

Persistan AF'de Mekanizmalar (Rotor, Multiple Wavelet, Endo/Epi Activation)

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Samsun

AF Mekanizmaları

Bilinenler

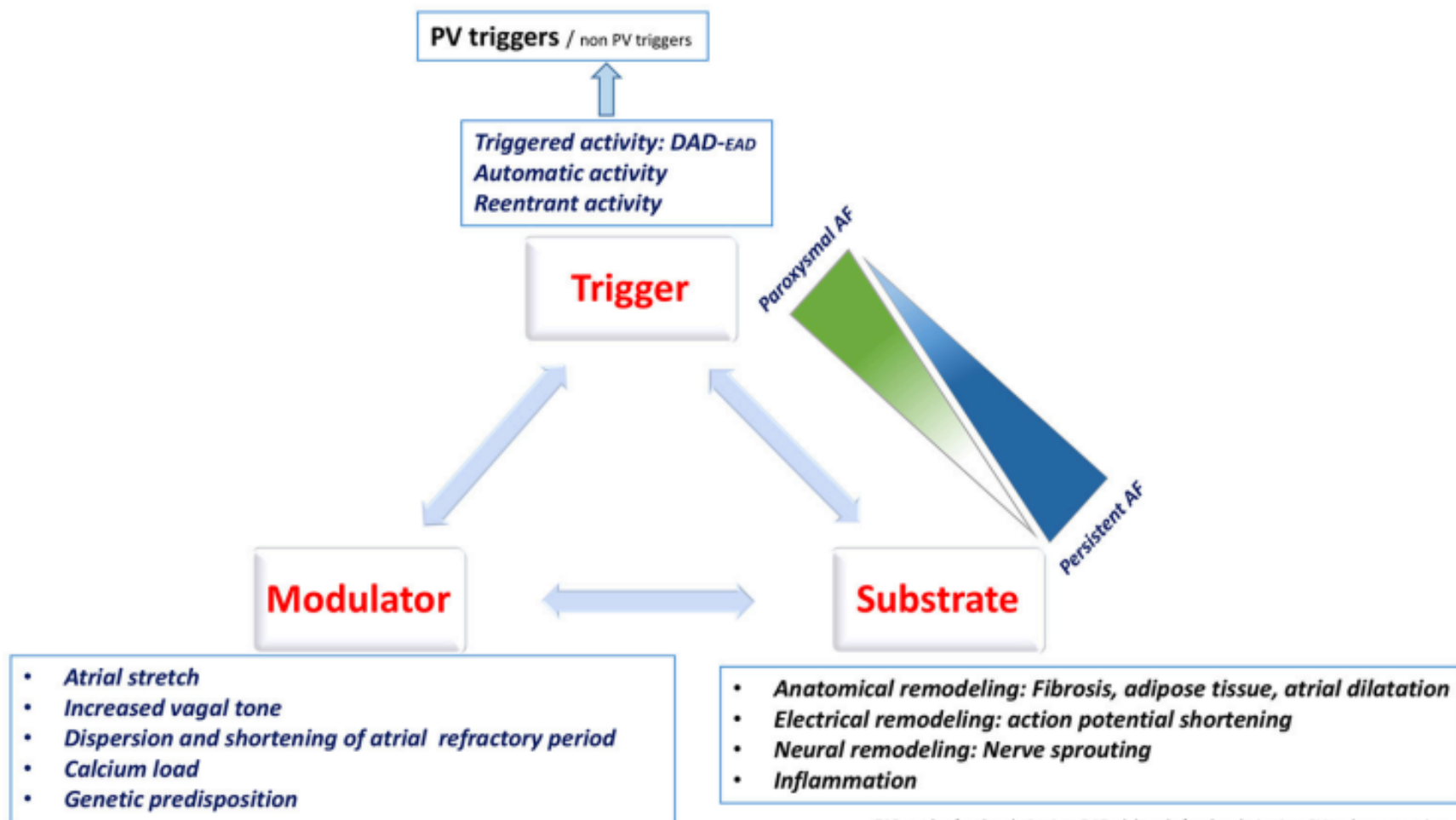
Bilinmeyenler



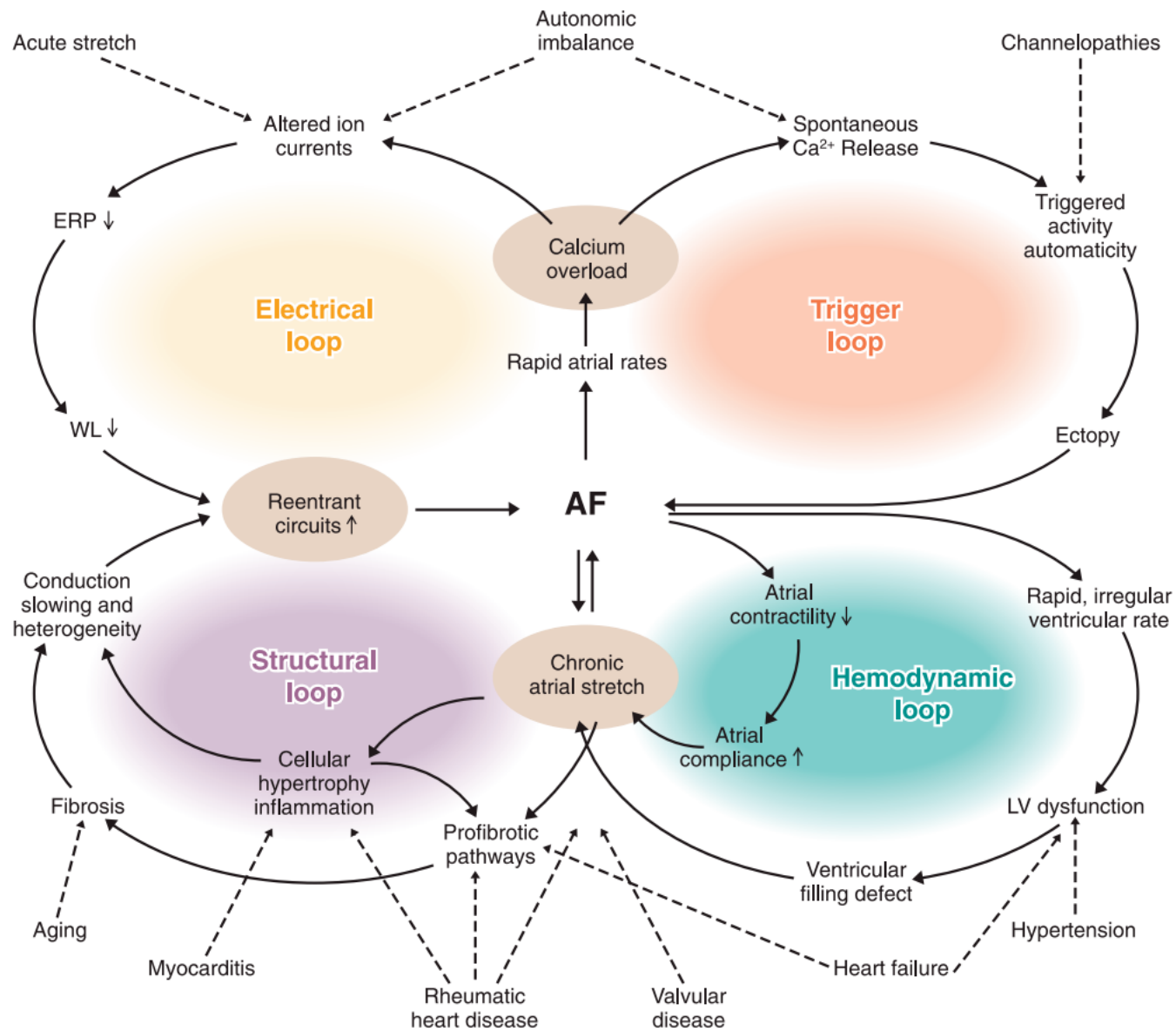
Atrial Fibrilasyon

- AF heterojen bir aritmi
- Mekanizması halen tam anlaşılabilmiş değil
- Tetikleyiciler– başlangıç
- Substrat – devam
- İyonik ve anatomik remodeling
- Genetik predispozisyon
- Nöro-humoral etkenler
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AF Patofizyolojisi



EAD: early afterdepolarization, DAD: delayed afterdepolarization, PV: pulmonary veins



SPONTANEOUS INITIATION OF ATRIAL FIBRILLATION BY ECTOPIC BEATS ORIGINATING IN THE PULMONARY VEINS

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AND JACQUES CLÉMENTY, M.D.

ABSTRACT

Background Atrial fibrillation, the most common sustained cardiac arrhythmia and a major cause of stroke, results from simultaneous reentrant wavelets. Its spontaneous initiation has not been studied.

Methods We studied 45 patients with frequent episodes of atrial fibrillation (mean [$\pm$ SD] duration, 344 ± 326 minutes per 24 hours) refractory to drug therapy. The spontaneous initiation of atrial fibrillation was mapped with the use of multielectrode catheters designed to record the earliest electrical activity preceding the onset of atrial fibrillation and associated atrial ectopic beats. The accuracy of the mapping was confirmed by the abrupt disappearance of triggering atrial ectopic beats after ablation with local radio-frequency energy.

Results A single point of origin of atrial ectopic beats was identified in 29 patients, two points of origin were identified in 9 patients, and three or four points of origin were identified in 7 patients, for a to-

mal atrial-tissue substrate.⁴⁻⁸ Complex approaches have been developed to interrupt wavelets, including extensive surgical or, recently, catheter-mediated atriotomy.⁹⁻²¹ There are, however, no data about the spontaneous initiation of atrial fibrillation. The triggers of atrial fibrillation may be focal targets for ablative therapy. We investigated the mode of initiation of spontaneous paroxysms of human atrial fibrillation by atrial ectopic beats, the characteristics of these triggering beats, and the effects of local ablation with radio-frequency energy.

METHODS

Characteristics of the Patients

The study population consisted of 45 patients enrolled consecutively (Table 1) who met the following criteria: the patient had to have atrial fibrillation resistant to more than two drugs, there had to be at least one episode of atrial fibrillation every two days, the patient had to be receiving anticoagulant treatment, the pa-

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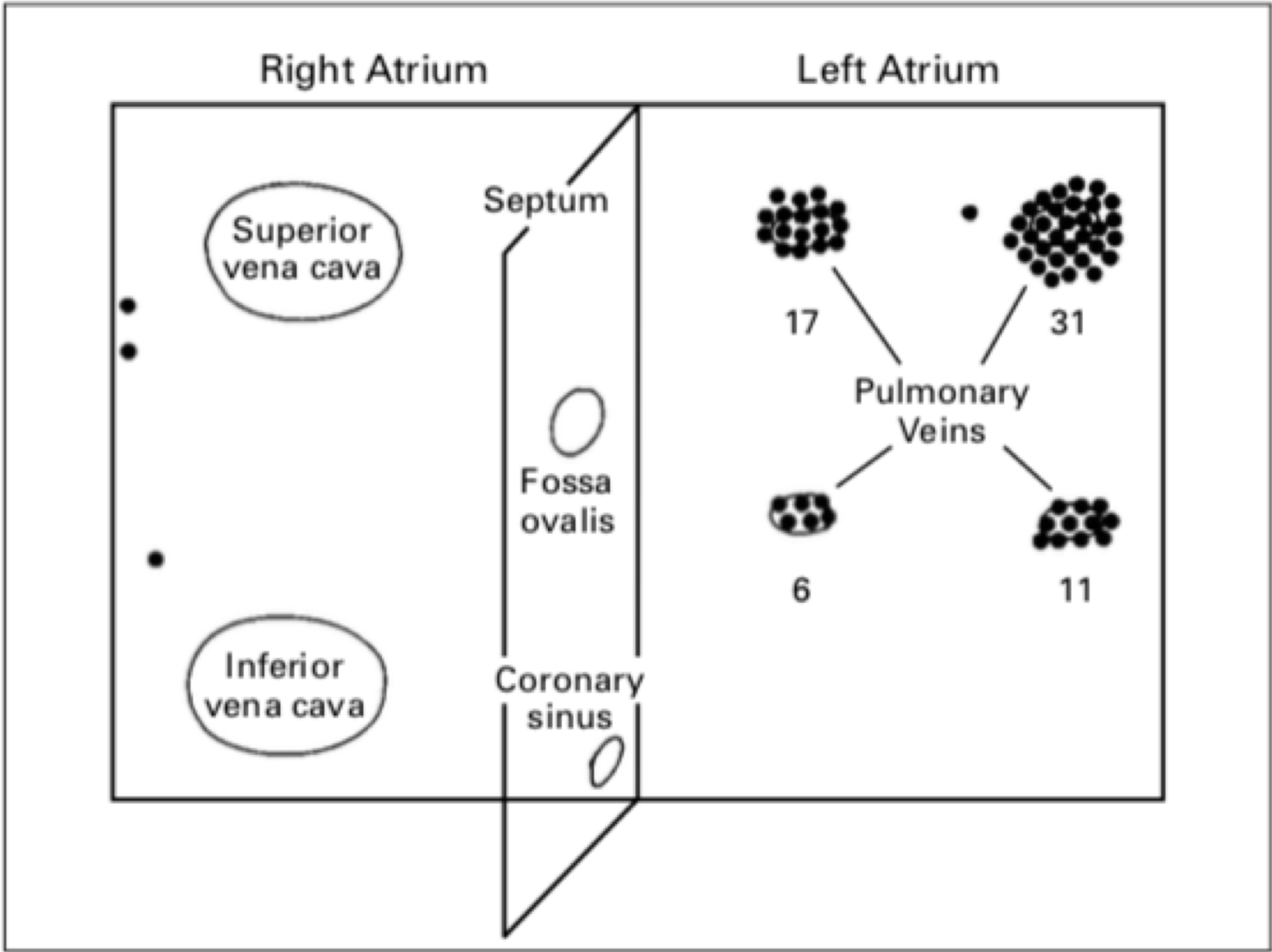
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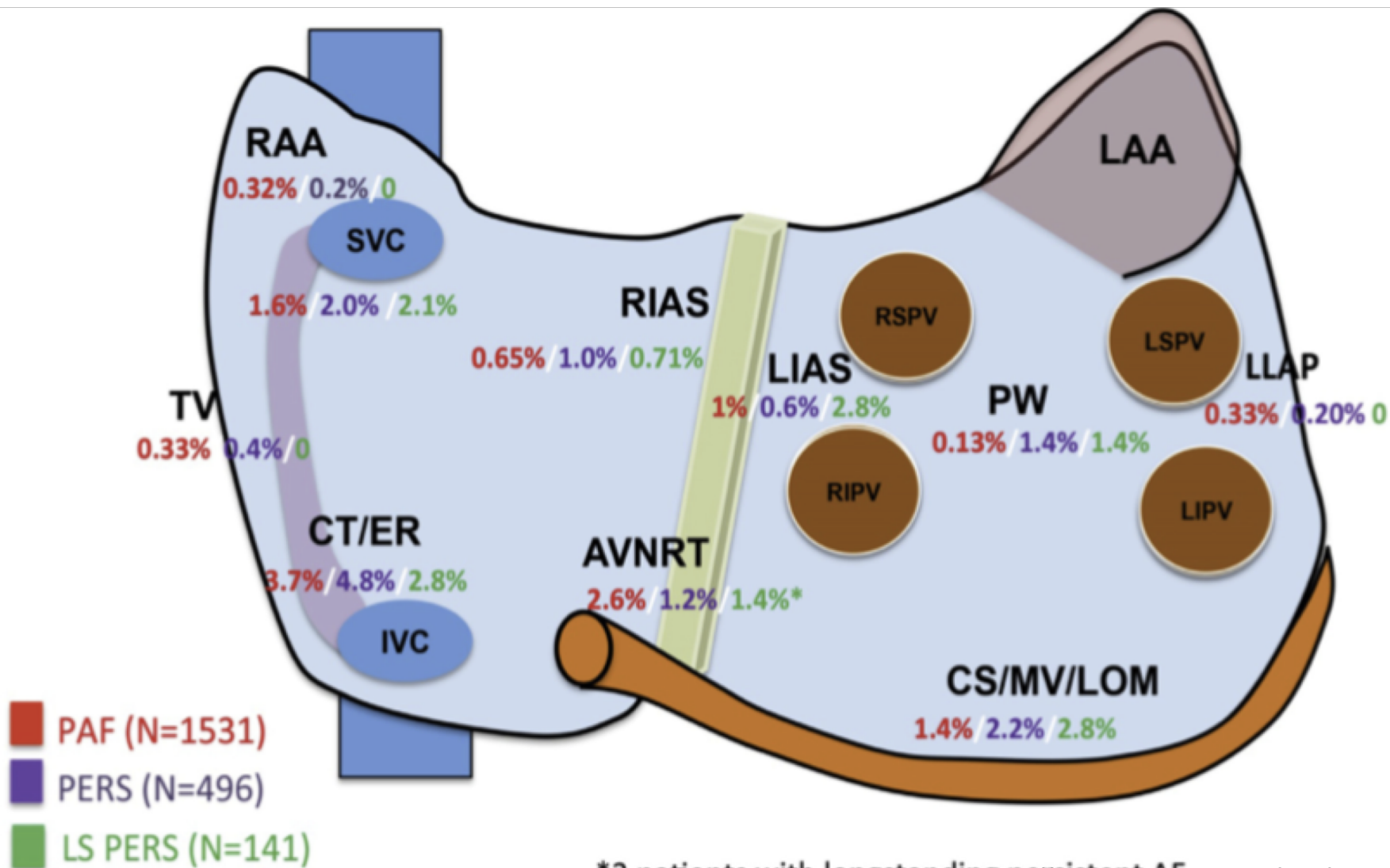
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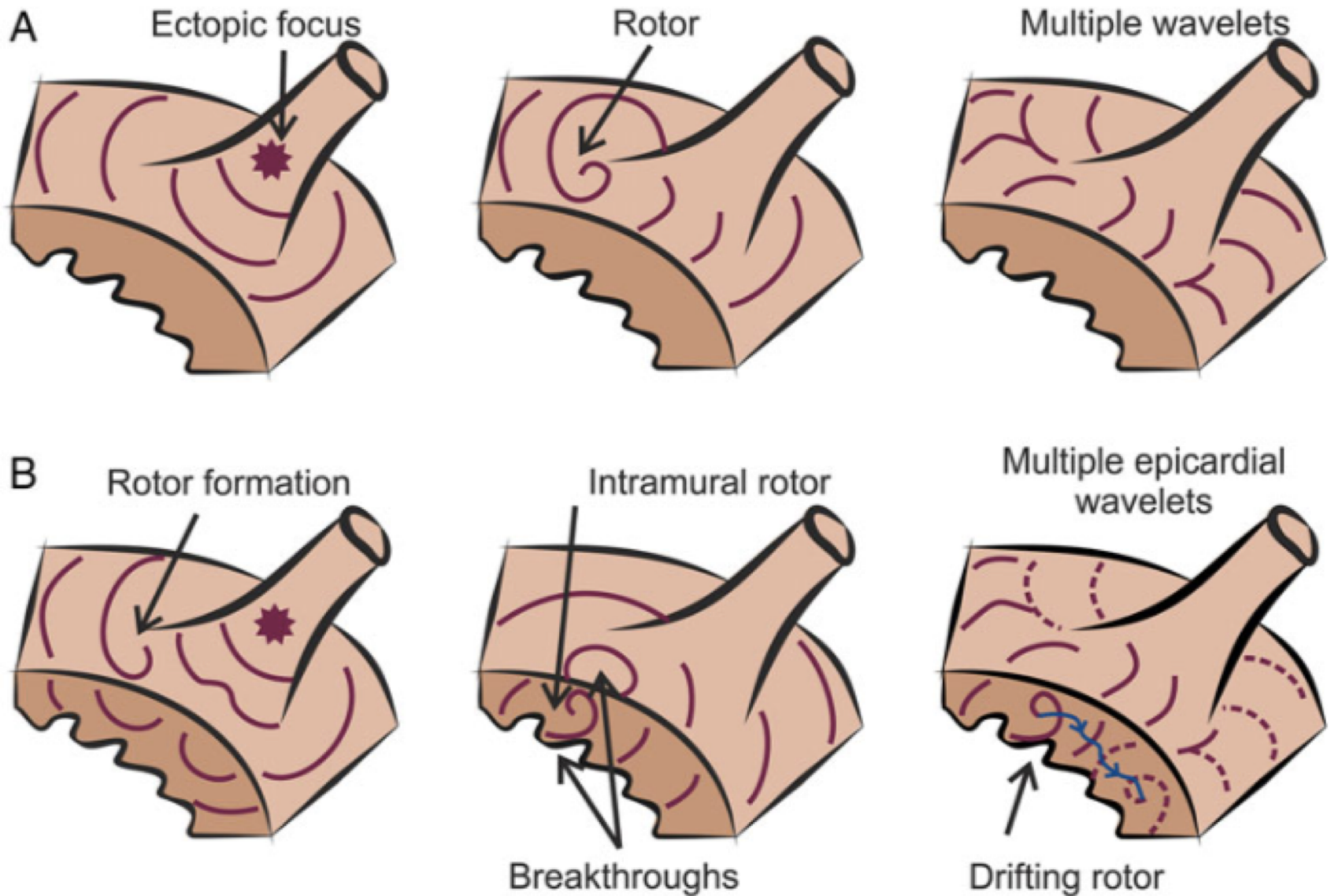
had to be at least one episode of atrial fibrillation every two days, the patient had to be receiving anticoagulant treatment, the pa-

PV-dışı tetikleyiciler



*2 patients with longstanding persistent AF
Santangeli et al. Heart Rhythm 2016

Persistan AF Mekanizmalar



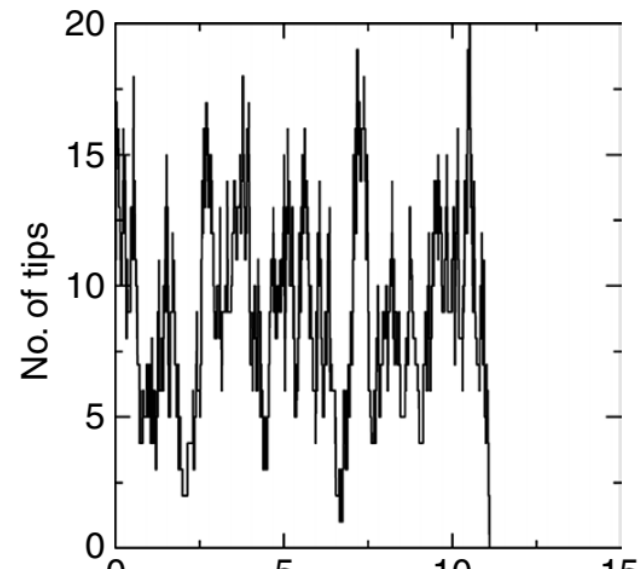
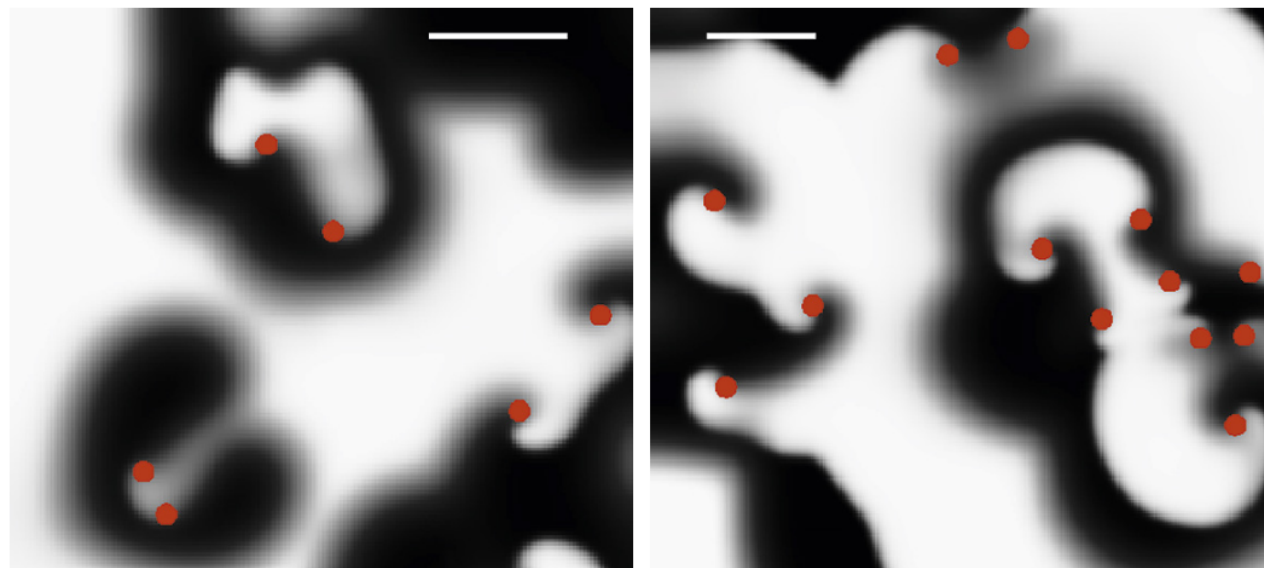
Multiple Wavelet – Çoklu Dalgacık Hipotezi

- Moe tarafından tanımlandı
- Eşzamanlı çoklu atrial reentran halkalar
- Başlatan ve devam ettiren farklı faktörler
- Atrial fibrilasyonun devamı için
 - Reentran halka sayısı
 - Atrial substrat → Atriyum boyutları, kütlesi, ileti hızı ve doku refrakterlik süresi

Multiple Wavelet – Çoklu Dalgacık Hipotezi

- Atriyum boyunca yayılan çoklu dalgalar , parçalanarak (wavebreak) yeni dalgacıklar oluşturuyor
- Teorik olarak dalgaların sayısı kritik seviyenin üzerinde kaldıkça AF devam ediyor

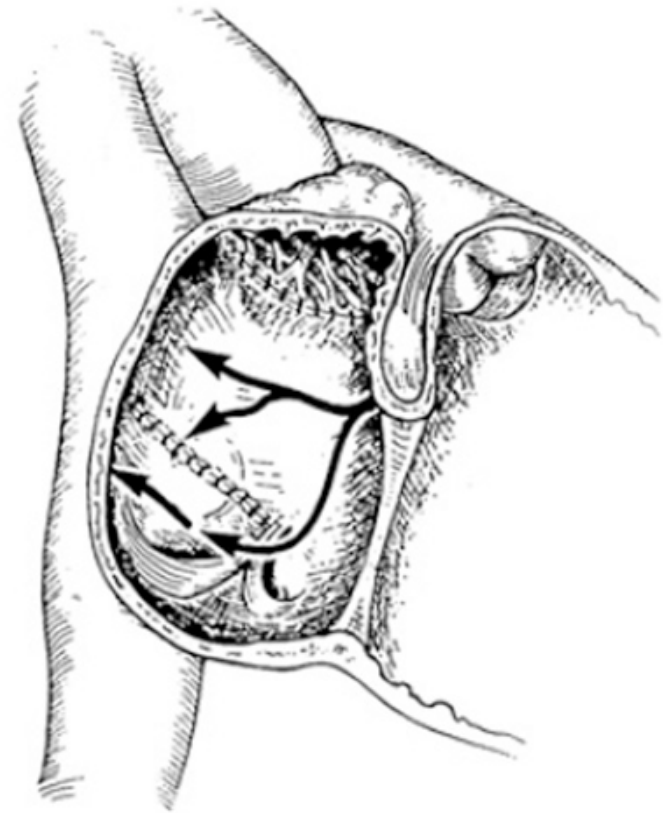
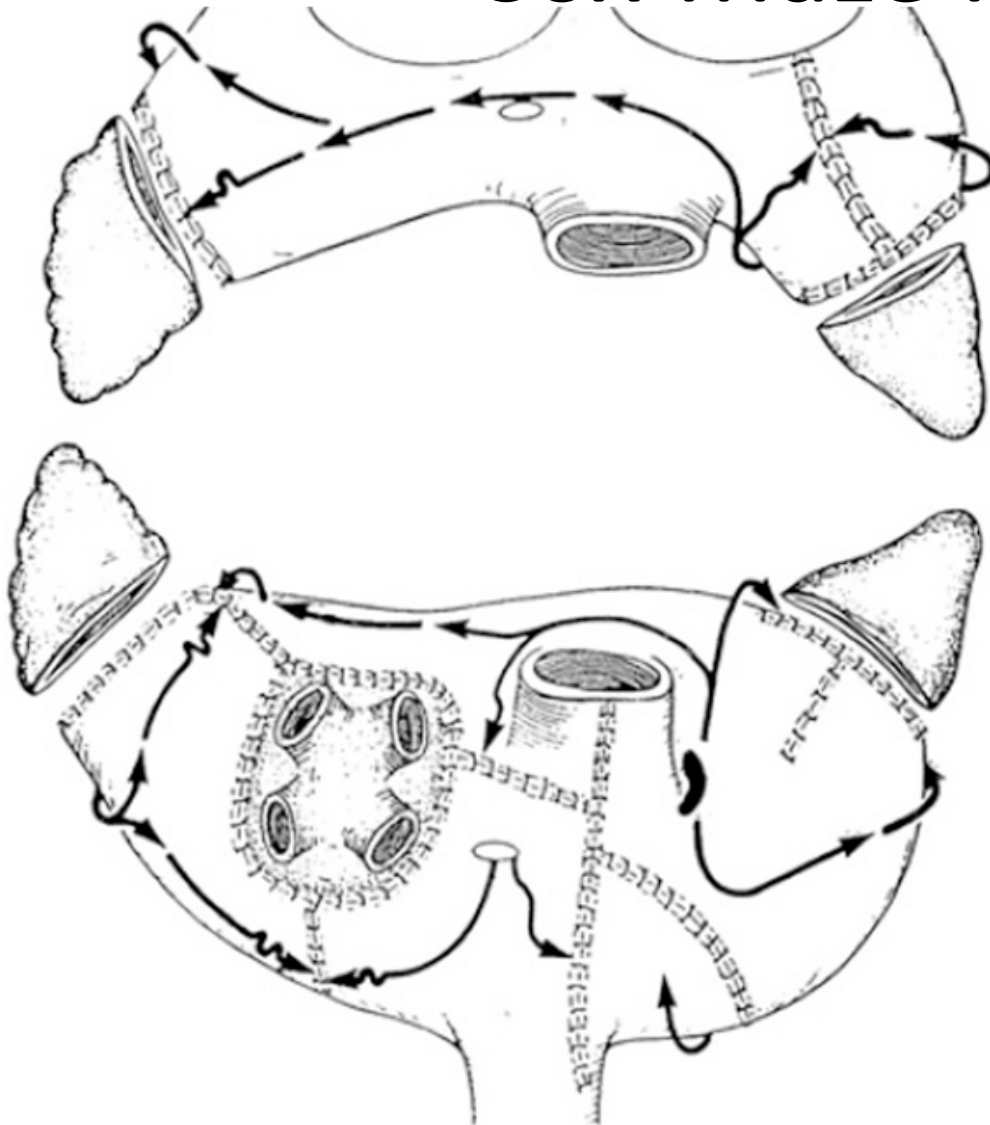
Multiple Wavelets



Deneyisel Modeller

- Allesie hayvan modellerinde AF'nin devamı için eşzamanlı 4-6 reentran halkanın yeterli
- Wang-Antiaritmik ilaçlar reentran halkaların sayısını azaltarak AF terminasyonu sağlıyor
- Cox → Cerrahi maze işleminin çok sayıda, küçük ve elektriksel olarak izole atriyal kompartman oluşturarak reentriyi önlemesi

Cox-Maze III işlemi



Dynamics of wavelets and their role in atrial fibrillation in the isolated sheep heart

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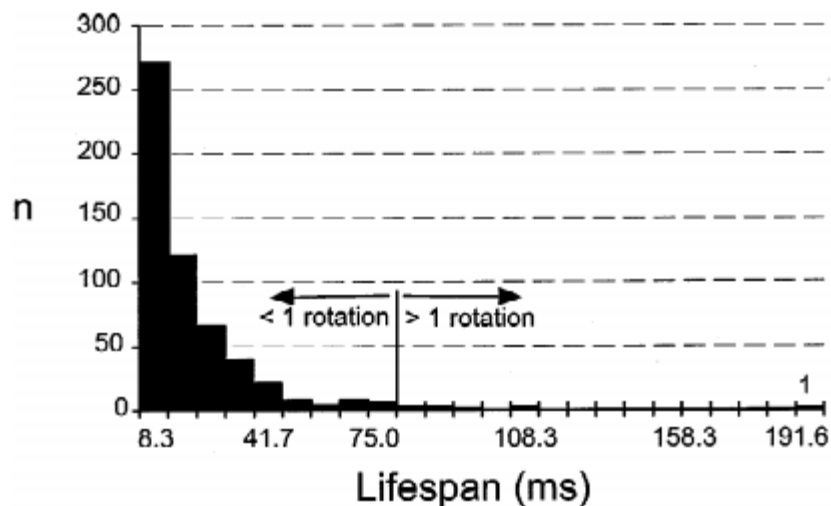
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Received 6 December 1999; accepted 28 June 2000



5. Conclusion

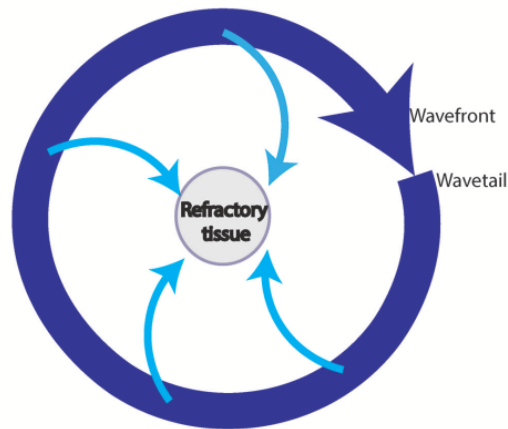
The limitations outlined above, notwithstanding, results from this study suggest that multiple wavelets are not critical for the maintenance of the arrhythmia, but instead, are the product of high frequency waves ‘breaking’ as they propagate through heterogeneous atrial tissue. At least in our model, random reentry of multiple unstable wavelets is not necessary to maintain AF. A single or small number of relatively stable ongoing reentry circuits generating high frequency waves can provide the ‘engine’ to generate numerous wavebreaks and wavelets that characterize fibrillatory conduction and AF in the isolated sheep heart.

Localized Drivers - Yerleşik Kaynak (Köken) Hipotezi

- Hiyerarşik elektriksel bir organizasyon içerisinde yerleşik kaynakların sürdürdüğü dizorganize elektriksel aktivite
- Hansen'e göre AF, yerleşik kaynakların hızlı tekrarlayan aktivitelerinin atriya yayılarak parçalanması sonucu ortaya çıkan fibrilatuar iletimin sonucu

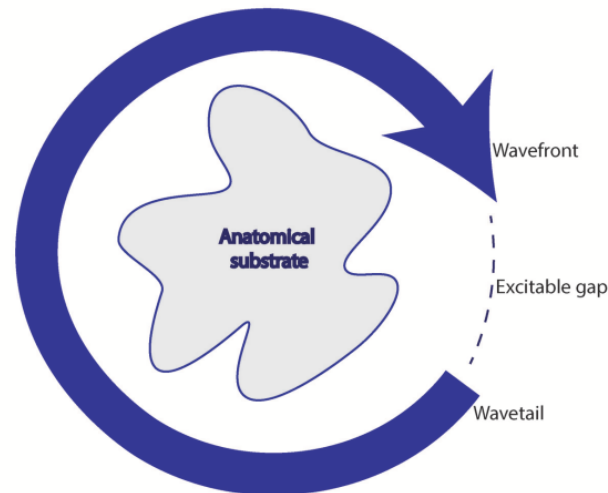
Localized Drivers

Functional reentry



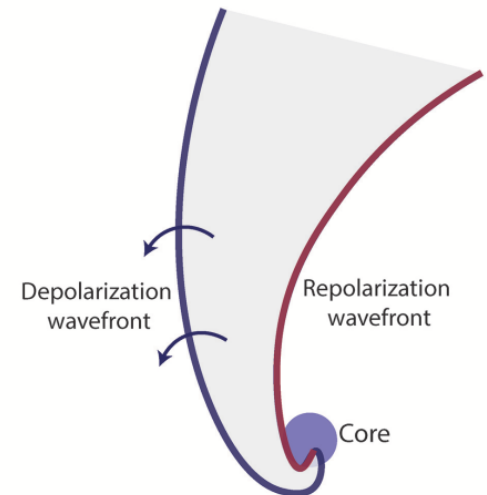
- 1- Length of circuit determined by conduction velocity and refractory period
- 2- Length of the circuit can change with alterations in the electrophysiological properties
- 3- No gap of full excitability (at the smallest circuit)
- 4- Shortcut of the circuit possible
- 5- Revolution time proportional to refractory period

Anatomical reentry



- 1- Length of the circular pathway determined by the perimeter of the anatomic obstacle
- 2- Length of the circular pathway fixed
- 3- Excitable gap between wavefront and the wavetail (dashed line)
- 4- Impulse can not shortcut the circuit
- 5- Revolution time inversely related to the conduction velocity

Spiral wave reentry



- 1- The point at which the depolarization and the repolarization curves meet has an undefined voltage state and is usually referred to as the phase singularity point.
- 2- Curvature of the depolarizing wavefront modulates the propagation velocity
- 3- Wave-tip trajectories can be circular or meandering

Leading Circle Modeli

- Allesie 1977
- Tek yönlü dairesel olarak hareket eden bir dalga cephesinin dairenin merkezinde neden olduğu sabit aktivasyonun bu merkezi daima refrakter hale getirmesi
- Merkezdeki bu refrakter bölge skar dokusuna benzer şekilde reentrinin devamını sağlayan fonksiyonel bir bariyer oluşturur

- Bu modelde, dokudaki tek yönlü blok bir uyarının tek yönlü dairesel hareketi başlatmasını sağlar
- Bu uyarı aynı anda dışa doğru hareket ederek çevre myokardı aktive ederken bir yandan da dairenin merkezini aktive eder

Leading Circle Model

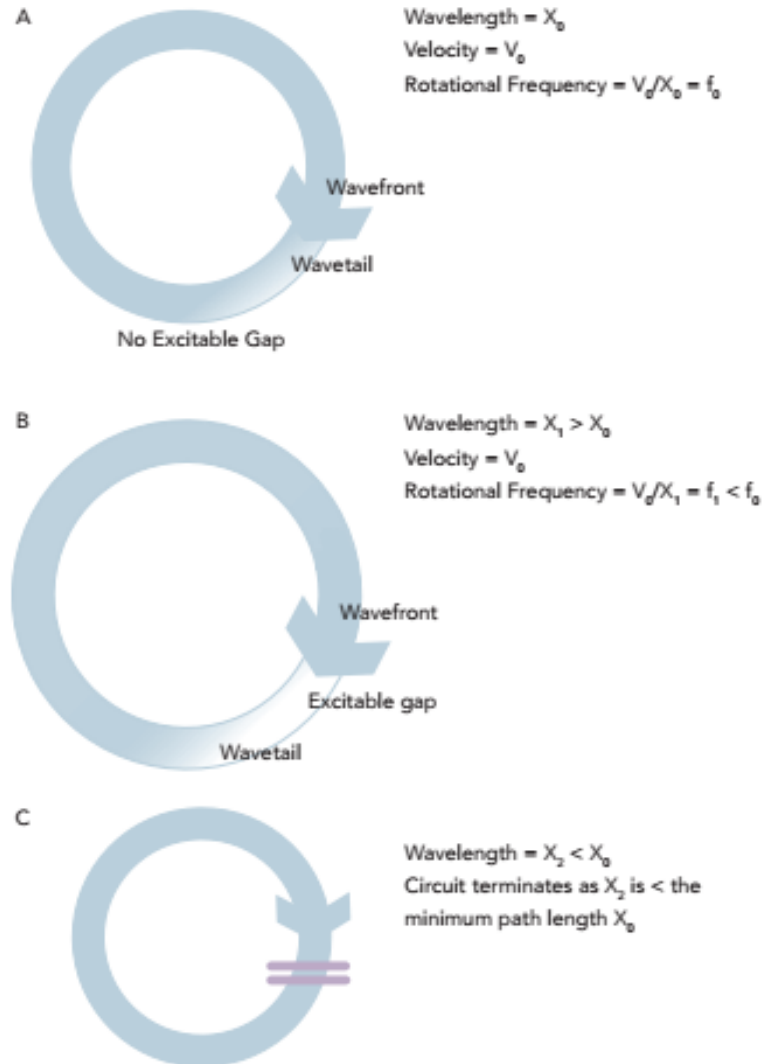
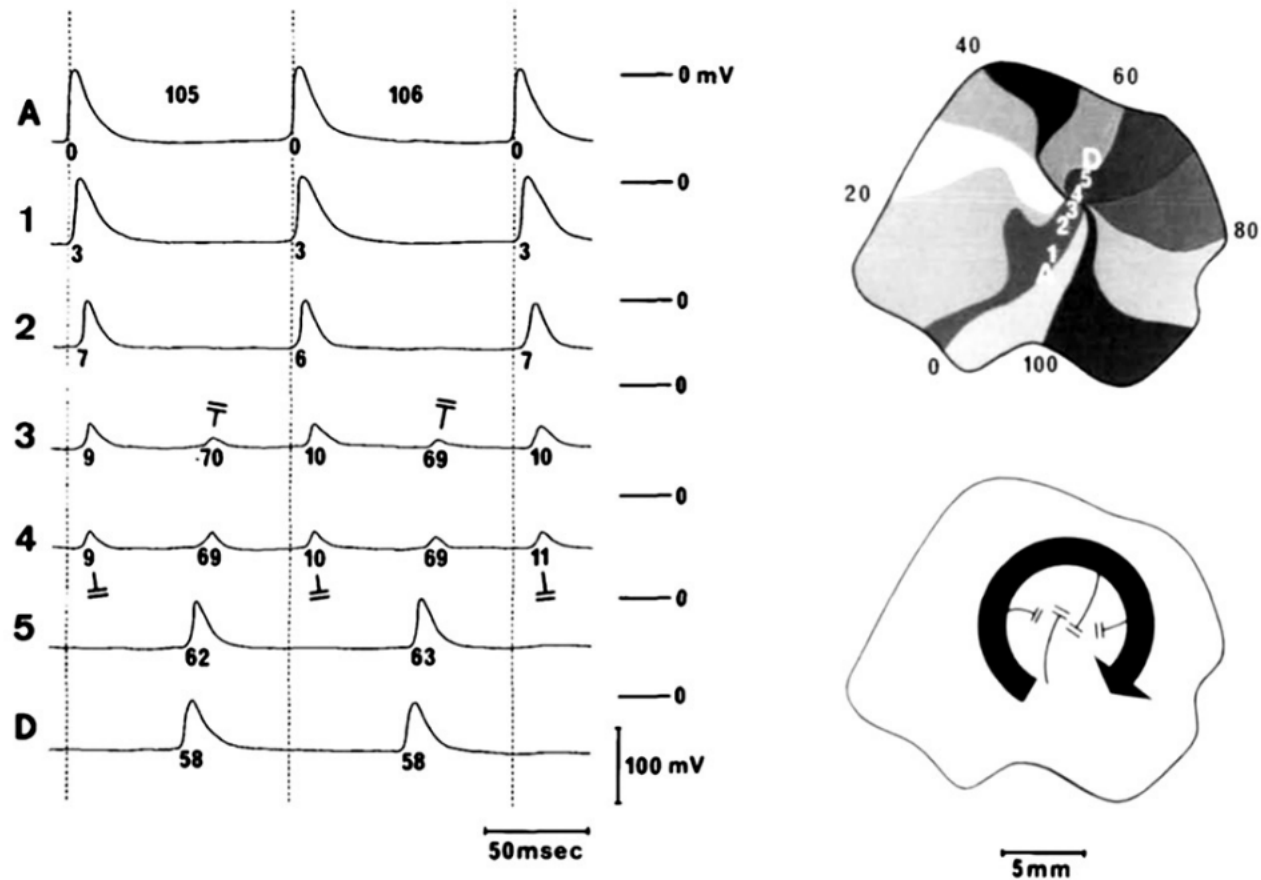
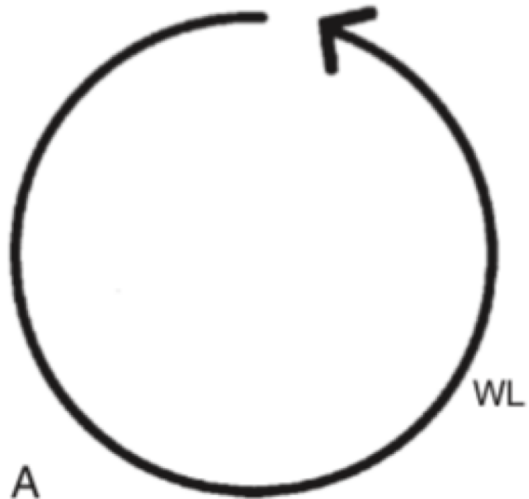


Figure 3: Experimental Evidence of Leading Circle Reentry



Membrane potentials located in a straight line (A through D) through a clockwise reentrant circuit in atrial tissue with a cycle length of 105 milliseconds. Fibres 3 and 4, which are located in the centre of the circle, are activated twice as often, but they do not reach normal amplitude and cannot propagate out of the centre of the circuit, rendering it functionally unexcitable because the tissue is continually depolarised. Reproduced with permission from Allesie et al.¹⁶

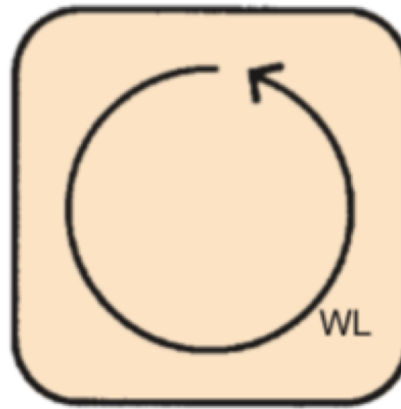


A

Wavelength (WL) =
refractory period x
conduction velocity

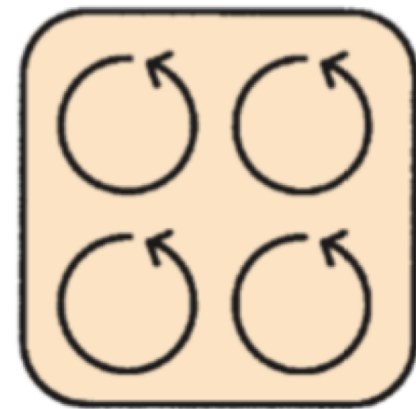
- minimal path length
for re-entry
- size of of functional re-entry
circuits (leading circle theory)

B



Normal atrial size
Normal WL
- AF not sustained

C



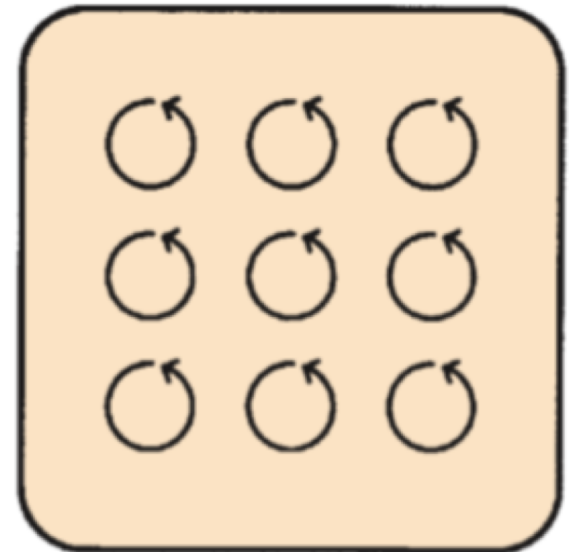
Normal atrial size
Short WL
- AF sustained

D



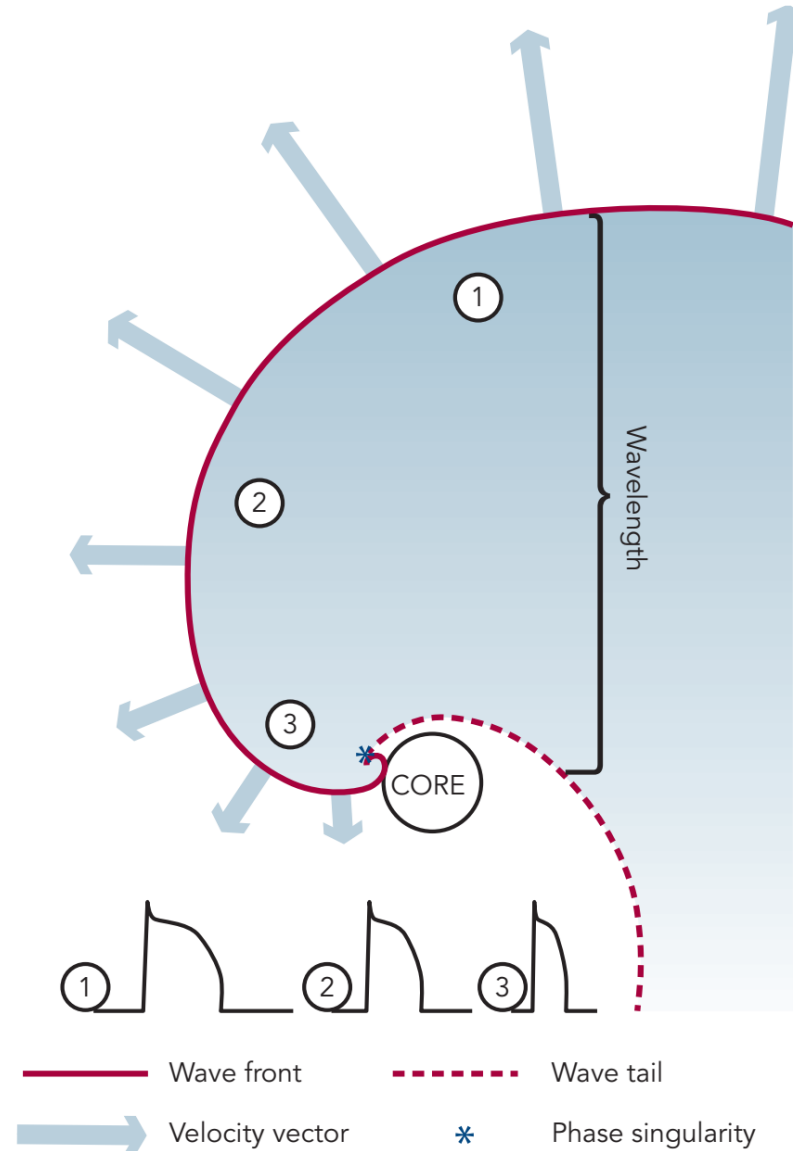
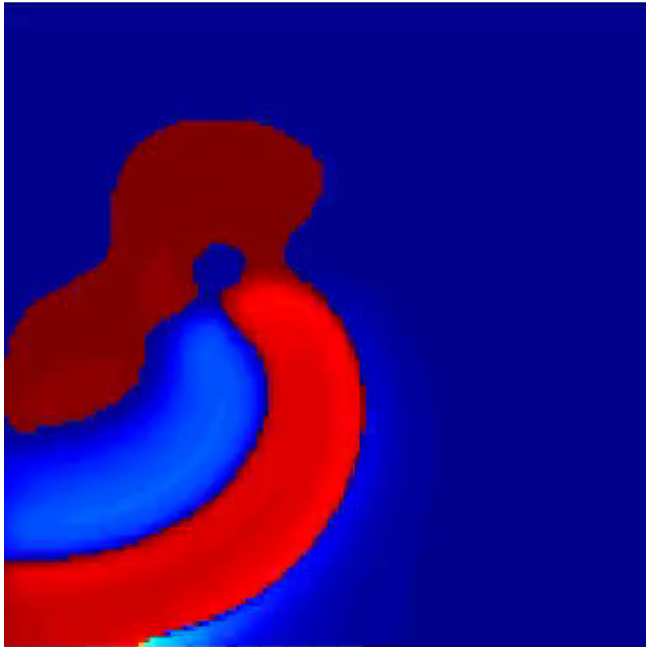
Drug-induced
WL ↑
- AF terminated

E



Enlarged atrium
Short WL
- AF very stable

Spiral Dalga Reentransi - Rotor



Rotor

- Rotor sabit bir akım kaynağı - gider uyumsuzluğu sayesinde hareket eder
- Bazı özel koşullarda farklı kompleks şekillerde hareket eder ve bu da rotorun hareket davranışları ve devamlılığında önemli etkileri vardır.
- Rotordaki PS'den uzaktaki bölgeler arasındaki gradientlerin oluşturduğu heterojen ileti özellikleri rotorun spiral şeklini korumasını sağlar

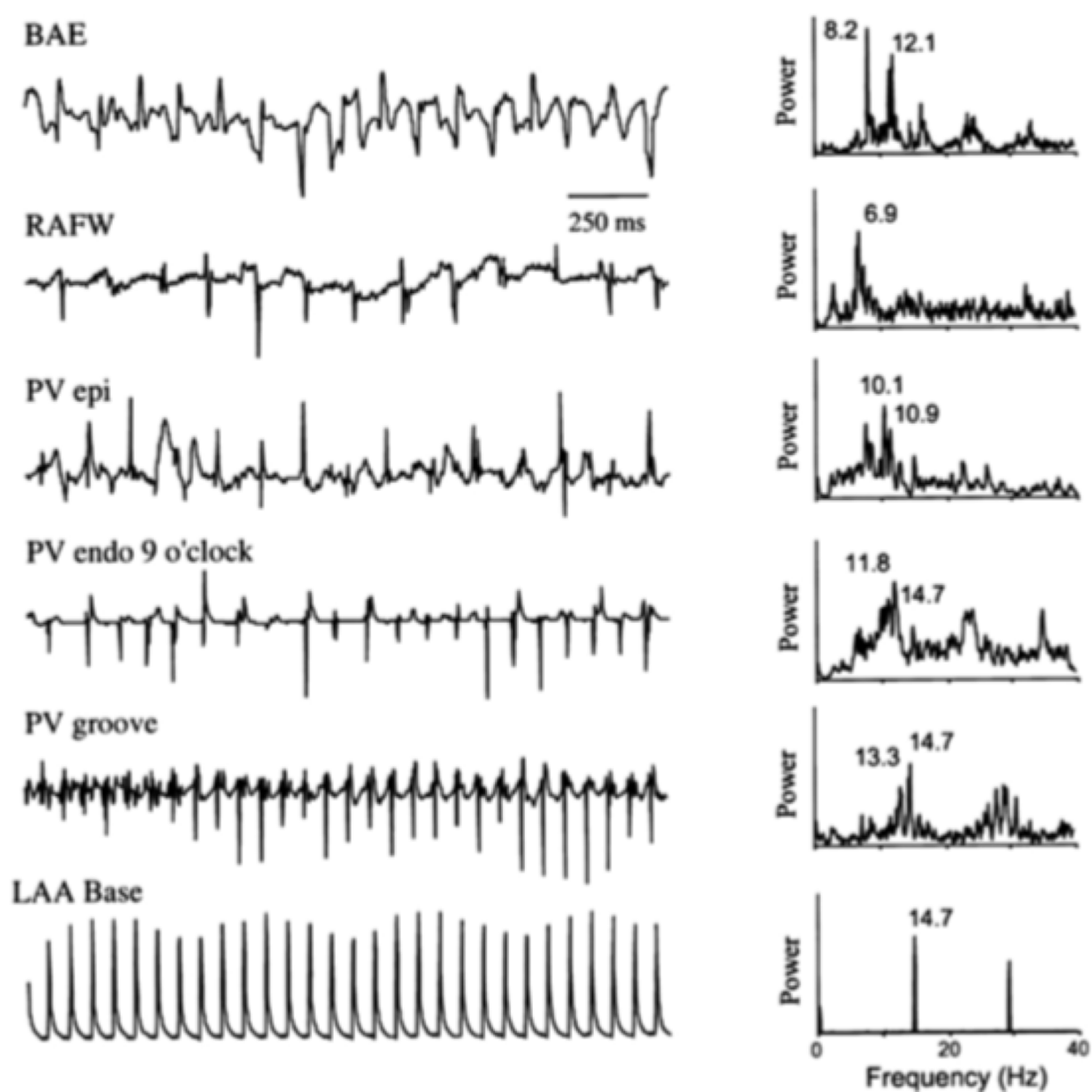
- Rotorlar teorik olarak bir öncül dalganın herhangi bir yapısal ya da elektriksel bir bariyer ile etkileşimi sonucu oluşur.
- Bu bariyerden geçiş öncül dalganın parçalanıp yeni dalgacıklar oluşturmasını sağlar → vortex shedding

- Bu dalgacıkların oluşturduğu rotorlar pulmoner venlerin etrafı ya da heterojen atriyal dokularda sabit kalıp stabil rotorları oluşturur
- Bazen de merkezden uzaklaşan wavefront – öncül dalga – anatomik ya da elektriksel olarak heterojen bölgelerde daha da parçalanarak fazla sayıda fibrilatuar aktivite oluşturabilir

Rotor Haritalama Çalışmaları

- Bu çalışmalarda AF kaotik ve dizorganize bir ritm olarak görünse de, bu durumun sınırlı sayıda yüksek frekanslı reentran döngülerin oldukça organize bir aktivitesi tarafından sürdürülmekte olduğu gösterilmiş

Figure 6: Simultaneously Recorded Electrograms, Pseudo-electrograms and Corresponding Fast Fourier Transformations During an AF Episode



A

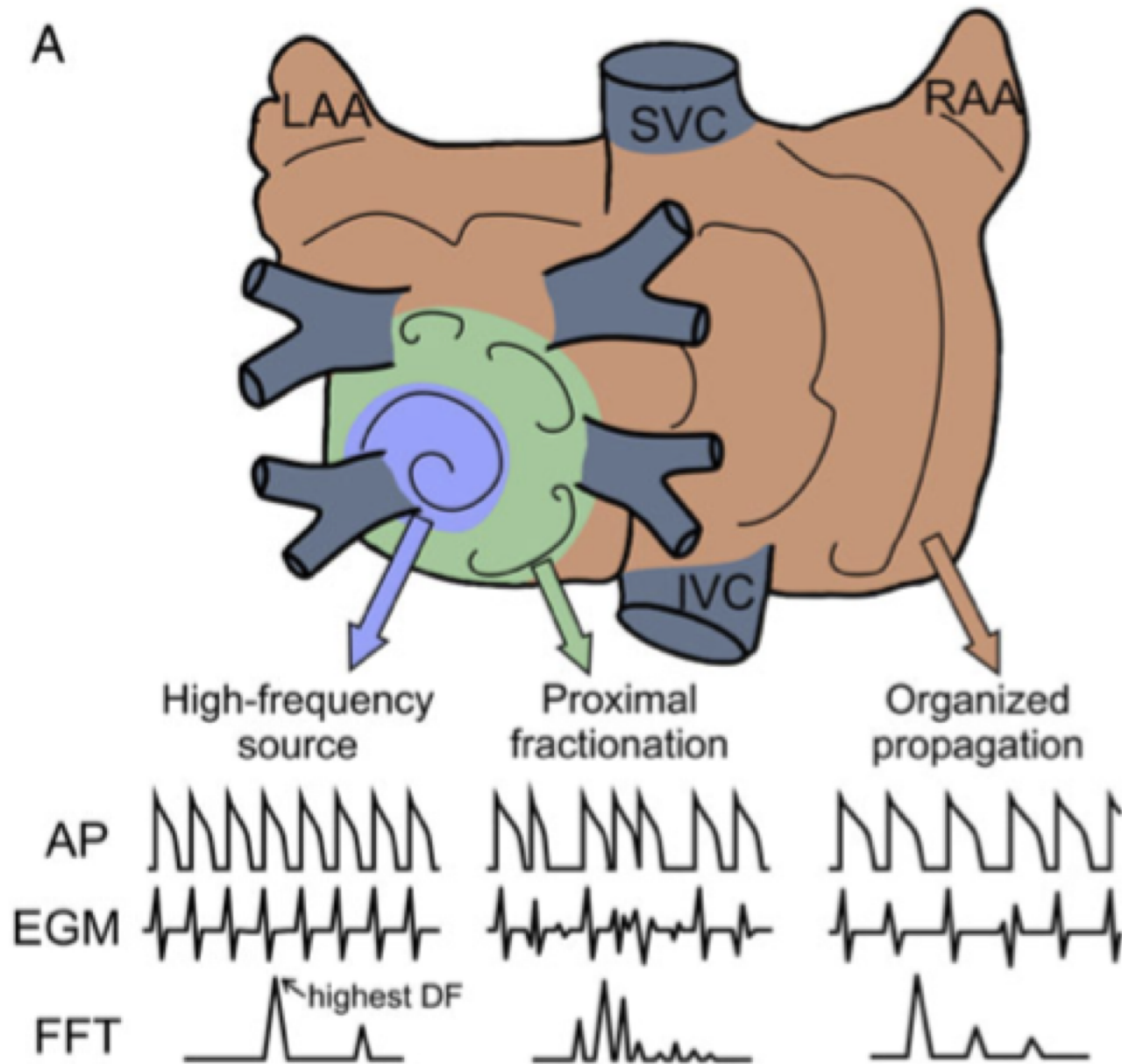
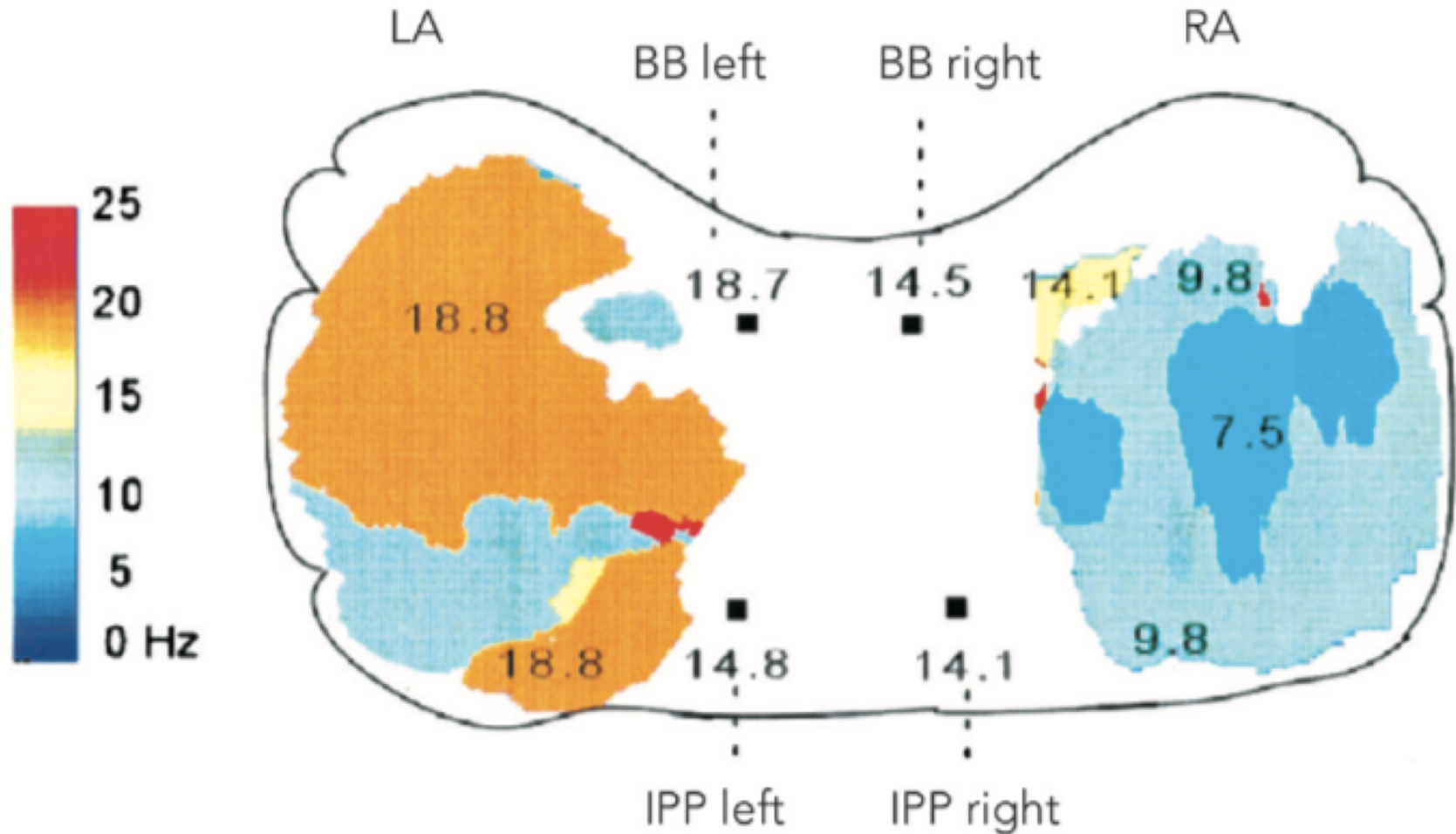


Figure 7: Left to Right Dominant Frequency Gradients in the Sheep Left and Right Atria

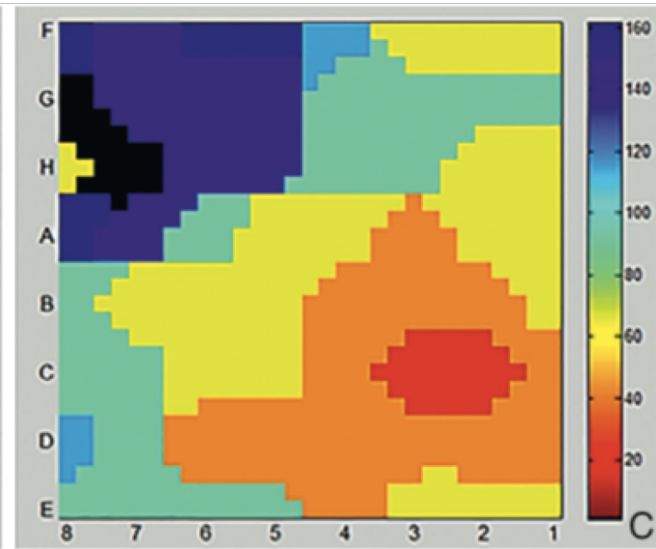
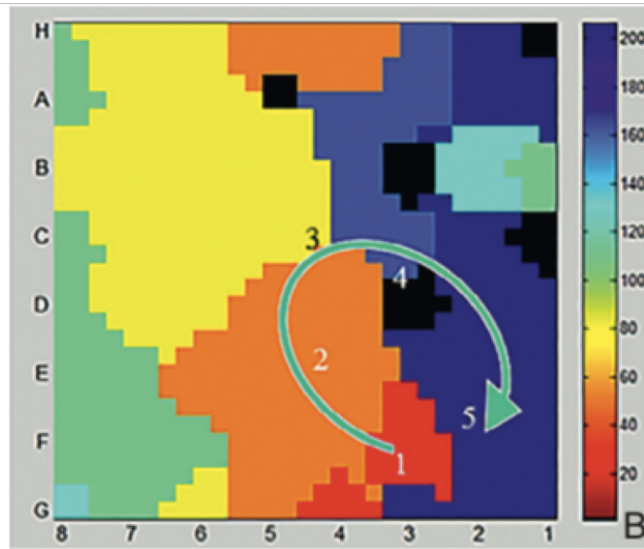
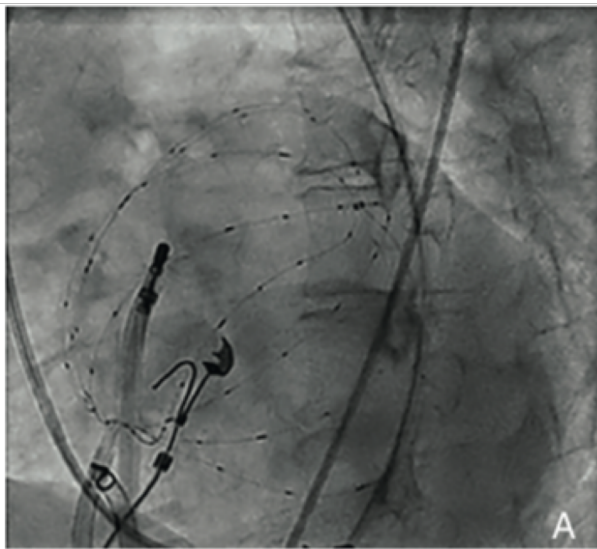


Numbers represent measured dominant frequencies at various atrial sites. BB = Bachmann's bundle; IPP = inferoposterior pathway; LA = left atrium, RA: right atrium; Reproduced with permission from Mansour et al.²⁹

İnvazif ve Noninvazif Haritalama

- Narayan ve ark. 64 pol-basket kateter (çap 48 mm, elektrod aralığı 4 mm; çap 60 mm, elektrod aralığı 5 mm) → FIRM (focal impulse and rotor modulation) haritalama
- ECGi-EKG görüntüleme-252 unipolar elektrod içeren vücut üzerinden kardiyak aktivite kaydı

FIRM Haritalama

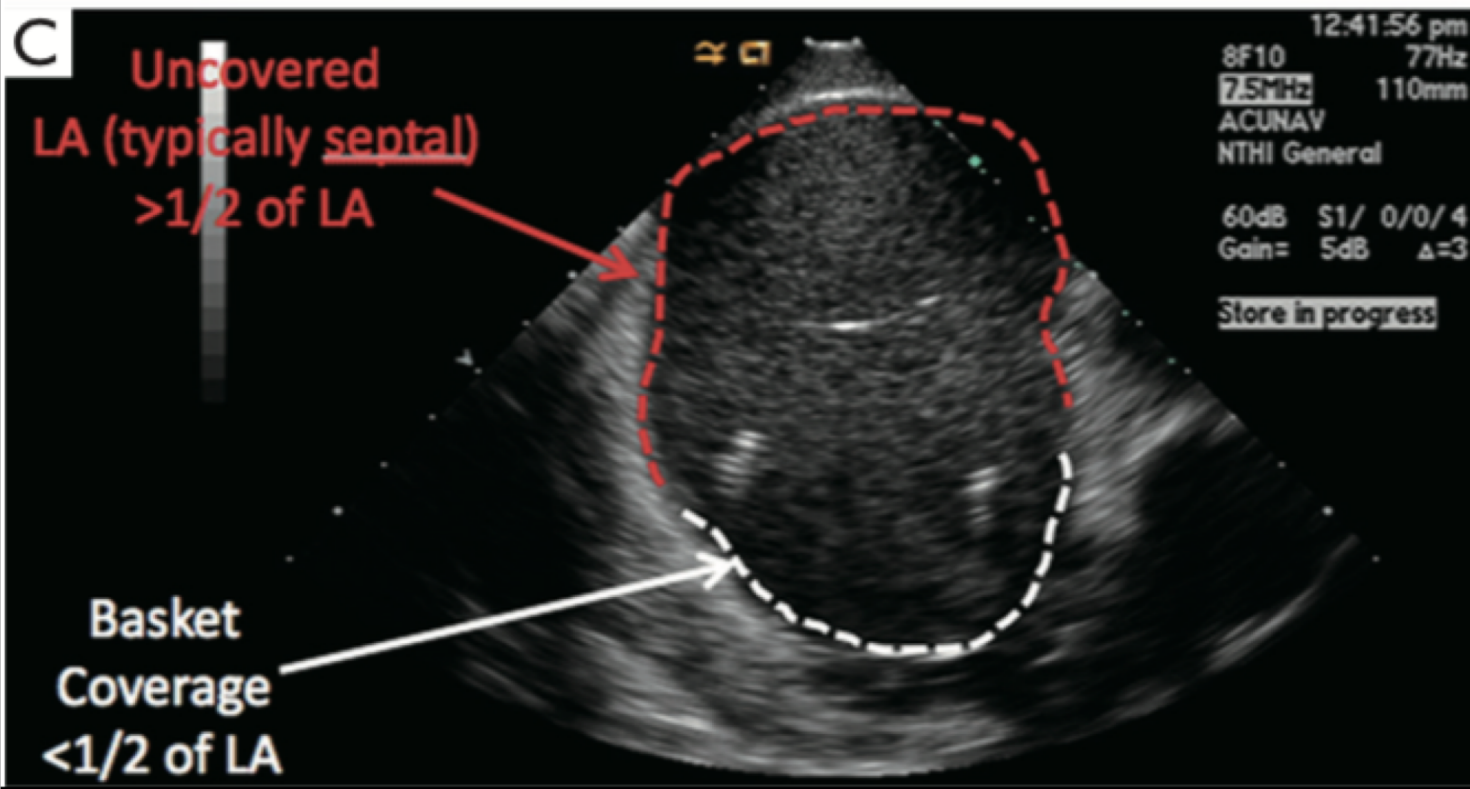
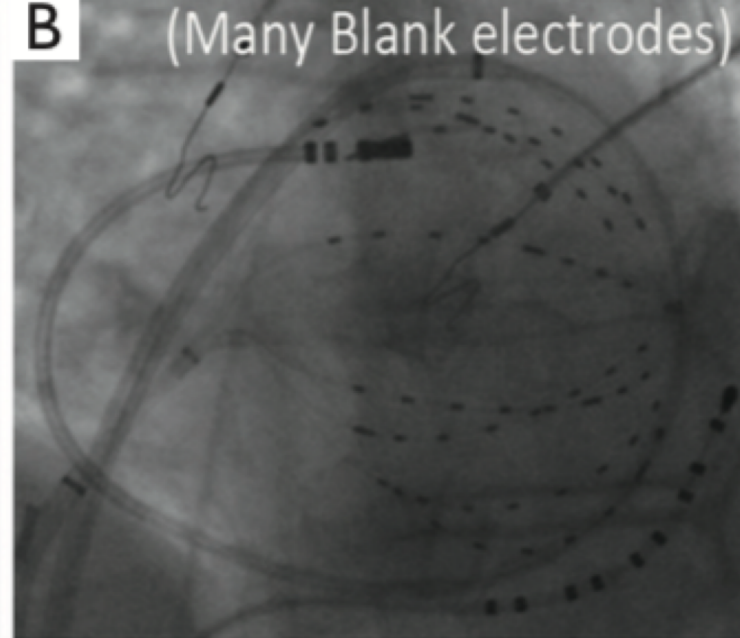
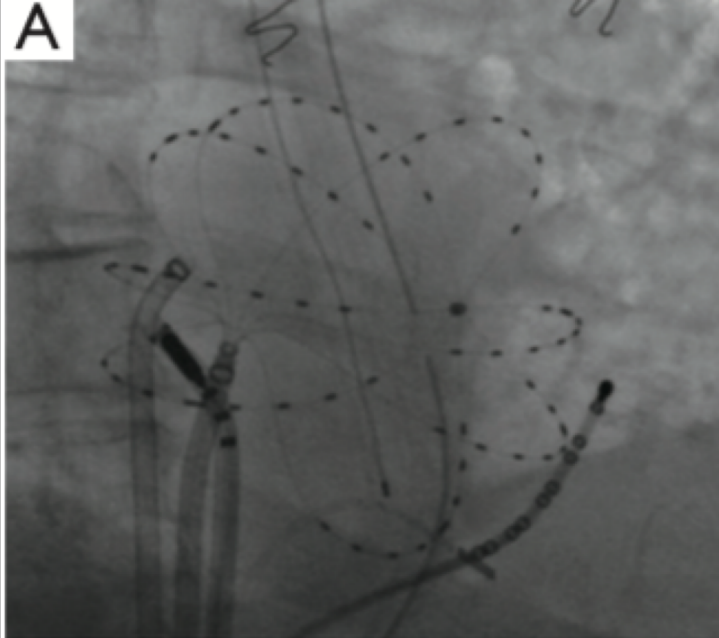


İnvazif - FIRM Haritalama

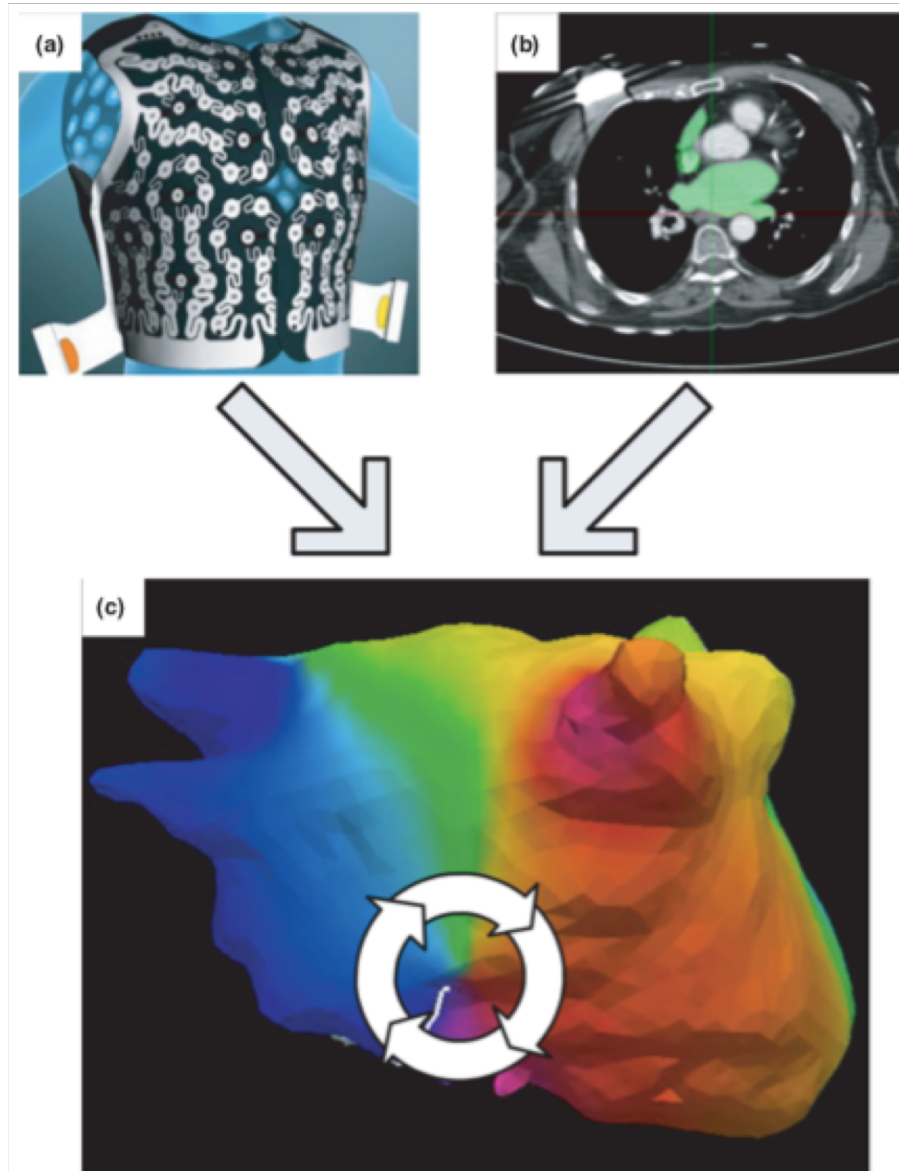
- Narayan ve ark. 64 pol kateter ile RA ve LA haritalaması
- Hastaların %97'sinde rotor ve fokal uyarılar
- %70 Rotor ve %76'sı LA yerleşimli

Kısıtlılıkları

- Eş zamanlı bi-atriyal analiz için 2 basket kateter gerekmesi
- Yetersiz elektrod teması ve uygunsuz yerleşim sinyal kalitesini azaltıyor
- Offline analiz gereksinimi - işlem süresini uzatıyor
- 2 ve 3 boyutlu haritalar arasındaki farklılıklar



EKG Görüntüleme - ECGi



Kısıtlılıkları

- Kardiyak sinyaller torakstaki yapılardan geçerken etkileniyor ve bulanık sinyaller kaydedilebiliyor
- İntramural ve endokardiyal aktiviteyi kaydetmiyor
- Mikroreentri, endoepikardiyal aktivasyon gibi mekanizmaları ayırt edebilmesi güç
- Septal aktiviteyi net analiz edemiyor

Endoepikardiyal Aktivasyon

- “Double Layer” – Çift katman hipotezi
- AF birbirini sürekli olarak besleyen iki ayrı disosiyasyon katmandaki çoklu dalgalar tarafından sürdürülmektedir
- Fibrilasyon dalgalarının ömrü kısa süreli olsa da iki katman arasındaki geçiş bölgelerinden çıkan yeni dalgalar AF’yi devam ettiriyor

Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans

Natasja de Groot, MD, PhD*; Lisette van der Does, MD*; Ameeta Yaksh, MD; Eva Lanthers, MD; Christophe Teuwen, MD; Paul Knops, BSc; Pieter van de Woestijne, MD; Jos Bekkers, MD, PhD; Charles Kik, MD; Ad Bogers, MD, PhD; Maurits Allessie, MD, PhD

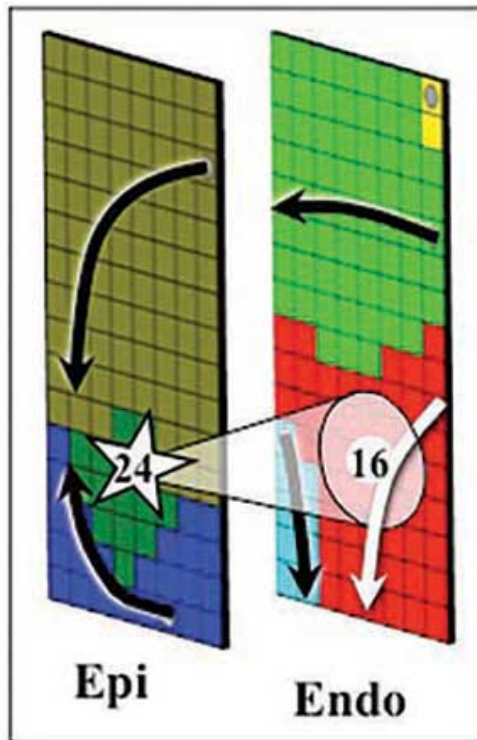
Background—The presence of focal fibrillation waves during atrial fibrillation (AF) can, besides ectopic activity, also be explained by asynchronous activation of the atrial endo- and epicardial layer and transmurally propagating fibrillation waves. To provide direct proof of endo-epicardial asynchrony, we performed simultaneous high-resolution mapping of the right atrial endo- and epicardial wall during AF in humans.

Method and Results—Intraoperative mapping of the endo- and epicardial right atrial wall was performed during (induced) AF in 10 patients with AF (paroxysmal: n=3; persistent: n=4; and longstanding persistent: n=3) and 4 patients without a history of AF. A clamp made of 2 rectangular 8×16 electrode arrays (interelectrode distance 2 mm) was inserted into the incision in the right atrial appendage. Recordings of 10 seconds of AF were analyzed to determine the incidence of asynchronous endo-epicardial activation times (≥ 15 ms) of opposite electrodes. Asynchronous endo-epicardial activation ranged between 0.9 and 55.9% without preference for either side. Focal waves appeared equally frequent at endocardium and epicardium (11% versus 13%; $P=0.18$). Using strict criteria for breakthrough (presence of an opposite wave within 4 mm and ≤ 14 ms before the origin of the focal wave), the majority (65%) of all focal fibrillation waves could be attributed to endo-epicardial excitation.

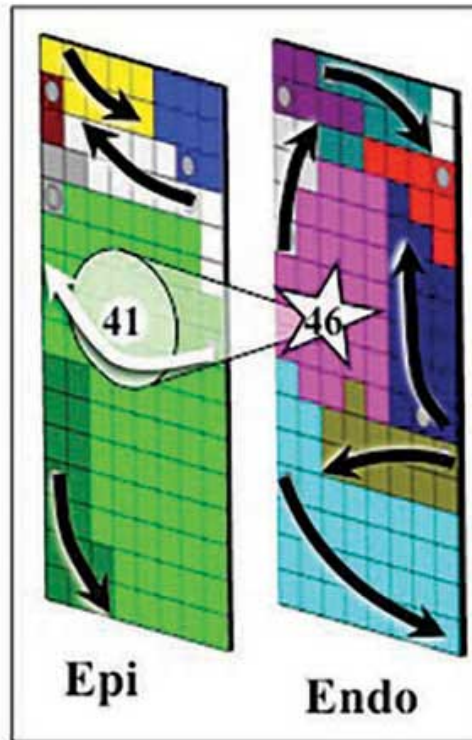
Conclusions—We provided the first evidence for asynchronous activation of the endo-epicardial wall during AF in humans. Endo-epicardial asynchrony may play a major role in the pathophysiology of AF and may offer an explanation why in some patients therapy fails. (*Circ Arrhythm Electrophysiol.* 2016;9:e003648. DOI: 10.1161/CIRCEP.115.003648.)

Endo-Epikardiyal Aktivasyon

**Epicardial
Breakthrough**



**Endocardial
Breakthrough**



**Endo + Epicardial
Breakthroughs**

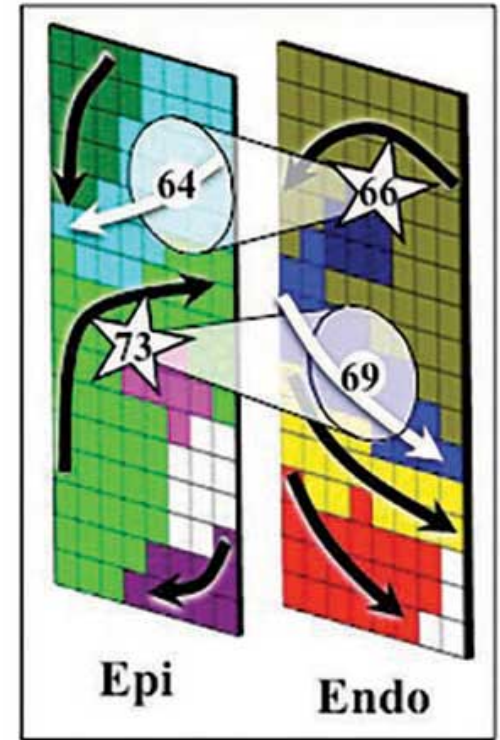


FIGURE 2. To assess the occurrence of endo-epicardial breakthrough, the opposite layer was examined for the presence of a fibrillation wave that could have served as a source for the focal wave.

Endo-Epicardial Breakthroughs Are Multiplication Sites

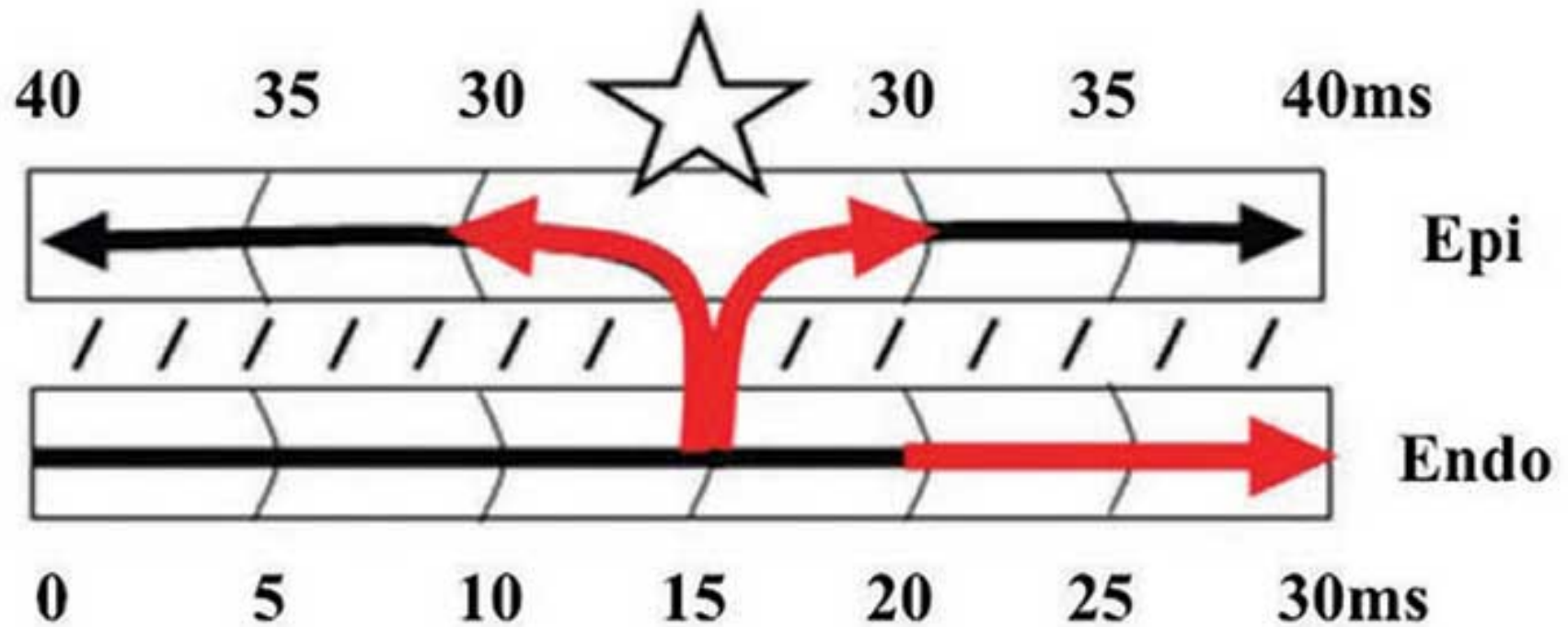


FIGURE 4. Since each breakthrough should be considered as a multiplication site, together all breakthroughs form a huge reservoir of 'new' fibrillation waves.

Sonuç olarak,

- AF mekanizmaları kompleks ve çok sayıda araştırma yapılmasına rağmen henüz tam olarak aydınlatılmış değil
- Deneysel olarak tanımlanmış mekanizmaların klinik pratikte açıklanması zor
- Daha gelişmiş haritalama metodları bu mekanizmaları anlamada yardımcı olabilir

Sonuç olarak

- AF'nin kişiden kişiye değişen mekanizmaları var.Hatta aynı hastada farklı zamanlarda farklı mekanizmalar söz konusu
- Kişiselleştirilmiş tedavinin geliştirilebilmesi için invazif-non invazif elektrofizyolojik ölçümler, biyokimyasal parametreler ve görüntüleme teknikleri ışığında atriyumdaki patofizyolojik değişiklikleri temel alan yeni bir sınıflamaya ihtiyaç var

Teşekkürler