

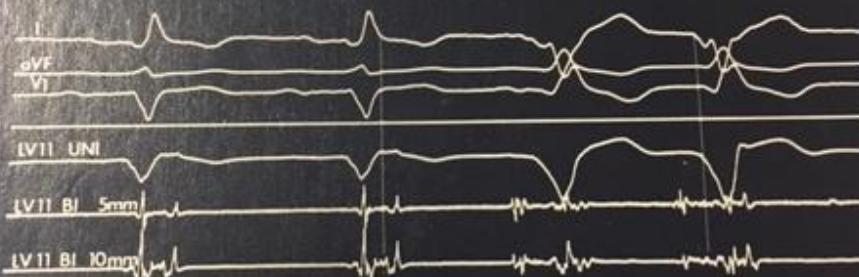
**AF ablasyonunda «sham» çalışma gibi
saçma bir şeye gerek yoktur**

**Prof. Dr. Fethi KILIÇASLAN
İstanbul Medipol Üniversitesi**

CLINICAL CARDIAC ELECTROPHYSIOLOGY

Techniques and Interpretations

Third Edition



MARK E. JOSEPHSON



LIPPINCOTT WILLIAMS & WILKINS

December, 11/12/04,

Dear Fethi,

".....And let the best be for your friend. If he must know the ebb of your tide, let him know it's flood also. Seach him always with hours to live, and not hours to kill....." Khalil Gibran

The Prophet

It was a pleasure to have you as a friend, partner, tutor, student and a Mentor. All the best for you in a successful, just progress
BP-Carrasco

truly yours
Nassef

AF ablasyonu

- AF Ablasyonun temel taşı pulmoner ven izolasyonudur.
- AF ablasyonu özellikle paroksismal AF'da yüz güldürücüdür.
- AF ablasyonu (uygun eğitim almış tecrübeli ekipleri olan merkezlerde yapılrsa) sinüs ritminin sürdürülmesinde antiaritmik ilaç tedavisinden daha etkilidir.
- Ciddi komplikasyonlarına ve maliyetine rağmen ablasyon AF'lu hastalarda en önemli ve en etkili tedavi seçenekidir.

Sham çalışma?

- Sham çalışmada (sham cerrahisi veya placebo cerrahi) kontrol grubunda cerrahi işlemin tedavi edici olduğu düşünülen aşaması yapılmaz.
- İlaçla yapılan çalışmalarda placebo ilaç kullanılırken cerrahi/girişim ile yapılan çalışmalarda sham cerrahisi/girişimi kullanılır.

* Critical review of sham surgery clinical trials: Confounding factors analysis
Annals of Medicine and Surgery 12 (2016) 21e26

Sham çalışma

- Plasebo etkisinde beyin aktif rol oynamaktadır. Bu etki tedavi edici özellikler gösterebilir.
- Ancak sham çalışma plasebo ilaç vermekten biraz daha farklıdır.
- Çünkü hasta aktif olarak işlem alındığı için hastaya zarar verme riski vardır.
- Bu nedenle tıbbi ve etik tartışmalara açıktır.

ORIGINAL

Impact
24-H
Results

Patients were blinded to whether they received renal artery denervation or only renal angiography (sham).



George L. Bakris, MD,* Raymond R. Townsend, MD,† Minglei Liu, PhD,‡ Sidney A. Cohen, MD, PhD,††
Ralph D'Agostino, PhD,§ John M. Flack, MD, MPH,|| David E. Kandzari, MD,¶ Barry T. Katzen, MD,#
Martin B. Leon, MD,** Laura Mauri, MD, MSc,†† Manuela Negoita, MD,‡ William W. O'Neill, MD,††
Suzanne Oparil, MD,§§ Krishna Rocha-Singh, MD,||| Deepak L. Bhatt, MD, MPH,¶¶
for the SYMPLICITY HTN-3 Investigators

AF'da sham çalışması?

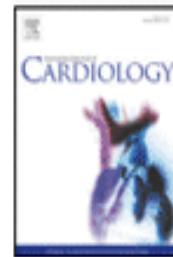
International Journal of Cardiology 211 (2016) 55-57



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Similarities between the renal artery and pulmonary vein denervation trials: Do we have to use sham procedures for atrial fibrillation catheter ablation trials?

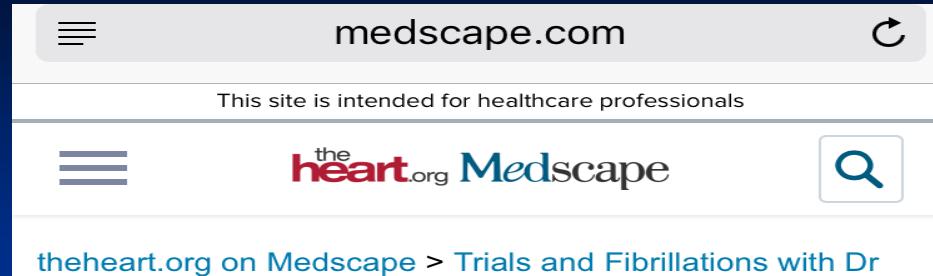


Ozcan Ozeke ^{*}, Serkan Cay, Firat Ozcan, Kazim Baser, Serkan Topaloglu, Dursun Aras

Turkiye Yuksek Ihtisas Training and Research Hospital, Department of Cardiology, Ankara, Turkey

- HT ve AF yaygın hastalıklardır.
- HT tedavisinde renal denervasyon ile ilgili ilk çalışma bulguları ümit verici iken SYMPLICITY HTN-3 çalışmasında renal denervasyonun tansiyon düşürücü etkisinin placebodan üstün olmadığı görülmüştür.
- AF tedavisinde kateter ablasyon ile çok ümit verici çalışmalar bildirilmesine rağmen AF nüksü önemli bir sorun olarak ortaya çıkmaktadır.
- Renal denervasyon sonrasında reinnervasyon görülmektedir. Buna karşılık AF ablasyonundan sonra PV rekonneksiyon görülmektedir.
- AF ablasyonunun placebo etkisi olabilir. Bu nedenle AF ablasyonunda sham çalışma önerilebilir.

- Similarities between the renal artery and pulmonary vein denervation trials: Do we have to use sham procedures for atrial fibrillation catheter ablation trials? Ozeke O et al. Int J Cardiol 2016;211:55-57.



- Ablation in the left atrium has never been tested against a true placebo.
- We are doing something with this procedure. The question is, would it be more effective than a sham procedure—especially if those judging its success were not ablation doctors.

ablation was no better than a sham procedure. Before the properly controlled trial, nearly all of the data and most of the experts predicted a new era in hypertension. Think about the massiveness of that reversal: millions of people have high blood pressure.

Çalışmalar

- SYMPLICITY HTN-3
 - 544 hasta (363 vs171)
- VPS-2 trial,:
 - 100 hasta (52 vs 48)
- Transplantation of embryonic dopamine neurons for severe Parkinson's disease, (Freed CR et al. N Engl J Med 2001;344:710-719.)
 - 40 hasta (20 vs 20)
- A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures (Buchbinder R et al. N Engl J Med 2009;361:557-568.)
 - 71 hasta (38 vs 40)

AF ablasyonunda sham çalışma gerekliliği?

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 total of 69 ectopic foci. Three foci were in the right atrium, 1 in the posterior left atrium, and 65 (94 percent) in the pulmonary veins (31 in the left superior, 17 in the right superior, 11 in the left inferior, and 6 in the right inferior pulmonary vein). The earliest activation was found to have occurred 2 to 4 cm inside the veins, marked by a local depolarization preceding the atrial ectopic beats on the surface electrocardiogram by 106 ± 24 msec. Atrial fibrillation was initiated by a sudden burst of rapid depolarizations (340 per minute). A local depolarization could also be recognized during sinus rhythm and abolished by radio-frequency ablation. During a follow-up period of 8 ± 6 months after ablation, 28 patients (62 percent) had no recurrence of atrial fibrillation.

Conclusions The pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of atrial fibrillation. These foci respond to treatment with radio-frequency ablation. (N Engl J Med 1998;339:659-66.)

20 yıl önce başladı....

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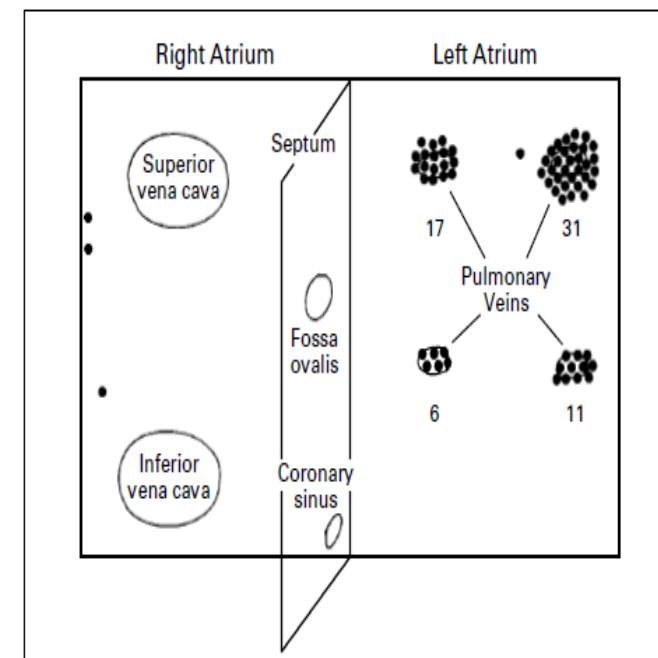


Figure 1. Diagram of the Sites of 69 Foci Triggering Atrial Fibrillation in 45 Patients.

Note the clustering in the pulmonary veins, particularly in both superior pulmonary veins. Numbers indicate the distribution of foci in the pulmonary veins.

●●●○ Turkcell LTE 22:29 🔍 ⌂ 🔋

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FILTER: None

SORT: Most recent

Search Results 11,207 items

Relationship of the lungs to the left atrium of particular relevance for ablation of atrial fibrillation.
Walsh KA, et al. J Interv Card Electrophysiol. 2017

[Electrical isolation of the left atrial appendage : Benefits and risks].
Bellmann B, et al. Herz. 2017. Article in German.

Acute Chest Pain and Broad Complex Tachycardia. A Non-typical Case of Pre-excited Atrial Fibrillation.
Arias RS, et al. Cardiol Res. 2011

Efficacy and effects on cardiac function of radiofrequency catheter ablation vs. direct current cardioversion of persistent atrial fibrillation with left ventricular systolic dysfunction.

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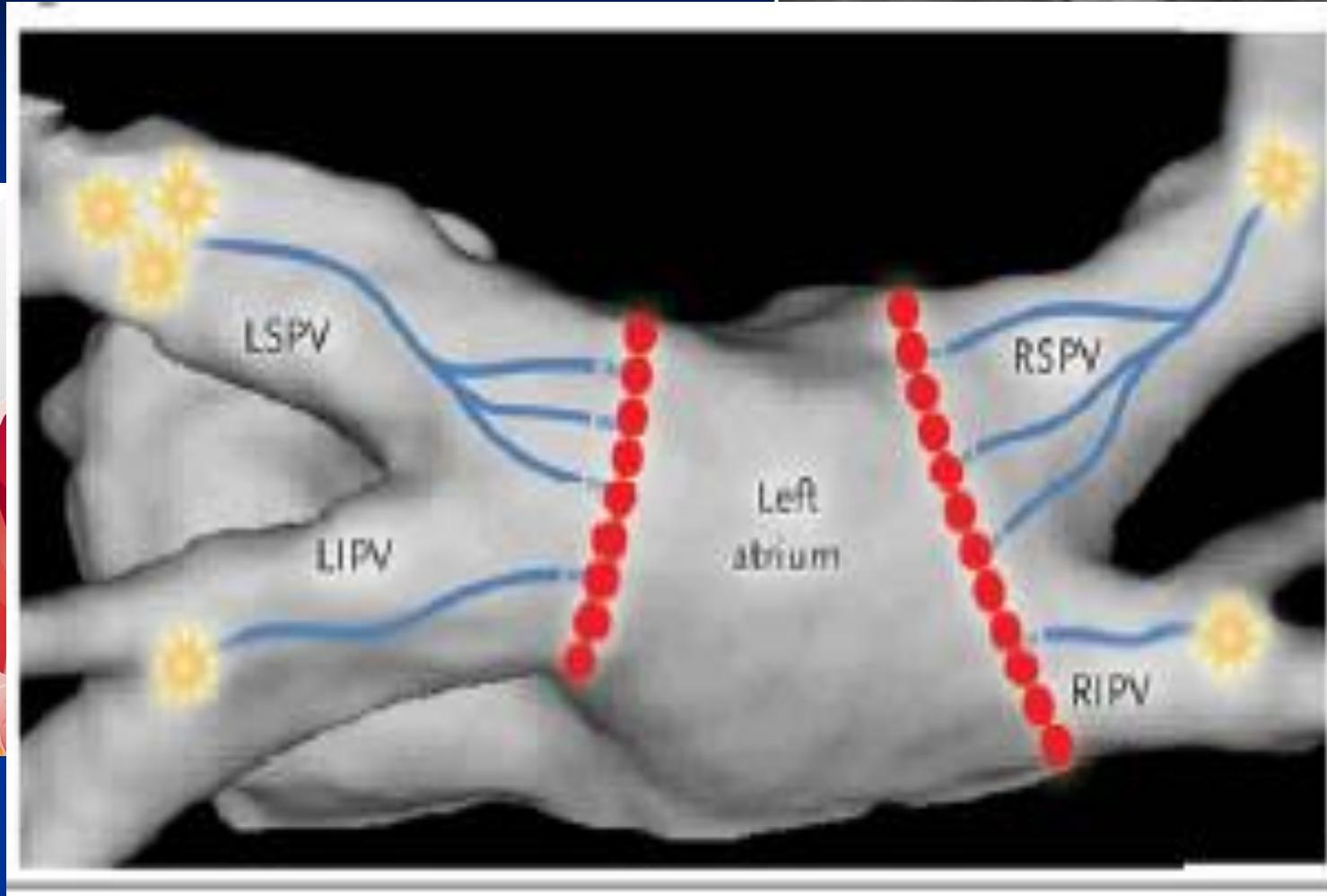
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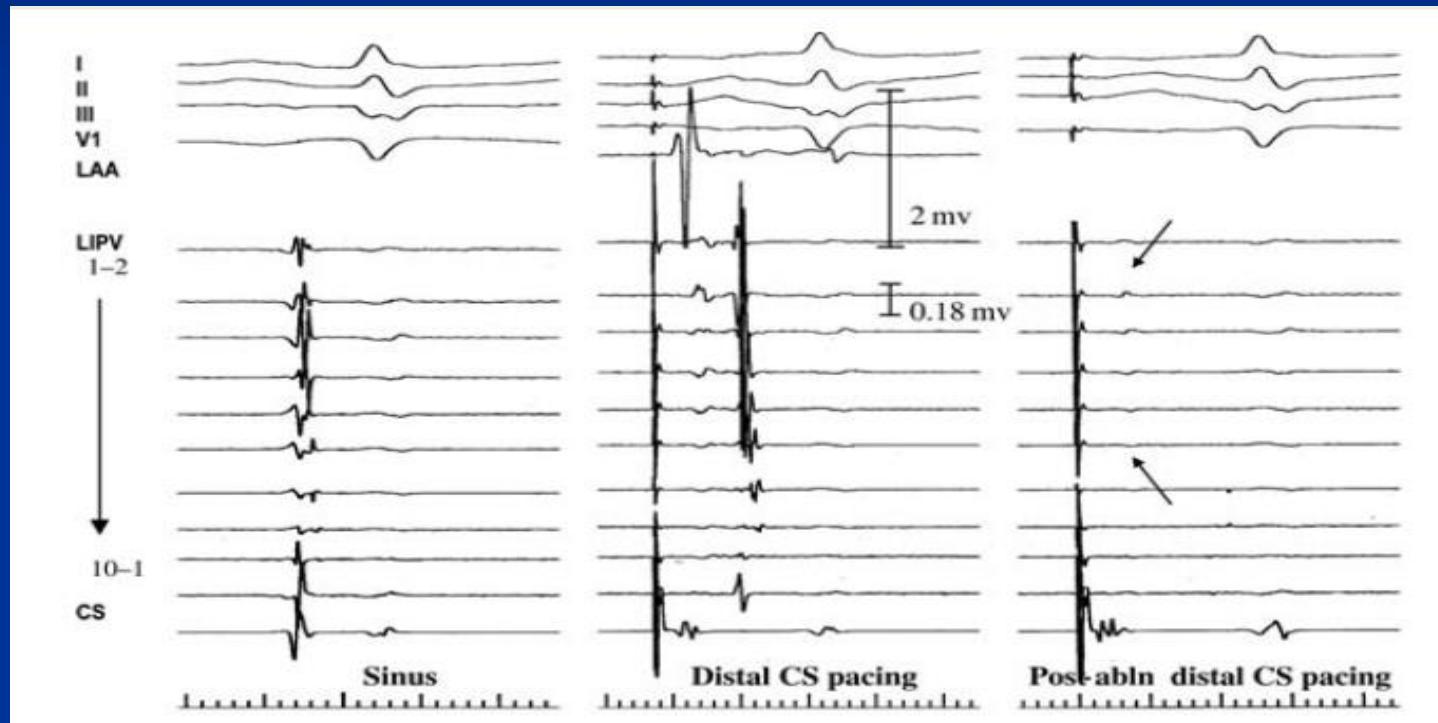
**Konvansiyonel
nokta-nokta RF
ablasyonu**

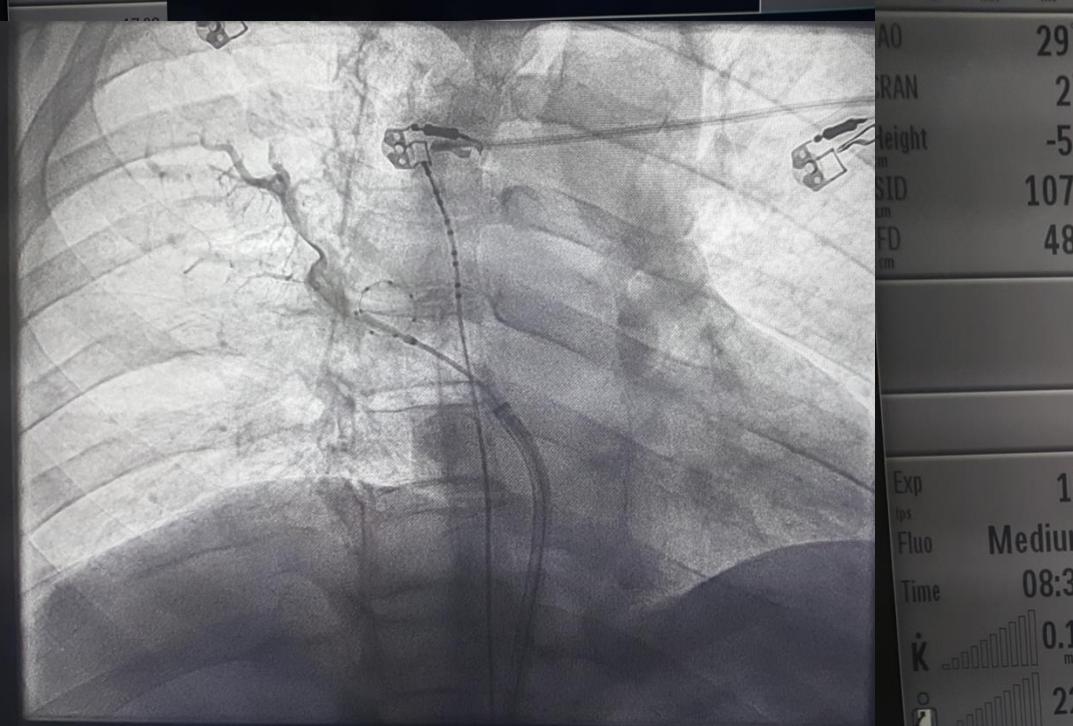
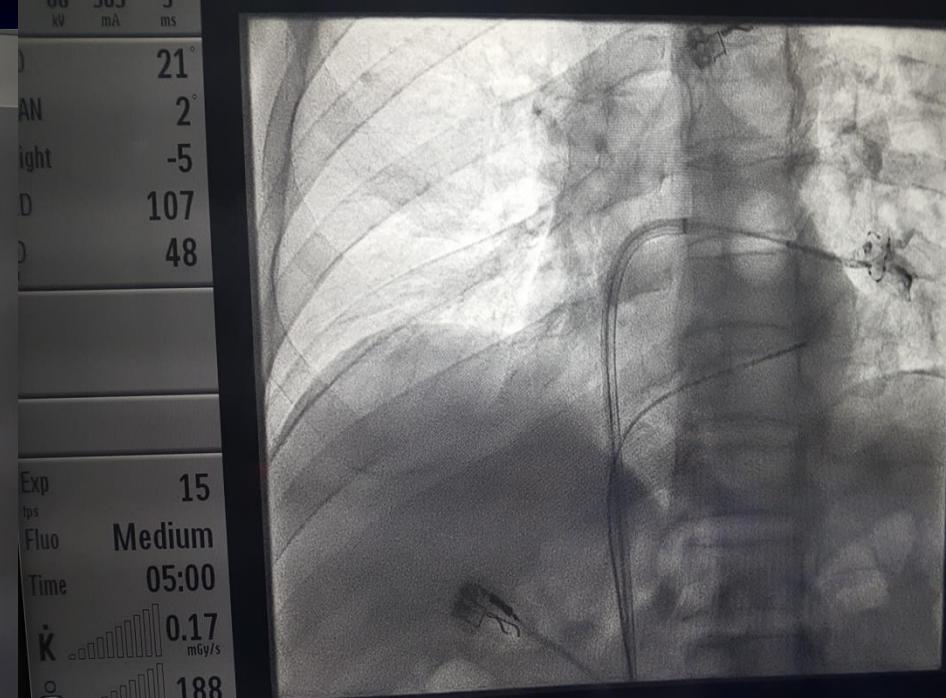
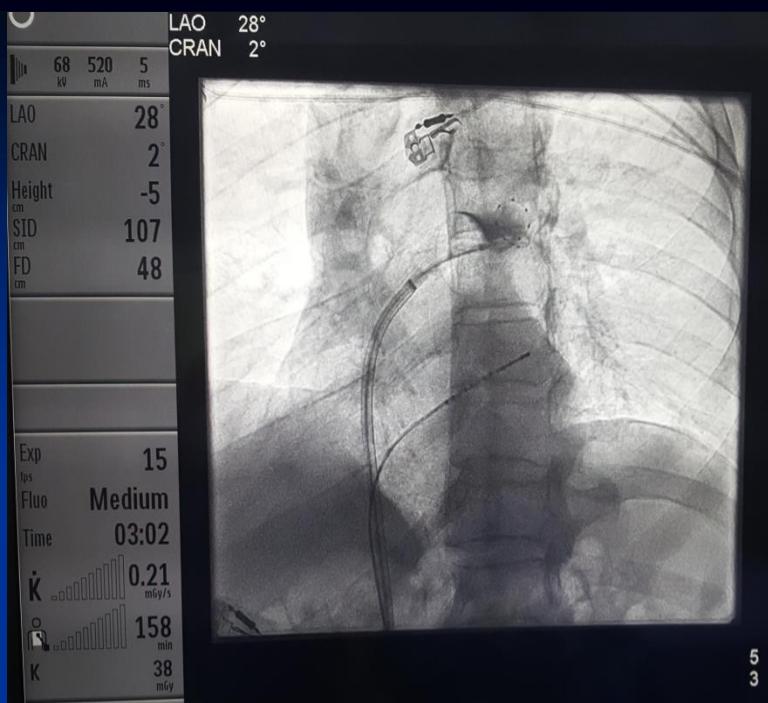
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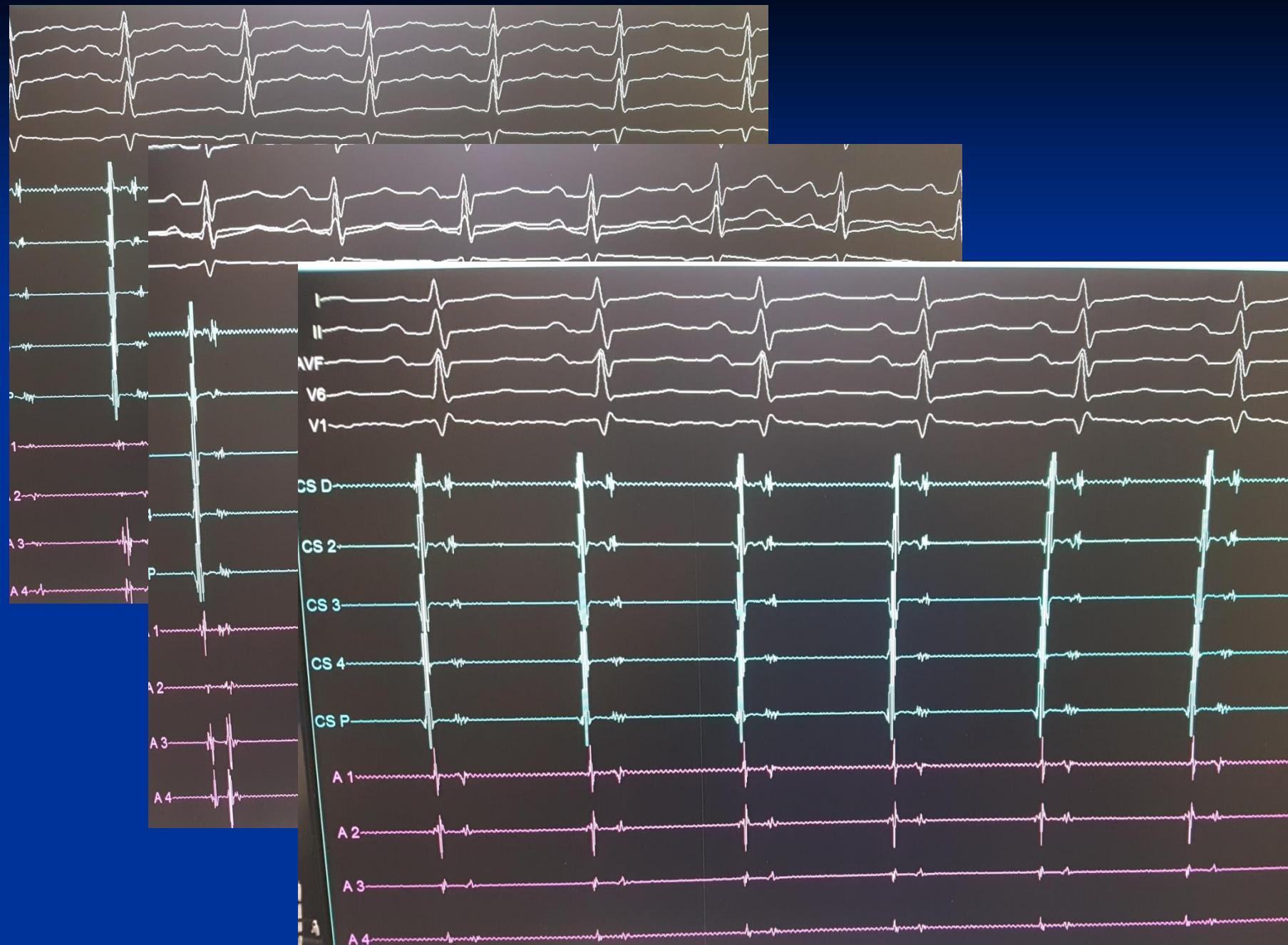
**Balon temelli
ablasyon**

- CRYO
- Ultrasound, Laser, HIFU
- Hotballoon RF









Arrhythmia/Electrophysiology

Response of Atrial Fibrillation to Pulmonary Vein Antrum Isolation Is Directly Related to Resumption and Delay of Pulmonary Vein Conduction

TABLE 2. Distribution of Document DINA Number by Author

Background—T
in conflicting
who could ma
antiarrhythmic

We also recruited PVAI. All patients with isolation of atrioventricular conduction defined as AP (n=44) did not have conduction with patients with normal group III, 267 developed in

Conclusions—The majority of patients with drug-free cure show no PV-LA conduction recurrence. Substantial A-PV delay is seen in patients able to maintain sinus rhythm on antiarrhythmic medication or cured of AF compared with patients who fail PVAI. (*Circulation*, 2005;112:627-635.)

TABLE 2. Distribution of Recurrent PVA Number by Patient Groups

No. Recurrent PVA	Group I	Group II	Group III
0	21 (81)	2 (5)	0 (0)
1	5 (19)	12 (32)	6 (14)
2	0 (0)	17 (46)	25 (57)
3	0 (0)	6 (16)	11 (25)
4	0 (0)	0 (0)	2 (4)

Numbers in each group column represent the number of patients with a specific number of recurrent PVA. Percentages are shown in parentheses.

nza, MD;
Saliba, MD:

as been debated (group I), patients present AF despite

• AF recurrence
• >3 months after
• with complete

l to PV (A-PV) recurrence was (n=37), and III

-left atrial (LA) $P=0.02$). In by $69 \pm 47\%$ for ate, A-PV block

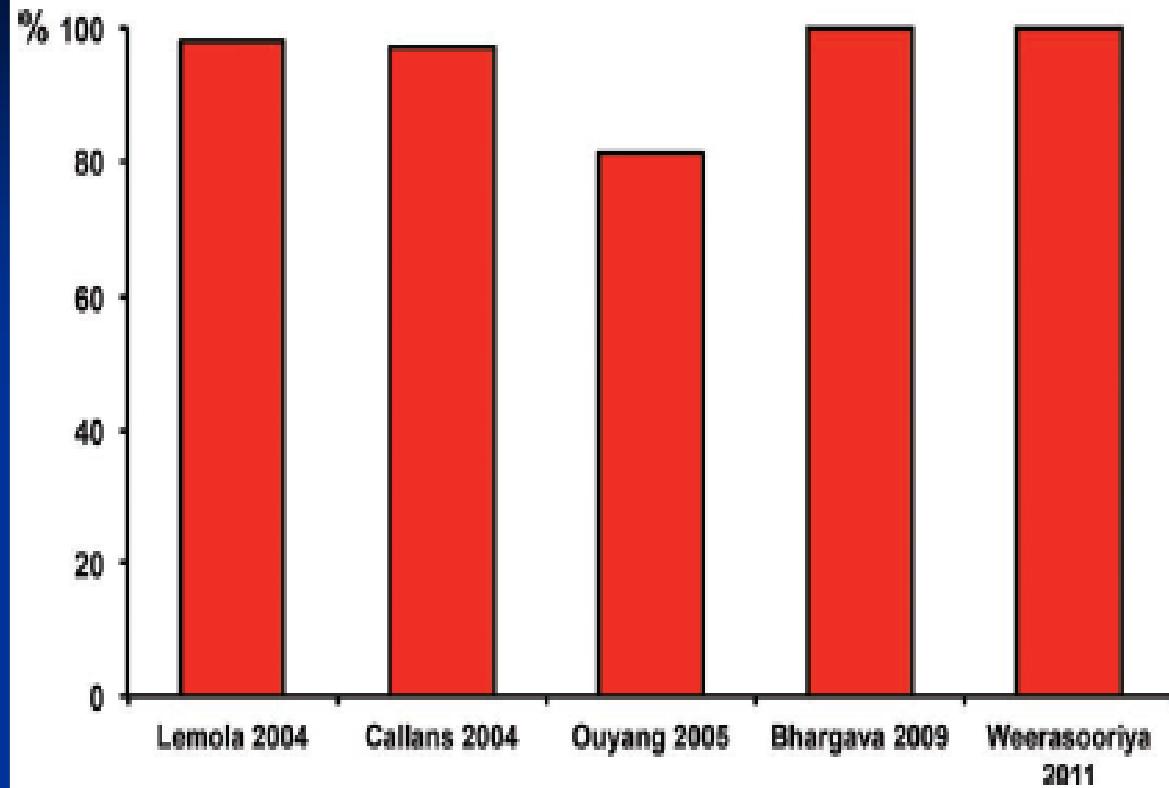


Figure 2. Prevalence of pulmonary vein reconnection in patients undergoing repeat catheter ablation procedures.



P. Santangeli, M.D.



D. Lin, M.D.

CATHETER ABLATION OF PAROXYSMAL ATRIAL FIBRILLATION: HAVE WE ACHIEVED CURE WITH PULMONARY VEIN ISOLATION?

Pasquale Santangeli, M.D.; David Lin, M.D.
Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

- Paroksismal AF'da PVI ile ortalama 5 yıllık takipte tek işlem ile %46,6 ve tekrarlı işlemler ile %79.5 aritmisi eliminasyonu sağlanmaktadır.
- Aritmi rekürrensinin en önemli nedeni PV rekonneksiyonudur. İkinci işlem uygulanan hastaların %92'sinde rekonneksiyon tespit edilmektedir. Bu hastalara rekonneksiyon hedef alan ikinci bir ablasyon yapılrsa işlem başarısı %81 olmaktadır.
- İlk işlemde ve ikinci işlemde PVI dışında ilave ablasyon yaklaşımlarının (lineer hat vb) ilave faydası yoktur.

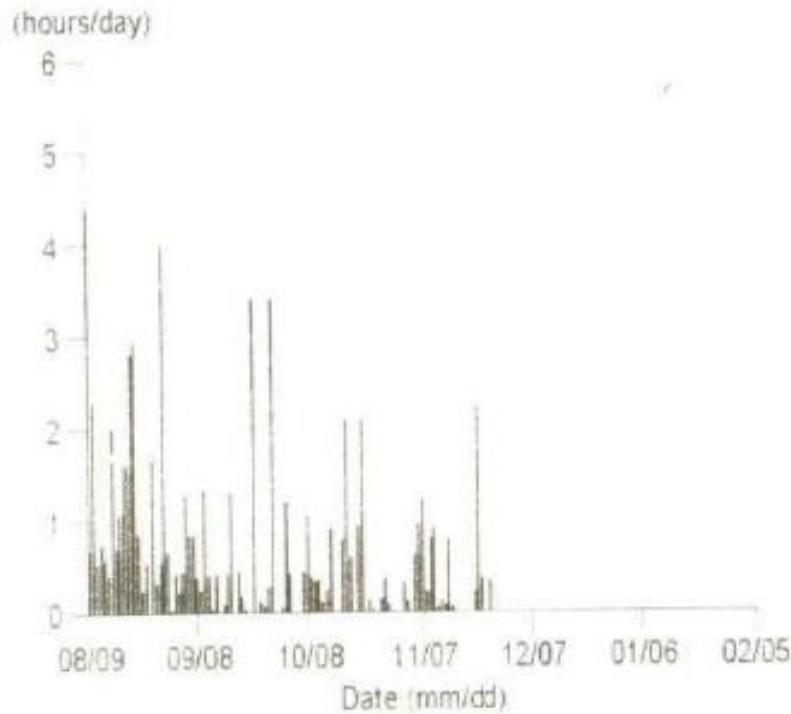
What have we learned of ablation procedures for atrial fibrillation?
Maurer1 T et al, J Intern Med 2016; 279: 439–448.

- Persistan AF atriyal fibrilasyon ve dilatasyona neden olarak AF'nin devamlılığını kolaylaştırmaktadır (atrial fibrillation begets atrial fibrillation).
- Persistan AF'da PV dışı odaklar ve LA substratı daha önemli yer tutmaktadır.
- Bu hastalarda tek başına PVI yeterli değildir. Sadece PVI ile 5 yıllık başarı oranı %24'dür.
- Başarıyı artttırmak için PV dışı tetkikleyicilerin ablasyonu ve substrat modifikasiyonu yapılmaktadır. Ancak ideal yaklaşım hala bilinmemektedir.
- Ancak persistan AF'da dahi AF ablasyonu antiaritmik tedaviden daha başarılıdır.

What have we learned of ablation procedures for atrial fibrillation?
Maurer1 T et al, J Intern Med 2016; 279: 439–448.

Atrial Arrhythmia Trend Report

Data Collection Period: 08/09/14 - 01/31/15 (Over Last 175 days)

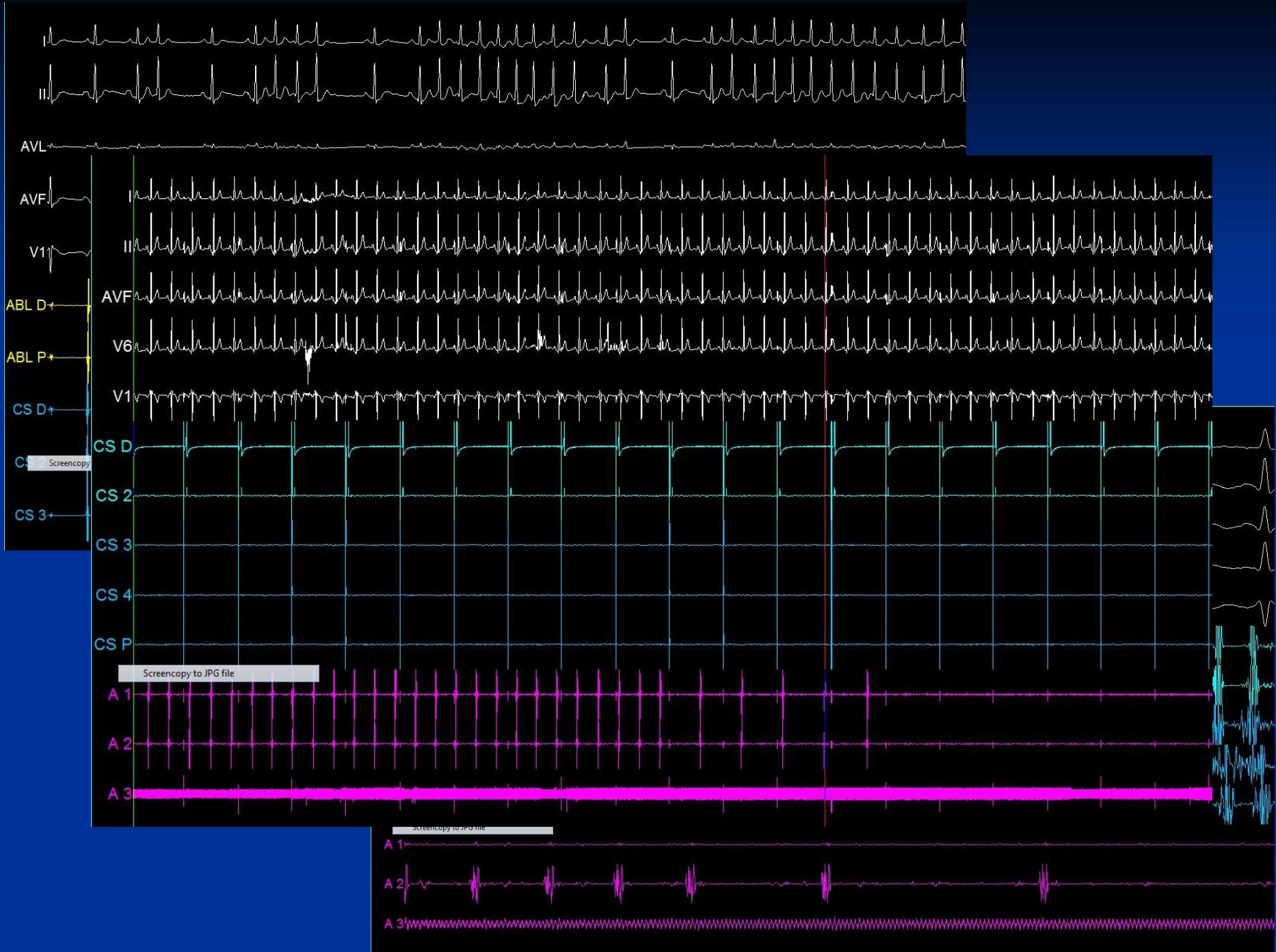


Initial Interrogation

Episode Trigger	Mode Switch
Detection Rate	175 bpm
Detection Duration	No Delay

Data Collected

Collected Daily	
Last follow-up	12/23/14



AF tedavisi için PVI?

- Bazı hastalarda kalıcı PVI'a rağmen neden AF nüksü VAR?
- Bazı hastalarda PV rekonneksiyona rağmen AF nüksü neden YOK?

Kalıcı PVI'a rağmen AF?

- Permanent PVI gösterilen hastalarda %29 oranında AF rekürrensi tespit edilmiştir.

Dukkipati SR, Neuzil P, Kautzner J, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. Heart Rhythm. 2012 Jun;9(6):919-25.

PV Dışı Tetikleyiciler

- Genel olarak PV dışı tetikleyicilerin oranı %14-28
- Özellikle kadınlarda ve sol atriyumu büyük olanlarda daha sık,
- En sık odaklar;
- ✓ Vena kava superior,
- ✓ Sol atriyum arka duvarı,
- ✓ Krista terminalis,
- ✓ Koroner sinüs,
- ✓ Marshall ligamenti,
- ✓ İnteratriyal septum,
- AVRT ve AVNRT gibi SVT'lerin de AF'yi başlattığı bildirilmiştir (%4)

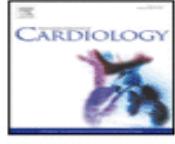
PV rekonneksiyona rağmen AF nüksü neden yok?

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Similarities between the renal artery and pulmonary vein denervation trials: Do we have to use sham procedures for atrial fibrillation catheter ablation trials?

Ozcan Ozeke *, Serkan Cay, Fırat Ozcan, Kazım Baser, Serkan Topaloglu, Dursun Aras

Turkiye Yüksel İhtisas Training and Research Hospital, Department of Cardiology, Ankara, Turkey

 CrossMark

Referans 33

- However, the observation that a substantial portion of patients had no further AF episodes after acute PV isolation despite re-connected PVs found at a repeat study during follow-up [33] suggesting the possible substrate modification aspect of circumferential PV isolation and/or placebo effects.

Persistence of Pulmonary Vein Isolation After Robotic Remote-Navigated Ablation for Atrial Fibrillation and its Relation to Clinical Outcome

STEPHAN WILLEMS, M.D., DANIEL STEVEN, M.D., HELGE SERVATIUS, M.D., BORIS A. HOFFMANN, M.D., IMKE DREWITZ, M.D., KAI MÜLLERLEILE, M.D., MUHAMMET ALI AYDIN, M.D., KARL WEGSCHEIDER, PH.D.,*

From the Depa

TABLE 2
Pattern of PV Reconnection during Follow-Up EPS in Patients with and without AF Recurrence

Reconducted PV	Free of AF Recurrence (n = 28)	AF Recurrence (n = 12)	P-Value
0 (%), (n))	32 (9)	0 (0)	
1 (%), (n))	21 (6)	0 (0)	
2 (%), (n))	29 (8)	58 (7)	
3 (%), (n))	11 (3)	33 (4)	
4 (%), (n))	7 (2)	8 (1)	
Mean	1.4	2.5	0.006

Methods
robotic ci
invasive e
Robotic P
time: 180
reduced a
12 [9–17]
electrical
showed a
conduction

with freedom from AF in all patients. At 3 months, 67% of patients were free of AF, while reablation of recovered PVs led to an overall freedom from AF in 81% of patients after 1 year.

Conclusion: Robotic PVI for PAF is safe, effective, and requires limited fluoroscopy while yielding comparable success rates to conventional ablation approaches with PV reconnection as a common phenomenon associated with AF recurrences. (*J Cardiovasc Electrophysiol*, Vol. 21, pp. 1079–1084, October 2010)

and Epidemiology,

EM) has been
the growing
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of PVI over

3 underwent
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nical course.
], procedure
significantly
4 [29–45] vs
and revealed
ce (n = 28)
nger LA-PV
is associated

OPEN

Pascal F.
Kati

Abstract: This systematic review was performed to investigate the ethical justification, methodological quality, validity and safety of placebo controls in randomized placebo-controlled surgical trials.

Central, MEDLINE, and EMBASE were systematically searched to identify randomized controlled trials comparing a surgical procedure to a placebo. “Surgical procedure” was defined as a medical procedure involving an incision with instruments. Placebo was defined as a blinded sham operation involving no change to the structural anatomy and without an expectable physiological response in the target body compartment.

Ten randomized placebo-controlled controlled surgical trials were included, all of them published in high-ranking medical journals (mean

Hüttner, MD,
Kati, MD,TABLE 1. Ethical Framework for the Use of Placebo in Clinical Trials¹⁵

Reference Question	27	28	29	30	31	32	33	34	35	36
Is there a valuable, clinically relevant question to be answered by a placebo controlled procedure trial?	+	+	+	+	+	+	+	+	+	+
Is the placebo control methodologically necessary to test the study hypothesis?	?	?	+	+	+	+	+	+	+	+
Has the risk of the placebo control been minimized?	?	?	?	?	?	+	+	+	+	+
Does the risk of a placebo control exceed a reasonable threshold of acceptable risk?	?	?	?	?	?	-	-	-	-	-
Is the risk of the placebo control justified by valuable knowledge to be gained?	?	?	+	+	+	+	+	+	+	+
Have research participants been adequately informed of and consented to the misleading involved in the administration of a placebo control?	?	?	?	?	?	+	+	?	?	+



Review

Critical review of sham surgery clinical trials: Confounding factors analysis



Massimo Ciccozzi ^{a, b}, Rosa Menga ^c, Giovanna Ricci ^d, Massimiliano Andrea Vitali ^{e, *}, Silvia Angeletti ^b, Ascanio Sirignano ^f, Vittoradolfo Tambone ^g

^a Department of Infectious, Parasitic, and Immune-Mediated Diseases, Epidemiology Unit, Reference Centre on Phylogeny, Molecular Epidemiology, and Microbial Evolution (FEMEM), National Institute of Health, 00161 Rome, Italy

^b Unit of Clinical Pathology and Microbiology, University Campus Bio-Medico of Rome, Italy

HIGHLIGHTS

- In sham surgery literature there's no assessment on confounding factors effect.
- Even if sham surgery has been used as control for over 30 years it isn't a standard.
- The validity of sham surgery is not completely supported by available literature.

Aklımda deli sorular

- AV tam blok tedavisinde kalıcı pacemaker tedavisini test eden bir sham çalışma yapılabilir mi?
- PVI paroksismal AF'da yüksek başarı sağlıyor ancak persistan AF'da başarı oranı düşük. Başarı placebo etkisine bağlı olsa paroksismal ve persistan AF'da PVI sonuçları neden bu kadar farklı?
- PVI gibi karmaşık, uzun ve riskli bir girişimde sham çalışması nasıl planlanacak? Bu kadar bilimsel veriye rağmen sham PVI etik sorun oluşturmaz mı?

Sonuç

- AF ablasyonunda sham çalışmaya gerek yoktur.
- Bunun yerine enerjimizi AF patofizyolojisini daha iyi anlamaya ve daha iyi ablasyon araçları ve metodları geliştirmeye harcamalıyız.