intensive care unit and later in a decision with the family, support was discontinued. A third patient died 5½ months after the ablation procedure from colon cancer.

TABLE 1. Demographics

	All patients	Paroxysmal (n = 60)	Persistent (n = 32)	Long-standing persistent (n = 22)	P value*
Age, mean $\pm$ standard deviation (median)	59.5 $\pm$ 10.6 (60.5)	59.7 $\pm$ 8.2 (60)	59.7 $\pm$ 10.6 (61.5)	58.3 $\pm$ 15.6 (60.5)	.86
Ejection fraction, % (median)	54.2 $\pm$ 9.5 (55.0)	54.8 $\pm$ 10.3 (57)	53.3 $\pm$ 8.8 (55)	53.7 $\pm$ 8.4 (55)	.79
Follow-up, d (median)	204 $\pm$ 41 (195)	201 $\pm$ 32 (195)	211 $\pm$ 50 (198)	200 $\pm$ 49 (197)	.49
Males, n (%)	79 (69.3%)	40 (66.7%)	25 (78.1%)	14 (63.6%)	.43
LA diameter, cm (median)	4.72 $\pm$ 0.83 (4.6)	4.59 $\pm$ 0.67 (4.5)	4.70 $\pm$ 1.10 (4.5)	5.06 $\pm$ 0.67 (4.95)	.10

LA, Left atrium. \*P value for continuous variables is analysis of variance comparing 3 groups (paroxysmal, persistent, and long-standing persistent); P value for the categorical variable "males" is the chi-square for distribution of males across groups.

## Rhythm

Complete rhythm documentation was available for the 114 patients at 6 months with ECG and LTM data. Long-term monitoring consisted of 24-hour Holter monitors in 22.8% (26/114) of the patients, 14- to 21-day event monitors in 59.7% (68/114), and pacemaker interrogations in 13.2% (15/114). A further 5 patients had AF picked up on the ECG and were coded as AF for the long-term monitoring also.

Table 3 show the rhythm results measured on ECG and LTM for patients treated by the surgical ablation. Because the strict definition of successful treatment requires that the patient has regained an NSR rhythm and also been able to discontinue any antiarrhythmic drugs, the table also shows the numbers reaching those goals. However, it should be noted that the decision to terminate antiarrhythmic drugs was often delayed until after the 6-month monitor was obtained.

Figures 1 and 2 graphs the fraction of patients with NSR on ECG and LTM rhythm analysis and compares these with the patient's perception of their rhythm. In patients who were diagnosed with paroxysmal AF before ablation, 86.7% (52/60) were in sinus rhythm at 6 months by LTM. ECG measurements overestimated the fraction in sinus rhythm, with 98.3% (59/60) being having ECG strips read as NSR. For patients classified as having persistent or long-standing persistent AF before surgery, the success rate at 6 months by LTM was worse than paroxysmal: 56.3% in persistent and 50.0% in long-standing persistent. The data from ECG measurements also overestimated the success rate by approximately 25% percentage points for persistent and 13.6% for long-standing persistent.

Because patients with NSR sometimes think that they are in AF,<sup>16-20</sup> we examined the data to see how accurate their

TABLE 2. Minor complications encountered in study

Transient nerve injury: 1.8% (2)	1 brachial plexus & 1 phrenic nerve
Renal failure: 1.8% (2)	Without dialysis
Pulmonary problems: 4.4% (5)	5 temporary respiratory distress
Pericarditis: 0.9% (1)	
Cardiac rhythm problems: 1.8% (2)	2 VFib
Coagulation problem: 0.9% (1)	

VFib, Ventricular fibrillation.

perceptions were. Data on patient perception was available on 105 patients (53/60 paroxysmal, 30/32 persistent, and 22/22 long-standing persistent). Based on their perception, only 3.8% (2/53) of the paroxysmal patients thought they were still in AF, whereas by LTM, 7 (13.3%) were actually in AF. Among patients with persistent or long-standing persistent AF preoperatively, patient perception of postoperative rhythm was even more unreliable, with few patients being able to reliably determine that they were still in AF.

## Role of Left Atrium Diameter

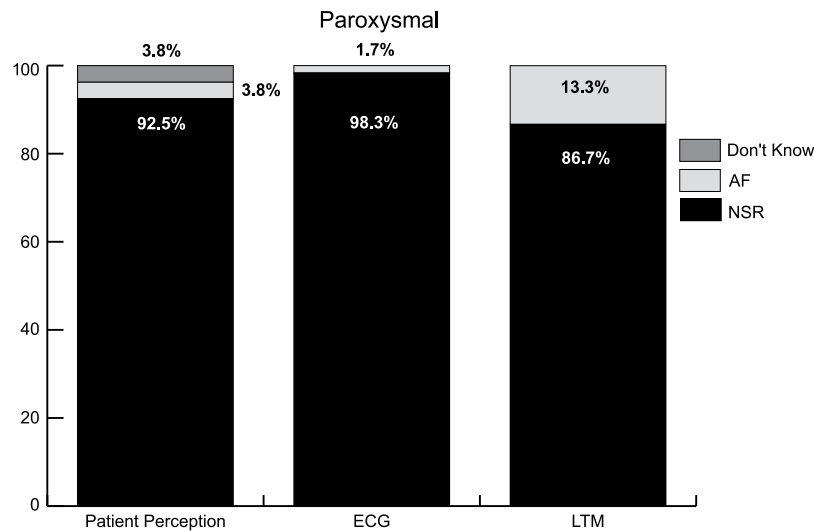
To address the question of whether a larger left atrium diameter increases the probability of failure rate for ablation, logistic regression was run with the LTM 6-month outcome as dependent variable. Neither left atrium diameter as a continuous variable or categorical ( $\leq 5$  cm vs  $> 5$  cm) was a statistically significant predictor of AF at 6 months, after controlling for the type of AF prior to ablation.

There was, however, a trend ( $P = .10$ ) toward a larger mean left atrium diameter across the groups from paroxysmal to long-standing persistent (Table 1). When the diameter was categorized above and below 5 cm, 36.4% (8/22) of long-standing persistent patients had diameters of  $> 5$  cm, whereas in the paroxysmal group, only 18.3% (11/60) had diameters that large.

TABLE 3. Patient rhythm and AAD status at 6 months after ablation

	Paroxysmal	Persistent	Long-standing persistent	P value
ECG NSR				
Patients in NSR	98.3% (59/60)	81.3% (26/32)	63.6% (14/22)	<.001
Also off AAD	80% (48/60)	68.8% (22/32)	36.4% (8/22)	<.001
LTM NSR				
Patients in NSR	86.7% (52/60)	56.3% (18/32)	50.0% (11/22)	<.001
Also off AAD	71.7% (43/60)	46.9% (15/32)	31.8% (7/22)	.002

AAD, Antiarrhythmic drugs; ECG, electrocardiogram; NSR, normal sinus rhythm; LTM, long-term monitor.



**FIGURE 1.** Outcomes for patients with paroxysmal atrial fibrillations (AF) as measured by electrocardiogram (ECG) and long-term monitor (LTM) along with patient perception. NSR, Normal sinus rhythm.

**Comparison of ECG and LTM Outcomes**

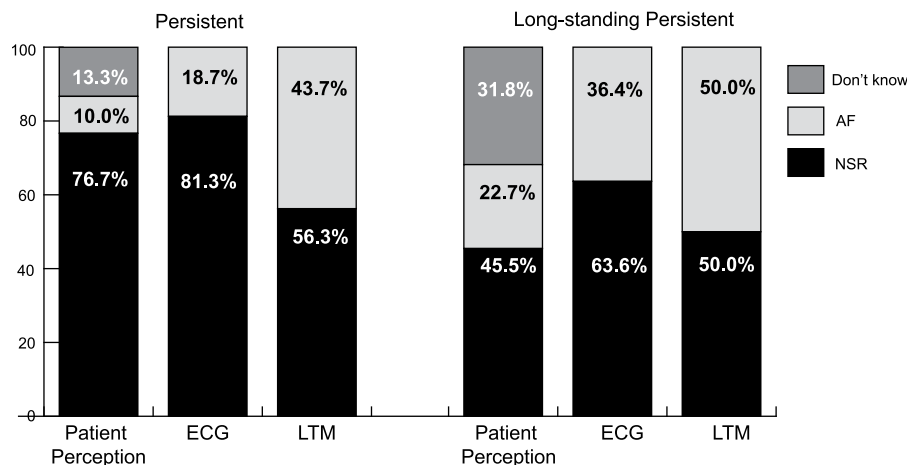
Using ECG to determine the outcome after ablation may or may not be accurate, depending on the circumstances. Because ECG represents a short window (typically 30 seconds), its ability to match LTM will depend on the outcome itself. Patients who no longer have AF will record NSR on both LTM and ECG. However, the problem arises in the group still having AF. Depending on whether the AF is sparse as might be seen in paroxysmal or fairly regular, the detection accuracy will fluctuate. The sensitivity of ECG (true AF detected in all patients with AF) varies from 13% in paroxysmal to 43% in persistent and 73% in long-standing persistent patients.

The results are shown graphically in Figure 3. For each type of AF, the LTM is the gold standard. ECG in all cases records NSR for patients with NSR on LTM; thus the specificity (recorded as NSR in those noted as NSR on LTM) is

100% in all cases. The graph shows the ability to correctly diagnose AF in patients who are known to still be having AF from the LTM.

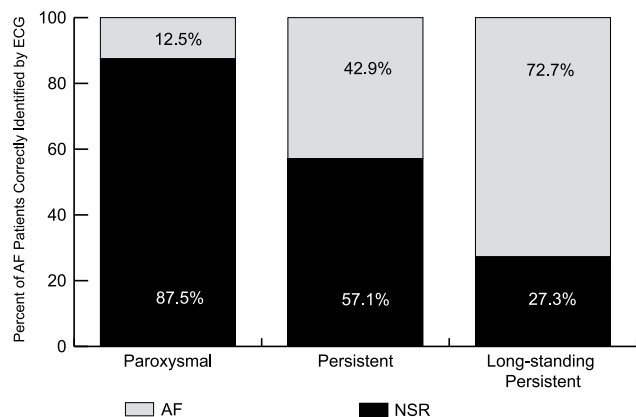
**DISCUSSION**

It has been shown previously<sup>21</sup> that there is up to a 40% difference in detection rates of AF when comparing implanted devices to random ECGs. Our data would confirm that the true burden of AF is not accurately assessed by random samplings of rhythm monitoring such as random ECGs. Nevertheless, most published literature today, prior to the HRS/EHRA/ECAS Expert Consensus Statement, does use interval random ECGs or short rhythm strips to determine the outcomes of treatment for AF. Previous literature also uses widely varying criteria for “success.” We adhered strictly to the Consensus Statement definitions and recommendations. In that context,



**FIGURE 2.** Outcomes for patients with persistent and long-standing persistent atrial fibrillations (AF) as measured by electrocardiogram (ECG) and long-term monitor (LTM) along with patient perception. NSR, Normal sinus rhythm.





**FIGURE 3.** The accuracy of electrocardiogram (ECG) in identifying patients known to still be in atrial fibrillations (AF). Patients are initially identified as in AF by long-term monitor. NSR, Normal sinus rhythm.

our success rate for patients with paroxysmal AF compares very favorably. Had we used only ECG to assess the success of surgery on patients with persistent and long-standing persistent AF (as many previous studies have done), treatment would have been deemed highly efficacious with a success rate of 81.5%. However, true success rates for persistent and long-standing persistent AF of 56.5% by longer-term monitoring leave room for improvement.

It is not too surprising that PV antral isolation and partial autonomic denervation would not be adequate treatment for a patient in persistent and long-standing persistent AF because of the associated changes in the left atrial substrate that occur in these conditions.<sup>22</sup> Electrical remodeling of the left atrium results in a fixed shortened refractory period and a shortened fibrillatory interval.<sup>23</sup> Atrial fibrosis has also been associated with AF.<sup>24</sup> Therefore, isolating the PV triggers alone is likely inadequate treatment for persistent and long-standing persistent AF. A more extensive lesion set similar to the left-sided Cox Maze-III may be necessary.

It is widely recognized that increasing left atrial size correlates with a lower success rate for ablation. That our data did not confirm this is surprising and may relate to the relatively small sample size.

Evidence-based data support both PV electrical isolation and targeted partial autonomic denervation in the treatment of AF. These techniques can be combined in a minimally invasive surgical approach. Early data suggest that this is an efficacious approach to the treatment of paroxysmal AF. Further studies are needed to firmly establish the safety of the procedure. Longer-term monitoring is essential to determine the true burden of AF. Minimally invasive techniques using a more extensive lesion set are being developed for the surgical treatment of long-standing persistent AF from an epicardial approach.

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## Discussion

**Dr T. Nitta** (*Tokyo, Japan*). First, I would like to praise the authors for presenting the data in a manner that strictly adheres to the consensus statement published in the *Heart Rhythm Journal* last year. Based on the statement, the major points we should follow when reporting are the patient follow-up protocol, definition of success for AF ablation, and assessment of postoperative cardiac rhythm. If one would like to have surgical outcomes compared to those of catheter ablation, the data must be reported in the same format based on an identical protocol.

The most striking message in this work was that there was a significant difference in the detection rates of AF between randomly recorded ECG and long-term rhythm monitoring. The true burden of AF was not accurately assessed by random samplings of rhythm monitoring from the regular ECG. I feel that we should reexamine our patients using the long-term monitoring methods, such as Holter monitoring and the event recorder, and reevaluate the outcomes after surgery. I have 2 questions for the authors of this excellent work.

First, how many patients actually had GP ablation? As I read your manuscript, you first mapped the GP, performed PV isolation, and then performed high-frequency burst pacing again to test the vagal response. Local GP ablation was performed only in the patients who showed remaining vagal responses after PV isolation. Given that you did not perform the GP ablation in all patients, I would like to know the impact of the GP ablation on the success rate of AF, and if there was any correlation between the location of GP ablation and success rate for each type of AF.

The second question is about the future of minimally invasive AF surgery. PV isolation alone or with GP ablation may not be an adequate treatment for persistent and long-standing persistent AF. Recent reports on catheter-based AF ablation have shown

that additional linear ablation or ablation of fractionated electrograms improves the success rate. As long as the lesion set is the same, catheter-based ablation will always be less invasive than surgical ablation. Do you think surgery should also move in the same direction, or should we return to the maze procedure as a way of dealing with advances of catheter-based ablation in the treatment of persistent or long-standing persistent AF?

Thank you for the privilege of discussing this work.

**Dr Edgerton** (*Dallas, Tex*). Thank you for your comments. With respect to the Chair, I will try to be brief.

I fear that perhaps we miscommunicated in the manuscript, and I will make sure that that is cleared up. All these patients were done identically at the 5 centers because we wanted to know that the results were translatable. Everyone had GP ablation. GPs were mapped before the ablation, the isolation of the pulmonary veins, then we went back and mapped for any surviving GPs and ablated all of those. So they were all done identically. I can't tell you the impact, therefore, of GP ablation.

To your second point, I refer back to Dr Turina's excellent lecture yesterday that showed when the arterial switch operation was begun, the mortality was 50%, yet he didn't give up, and we have learned from this and moved on. We have designed now a technique to perform, through a minimally invasive approach, the full left atrial lesion set that Dr Cox designed for the maze III. I have 20 patients who have 6-month long-term monitoring. I am presenting that tomorrow at the Heart Rhythm Society. So we have moved on to now perform the full left-sided maze lesion set. For patients with long-standing AF, the results are significantly improved over what we presented here, and although there were only small numbers of patients, we think the early results are promising.

Thank you for your comments.