

Online Appendix for the following *JACC* article

TITLE: Treatment of Atrial Fibrillation by the Ablation of Localized Sources: The Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation (CONFIRM) Trial

AUTHORS: Sanjiv M. Narayan, MD, PhD, David E. Krummen, MD, Kalyanam Shivkumar, MD, PhD, Paul Clopton, MS, Wouter-Jan Rappel, PhD, John M. Miller, MD

APPENDIX

SUPPLEMENTARY METHODS

Details of Electrophysiological Study

Patients were studied in the fasted state. Electrophysiology study was performed after discontinuing anti-arrhythmic medications for 5 half lives, or >60 days for amiodarone (median 230 days for all patients) (Table 1 of main manuscript). Catheters were advanced from peripheral veins to the coronary sinus and, after trans-septal puncture guided by intracardiac echocardiography, a 64-pole basket catheter (Constellation, Boston Scientific, Massachusetts) was advanced to the left atrium in all patients. The last 73 subjects also had 64 pole basket mapping of the right atrium once technical constraints were overcome. The 64-pole basket catheter (Constellation) was advanced through an 8.5F SL1 sheath (Daig Medical, Minnetonka, Minnesota) to map the atria with a wide field of view. Insertion of the basket or its exchange with other catheters through an existing sheath typically required <1 minute, and subsequent positioning for optimal electrode contact (1) <5 minutes. Figure 1 of the main text illustrates such a case in a patient with persistent AF, providing simultaneous recordings from 128 biatrial basket electrodes, 10 coronary sinus electrodes, and an additional “roving” catheter (139 in total). Baskets were manipulated to ensure optimal tissue contact confirmed by fluoroscopy, direct visualization on intracardiac echocardiography and electrogram quality as recently illustrated (1). A digital atrial shell was created to guide clinical (not FIRM) ablation for all patients using either the NavX (St. Jude, Minneapolis, Minnesota) or Carto (Biosense-Webster, Diamond Bar, California) systems. Intravenous heparin was infused to achieve an activated clotting time >350 s in all cases.

Electrophysiological Data Used for Computational Mapping

The methods underlying computational mapping have recently been described (1). Briefly, in FIRM-blinded subjects, a deflectable 7F monophasic action potential catheter (MAP [EP Technologies, Sunnyvale, California]) was used to record MAPs from the atria in parallel with basket recordings used to define the dynamics of atrial repolarization (2,3), and develop and validate computational maps of AF. Briefly, FIRM-blinded subjects were studied in sinus rhythm, and those in AF were cardioverted to sinus rhythm electrically using external paddles (200 to 300 J biphasic waveforms, Physiocontrol, Washington). If cardioversion was acutely unsuccessful or AF recurred, we proceeded directly to conventional ablation (see main text).

From sinus rhythm, pacing was performed from the left or right superior pulmonary vein using the proximal poles of the MAP catheter (2-4). Pacing at twice diastolic threshold was performed to deliver single extrastimuli in 27 subjects (2), and burst pacing to the point of AF onset in 25 subjects (3). Subjects then proceeded to conventional ablation.

Intracardiac signals from the atrium were recorded either as unipoles (or bipoles to reduce far-field artifact). AF activation was mapped using basket electrodes with 4 to 6 mm spacing (Constellation), providing theoretically sufficient spatial resolution to detect reentrant circuits in human atria (2,3,5,6).

Signals were exported from recording systems at 16 bit (Bard Pro, Billerica, Massachusetts) or 12-bit (Prucka, GE Healthcare, Milwaukee, Wisconsin) digital resolution at each recruiting center, and processed in blinded fashion using custom software written by SMN

and WJR in Labview (National Instruments, Austin, Texas) and Matlab (The Mathworks, Natick, Massachusetts) on multicore personal computers.

Use of Repolarization and Conduction Data For Computational Analyses

In offline analysis in FIRM-blinded subjects, we defined the dynamic rate-response of human atrial conduction and repolarization (action potential duration [APD]). APD was measured for progressively early extrastimuli and faster pacing rates to define APD restitution curves (7) in human left atria, as we recently reported (2,3). Conduction time from the pacing site to each defined basket electrode position was also measured to define the rate-response (restitution) of atrial conduction regionally within human atrium as also recently reported (6).

A major challenge in interpreting complex signals during human AF is that signals vary in rate and shape such that traditional rate measurements may be erroneous (8). Accordingly, we analyzed regional variations in the tissue factors that determine the minimum tissue wavelength of a reentrant circuit, $\lambda = \text{refractory period} \times \text{conduction velocity}$ (9). We used APD restitution to define the shortest refractory period (i.e., minimum APD) for each patient (2,3). Minimum APD indicates the shortest time atrial activation time, and was used to identify signal deflections separated by a shorter interval that could not reflect successive local AF activations at that electrode location. To identify conduction velocity, the second component of λ , we used regional conduction restitution (6) to define regions of slow atrial conduction at rapid rates. This information was also used to identify signal deflections that were unlikely to represent local atrial activation.

Computational Maps of AF Rotors and Focal Impulses

AF signals were processed by linear detrending, removal of QRS artifact (10) and spatial averaging. Sequences of activation at multiple electrodes in both atria were then used directly to create isochronal maps of AF as shown in Figures 1 and 2 of the main text. Algorithms and software were designed to continually associate electrogram sequences such that rotors or focal beat sources, when identified, could be tracked if they migrated.

With continued algorithmic improvements, computational (FIRM) mapping time reduced to the point where intraprocedural mapping was possible to enable FIRM-guided ablation. With continued improvements, FIRM mapping time has reduced to <10 minutes.

Details of Ablation Technique

In FIRM-guided subjects, *AF ablation commenced with FIRM* to eliminate rotors or focal impulses by direct ablation or transection, depending on location. The endpoint of FIRM ablation at each site was acute AF termination, slowing of AF rate by >10%, or 10 minutes of ablation, whichever came first. The cutpoint used for AF slowing (>10% prolongation of AF CL, or 15–20 ms prolongation in a typical AF case) is more conservative than previous reports that used AF CL prolongation >6 ms (\approx 3% to 4% of typical AF cycle length) to indicate meaningful slowing during ablation (11). Radiofrequency ablation was delivered using a 3.5-mm tip irrigated catheter (Thermocool, Biosense-Webster) at 25 to 35 W or, in heart failure subjects, an 8-mm tip non-irrigated catheter (Blazer, Boston Scientific) at 40 W to 50 W to a target temperature of 50° to 52°C.

For each source, the catheter was maneuvered to the electrode site overlying the source identified by fluoroscopy or digital atrial maps. Radiofrequency applications for FIRM ablation were made for 15 to 30 s at any given location, moving the catheter within the area indicated by maps to represent the rotor core or focal impulse origin, for a total ablation time of ≤ 10 minutes. If AF terminated, attempts were made to reinitiate AF and, if successful, maps were recomputed and FIRM was repeated for up to 30 minutes of radiofrequency application. A case report of successful acute AF termination by FIRM ablation at right atrial then left atrial rotors has recently been published with a video recording of the case in an accompanying online supplement (12). Conventional ablation was then performed.

Conventional ablation (13), performed after FIRM ablation in the FIRM-guided group, and as sole therapy in the FIRM-blinded group, comprised wide area circumferential ablation to isolate the left and right pulmonary veins in pairs, with verification of pulmonary vein isolation using a circular mapping catheter (Lasso, Biosense-Webster). Ablation power, temperatures, and duration parameters were as noted for the FIRM-guided group. Cases of persistent AF also received a left atrial roof line, and atrial tachycardia or flutter were also ablated appropriately. For example, patients with cavotricuspid or mitral annular flutter had lesions applied to create bidirectional block across each respective isthmus. No other ablation was performed. If AF persisted after completion of the ablation protocol in each group, cardioversion was performed.

SUPPLEMENTARY FIGURES 1 and 2

These figures illustrate monitoring in the CONFIRM trial for silent as well as symptomatic AF after ablation using implanted continuous ECG monitors combined with regular clinic visits.

Supplementary Figure 1. Continuous absence of AF For 15 months post-AF ablation using an implanted ECG monitor with AF autodetection (Reveal XT, Medtronic, MN), in a 57-year-old with persistent AF for 4 years, mild left ventricular dysfunction (ejection fraction 45%), and CHADS2 score = 3.

NOTE DATED: 09/30/2010 13:18
LOCAL TITLE: MED/CARD/ELECTROPHYSIOLOGY
STANDARD TITLE: CARDIOLOGY NOTE
VISIT: 09/30/2010 13:00 LJ MED CARDIO ARRHYTHMIA

6 month

loop recorder interrogation:
MDT Reveal
No AF noted

Date of Visit: 27-Dec-2010 11:01:34
SW007 Software Version 7.0
Copyright © Medtronic, Inc. 2007

Initial Interrogation: Quick Look Page 1

Device Status (Implanted: 19-Mar-2010)

Battery Status	Good	<u>9 mo</u>
Episodes (27)		
Symptom	0	
FVT	0	
VT	7	
Asystole	0	
Brady	8	
AT/AF		
AT	0	
AF	12	
% of Time AT/AF	<0.1 %	

Date of Visit: 28-Mar-2011 10:56:46
SW007 Software Version 7.0
Copyright © Medtronic, Inc. 2007

Initial Interrogation: Quick Look Page 1

Device Status (Implanted: 19-Mar-2010)

Battery Status	Good	<u>12 mo</u>
Episodes (24)		
Symptom	0	
FVT	0	
VT	8	
Asystole	0	
Brady	15	
AT/AF		
AT	0	
AF	1	
% of Time AT/AF	<0.1 %	

Date of Visit: 30-Jun-2011 14:07:17
SW007 Software Version 7.0
Copyright © Medtronic, Inc. 2007

Initial Interrogation: AT/AF Summary Page 1

Prior Session	Last Session
27-Dec-2010 to 28-Mar-2011	28-Mar-2011 to 30-Jun-2011
91 days	94 days

15 mo

AT/AF Summary

% of Time AT/AF	<0.1 %	<0.1 %
Average AT/AF time/day	<0.1 hours/day	<0.1 hours/day

Supplementary Figure 2. Absence of AF at 9 months after FIRM-guided AF ablation for highly symptomatic drug-refractory paroxysmal AF in a 54-year-old man, using an implanted continuous ECG monitor with AF autodetection algorithm (Reveal XT, Medtronic, MN).

Date of Visit: 10-Jan-2011 10:49:41
SW007 Software Version 7.0
Copyright © Medtronic, Inc. 2007

Initial Interrogation: Quick Look

Page 1

Device Status (Implanted: 03-Dec-2010) 1 month

Battery Status Good

Episodes (6)

Symptom	0
FVT	0
VT	2
Asystole	0
Brady	0
AT/AF	
AT	0
AF	4
% of Time AT/AF	0.4 %

Date of Visit: 15-Mar-2011 13:21:18
SW007 Software Version 7.0
Copyright © Medtronic, Inc. 2007

Initial Interrogation: Quick Look

Page 1

Device Status (Implanted: 03-Dec-2010) 3 month

Battery Status Good

Episodes (1)

Symptom	0
FVT	0
VT	0
Asystole	0
Brady	0
AT/AF	
AT	0
AF	1
% of Time AT/AF	<0.1 %

Date of Visit: 16-Jun-2011 14:05:43
SW007 Software Version 7.0
Copyright © Medtronic, Inc. 2007

Initial Interrogation: Quick Look

Page 1

Device Status (Implanted: 03-Dec-2010) 6 month

Battery Status Good

Episodes (0)

Symptom	0
FVT	0
VT	0
Asystole	0
Brady	0
AT/AF	
AT	0
AF	0
% of Time AT/AF	0.0 %

Date of Visit: 22-Sep-2011 13:38:54
FullView SW007 Software Version 7.1
Copyright © Medtronic, Inc. 2010

Initial Interrogation: Quick Look

Page 1

Device Status (Implanted: 03-Dec-2010) 9-month

Battery Status Good

Episodes (1)

Symptom	0
FVT	0
VT	0
Asystole	0
Brady	0
AT/AF	
AT	0
AF	1
% of Time AT/AF	<0.1 %

SUPPLEMENTARY REFERENCES

1. Narayan SM, Krummen DE, Rappel W-J. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol* 2012;23. In press.
2. Narayan SM, Kazi D, Krummen DE, Rappel W-J. Repolarization and activation restitution near human pulmonary veins and atrial fibrillation initiation: a mechanism for the initiation of atrial fibrillation by premature beats. *J Am Coll Cardiol* 2008;52:1222-30.
3. Narayan SM, Franz MR, Clopton P, Pruvot EJ, Krummen DE. Repolarization alternans reveals vulnerability to human atrial fibrillation. *Circulation* 2011;123:2922-30.
4. Franz MR, Chin MC, Sharkey HR, Griffin JC, Scheinman MM. A new, single-catheter technique for simultaneous measurement of action potential duration and refractory period *in vivo*. *J Am Coll Cardiol* 1990;16:878-86.
5. Ideker RE, Rogers JM, Fast V, Li L, Kay GN, Pogwizd SM. Can mapping differentiate microreentry from a focus in the ventricle? *Heart Rhythm* 2009;6:1666-9.
6. Lalani G, Schricker A, Gibson M, Rostamian A, Krummen DE, Narayan SM. Dynamic conduction slowing precedes human atrial fibrillation initiation: insights from bi-atrial basket mapping on transitions to atrial fibrillation. *J Am Coll Cardiol* 2012;59:595-606.
7. Franz MR, Swerdlow CD, Liem LB, Schaefer J. Cycle length dependence of human action potential duration *in vivo*. Effects of single extrastimuli, sudden sustained rate

- acceleration and deceleration, and different steady-state frequencies. *J Clin Invest* 1988;82:972-9.
8. Elvan A, Linnenbank A, van Bommel M, et al. Dominant frequency of atrial fibrillation correlates poorly with atrial fibrillation cycle length. *Circ Arrhythm Electrophysiol* 2009;2:634-44.
 9. Rensma P, Allesie M, Lammers W, Bonke F, Schalij M. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res* 1988;62:395-410.
 10. Ng J, Kadish AH, Goldberger JJ. Technical considerations for dominant frequency analysis. *J Cardiovasc Electrophysiol* 2007;18:757-64.
 11. Takahashi Y, O'Neill MD, Hocini M, et al. Characterization of electrograms associated with termination of chronic atrial fibrillation by catheter ablation. *J Am Coll Cardiol* 2008;51:1003-10.
 12. Narayan SM, Patel J, Mulpuru S, Krummen DE. Focal impulse and rotor modulation (FIRM) ablation of sustaining rotors abruptly terminates persistent atrial fibrillation to sinus rhythm with elimination on followup. *Heart Rhythm* 2012;9. In press.
 13. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the

European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm 2012;9:632-96.e21.