Ablation of Ganglionic Plexi During Combined Surgery for Atrial Fibrillation

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Ann Thorac Surg 2008;86:1659-1663
DOI: 10.1016/j.athoracsur.2008.06.077

Ablation of Ganglionic Plexi During Combined Surgery for Atrial Fibrillation

Nicolas Doll, MD, PhD, Patrick Pritzwald-Stegmann, MD, Markus Czesla, MD, Joerg Kempfert, MD, Monika Anna Stenzel, MD, Michael A. Borger, MD, PhD, and Friedrich-Wilhelm Mohr, MD, PhD

Departments of Cardiac Surgery and Cardiology, Heart Center Leipzig, University of Leipzig, Leipzig, Germany

Purpose. **Recent investigations into the treatment of atrial fibrillation have suggested improved outcomes after concomitant pulmonary vein isolation (PVI) and ganglionic plexi (GP) ablation. We investigated the impact of left atrial ablation with substrate modification (left atrial maze) or epicardial PVI, combined with GP mapping and ablation, in patients with paroxysmal or longstanding persistent atrial fibrillation undergoing additional off-pump or on-pump cardiac surgery.**

Description. **Twelve patients aged 74.9 ± 3.8 years, with atrial fibrillation for 4.5 ± 1.5 years, underwent left atrial maze or epicardial PVI, along with GP mapping and ablation during coronary bypass grafting with or without valve surgery. The GP mapping used high-frequency bipolar stimulation. The GP ablation and PVI were achieved using bipolar radiofrequency ablation. Conduction block was confirmed by pacing.**

Evaluation. **At 1-year follow-up, 83% of patients were in sinus rhythm. Echocardiography confirmed satisfactory bi-atrial contraction. Exercise-induced heart rate variability was appropriate. There were no early deaths.**

Conclusions. **Epicardial PVI, left atrial maze, GP mapping, and ablation for the treatment of atrial fibrillation can be effectively and safely performed during surgery for other cardiac pathologies.**

(Ann Thorac Surg 2008;86:1659–63)

The role of the autonomic nervous system in the triggering or maintenance of atrial fibrillation (AF), or both, is being increasingly recognized [1]. The intrinsic cardiac autonomic nervous system is composed of axons and autonomic ganglia grouped into ganglionic plexi (GP) within the epicardial fat pads of the heart [2]. The importance of autonomic tone before the onset of paroxysmal AF seems to involve a shift from sympathetic to parasympathetic predominance [3], and the attenuation of this parasympathetic influence seems to provide additional benefit after ablation therapy [4]. Recent studies have demonstrated that GP stimulation can convert subthreshold isolated foci of premature depolarization in the pulmonary veins into AF-inducing triggers [2] and provide a substrate for pulmonary veins firing into AF [5]. Advancements in epicardial electrophysiological mapping and isolation of GPs have been reported to allow effective identification and ablation using bipolar radiofrequency isolation in patients undergoing stand-alone minimally invasive surgery for AF [6]. Surgical removal of GP-containing tissue during concomitant coronary artery bypass grafting (CABG) surgery in the prevention of post-operative AF has also shown positive results [7]. Paroxysmal AF is often treated with pulmonary vein isolation alone, whereas successfully treating longstanding persistent AF requires substrate modification with a Cox maze III operation or one of its derivatives [1]. Therefore, we commenced a study to investigate the impact of left atrial ablation with substrate modification or epicardial PVI, combined with GP mapping and ablation, in patients with paroxysmal or longstanding persistent AF undergoing concomitant off-pump or on-pump cardiac surgery.

Technology

The ethics committee of the University of Leipzig approved the study protocol, consent process, and operative procedure. From September to December 2006, 6 male and 6 female patients (mean age, 74.9 ± 3.8 years) who suffered from either paroxysmal or longstanding persistent AF of 4.5 ± 1.5 years duration, underwent GP mapping and ablation at the time of concomitant elective cardiac surgery. The primary surgeries were seven CABG procedures, two aortic valve replacements, one mitral

Accepted for publication June 2, 2008.

Address correspondence to Dr Doll, Heart Center Leipzig, Department of Cardiac Surgery, University of Leipzig, Struempellstr. 39, Leipzig, 04289, Germany; e-mail: dolln@medizin.uni-leipzig.de.

Published by Elsevier Inc

0003-4975/08/$34.00
doi:10.1016/j.athoracsur.2008.06.077

Ann Thorac Surg
2008;86:1659–63

Table 1. Patient Characteristics

Characteristic	Number of Patients (%)
Diabetes mellitus	7 (58.3)
Pulmonary hypertension	1 (8.3)
Hypertension	11 (91.7)
Hyperlipidemia	8 (66.7)
Obstructive airway disease	2 (16.7)
Chronic renal insufficiency	1 (8.3)
Previous cardiac operations	0 (0)
Previous AF cardioversion	0 (0)
Previous catheter ablation	0 (0)
Previous emboli	0 (0)
Implanted cardioverter-defibrillator	0 (0)
Anticoagulation	11 (91.7)
0. Anti-arrhythmic medications	4 (33.3)
1. Anti-arrhythmic medications	6 (50.0)
2. Anti-arrhythmic medications	2 (16.7)

valve repair with CABG, one combined aortic valve replacement with mitral valve repair and CABG, and one aortic valve replacement with CABG. Five of the isolated CABG patients underwent an off-pump procedure. Six patients suffered from paroxysmal AF (group 1) and were treated with bilateral PVI using epicardial bipolar radiofrequency ablation (AtriCure Inc, Cincinnati, OH). The 6 patients with longstanding persistent AF (group 2) underwent a left atrial ablation procedure in which a left atrial substrate modification was performed by creating additional left atrial connecting lines. The GP stimulation and ablation was performed before clamping the pulmonary veins. The conduction block was always confirmed before aortic cross clamping. In all pump cases, the block was measured on pump. Further patient characteristics are listed in Table 1.

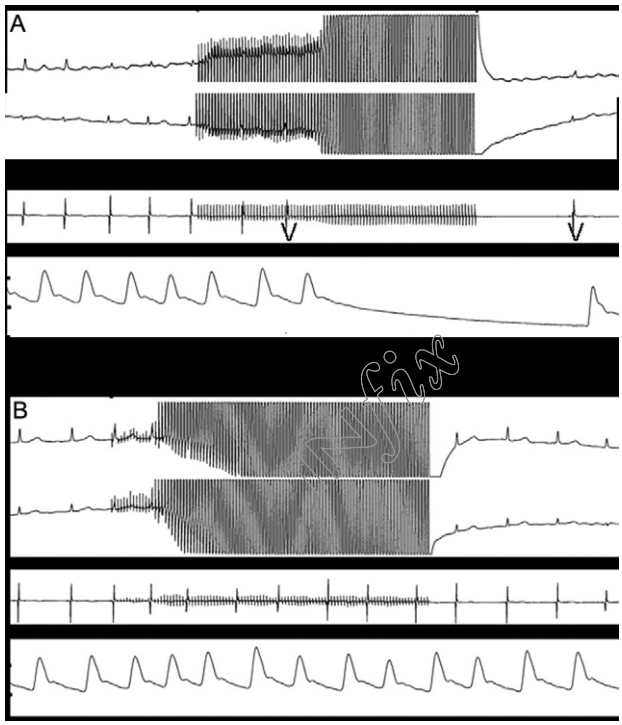

Fig 2. (A) Stimulation of ganglionic plexus (GP) with resultant vagal response before ablation. (B) Stimulation of GP after ablation without a resultant vagal response.

Device Description

Mapping of the conduction block was always confirmed before cross clamping. In all pump cases the block was measured on pump with the Pacing Box (Pace 203H [Osypka, Rheinfelden, Germany]) while observing the following protocol and settings at a pulse width of 1.5 msec, a pulse rate of 1,000 impulses/minute, and a pulse

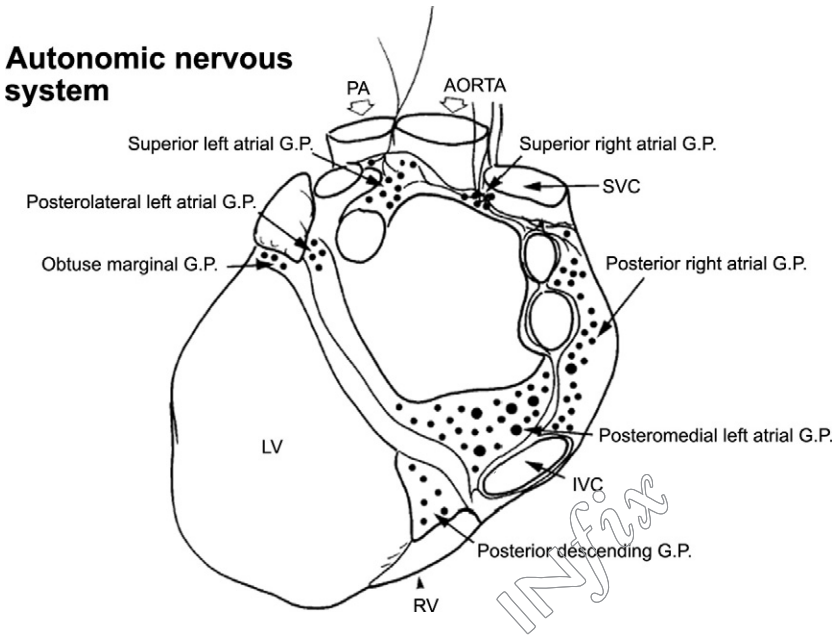

Fig 1. Schematic human heart; posterior view. General anatomical location of ganglionic plexi indicated by the black dots. These are contained in the "fat pads" that the surgeon visualizes. (GP = ganglionic plexus; IVC = inferior vena cava; LV = left ventricle; PA = pulmonary artery; RV = right ventricle; SVC = superior vena cava). (Adapted from Gross and microscopic anatomy of the human intrinsic cardiac nervous system, Anat Rec, Vol 247, No 2, 1997, 289–98. Copyright © 1997. Reprinted with permission of Wiley-Liss Inc, a subsidiary of John Wiley & Sons, Inc.)

Table 2. Intraoperative Data

Intraoperative Procedures	Group 1 (n = 6) Paroxysmal AF	Group 2 (n = 6) Longstanding Persistant AF
CABG	n = 5	n = 2
AVR	n = 1	n = 1
CABG + AVR		n = 1
CABG + MVR		n = 1
CABG + AVR + MVR		n = 1
Operative time	217 ± 22 min	249 ± 83 min
Cross-clamp time	52 min (n = 1)	81 ± 38 min
CPB time	97 ± 1 min (n = 1)	149 ± 49 min
Number of ganglia ablated	9 ± 4	10 ± 3
Patients in sinus rhythm at end of procedure	n = 6	n = 6
Pacemaker mode at end of procedure	AAI (n = 2)	AAI (n = 6)
Need for IABP	n = 0	n = 0

AF = atrial fibrillation; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; MVR = mitral valve repair; PVI = pulmonary vein isolation.

amplitude of 18V. High-frequency stimulation was performed at each anatomical location known to contain GPs (Fig 1). The occurrence of temporary asystole or a decrease of 50% in the native heart rate was defined as successful detection of a GP (Fig 2A). After GP ablation, the site was high-frequency stimulated again to confirm the absence of a vagal response (Fig 2B). The GP ablation was performed until no further GPs could be detected.

In this study a bipolar device (Isolator Clamp [Atricure Inc]) was used to isolate the pulmonary veins. The device consisted of a hand piece with two 5 cm × 1 mm electrodes embedded in each jaw. Located at 1 mm from the electrodes was a thermocouple, which recorded myocardial tissue temperature. The Isolator Clamp was connected to a generator that generated bipolar radiofrequency energy delivered at 75 Volts and 650 mAmps. Ablation of the target tissue was performed by clamping the tissue between the jaws of the device until a built-in algorithm within the system recognized a decrease in tissue conductance between the two electrodes to a stable minimum value. Ablation was terminated after a period of 3 seconds after this minimum value was obtained. In all cases, electrical isolation of the pulmonary veins was confirmed by pacing before and after ablation using the MAXPEN3 (Atricure Inc). The results were expressed as mean ± standard deviation (SD) for continuous variables and as proportions for categorical variables throughout the article.

Technique

There were no intraoperative or early postoperative deaths. At second follow-up performed at 13.9 ± 1.5 months postoperatively, there was one death noted in group 1. The patient, who had previously been treated for a mammary carcinoma with radiation therapy, died 5 months postoperatively due to right heart failure. We were unable to obtain electrocardiographic and echocardiography follow-up for 1 patient in each group due to patient refusal. One patient in group 2 was lost to follow-up.

The mean operative time was 233 ± 61 min in all patients, whereas cardiopulmonary bypass and aortic cross-clamp times were 136 ± 47 minutes and 77 ± 36 minutes, respectively, in those patients who were operated on pump. An average of 9 ± 4 ganglia was ablated. For further intraoperative details, see Table 2. At the conclusion of surgery all patients were in sinus rhythm. Eight patients were temporarily paced atrially because of relative bradycardia. Seven patients had a recurrence of AF prior to discharge; of these, 4 were successfully cardioverted, resulting in 9 of the total 12 patients (75%) going home in sinus rhythm. Mean hospital length of stay was 11 ± 3 days postoperatively.

At first follow-up, 78 ± 38 days postoperatively, 10 of 12 patients (83%) were in sinus rhythm. The 2 patients with longstanding persistent AF at discharge remained in this rhythm throughout follow-up. Heart rate variability was preserved (67 ± 19 and 59 ± 12 bpm at rest; 97 ± 27 and 99 ± 26 bpm with exercise; all at first and second follow-up, respectively). At second follow-up no patient had reverted to AF since discharge. All patients with paroxysmal AF were in sinus rhythm during second follow-up, whereas 3 of 4 patients (75%) with longstanding

Table 3. Postoperative Telemetry and Echocardiography

7-Day Holter Monitor	SR	HR Min	HR Max	HR Mean
1st follow-Up (n = 7)	83%	56 ± 18	113 ± 53	75 ± 24
2nd follow-Up (n = 8)	88%	59 ± 12	99 ± 26	71 ± 17

Echocardiography	Preop	Postop	1st Follow-Up	2nd Follow-Up
LA diameter (mm)	45 ± 8	46 ± 9	49 ± 10	49 ± 5
LV ejection fraction (%)	53 ± 14	55 ± 17	52 ± 12	59 ± 10
LV end-diastolic volume (mL)	90 ± 35	101 ± 31	98 ± 32	81 ± 29

HR = heart rate in beats per minute; LA = left atrial; LV = left ventricular; min = minimum; max = maximum; SR = sinus rhythm; values expressed ± standard deviation; preop = preoperative; postop = postoperative.

persistent AF who were available for follow-up were in sinus rhythm. For further telemetry results, see Table 3.

Echocardiography demonstrated bilateral atrial contraction in all patients who were in sinus rhythm. Atrial size did not significantly change postoperatively (see Table 3). Left ventricular ejection fraction increased from 53 ± 14% preoperatively to 59 ± 10% at second follow-up. Left ventricular end-diastolic volume decreased on follow-up from 90 ± 35 mL preoperatively to 81 ± 29 mL postoperatively.

Anticoagulation therapy was able to be markedly reduced postoperatively with only 38% of patients being treated at second follow-up compared with 92% preoperatively. Amiodarone was required in 3 patients immediately postoperatively. However, this could be successfully weaned, leaving only 1 patient in group 2 with longstanding persistent AF on this therapy. There were 58% of the patients who received beta-blocker therapy preoperatively, which increased to 88% at the second follow-up, and this was the sole form of anti-arrhythmic therapy in all but 1 patient.

Complications included 1 patient who had a resternotomy for bleeding, 1 who had sternal wound infection, and 1 who suffered left-sided hemiparesis immediately after aortic valve replacements. At second follow-up, 1 patient had suffered a stroke, despite anticoagulation. It was a 71-year-old woman who had suffered from longstanding persistent atrial fibrillation, but at the time of follow-up she was in sinus rhythm. Severe carotid stenosis was believed to have been the causative factor. This was likely the progression of pre-existing disease that was not an indication for intervention at the time of cardiac surgery. She received a full left atrial lesion set with a left atrial substrate modification by creating additional left atrial connecting lines. In all patients with longstanding persistent atrial fibrillation, the left atrial appendage was resected.

Clinical Experience

There is good evidence that derivatives of the Cox maze procedures using bipolar radiofrequency ablation devices are safe and effective in the treatment of AF [8], and that PVI alone can also be more effective than conservative treatment [6]. These procedures may be safely combined with surgery for other cardiac pathologies [8]. Because our patients had concomitant cardiac pathology requiring surgical intervention, there was a clear indication to treat the AF surgically at the time of surgery. Hence, our patients did not undergo prior invasive treatments for AF, such as catheter-based PVI ablation.

Comment

Animal studies have suggested that GP ablation alone may not achieve long-term suppression of AF [9]. However, other investigators argue that GP ablation does in fact play a key role in AF modulation [5]. Nevertheless, there is increasing clinical evidence in humans that in lone AF, GP ablation in addition to PVI is safe and effective [6]. The results of this study suggest that not only is GP isolation safe when performed during concomitant surgery for AF and other cardiac pathologies, but it seems to increase efficacy of freedom from long-term AF. There was 100% freedom from AF in those patients treated with PVI for paroxysmal AF and 75% in those suffering from longstanding persistent AF who underwent left atrial ablation with substrate modification. The efficacy of PVI alone when concomitant cardiac disease is present has been questioned [8]. Although our numbers are small, PVI combined with GP ablation may be more effective in this setting than first believed. Exercise variability remained intact in both groups, despite ablating all GPs that could be intraoperatively identified.

It is unclear whether there will be a regeneration of the ablated ganglion tissue, and there is diverging evidence for and against the role of GPs in long-term freedom from AF. Oh and colleagues [9] showed that there is regeneration of GP activity 4 weeks after ablation in dog hearts. However, Scherlag [10] suggested that the ablation performed was only partial. We believe that this issue would best be addressed by further long-term evaluation in a chronic animal study using the technique we used in the current study that is ablating all identifiable GPs.

Although we recognize that the small patient group is a limitation of our study, our outcomes and those of others [6] indicate that GP ablation is sufficiently safe to extend its use to larger patient populations. Therefore, we have commenced a prospective randomized study to further evaluate this procedure. A total of 100 patients undergoing surgery for concomitant cardiac pathologies will be randomized to undergo standard left atrial ablation and substrate modification for longstanding persistent AF or PVI isolation only for paroxysmal AF with GP ablation (n = 50) or without GP ablation (n = 50). We hope that the results of this trial will shed further light on the effect of GP ablation on increased long-term efficacy of concomitant procedures to treat AF.

Disclosures and Freedom of Investigation

The bipolar ablation device was purchased by the Heart Center Leipzig, Leipzig, Germany. The authors have performed a free and independent evaluation of this new technology. Doctors Doll, Pritzwald-Stegmann, Czesla, Kempfert, Stenzel, Borger, and Mohr have no financial relationship with the company Atricure.

We would like to thank Dr Gaynor from Atricure for his support and advisory function.

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Disclaimer

The Society of Thoracic Surgeons, the Southern Thoracic Surgical Association, and *The Annals of Thoracic Surgery* neither endorse nor discourage use of the new technology described in this article.

INVITED COMMENTARY

Four years ago, while visiting The University of Oklahoma and performing and demonstrating minimally invasive pulmonary vein isolation to Dr Jackman and the Oklahoma arrhythmia team, I toured the Oklahoma arrhythmia center. Purely by chance, we observed Dr Ben Scherlag performing ganglionic plexi (GP) ablation in the canine model using alcohol injections into the canine fat pads. Ben was then kind enough to accept an invitation to visit us in Cincinnati with his equipment, where we performed the first ever GP testing and isolation in a human during a minimally invasive pulmonary vein isolation procedure (MiniMaze). We did not inject alcohol into the fat pads as Ben had done in the laboratory, but instead we used neurosurgical bipolar forceps to cauterize the fat pads around the pulmonary veins. After that case, we routinely added GP testing and isolation to the MiniMaze procedure, evolving from bipolar forceps application of cautery to the fat pads to a bipolar pen application. We reported our GP technique in this journal [1].

The article by Doll and colleagues [2] is significant as it lays the foundation for a randomized study of concomitant surgical AF treatment with and without GP fat pad isolation. Bipolar clamp treatment alone (without specific fat pad lesions with a pen) creates epicardial lesions that block some of the autonomic activity. The questions yet to be answered are as follows: (1) How much autonomic activity is blocked by pulmonary vein isolation alone? (2) How much does fat pad isolation add to pulmonary vein isolation? To date, we have not shown that the addition of the specific fat pad lesions improves the cure of AF. In fact, in our own series of minimally invasive stand-alone procedures (MiniMaze), the initial 20 cases were performed before we started the specific GP testing and isolation. This included the very first patient in the series who was longstanding, persistent, and who is now 5 years out from the MiniMaze and is AF free. He had only clamp isolation of the pulmonary veins. It may well be true that bipolar clamp isolation of the pulmonary veins results in enough GP isolation. We really may be comparing only the extent of GP isolation when we compare isolation of the pulmonary veins alone versus isolation of the pulmonary veins with "additional" fat pad isolation. How much is enough? We do not know. We also do not know if fat pad isolation alone, without pulmonary vein isolation will be enough to cure AF in some subsets of patients.

It seems, at least in humans, in the case of the importance of specific fat pad GP ablation during PV isolation, we have a mountain of theory based on a molehill of evidence. Doll and colleagues' [2] article based on the follow-up of 8 of 12 patients at 1 year will not shed light on this conundrum. However, their planned randomized study is a great idea.

Dr Wolf discloses that he has a financial relationship with Atricure.

Randall K. Wolf, MD

Capital University
Beijing, China
Deaconess Hospital
311 Straight St
Cincinnati, OH 45219
e-mail: randallwolf@dataquesthealthcare.com

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