

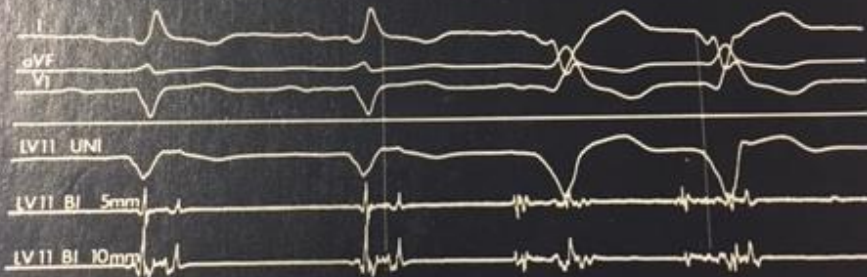
**AF ablasyonunda «sham» çalışma gibi
saçma bir şeye gerek yoktur**

Prof. Dr. Fethi KILIÇASLAN
İstanbul Medipol Üniversitesi

CLINICAL CARDIAC ELECTROPHYSIOLOGY

Techniques and Interpretations

Third Edition



MARK E. JOSEPHSON



LIPPINCOTT WILLIAMS & WILKINS

Dear Fethi,

Cleveland, 11/12/04

".....And let the best be for your friend. If he must know the ebb of your tide, let him know its flood also. Seek 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, fast progress.
truly yours
BP-Carroll
Nassir

AF ablasyonu

- AF Ablasyonun temel taşı pulmoner ven izolasyonudur.
- AF ablasyonu özellikle paroksismal AF'da yuz guldurucudur.
- AF ablasyonu (uygun eđitim almıř tecrübeli ekipleri olan merkezlerde yapılırsa) sinüs ritminin sürdürülmesinde antiaritmik ilaç tedavisinden daha etkilidir.
- Ciddi komplikasyonlarına ve maliyetine rağmen ablasyon AF'lu hastalarda en önemli ve en etkili tedavi seçeneđidir.

Sham alıřma?

- Sham alıřmada (sham cerrahisi veya placebo cerrahi) kontrol grubunda cerrahi iřlemin tedavi edici olduėu dūřnūlen ařaması yapılmaz.
- İlala yapılan alıřmalarda plasebo ila kullanılırken cerrahi/giriřim ile yapılan alıřmalarda sham cerrahisi/giriřimi kullanılır.

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

Sham alıřma

- Plasebo etkisinde beyin aktif rol oynamaktadır. Bu etki tedavi edici zellikler gsterebilir.
- Ancak sham alıřma plasebo ila vermekten biraz daha farklıdır.
- ünkü hasta aktif olarak iřlem alındığı iin hastaya zarar verme riski vardır.
- Bu nedenle tıbbi ve etik tartiřmalara aıktır.

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 SYMPPLICITY HTN-3 Investigators

AF'da sham alıřması?

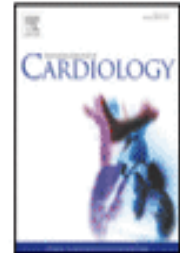
International Journal of Cardiology 211 (2016) 55–57



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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?

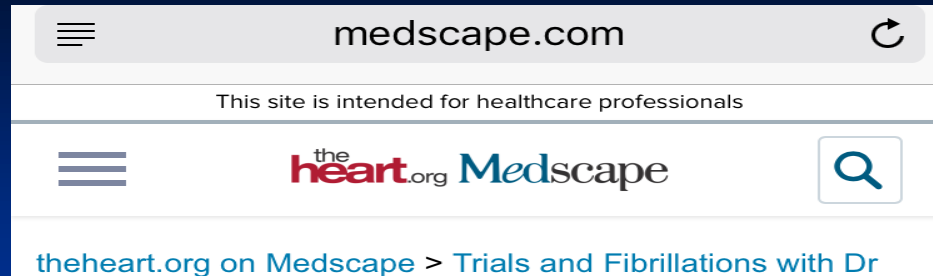


Ozcan Ozeke *, Serkan Cay, Firat Ozcan, Kazim Baser, Serkan Topaloglu, Dursun Aras

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 plasebodan 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 plasebo 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 vs 171)
- 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 gerekli mi?

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....

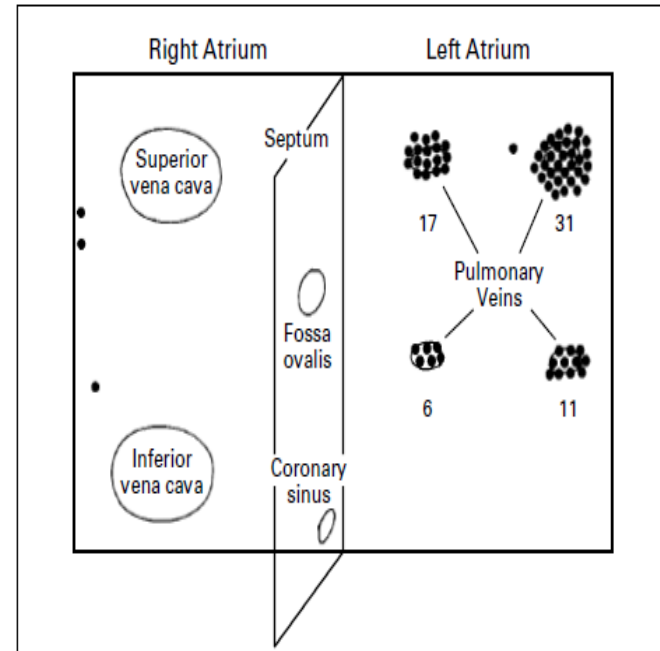


Figure 1. Diagram of the Sites of 69 Foci Triggering Atrial Fibrillation in 45 Patients.

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

PubMed atrial fibrillation ablation

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.

AF ABLASYONU

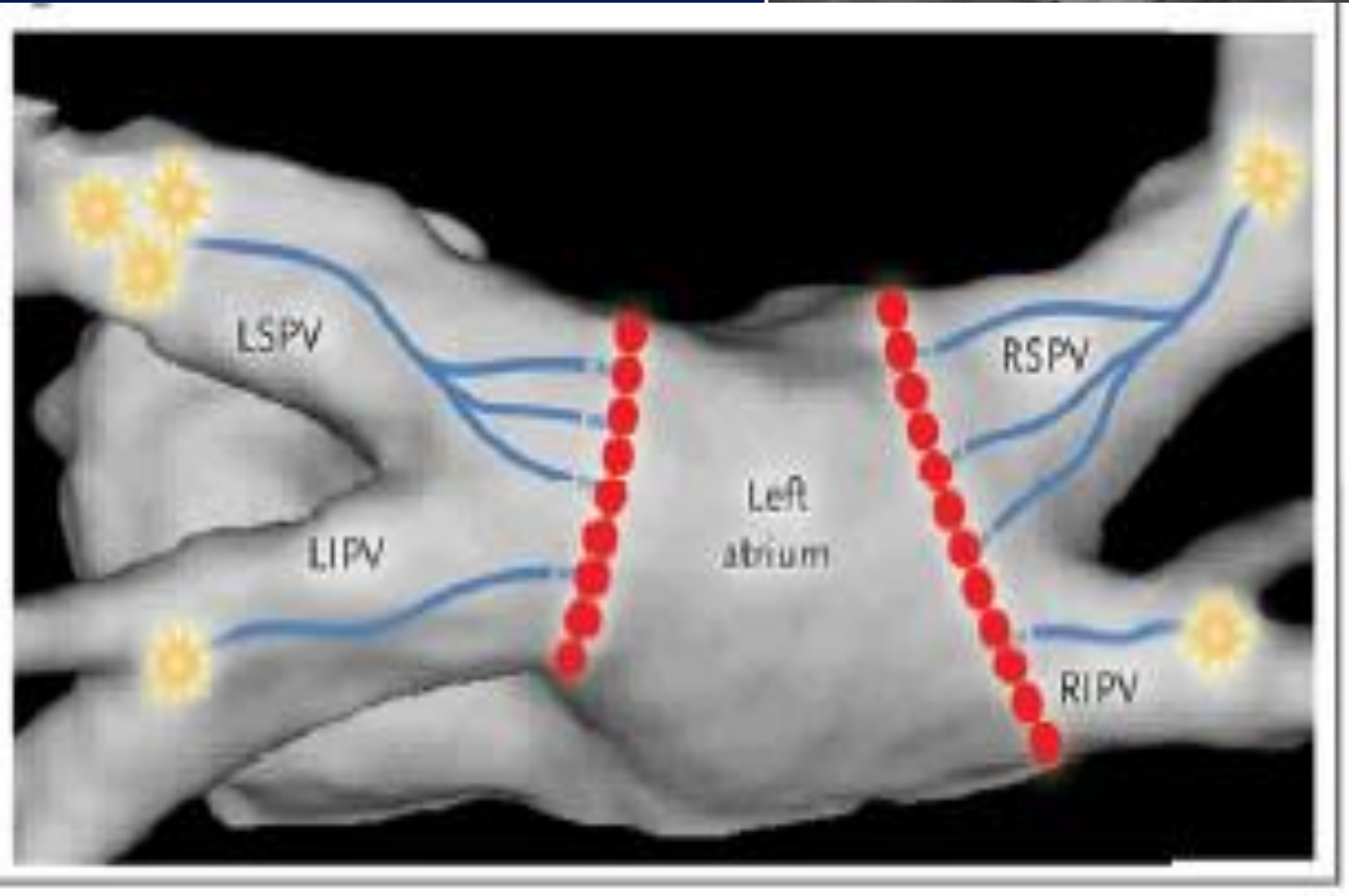
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graph TD; A[AF ABLASYONU] --> B[Konvansiyonel nokta-nokta RF ablasyonu]; A --> C[Balon temelli ablasyon];
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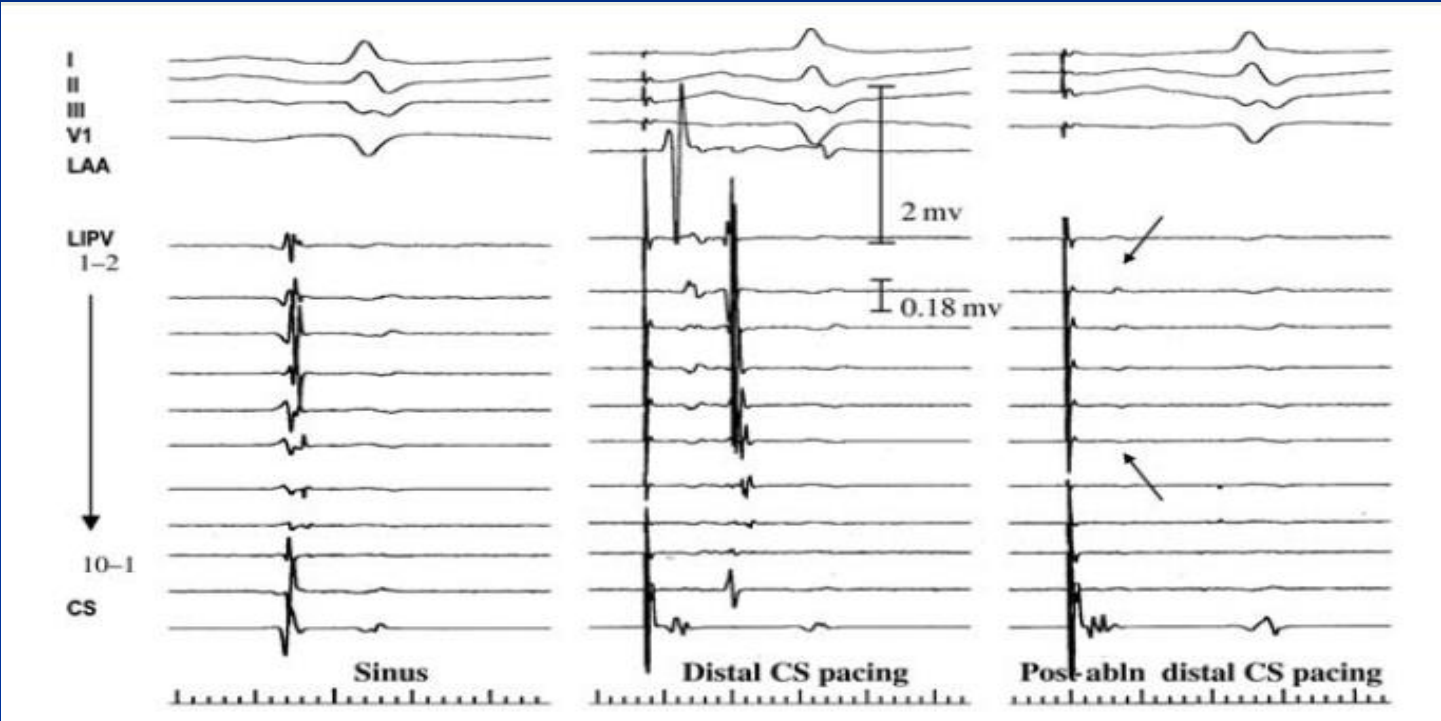
Konvansiyonel nokta-nokta RF ablasyonu

- Ensite
- CARTO

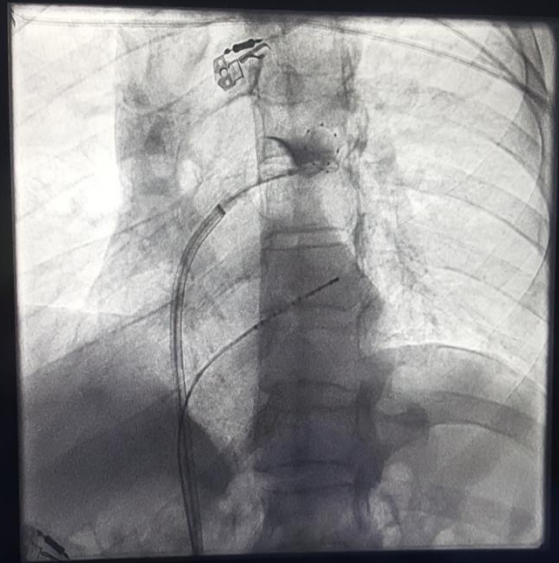
Balon temelli ablasyon

- CRYO
- Ultrasound, Laser, HIFU
- Hotballoon RF





LAO 28°
CRAN 2°
Height -5
SID 107
FD 48



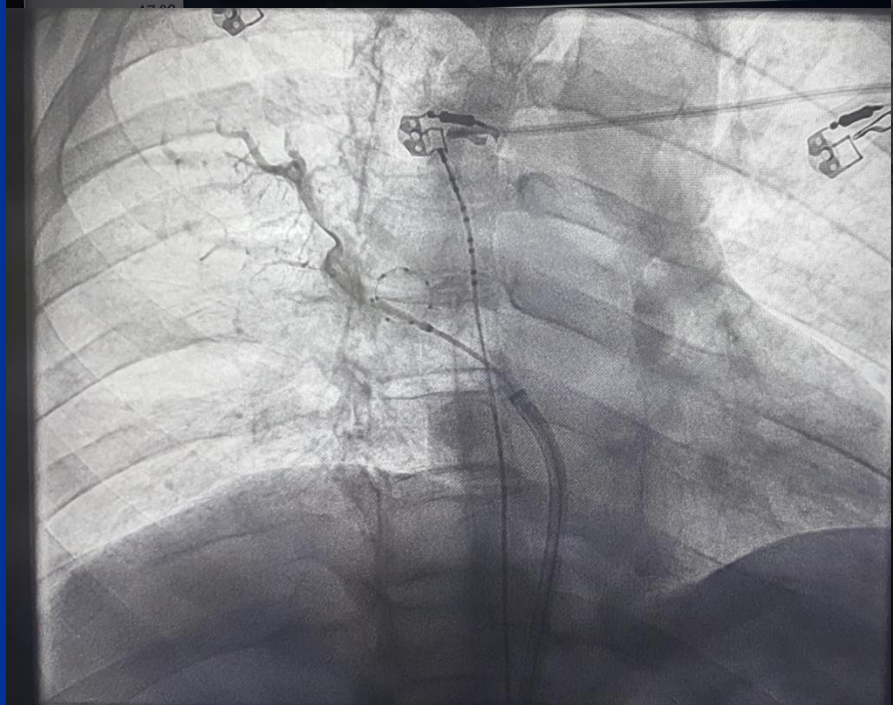
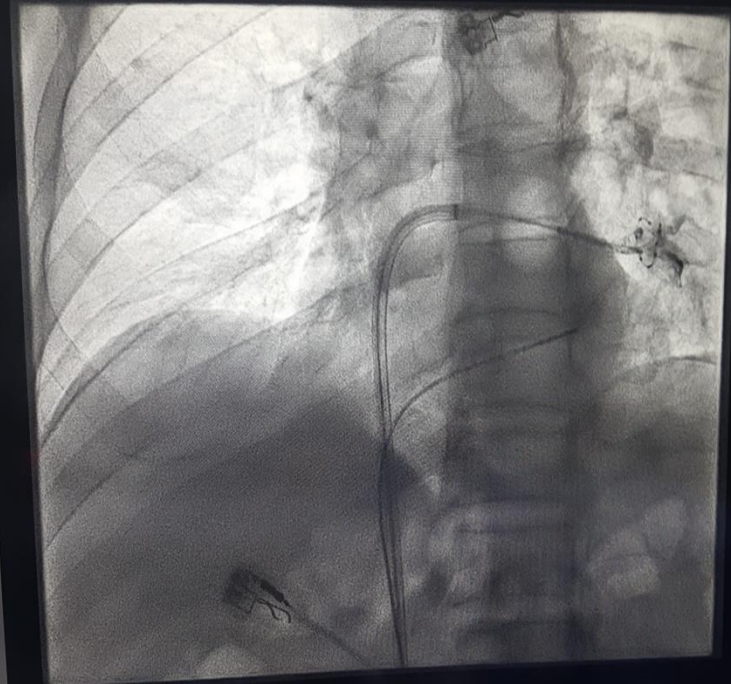
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01/09/1961
31/01/2017

21°
2°
-5
107
48

Exp 15
Fluo Medium
Time 03:02
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158 min
K 38 mGy

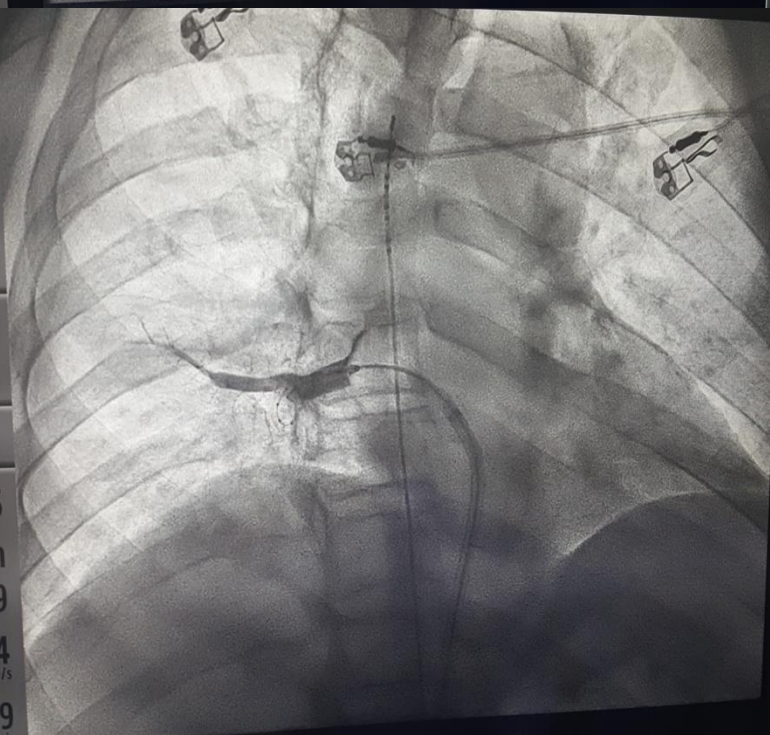
5
3

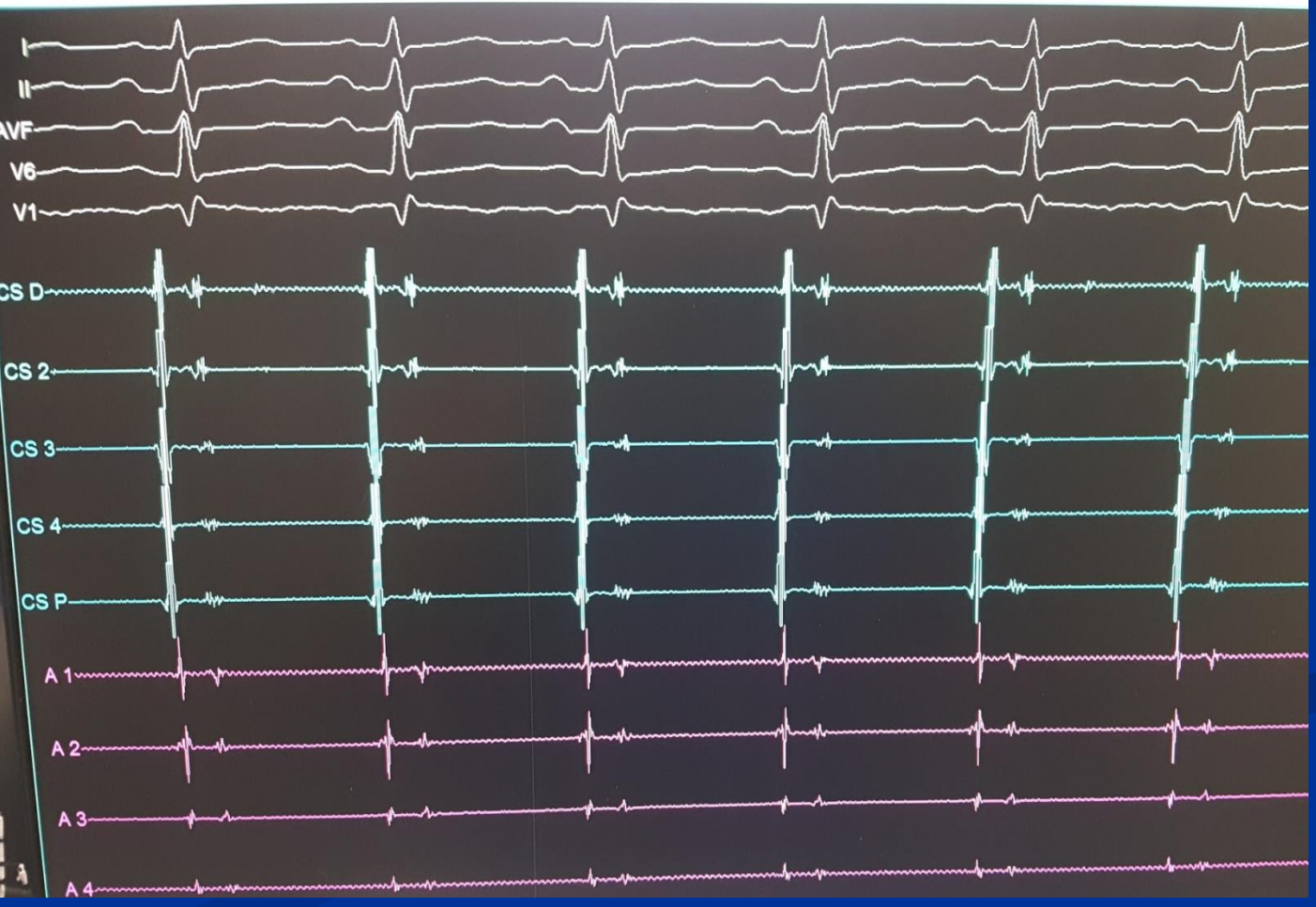
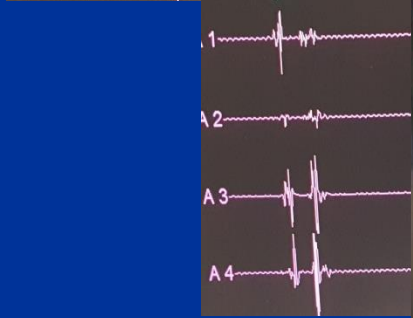
Exp 15
Fluo Medium
Time 05:00
K 0.17 mGy/s
188 min



LAO 29°
CRAN 2°
Height -5
SID 107
FD 48

Exp 15
Fluo Medium
Time 08:39
K 0.14 mGy/s
229 min





Arrhythmia/Electrophysiology

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

Atul Verma, MD; Fethi Kilicaslan, MD; Ennio Pisano, MD; Nassir F. Marrouche, MD;

Raffaele F.

nza, MD;

David O. Ma

Saliba, MD;

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.

Background—There is a long history of debate in conflicting studies regarding the efficacy of antiarrhythmic drugs in patients who could not be cured of AF by PVAI. We also recruited patients who were not cured by PVAI. All patients underwent antral isolation of all pulmonary veins. Conduction delay was defined as AF recurrence within 3 months (n=44) did not recur. Conduction was defined as AF recurrence within 3 months in group III, 267 patients developed in

as been debated (group I), patients with recurrent AF despite AF recurrence. >3 months after with complete block to PV (A-PV) recurrence was (n=37), and III left atrial (LA) to I (P=0.02). In by 69±47% for late, A-PV block

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.)

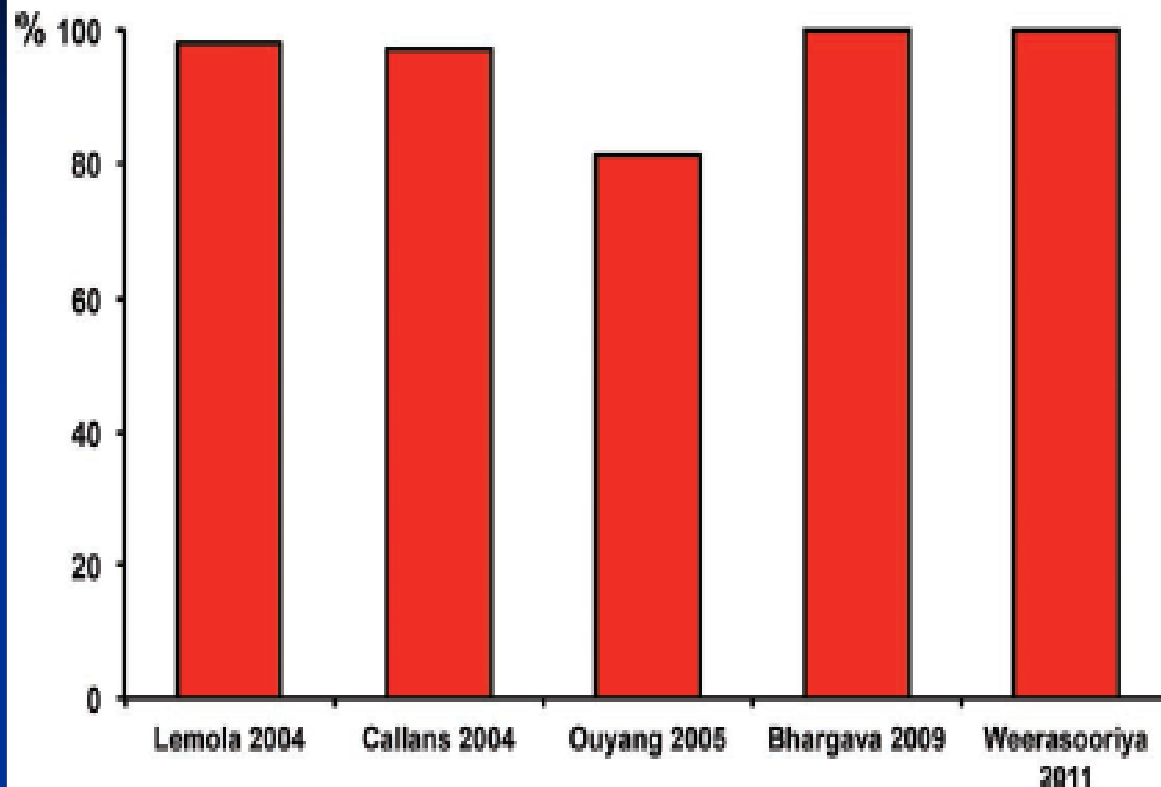


Figure 2. Prevalence of pulmonary vein reconnection in patients undergoing repeat catheter ablation procedures.



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

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

- Persistan AF atriyal fibrilasyon ve dilatasyona neden olarak AF'nin devamlılığını kolaylařtırmaktadır (atrial fibrillation begets atrial fibrillation).
- Persistan AF'da PV dıřı odaklar ve LA substratı daha önemli yer tutmaktadır.
- Bu hastalarda tek başına PVI yeterli deęildir. Sadece PVI ile 5 yıllık başarı oranı %24'dür.
- Başarıyı arttırmak için PV dıřı tetkikleyicilerin ablasyonu ve substrat modifikasyonu yapılmaktadır. Ancak ideal yaklařım 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.

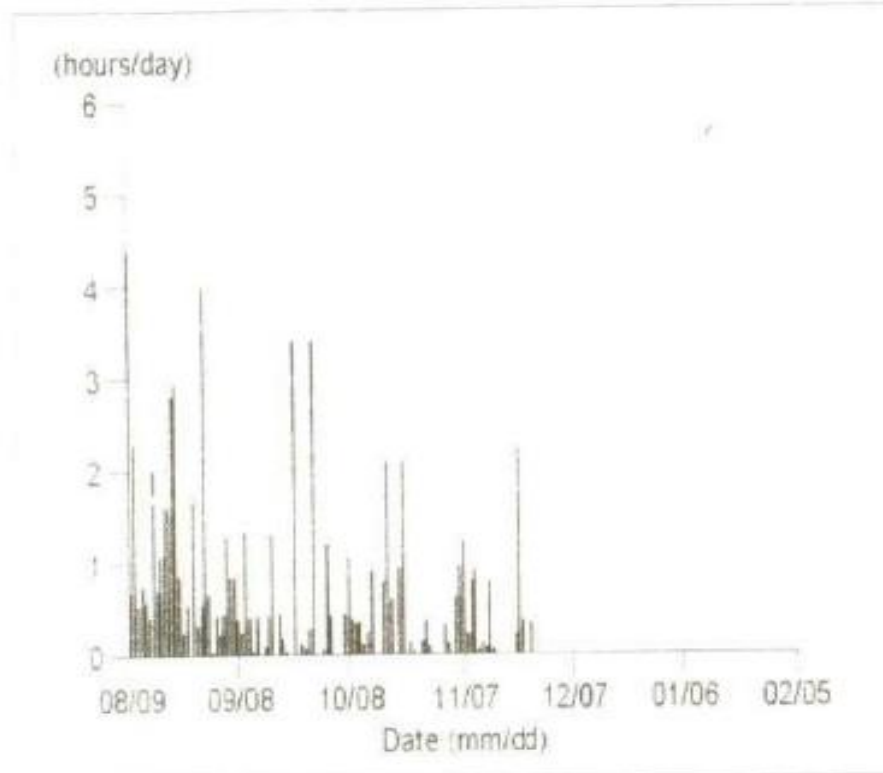
Pacemaker Model: Medtronic Adapta ADDR01
Serial Number: NWB947305

Software SW003 7.3
Copyright (c) Medtronic, Inc. 2005

Atrial Arrhythmia Trend Report

Page 1

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

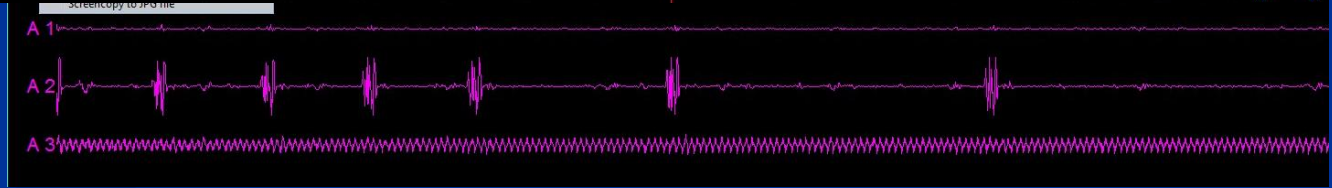
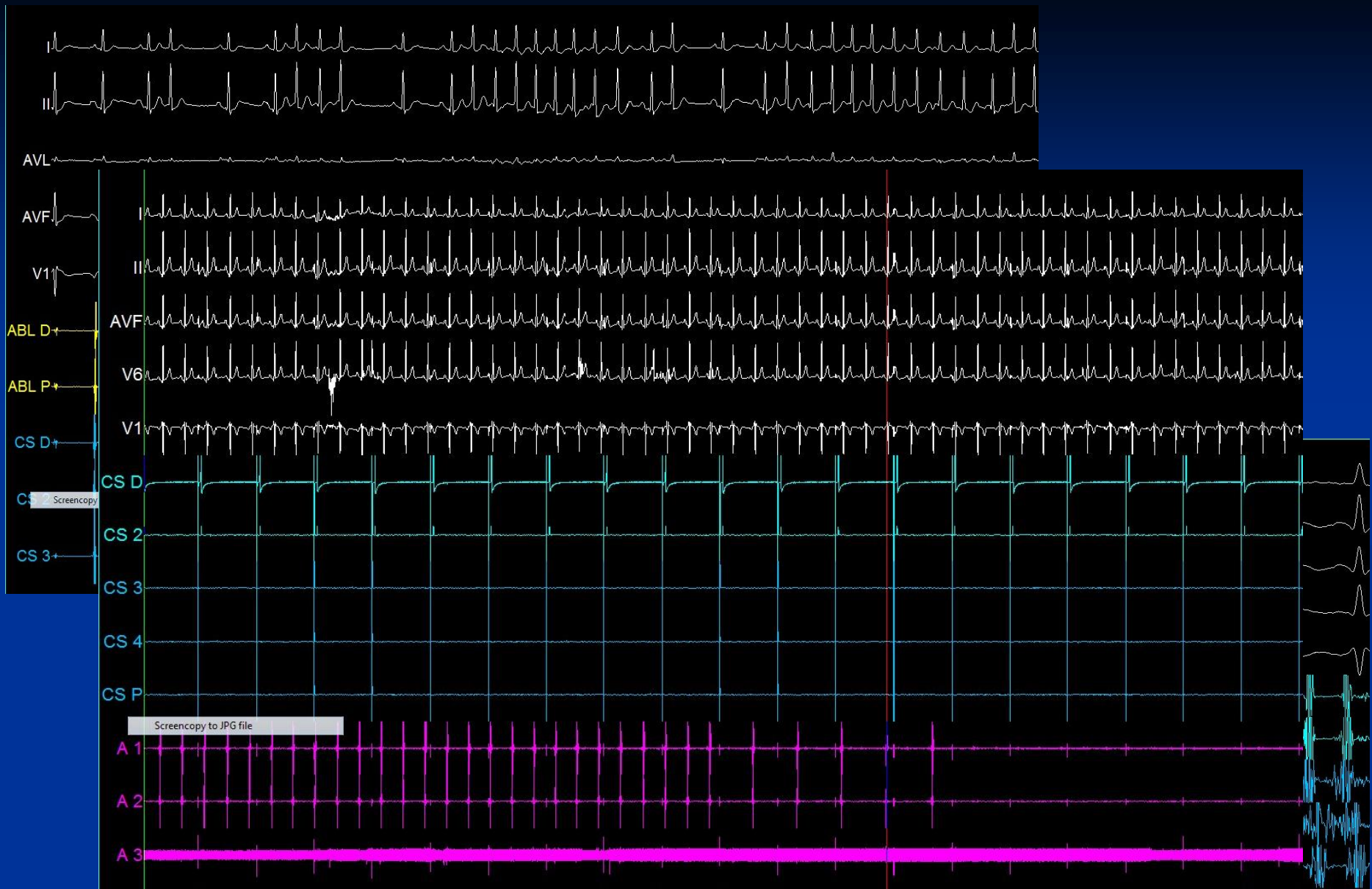


Initial Interrogation

| | |
|--------------------|-------------|
| 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?



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.,*

TABLE 2
Pattern of PV Reconduction 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 |

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 reconduction as a common phenomenon associated with AF recurrences. (*J Cardiovasc Electrophysiol*, Vol. 21, pp. 1079-1084, October 2010)

OPEN

Pascal I
Kati

Hüttner, MD,
rich, MD,

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

TABLE 1. Ethical Framework for the Use of Placebo in Clinical Trials¹⁵

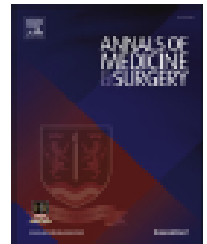
| Reference Question | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
|---|----|----|----|----|----|----|----|----|----|----|
| Is there a valuable, clinically relevant question to be answered by a placebo controlled procedure trial? | + | + | + | + | + | + | + | + | + | + |
| Is the placebo control 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? | ? | ? | ? | ? | ? | + | + | ? | ? | + |



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journal homepage: www.annalsjournal.com



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

H I G H L I G H T S

- 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 plasebo 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.