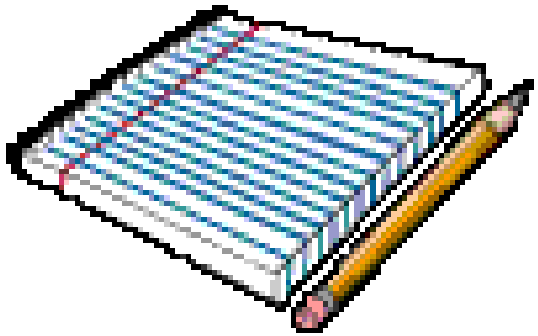
# ATRİYAL FİBRİLASYONUN MEKANİZMALARI

## - Rotorlar -

Özgür Aslan

DEÜTF, Kardiyoloji A.D.



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Cardiovascular Research (2011) **89**, 766–775
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**SPOTLIGHT REVIEW**

# Déjà vu in the theories of atrial fibrillation dynamics

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## 1. Introduction

> The history of the recognition of fibrillation of the auricles will impress you with the dimness of our eyes and the opacity of the obstacles which embarrass our vision.
>
> Sir Thomas Lewis

Sir Thomas Lewis made the above statement in a lecture he delivered in 1912 at University College Hospital in London, UK.[1] It is quoted here because it remains so relevant in the twenty-first century. It seems that today we remain as blind to the facts about atrial fibrillation (AF), as investigators in Lewis' time were 100 years ago. We carry on conspicuously in the dark about the nature of persistent AF.

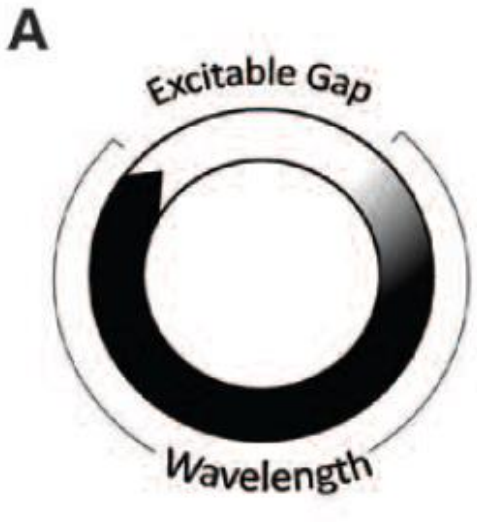
# «Reentry»

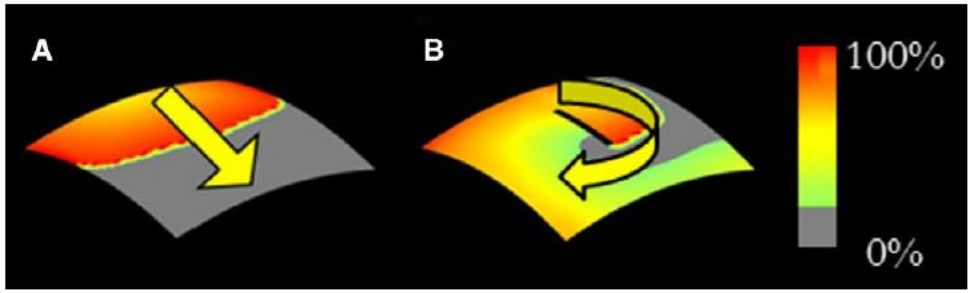
## Uyarının YAYILMASI («*Impulse Propagation*»)

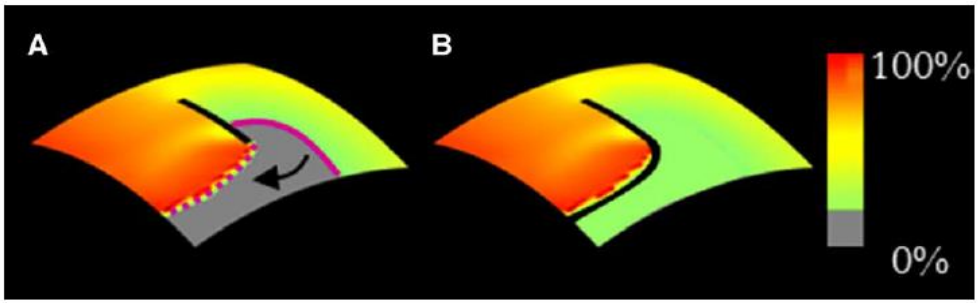
- **Hücrenin Uyarılması («Cell Excitation»)**
  - İçe doğru akımların dışa doğru akımları aşması !
  - Eşik –aktivasyon (aksiyon) potansiyeli
  - Depolarizan akımlar (Na, ve Ca ) ve
  - Dışa doğru akımlar ile dengelenme
- **Yayılma («Propogation»)**
  - Bir hücreden komşularına sıçrayan depolarizan akımdan kaynaklanan uyarılma
  - **İletim hızı («conduction velocity»)**
    - Hücrede aksiyon potansiyelinin oluşma süresi uzadığına komşu hücrenin uyarılması da gecikir (yayılma yavaşlar) !

# «Reentry»

- Devam eden elektriksel aktivite, «uyarının sürekli yayılması»nın sonucudur
- Aktivasyon dalgası kapalı bir devrede yayılır
  - Reentry içindeki hücreler tekrar uyarılırlar
  - Bir uyarı dalgası uyarı yönünü değiştiremez
    - Hücrelerin Refrakterliği
  - Başladığı yere dönebilme

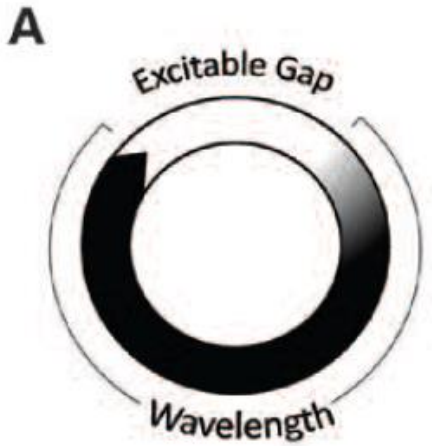


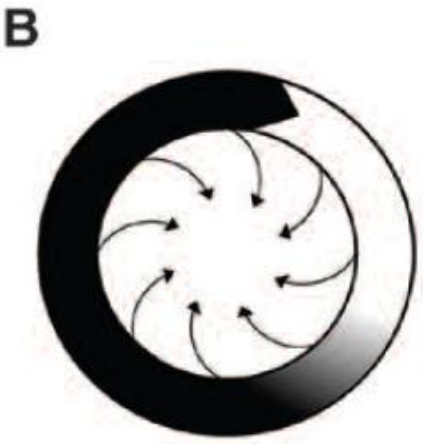



# «Reentry»

- **Anatomik reentry**
  - Halka tipi
  - Uyarılabilir bir bağlantı noktası («gap»)
  - Dalga boyu = Refrakter periyod X İletim hızı
    - Yayılan dalganın (depolarize olmuş hücreler bütünü) uzaysal dağılımı



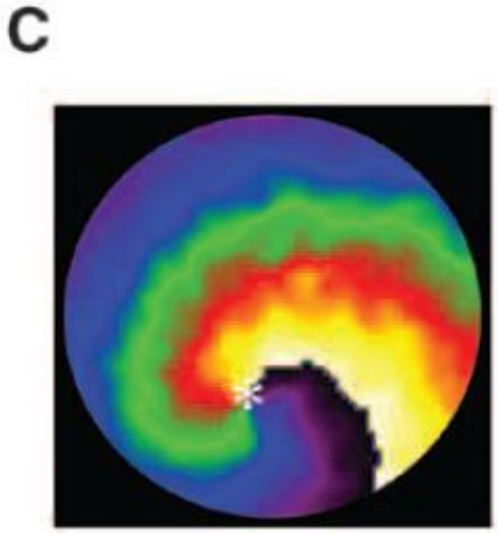

- **Fonksiyonel reentry**
  - «Leading circle» hipotezi
    - Anatomik engele gerek yoktur
    - Tam olarak uyarılabilir bir bağlantı noktası («gap») yoktur !
    - Halkanın iç kısmında merkeze doğru uyarılma sonucu refrakterlik !

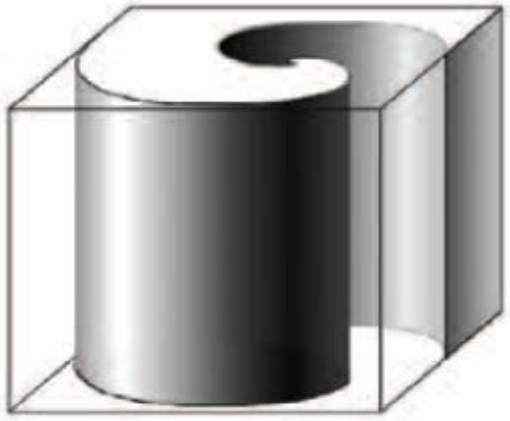



*Pandit SV, Jalife J. Rotors and the Dynamics of Cardiac Fibrillation Circ Res. 2013;112:849-862.*

# Rotor ?

- Bir çeşit fonksiyonel reentry !
  - *Davidenko 1990; Jalife; Narayan; Chen*
- Kavisli dalga kümesi ve dalganın kuyruğu bir «teklik» («singularity») noktasında buluşur !
- Dokunun merkezi refrakter değildir !
- **Rotorlar** = *«Fibrilasyonun devamını sağlayan, düzenleyici kaynaklar veya yürütücüler» ?*
- ***«Spiral dalga»***
  - Dönmekte olan rotorun kendi çevresinde oluşturduğu kavisli elektriksel girdapların 2-boyutlu temsili
- ***«Scroll – Kıvrım – dalga»***
  - Bir spiral dalganın 3-boyutlu temsili
  - Dönüş merkezi, spiral ucun dönüş yörüngesinin oluşturduğu lifsi bir çukurluktur
    - Spiralin merkezi !!



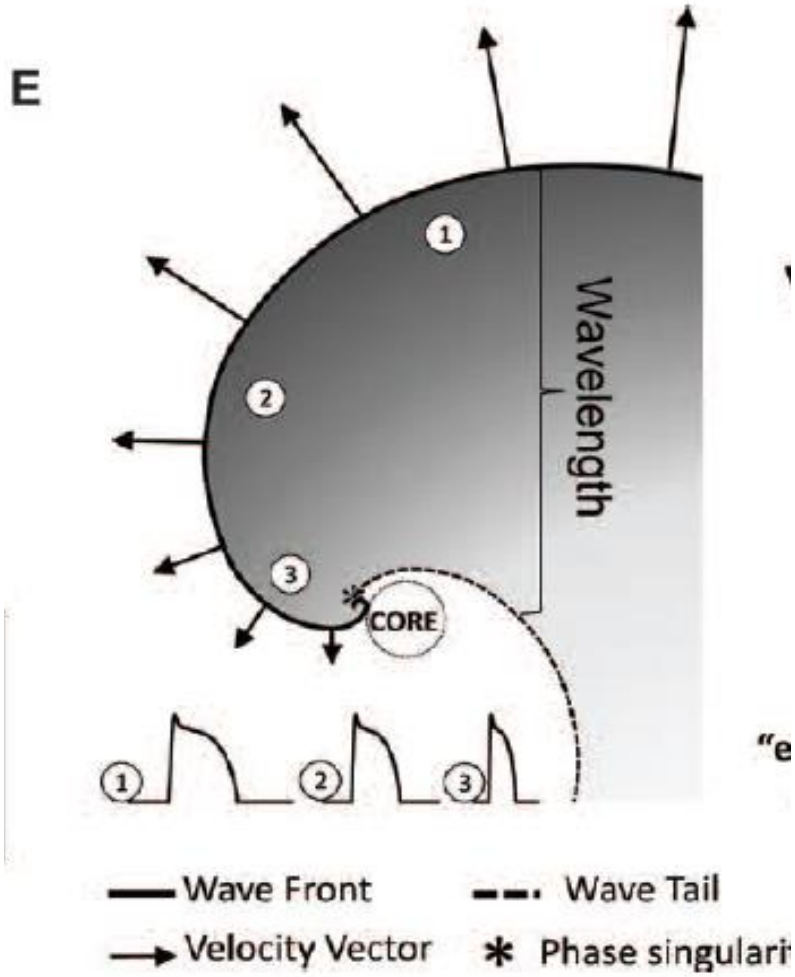




*Jalife J Cardiovasc Res 2011;89:766-775*
*Pandit SV, Jalife J. Rotors and the Dynamics of Cardiac Fibrillation Circ Res. 2013;112:849-862.*

# Rotor ?

## «Spiral dalga»

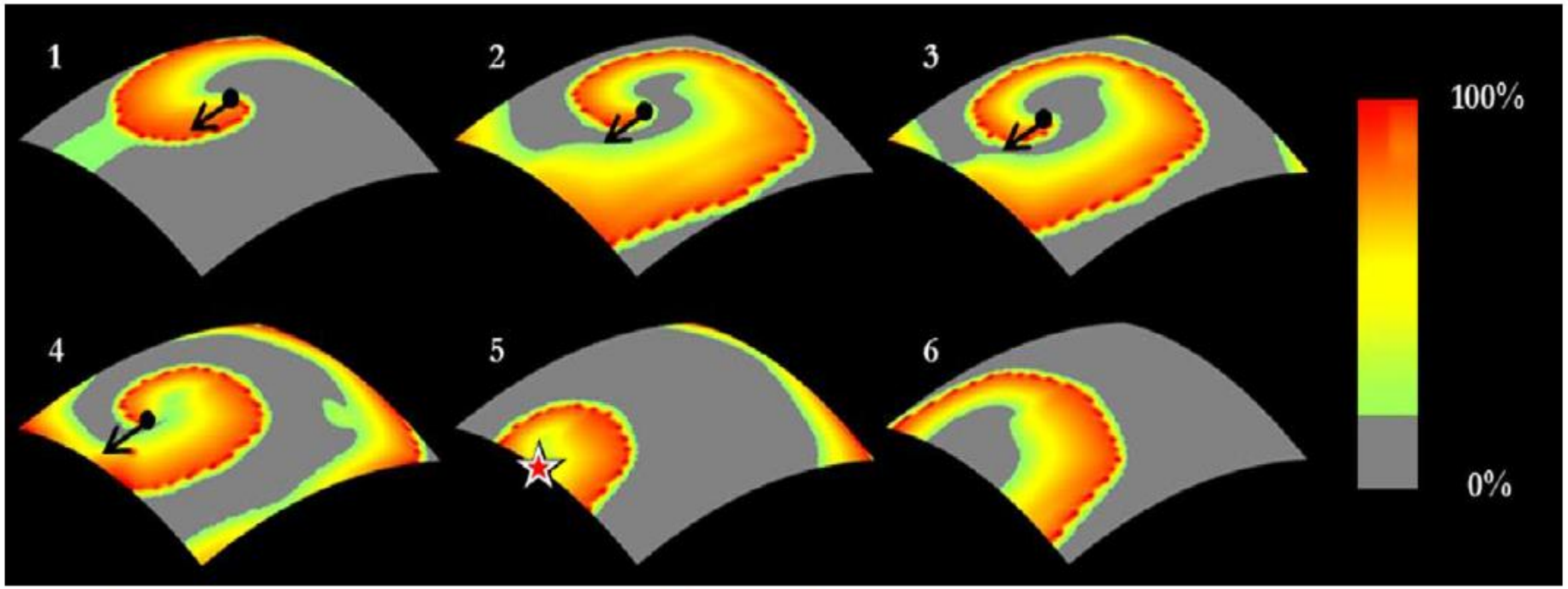
- **Dalga kümesi**
  - elektriksel uyarı ilerledikçe depolarize olan hücrelerin oluşturduğu alanı temsil eder
- **Dalganın kuyruğu**
  - tam olarak uyarılmış bulunan (aksiyon potansiyelin tepesi) ve dinlenmeye başlayan (repolarizasyon) hücrelerden oluşur
- **Kavisli ön-uç**
  - Kavis spiral merkeze doğru giderek keskinleşir !
  - Kavis arttıkça iletim hızı yavaşlar
- **Spiralin merkezi**
  - İletinin yayılamadığı nokta !
  - Çevresinde dönüşün gerçekleştiği uyarılamayan merkez
  - Merkez çevresinde iletim homojen olmaz ise merkez sabit kalmaz !



# Rotor ?

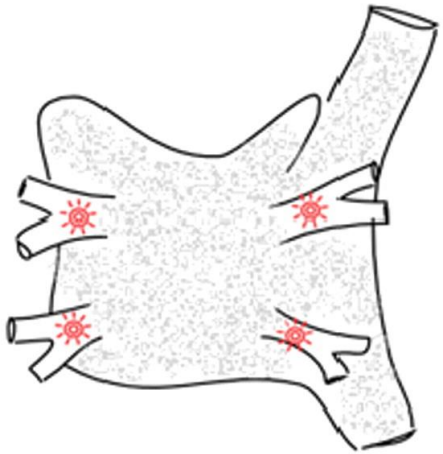
## «Spiral dalga»

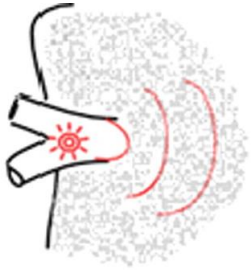
- Rotorlar tarafından çıkarılan spiral dalgalar kalp içindeki anatomik ve fonksiyonel engellere rastladığında :
  - Spiralin kenarı uyarılamayan bir dokuya rastladığında dalga kırılır / söner ?
  - Yeni dalgacıklar oluşup, dalga uçları da dönmeye başlarsa «çocuk-dalgalar» ortaya

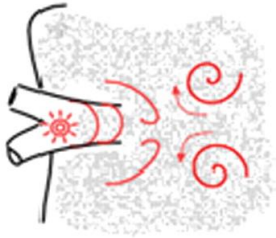


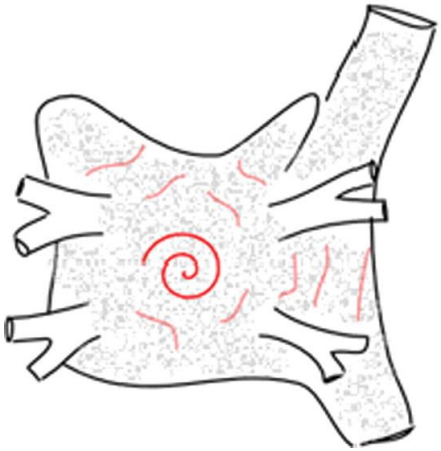

*Jalife J, Berenfeld O. Molecular mechanisms and global dynamics of fibrillation: J Theor Biol 2004;230:475–487*

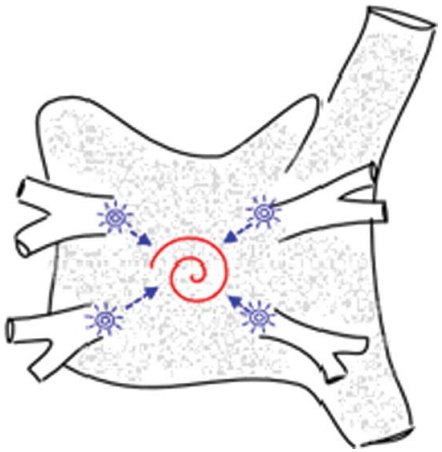
# Fokal tetikleyiciler / Rotor





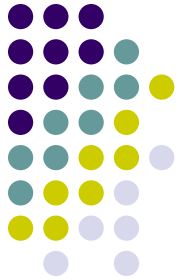






Calkins H et al. Europace 2012

# Rotorlar
## - *İnsanda nasıl saptanabilir ?* -

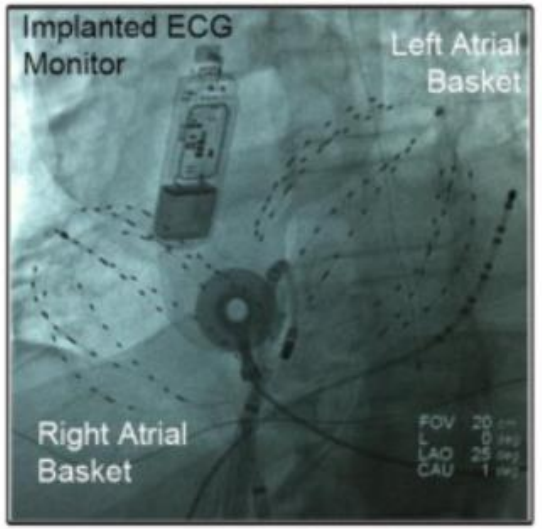


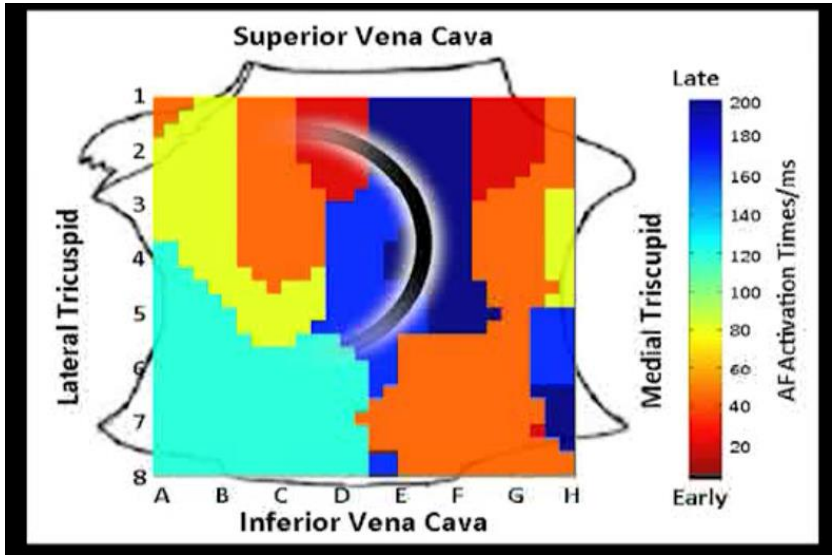
- «FIRM (*Focal Impulse and Rotor Modulation*)»
- «*Noninvasive Panoramic Mapping*»
- «*Beat-to-beat nonlinear measurement of the repetitiveness of the electrogram morphology*»

# FIRM: Focal impulse and rotor modulation

- AF sırasında, her iki atriyumdan, basket kateter aracılığıyla, eş zamanlı, temasa dayalı elektrogram kayıtları
- 64 pollü basket kateter
- Özel yazılım (Topera)
  - Sinyal ileti hızı ve repolarizasyon parametreleri
- Lokalizasyon ve ablasyon

# FIRM: Topera's RhythmView™



# Treatment of Atrial Fibrillation by the Ablation of Localized Sources

## CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial

Sanjiv M. Narayan, MD, PHD,*† David E. Krummen, MD,*† Kalyanam Shivkumar, MD, PHD,‡ Paul Clopton, MS,† Wouter-Jan Rappel, PHD,§ John M. Miller, MD‖

*San Diego and Los Angeles, California; and Indianapolis, Indiana*

**Objectives** We hypothesized that human atrial fibrillation (AF) may be sustained by localized sources (electrical rotors and focal impulses), whose elimination (focal impulse and rotor modulation [FIRM]) may improve outcome from AF ablation.

**Background** Catheter ablation for AF is a promising therapy, whose success is limited in part by uncertainty in the mechanisms that sustain AF. We developed a computational approach to map whether AF is sustained by several meandering waves (the prevailing hypothesis) or localized sources, then prospectively tested whether targeting patient-specific mechanisms revealed by mapping would improve AF ablation outcome.

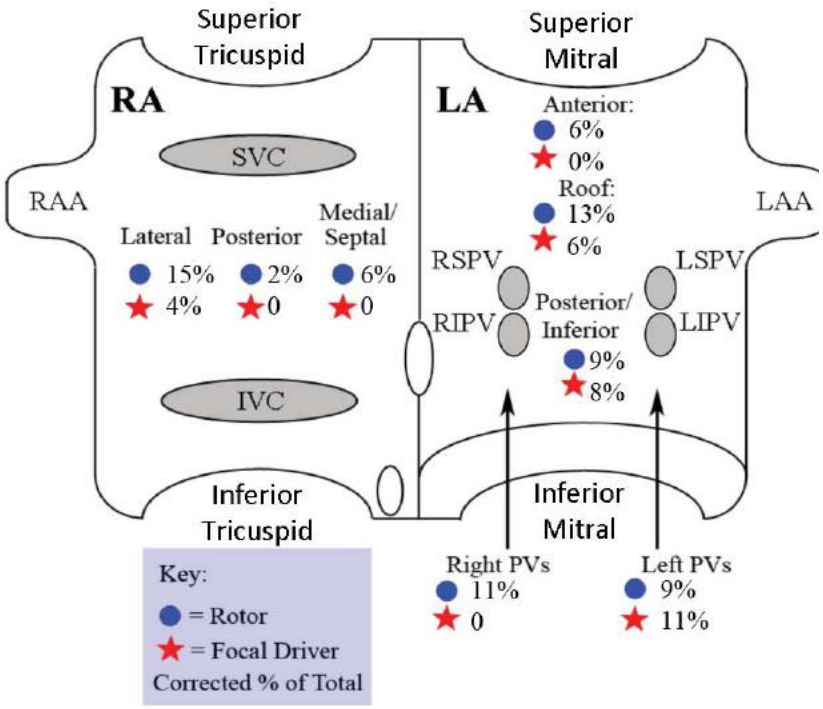
**Methods** We recruited 92 subjects during 107 consecutive ablation procedures for paroxysmal or persistent (72%) AF. Cases were prospectively treated, in a 2-arm 1:2 design, by ablation at sources (FIRM-guided) followed by conventional ablation ($n = 36$), or conventional ablation alone ($n = 71$; FIRM-blinded).

**Results** Localized rotors or focal impulses were detected in 98 (97%) of 101 cases with sustained AF, each exhibiting $2.1 \pm 1.0$ sources. The acute endpoint (AF termination or consistent slowing) was achieved in 86% of FIRM-guided cases versus 20% of FIRM-blinded cases ($p < 0.001$). FIRM ablation alone at the primary source terminated AF in a median 2.5 min (interquartile range: 1.0 to 3.1 min). Total ablation time did not differ between groups ($57.8 \pm 22.8$ min vs. $52.1 \pm 17.8$ min, $p = 0.16$). During a median 273 days (interquartile range: 132 to 681 days) after a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%; $p < 0.001$) after a single procedure than FIRM-blinded cases with rigorous, often implanted, electrocardiography monitoring. Adverse events did not differ between groups.

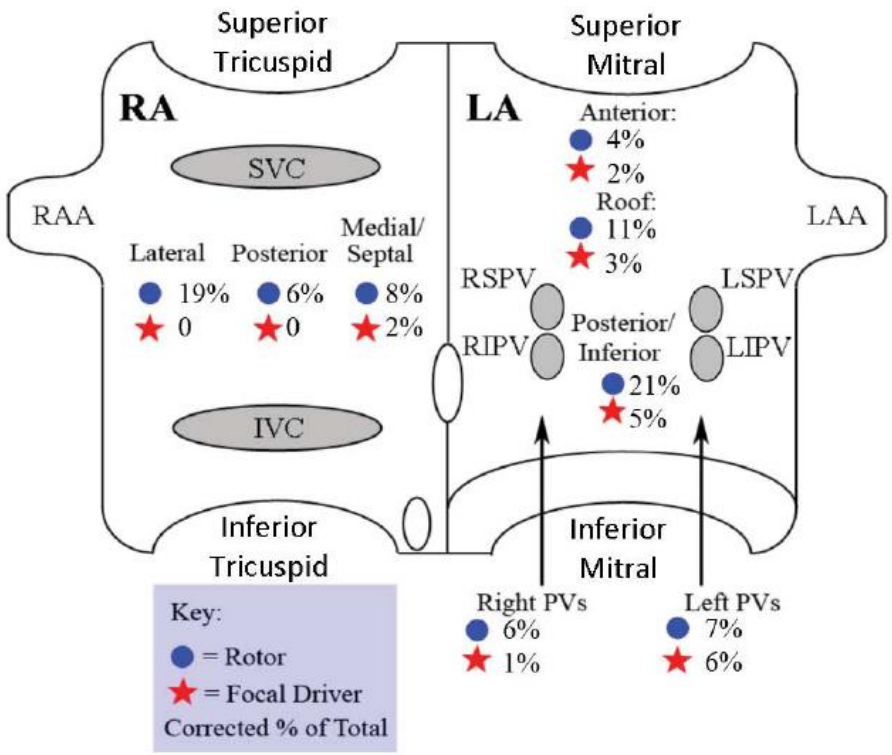
**Conclusions** Localized electrical rotors and focal impulse sources are prevalent sustaining mechanisms for human AF. FIRM ablation at patient-specific sources acutely terminated or slowed AF, and improved outcome. These results offer a novel mechanistic framework and treatment paradigm for AF. (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation [CONFIRM]; NCT01008722) (J Am Coll Cardiol 2012;60: 628–36) 

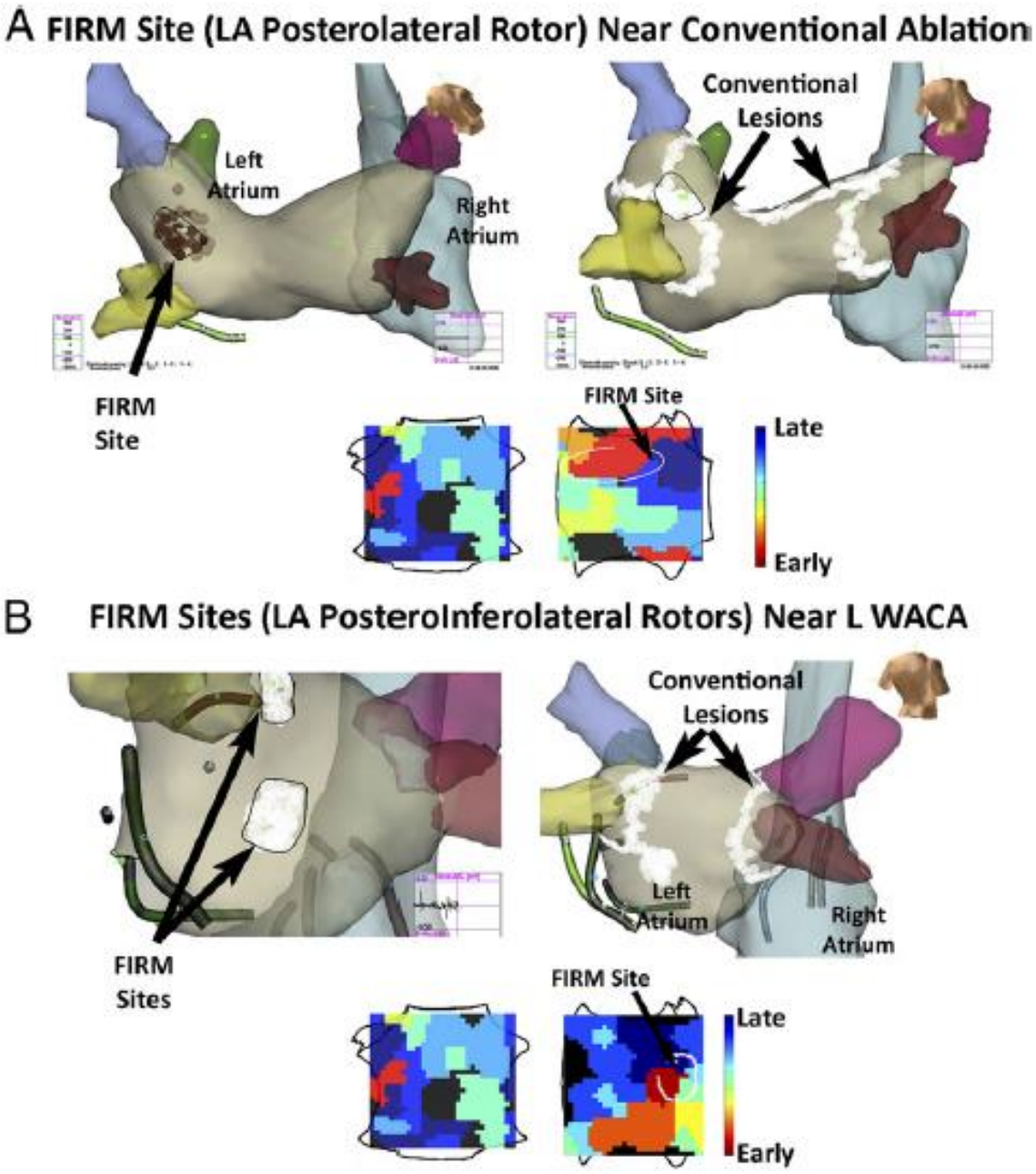
# CONFIRM çalışması

A. AF Source Locations - CONFIRM Paroxysmal AF




B. AF Source Locations - CONFIRM Persistent AF






Journal of the American College of Cardiology, Volume 62, Issue 2, 2013, 138 - 147

# Noninvasive Panoramic Mapping of Human Atrial Fibrillation Mechanisms: A Feasibility Report

MICHEL HAISSAGUERRE, M.D.,* MELEZE HOCINI, M.D., ASHOK J. SHAH, M.D., NICOLAS DERVAL, M.D., FREDERIC SACHER, M.D., PIERRE JAIS, M.D., and REMI DUBOIS, PH.D.

From the * Hôpital Cardiologique du Haut-Lévêque and the Université Victor Segalen Bordeaux II, Bordeaux, France

**Noninvasive Panoramic Mapping of Human Atrial Fibrillation Mechanisms.** ***Introduction:*** **Recent developments in body surface mapping and computer processing have allowed noninvasive mapping of atrial activation responsible for various cardiac arrhythmias with increasingly greater resolution. We developed specific algorithms to identify localized sources and atrial propagation occurring simultaneously during ongoing atrial fibrillation (AF).**

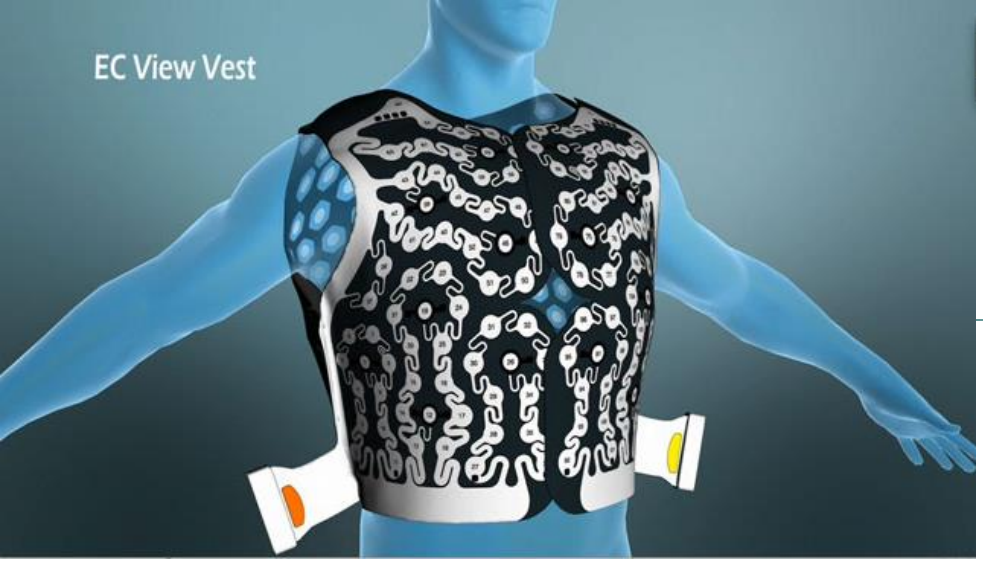
***Methods and Results:*** **We report the feasibility of noninvasive panoramic mapping of human AF mechanisms and its validation by successful ablation. We used a commercially available mapping system using an array of 252 body surface electrodes and noncontrast thoracic CT scan to obtain high-resolution images of the biatrial geometry and the relative electrode positions. On the surface unipolar electrograms acquired during AF we developed specific signal-analysis process combining filtering, wavelet transform, and phase mapping. At least 5 windows with spontaneous, long ventricular pauses were selected for mapping. The incidence, location and characteristics of localized sources (foci and rotors) were assessed on the cumulative duration of all recorded windows. In a patient with paroxysmal AF, noninvasive maps showed multiple single or repetitive discharges from 3 pulmonary veins (PVs), a rotor meandering along the right venous ostia, and their mutual interplay. All areas outside the left posterior wall were passively activated. AF terminated during isolation of right PV. In a patient with persistent AF for 7 months, a rotor was identified recurrently, drifting in the left atrial inferior and posterior wall and in the roof. It was not stationary for more than 2 rotations. The right atrial free wall was activated over the Bachman's bundle by a passive wavefront propagating in a counterclockwise pattern. Ablation at the rotor locations abruptly converted AF into atrial tachycardia after 10 minutes of radiofrequency application. Further mapping and ablation confirmed a counterclockwise cavotricuspid isthmus—dependent flutter.**

***Conclusions:*** **This report demonstrates the feasibility of noninvasive panoramic mapping of AF in identifying active sources, which include unstable rotors and PV foci, and its validation by ablation results.**
*(J Cardiovasc Electrophysiol, Vol. 24, pp. 711-717, June 2013)*

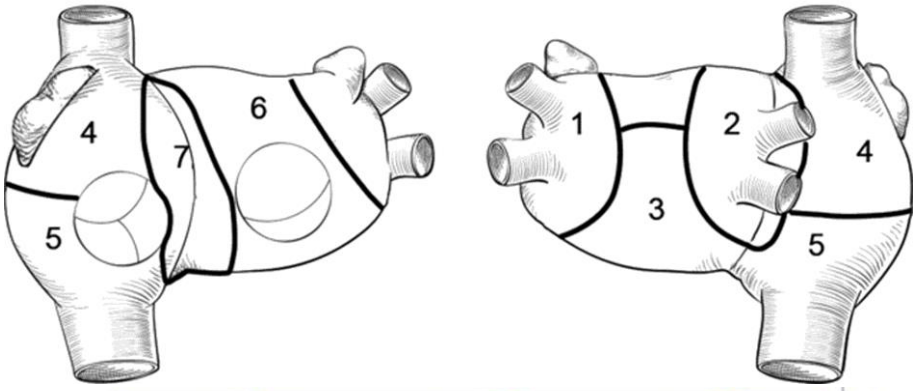
# «Noninvasive panaromic mapping»

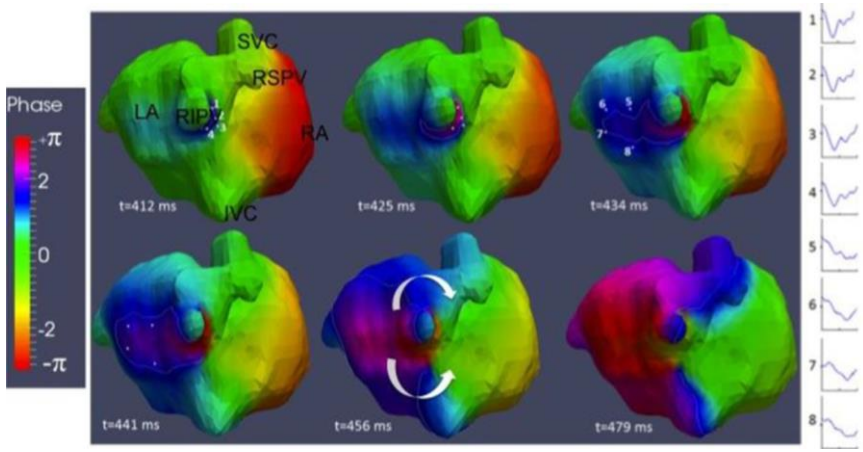
- ECVue, Cardioinsight Tech
  - 252 elektrodlu doğrudan haritalama yöntemi («ECG imaging»)
- Unipolar gövde potansyellerinin 3-D BT görüntüleri üzerinde rekonstrüksiyonu
  - Sinyaller ventriküler pauseler sırasında  elde ediliyor
- Atriyal geometri 7 bölüme ayrılır
- «Driver» : Rotorlar veya spontan fokal deşarjlar
  - **«Driver density maps»**
- Endokardiyal + epikardiyal sinyaller bütünü («scroll wave ?»

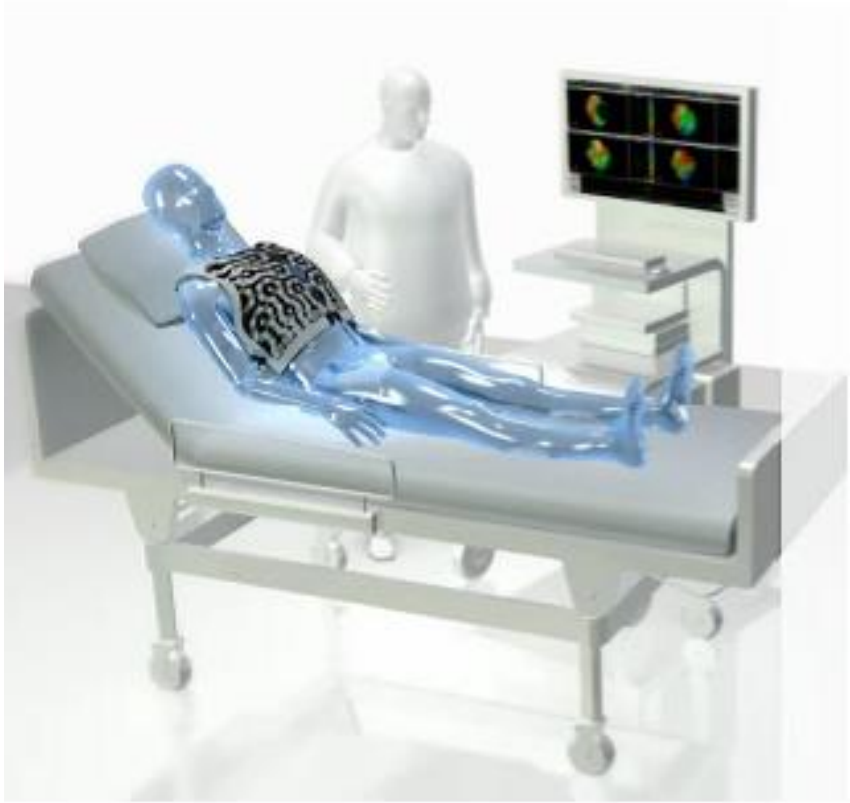
*Narayan SM, et al. J Am Coll Cardiol. 2012;60(7):628-636*




# ECVue, Cardioinsight Technologies



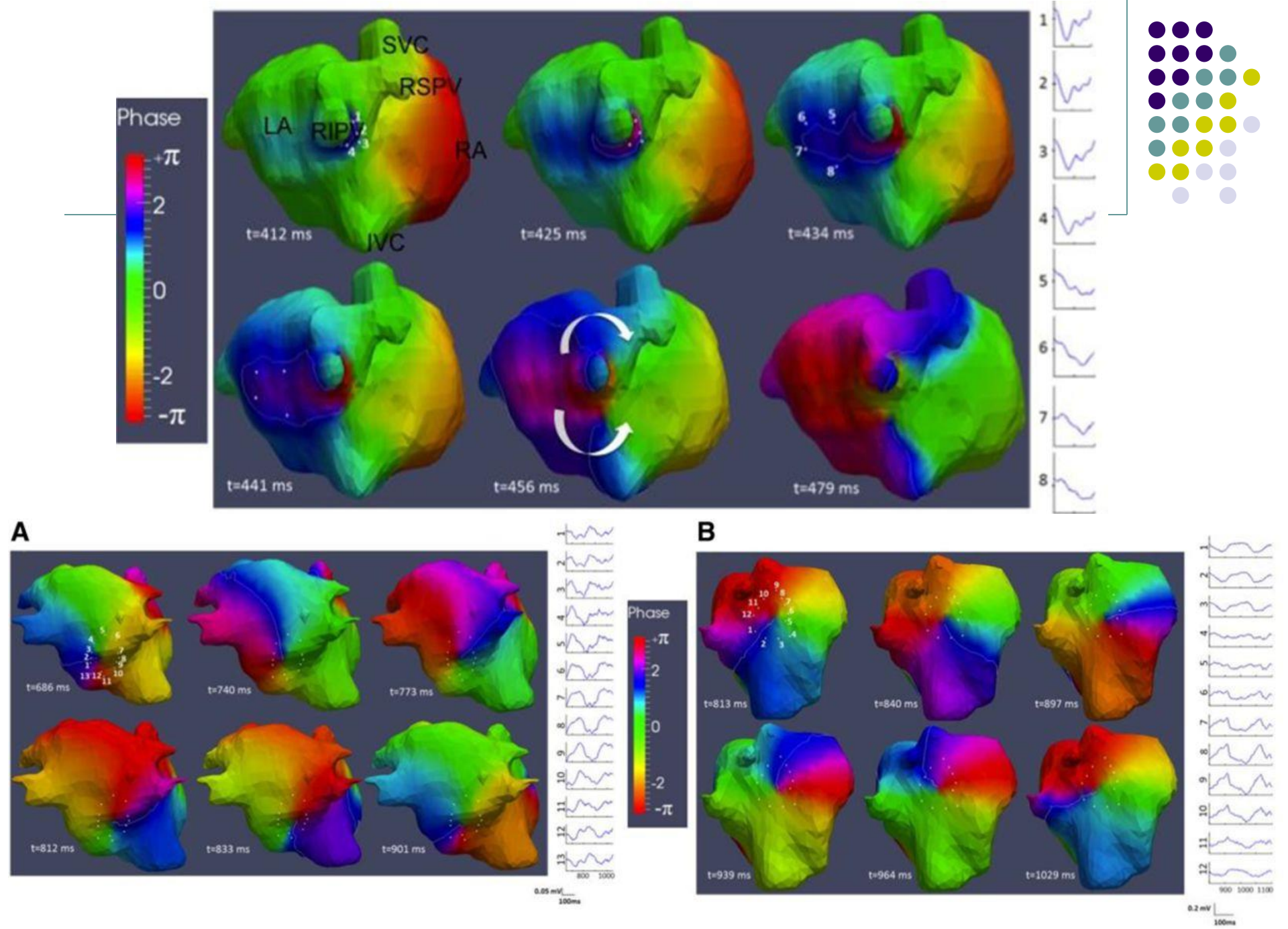
# Driver Domains in Persistent Atrial Fibrillation

Michel Haissaguerre, MD; Meleze Hocini, MD; Arnaud Denis, MD; Ashok J. Shah, MD; Yuki Komatsu, MD; Seigo Yamashita, MD; Matthew Daly, MD; Sana Amraoui, MD; Stephan Zellerhoff, MD; Marie-Quitterie Picat, MD; Adam Quotb, PhD; Laurence Jesel, MD; Han Lim, MD; Sylvain Ploux, MD; Pierre Bordachar, MD; Guillaume Attuel, PhD; Valentin Meillet, MSc; Philippe Ritter, MD; Nicolas Derval, MD; Frederic Sacher, MD; Olivier Bernus, PhD; Hubert Cochet, MD; Pierre Jais, MD; Remi Dubois, PhD

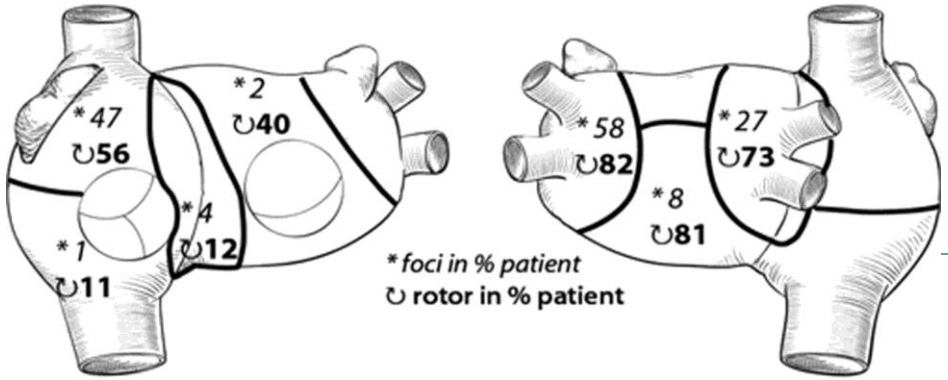
***Background***—Specific noninvasive signal processing was applied to identify drivers in distinct categories of persistent atrial fibrillation (AF).

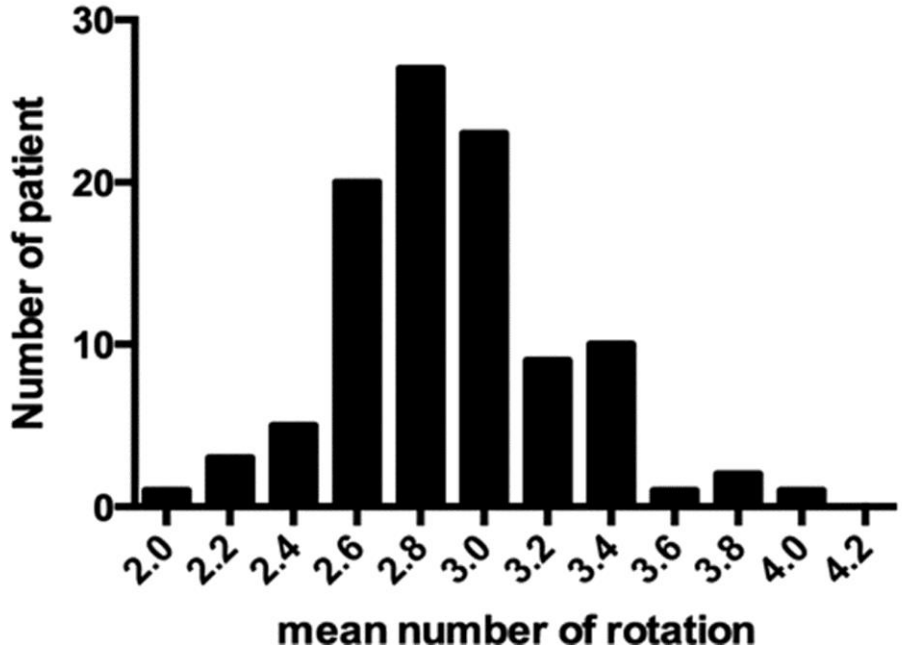
***Methods and Results***—In 103 consecutive patients with persistent AF, accurate biatrial geometry relative to an array of 252 body surface electrodes was obtained from a noncontrast computed tomography scan. The reconstructed unipolar AF electrograms acquired at bedside from multiple windows (duration, 9±1 s) were signal processed to identify the drivers (focal or reentrant activity) and their cumulative density map. The driver domains were catheter ablated by using AF termination as the procedural end point in comparison with the stepwise-ablation control group. The maps showed incessantly changing beat-to-beat wave fronts and varying spatiotemporal behavior of driver activities. Reentries were not sustained (median, 2.6 rotations lasting 449±89 ms), meandered substantially but recurred repetitively in the same region. In total, 4720 drivers were identified in 103 patients: 3802 (80.5%) reentries and 918 (19.5%) focal breakthroughs; most of them colocalized. Of these, 69% reentries and 71% foci were in the left atrium. Driver ablation alone terminated 75% and 15% of persistent and long-lasting AF, respectively. The number of targeted driver regions increased with the duration of continuous AF: 2 in patients presenting in sinus rhythm, 3 in AF lasting 1 to 3 months, 4 in AF lasting 4 to 6 months, and 6 in AF lasting longer. The termination rate sharply declined after 6 months. The mean radiofrequency delivery to AF termination was 28±17 minutes versus 65±33 minutes in the control group ($P<0.0001$). At 12 months, 85% patients with AF termination were free from AF, similar to the control population (87%,); $P$=not significant.

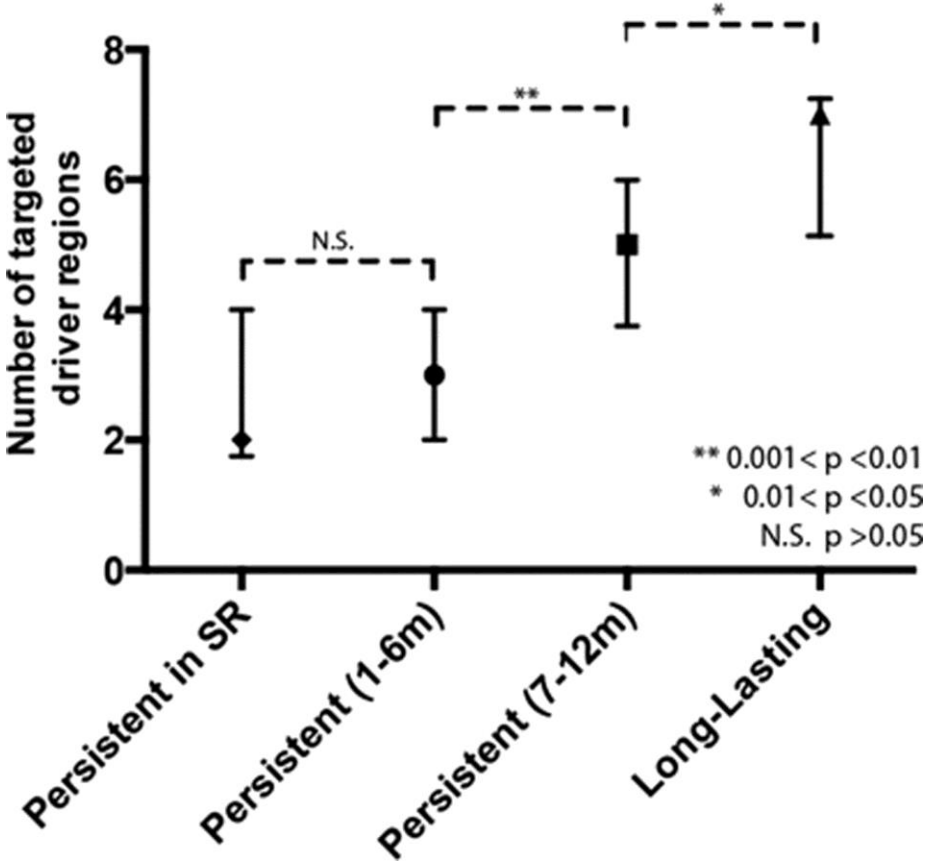
***Conclusions***—Persistent AF in early months is maintained predominantly by drivers clustered in a few regions, most of them being unstable reentries. (***Circulation*. 2014;130:530-538.**)




*Haissaguerre M et al. Circulation. 2014;130:530-538*




*Haissaguerre M et al. Circulation. 2014;130:530-538*

# Rotor ? – Kavramlar -

**Narayan grubu**

**«FIRM (Focal Impulse and Rotor Modulation)»**

- Kararlı AF rotorları
- Fokal kaynaklar

**Haissaguerre grubu**

**«Driver Domains»**

- Kararsız reentry ler
- Fokal kırılma/yayılma bölgeleri

# «Beat-to-beat nonlinear measurement of the repetitiveness of the electrogram morphology»

## Prevalence, Characteristics, Mapping, and Catheter Ablation of Potential Rotors in Nonparoxysmal Atrial Fibrillation

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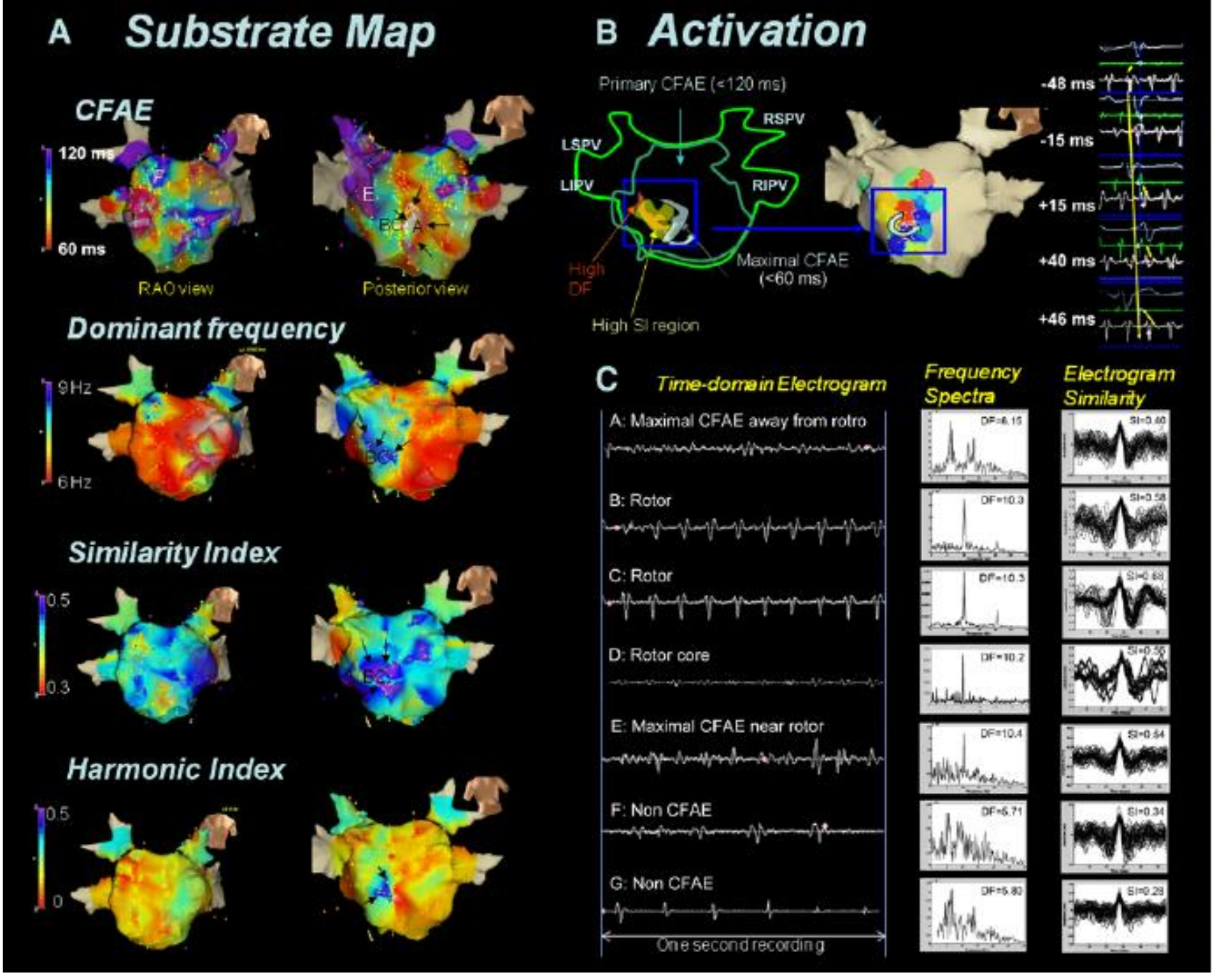
***Background***—Identification of critical atrial substrates in patients with nonparoxysmal atrial fibrillation (AF) failing to respond to pulmonary vein isolation is important. This study investigated the signal characteristics, substrate nature, and ablation results of rotors during AF.

***Methods and Results***—In total, 53 patients (age=55±8), 31 with persistent AF and 22 with long-lasting AF, underwent pulmonary vein isolation and substrate modification of complex fractionated atrial electrograms. Small-radius-reentrant rotors were identified from signal analyses of the dominant frequency and fractionation interval and nonlinear analyses (newly developed, beat-to-beat nonlinear measurement of the repetitiveness of the electrogram morphology >6 seconds). In 15% of the patients, activation maps demonstrated occurrences of rotor-like small-radius reentrant circuits (n=9; 1.1 per patient; cycle length=110±21 ms; diameter=11±6 mm) with fibrillation occurring outside these areas. Rotors were identified by conventional point-by-point mapping and signal analyses and were subsequently eradicated by catheter ablation in these patients. Persistent AF for <1 year, a smaller left atrial size, substrates with higher mean voltages and shorter total activation durations predicted a higher incidence of rotors (all $P<0.05$). In the multivariable model, areas of reentrant circuits exhibited a higher dominant frequency, kurtosis, and higher degree of a beat-to-beat electrogram similarity than areas without or outside the rotors (all $P<0.05$).

***Conclusions***—Rotor-like re-entry with fibrillatory conduction was found in a limited number of patients with nonparoxysmal AF after pulmonary vein isolation. Those areas were characterized by rapid repetitive activity with a high degree of electrogram similarity. (***Circ Arrhythm Electrophysiol.* 2013;6:851-858.**)

**Key Words:** atrial fibrillation ■ atrium ■ catheter ablation ■ electrocardiography ■ mapping


A Substrate Map
CFAE
120 ms
60 ms
RAO view
Posterior view
Dominant frequency
9 Hz
6 Hz
Similarity Index
0.5
0.3
Harmonic Index
0.5
0
B Activation
Primary CFAE (<120 ms)
LSPV
RSPV
LIPV
RIPV
High DF
High SI region
Maximal CFAE (<60 ms)
-48 ms
-15 ms
+15 ms
+40 ms
+46 ms
C
Time-domain Electrogram
Frequency Spectra
Electrogram Similarity
A: Maximal CFAE away from rotro
B: Rotor
C: Rotor
D: Rotor core
E: Maximal CFAE near rotor
F: Non CFAE
G: Non CFAE
One second recording

Original Article

# Noninvasive Localization of Maximal Frequency Sites of Atrial Fibrillation by Body Surface Potential Mapping

Maria S. Guillem, PhD; Andreu M. Climent, PhD; Jose Millet, PhD; Ángel Arenal, MD, PhD; Francisco Fernández-Avilés, MD, PhD; José Jalife, MD; Felipe Atienza, MD, PhD*; Omer Berenfeld, PhD*

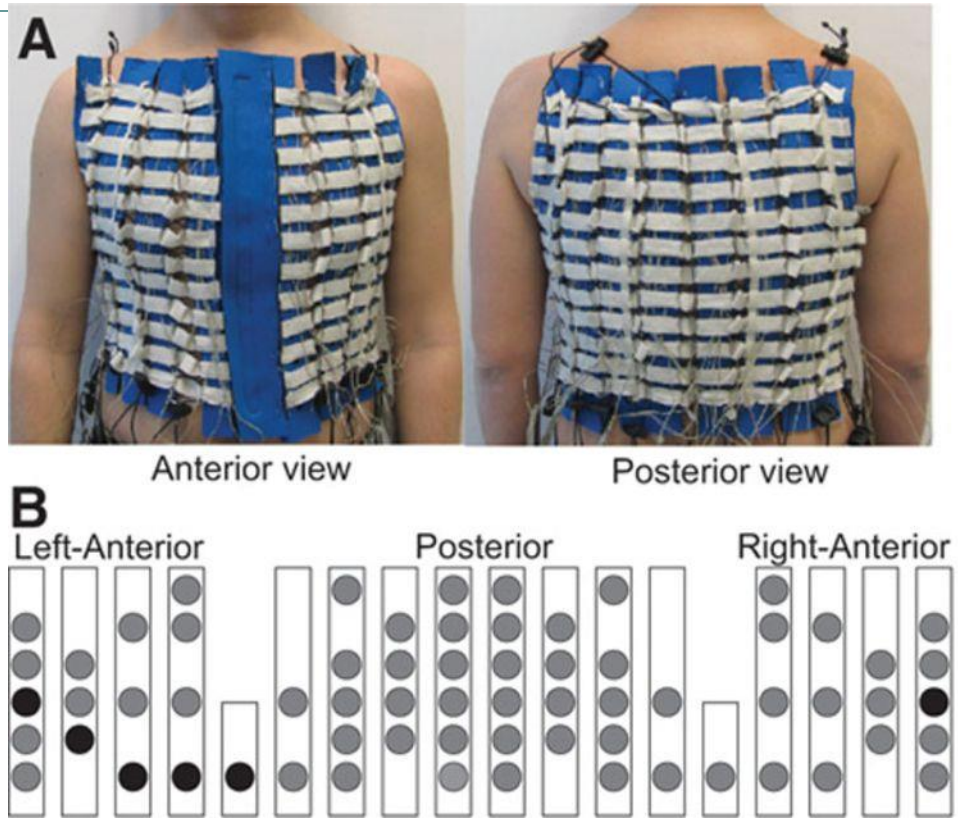
***Background***—Ablation of high-frequency sources in patients with atrial fibrillation (AF) is an effective therapy to restore sinus rhythm. However, this strategy may be ineffective in patients without a significant dominant frequency (DF) gradient. The aim of this study was to investigate whether sites with high-frequency activity in human AF can be identified noninvasively, which should help intervention planning and therapy.

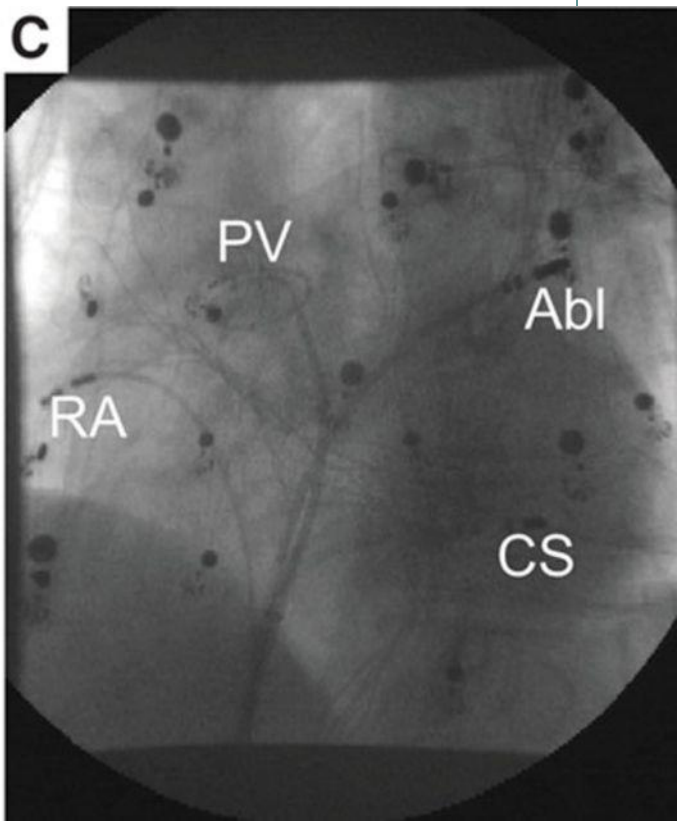
***Methods and Results***—In 14 patients with a history of AF, 67-lead body surface recordings were simultaneously registered with 15 endocardial electrograms from both atria including the highest DF site, which was predetermined by atrial-wide real-time frequency electroanatomical mapping. Power spectra of surface leads and the body surface location of the highest DF site were compared with intracardiac information. Highest DFs found on specific sites of the torso showed a significant correlation with DFs found in the nearest atrium ($\rho$=0.96 for right atrium and $\rho$=0.92 for left atrium) and the DF gradient between them ($\rho$=0.93). The spatial distribution of power on the surface showed an inverse relationship between the frequencies versus the power spread area, consistent with localized fast sources as the AF mechanism with fibrillatory conduction elsewhere.

***Conclusions***—Spectral analysis of body surface recordings during AF allows a noninvasive characterization of the global distribution of the atrial DFs and the identification of the atrium with the highest frequency, opening the possibility for improved noninvasive personalized diagnosis and treatment. (***Circ Arrhythm Electrophysiol*. 2013;6:294-301.**)

**Key Words:** atrial fibrillation ■ body surface potential mapping ■ catheter ablation ■ Fourier analysis

**67 kanallı vücut yüzey elektrodu kaydı**
**15 endokardiyal kayıt**




Guillem M S et al. Circ Arrhythm Electrophysiol. 2013;6:294-301

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doi:10.1093/europace/eut038



# Non-invasive identification of stable rotors and focal sources for human atrial fibrillation: mechanistic classification of atrial fibrillation from the electrocardiogram

**Aled R. Jones[1], David E. Krummen[2,3], and Sanjiv M. Narayan[2,3]***

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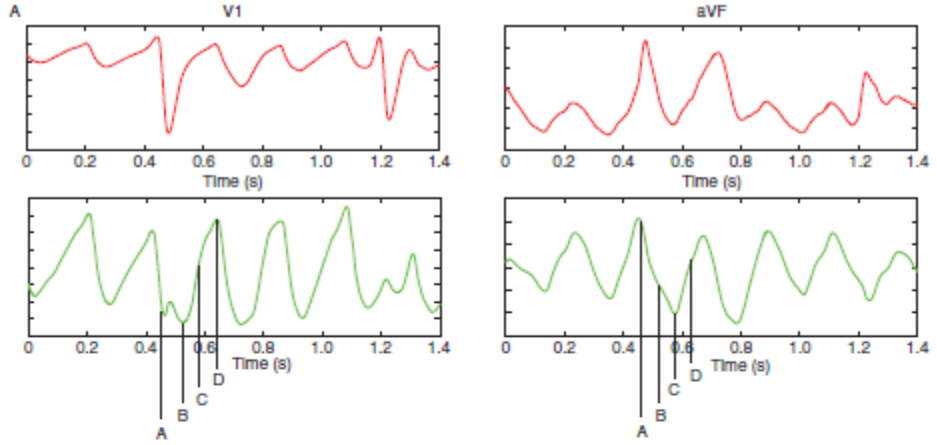
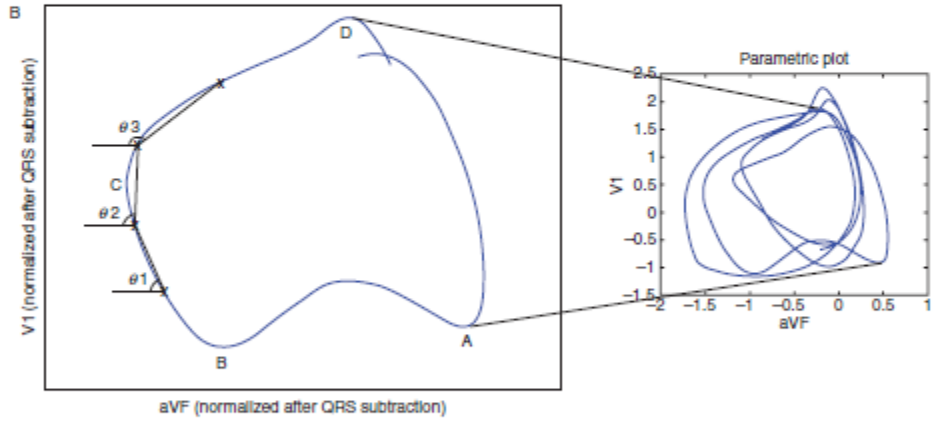
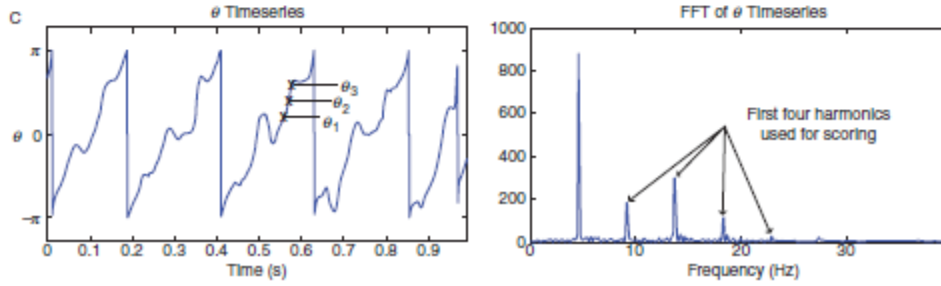
**Aims** To develop electrocardiogram (ECG) tools to quantify the number of sources for atrial fibrillation (AF), i.e. spatially stable rotors and focal impulses, and whether they lie in right or left atrium. Intracardiac mapping has recently shown that paroxysmal and persistent AF is sustained by rotors or focal sources that are stable in location and thus targets for limited ablation [focal impulse and rotor modulation (FIRM)] to eliminate AF. Importantly, the numbers and locations of concurrent sources determine both the complexity of AF and the approach for ablation.

**Methods and results** In 36 AF patients ($n = 29$ persistent, $63 \pm 9$ years) in the CONventional ablation with or without Focal Impulse and Rotor Modulation (CONFIRM) trial, we developed phase lock (PL) to quantify spatial repeatability of ECG 'F-waves' between leads over time. Phase lock spectrally quantifies the angle $\theta$ between F-wave voltages in planes formed by ECG leads I, aVF, and V1 at successive points in time. We compared PL with ECG spectral dominant frequency (DF) and organizational index (OI) to characterize stable rotors and focal sources validated by intracardiac FIRM mapping.



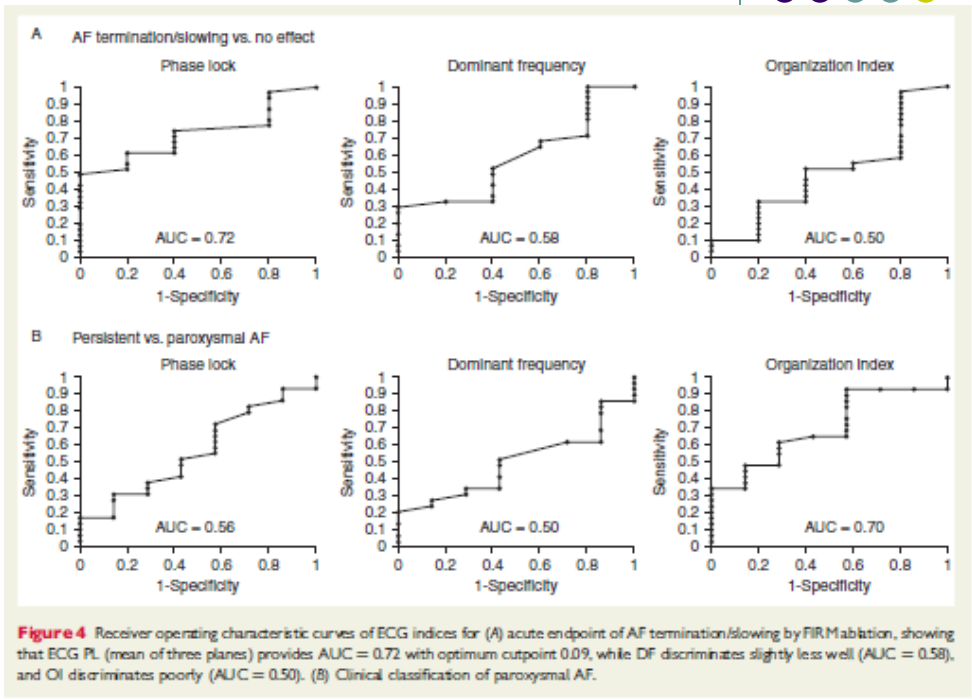




**Figure 4** Receiver operating characteristic curves of ECG indices for (*A*) acute endpoint of AF termination/slowing by FIRM ablation, showing that ECG PL (mean of three planes) provides AUC = 0.72 with optimum cutpoint 0.09, while DF discriminates slightly less well (AUC = 0.58), and OI discriminates poorly (AUC = 0.50). (*B*) Clinical classification of paroxysmal AF.

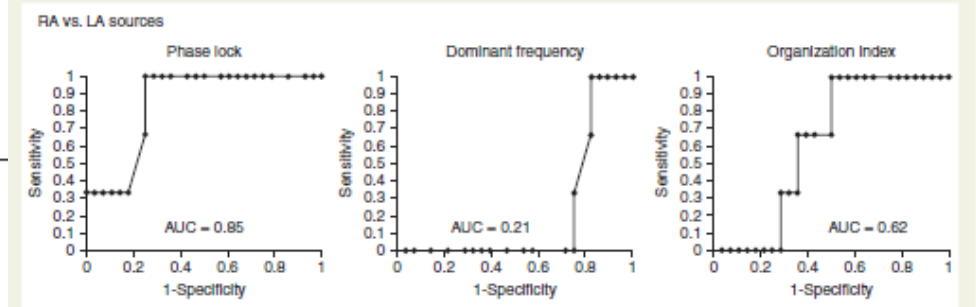



**Figure 5** Electrocardiogram PL identifies RA from LA primary AF sources (where FIRM terminated or substantially organized AF). (*A*) Mean PL in any plane provided AUC = 0.85; by comparison, plane of mean, (*B*) DF, and (*C*) OI are less predictive.

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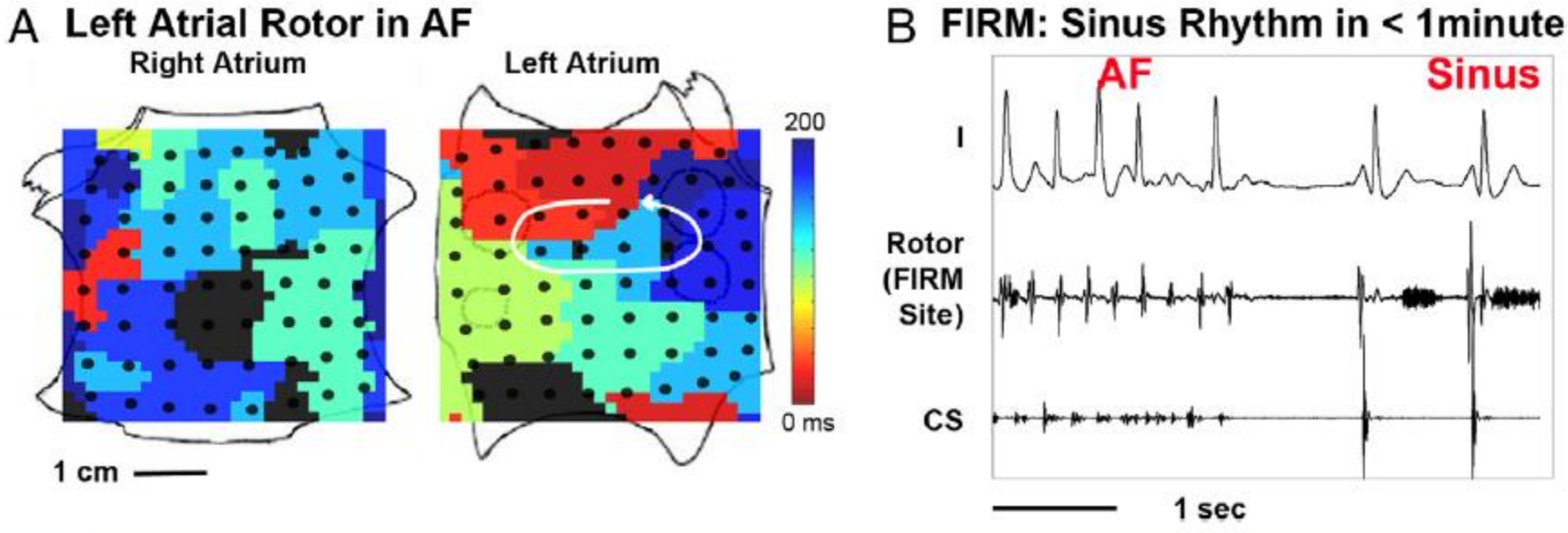



**Figure 2** Acute Termination of AF to Sinus Rhythm By FIRM Ablation

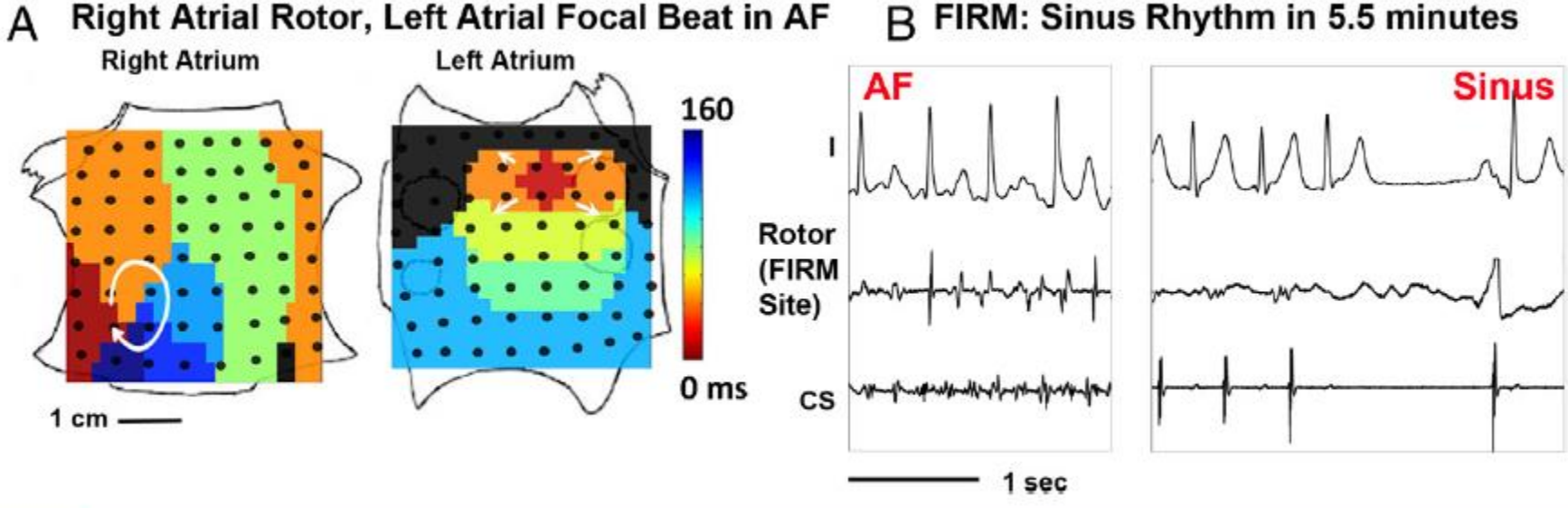



**Figure 3** Acute Termination of AF, 2 Sources, to Sinus Rhythm by FIRM Ablation

# Rotor - Karşıt görüş ?!

**«Wishful thinking or scientific fact?»**

- «*Narayan & Jalife (2014) tarafından öne sürülen 'kararlı rotor' fikri temelde Narayan ve ark. nın çalışmalarına dayanır !*»
  - Narayan TOPERA'nın mucididir !
  - TOPERA bir yazılım ile, basket kateterle elde edilmiş olan görece az sayıda düşük rezolusyonlu sinyali işleyerek bilgi verir

- «*Yüksek rezolusyonlu haritalama teknikleri kararlı rotorları gösterememiştir !*»
  - Allessie *et al*. 2010; de Groot *et al.* 2010; Lee *et al*. 2014

- *«Yürütücü rotorların elektrogram kanıtları yoktur!»*

- «*Panaromik bakış» ile elde edildiği söylenen, atriyumu düzensizce yöneten büyük tek bir rotor yüksek rezolusyonlu haritalamada çok ender saptanıyor* !»

- «*Düşük yoğunluklu kayıt mı kompleksiteyi kaçırıyor yoksa yüksek yoğunluklu haritalama mı fazlaca ayrıntıya gömülüyor* ?»

*M Allessie and N de Groot . CROSSTALK. J Physiol 592.15 (2014) p 3173 3173*

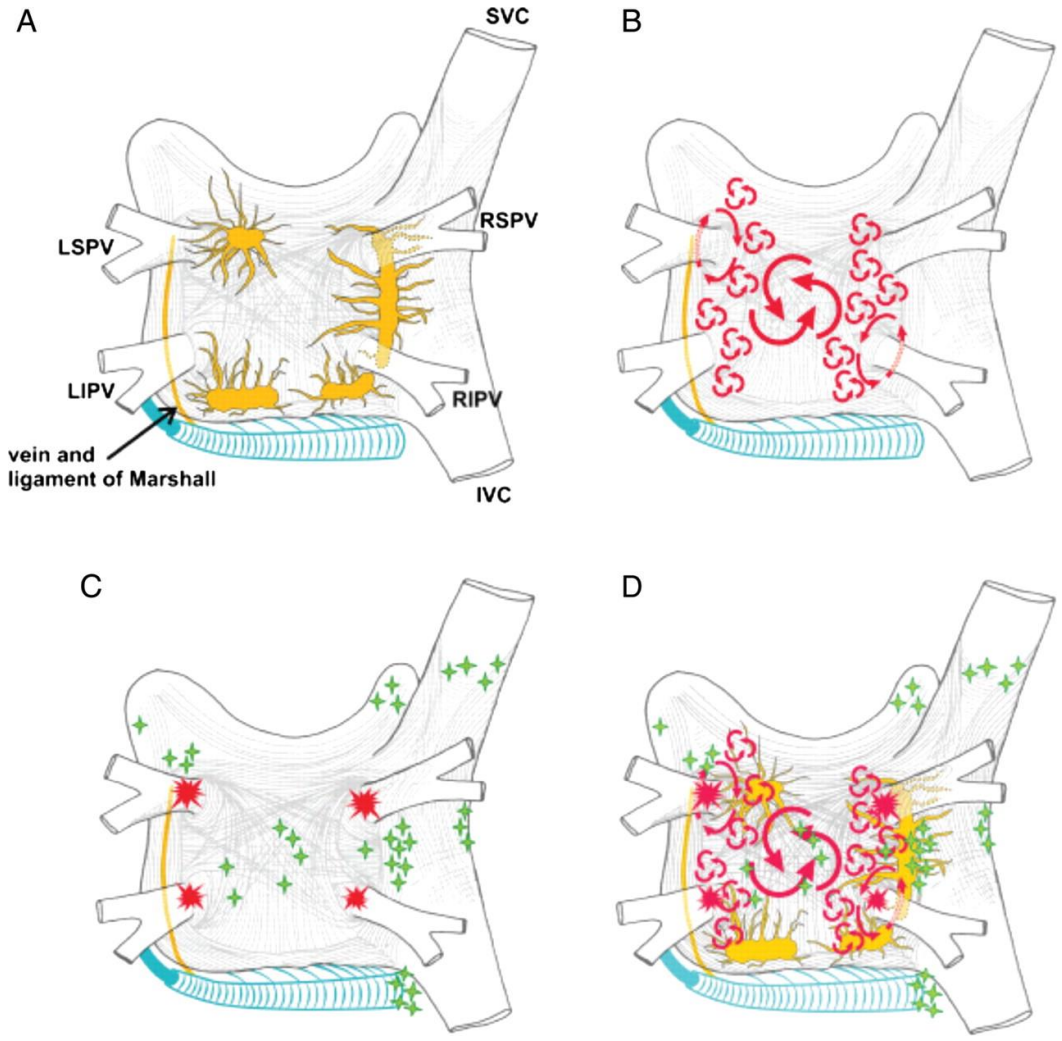
# AF'nin mekanizmaları

## Bundan sonrası ?

- PAF için  çoğunlukla önemli olan «ektopik odaksal deşarjlar» !
  - Anormal otomatizma mı ?  Mikroreentry mi ?
- Reentry
  - Yüksek hızlı elektriksel girdaplar biçiminde reentry ? (**Rotorlar** !)
    - Deneysel kanıtlar !
  - Tüm AF tiplerinde var mı ?
- ***Deneysel çalışmaların açıkları (Yeni araştırma alanları ?)***
  - Altta yatan hastalıkların rolü ?
    - HT
    - Kalp Yet.
    - KAH
  - Dejeneratif süreç (İnflamasyon – Fibrozis) ve Biçimlenme ?
    - Altta yatan hastalıkların ilerlemesiyle ?
    - Yaşlanma ?
    - AF'nin nedeni ? / sonucu ?

*Jalife J Cardiovasc Res 2011;89:766-775*

# AF’nin mekanizmaları




Calkins H et al. Europace 2012