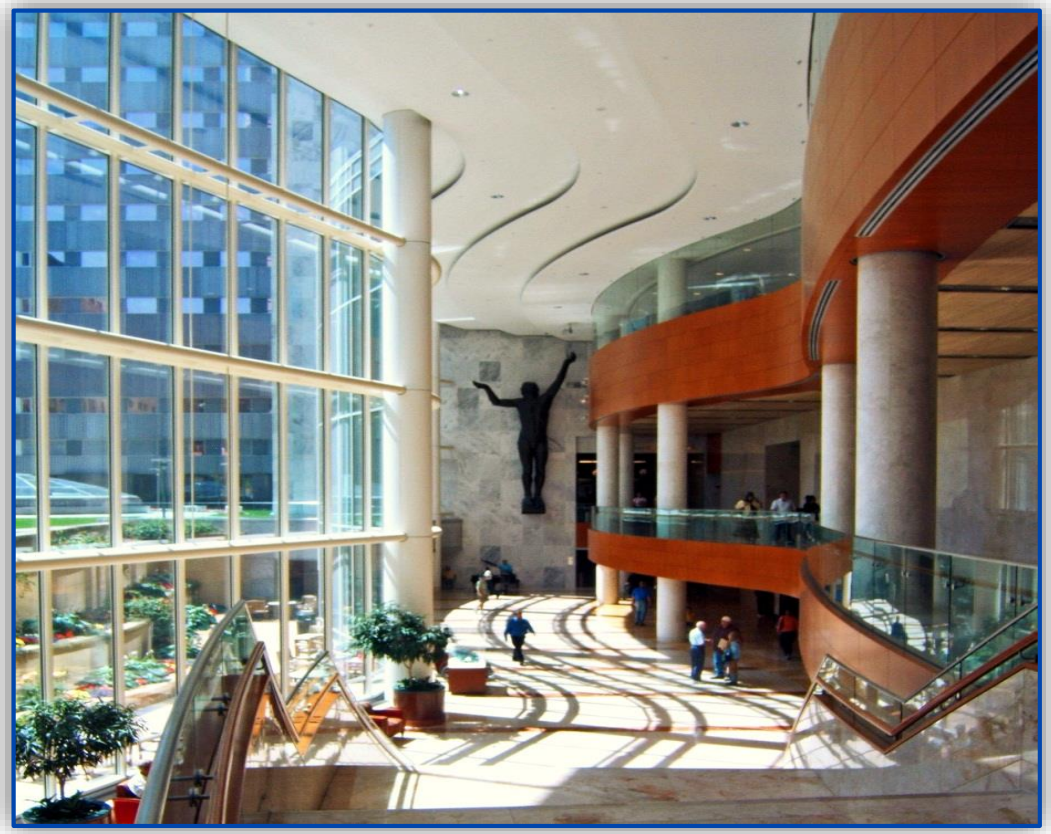
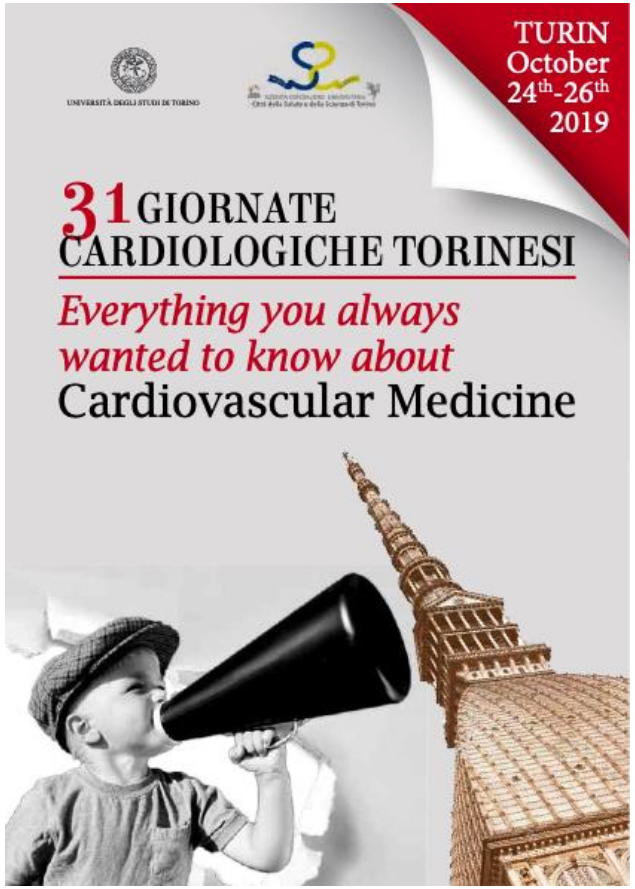




Atrial Fibrillation as a vascular disease

Amir Lerman, MD

Barbara Woodward Lips Endowed Professor

Director Cardiovascular Research Center

Mayo Clinic, Rochester, MN

MAYO CLINIC

Research

JAMA | Original Investigation

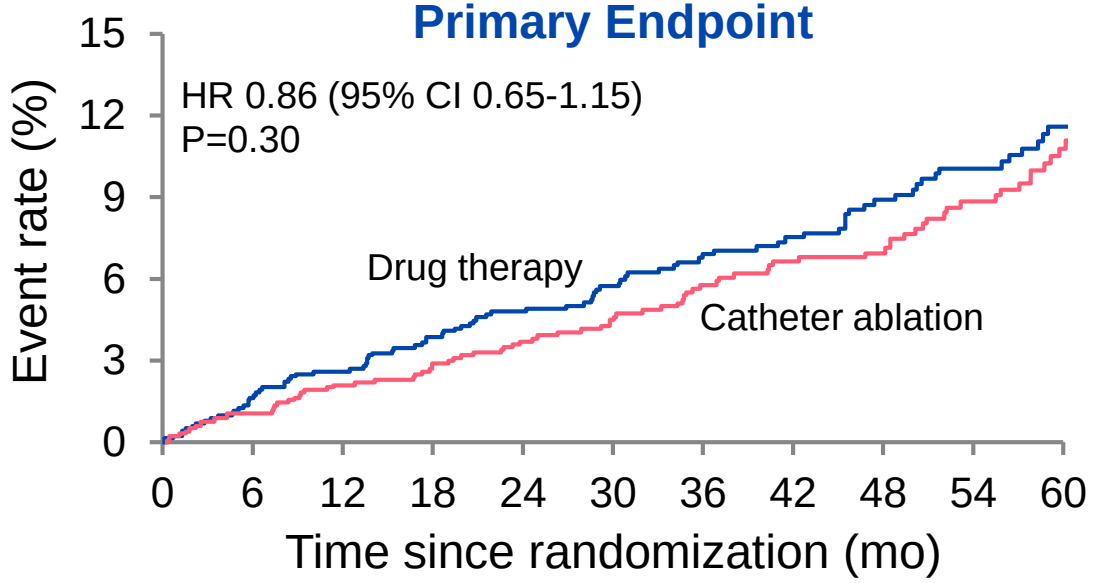
Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation

The CABANA Randomized Clinical Trial

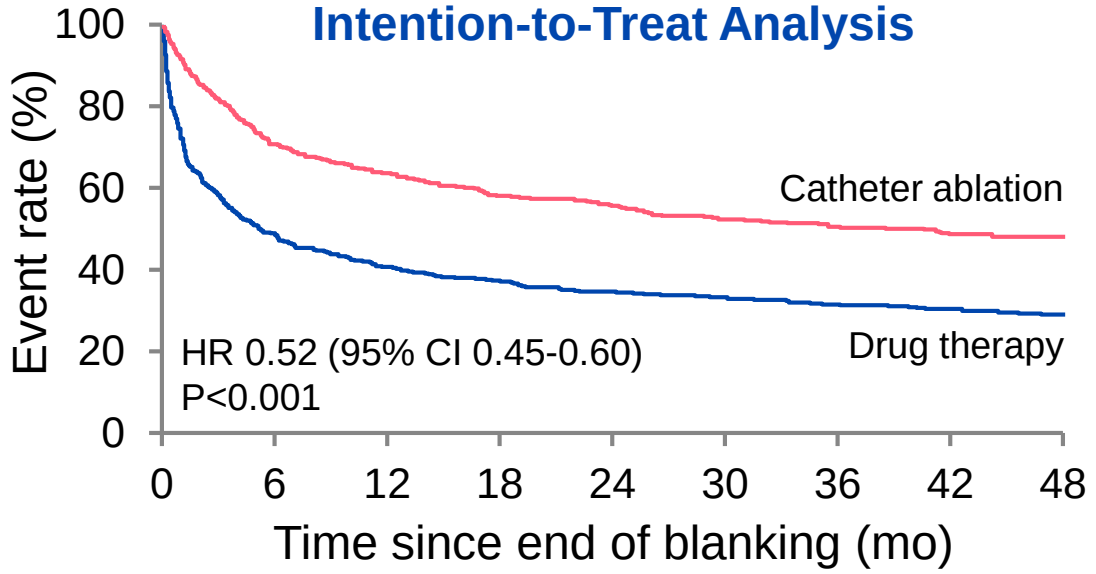
A total of 2204 symptomatic patients with AF aged 65 years and older or younger than 65 years with ≥1 risk factors for stroke were enrolled from November 2009-April 2016, with follow-up through December 31, 2017

Baseline characteristics	Catheter ablation (%) n=1108	Drug therapy (%) n=1096
HTN or LVH	73.4	84.7
HTN	79.1	82.2
LVH	38.7	42.1
Diabetes	25.3	25.7
Sleep apnea	23.6	22.5
CAD	18.8	19.7
Heart failure	15.7	14.9

K-M Estimates of Incidence of Primary Endpoint



Recurrent AF After Blanking by Intention-to-Treat Analysis



Packer et al: JAMA 321:1261, 2019

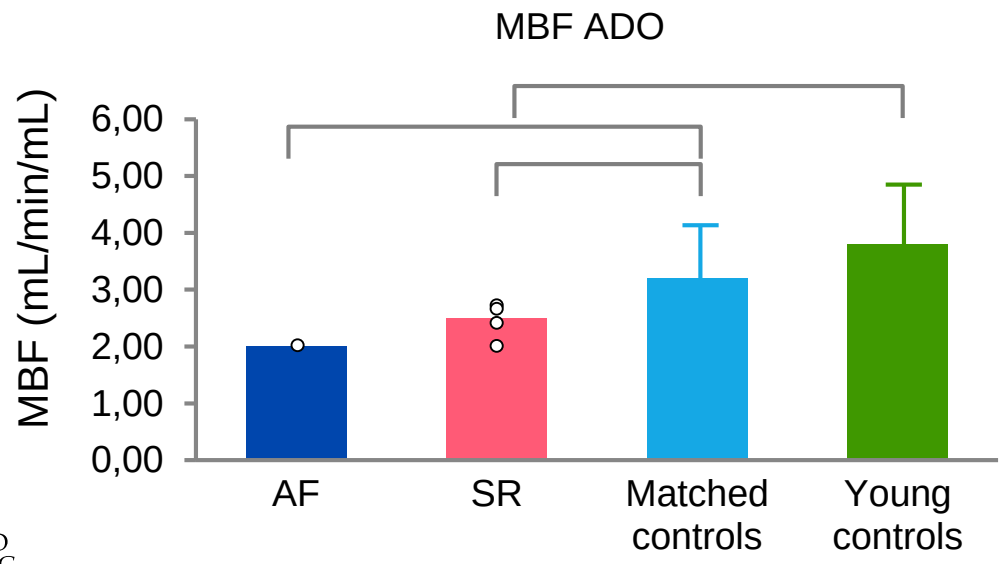
MAYO CLINIC

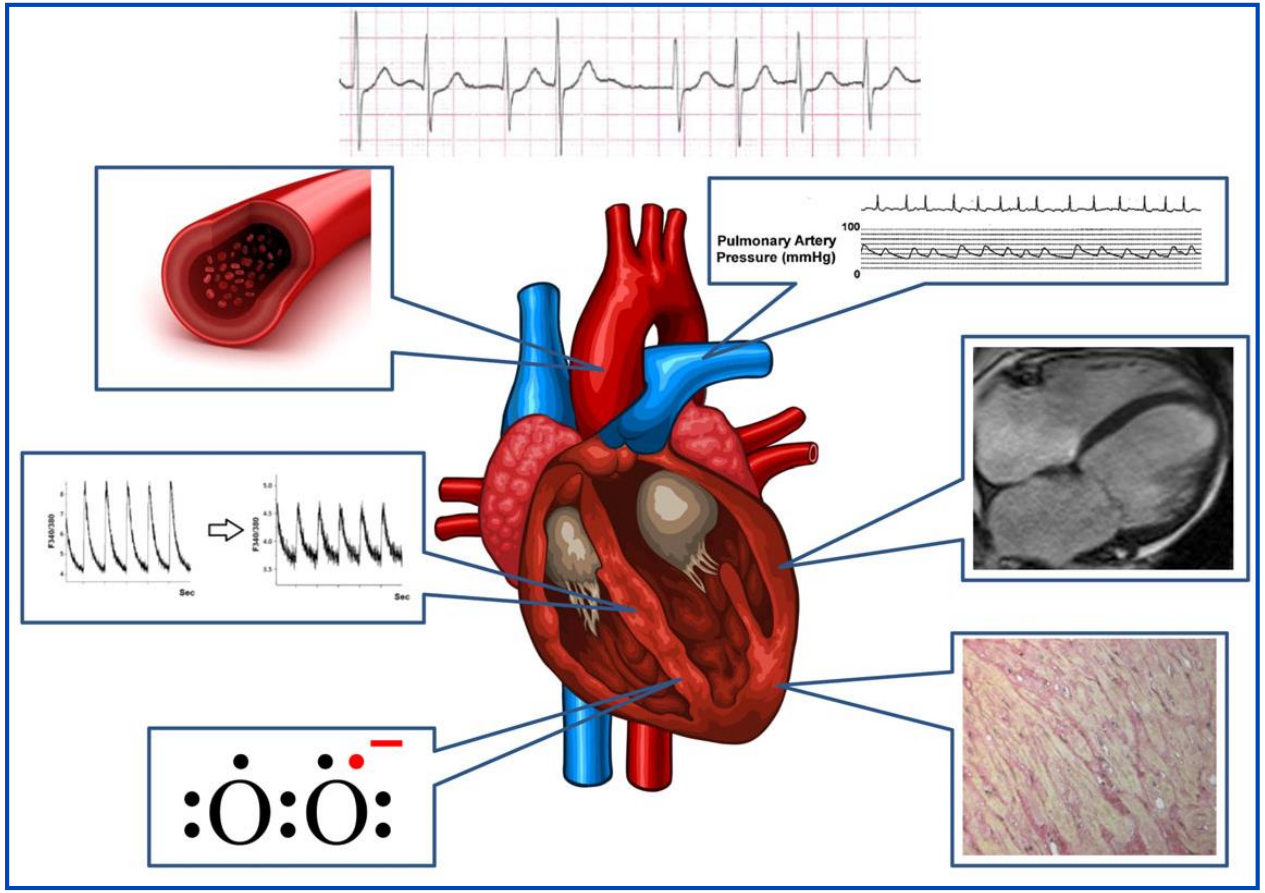
Atrial fibrillation: effects beyond the atrium?

Rohan S. Wijesurendra* and Barbara Casadei

It is increasingly recognized that AF is more than an atrial disease, being associated with systemic inflammation, endothelial dysfunction, and adverse effects on the structure and function of the left ventricular myocardium that may be prognostically important.

Myocardial Blood Flow in Patients by PET during AF and during SR after Cardioversion (SR) in Comparison With Age-/Risk-matched and Young Controls as Measured at Under Adenosine for Assessment of Perfusion Reserve





Systemic Effects of AF. Clockwise from Top Right: Adverse Hemodynamic Effects; Ventricular Remodeling and Dysfunction; Diffuse and Focal Myocardial Fibrosis; Ventricular Oxidative Stress; Impaired Ventricular Calcium Handling; Inflammation and **Impaired Endothelial Function**, Myocardial Perfusion, and Perfusion Reserve.

Wijesurendra: Cardiovascular Research 105, 238, 2015

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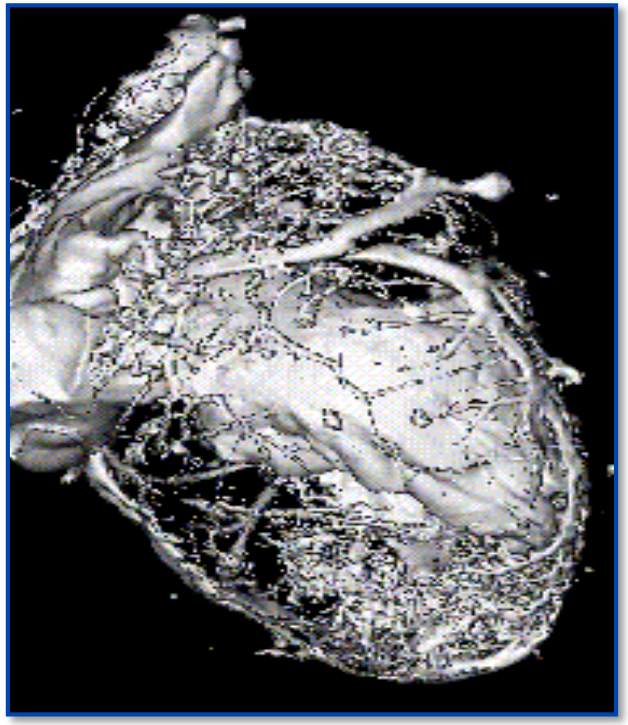
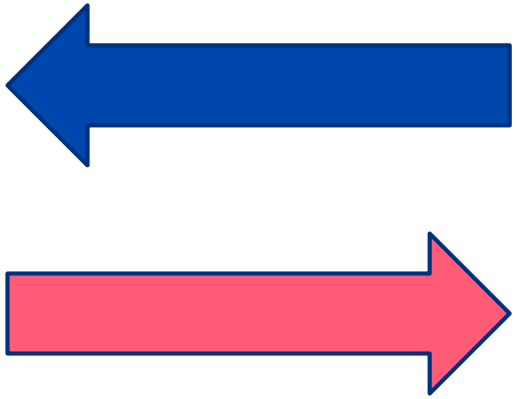
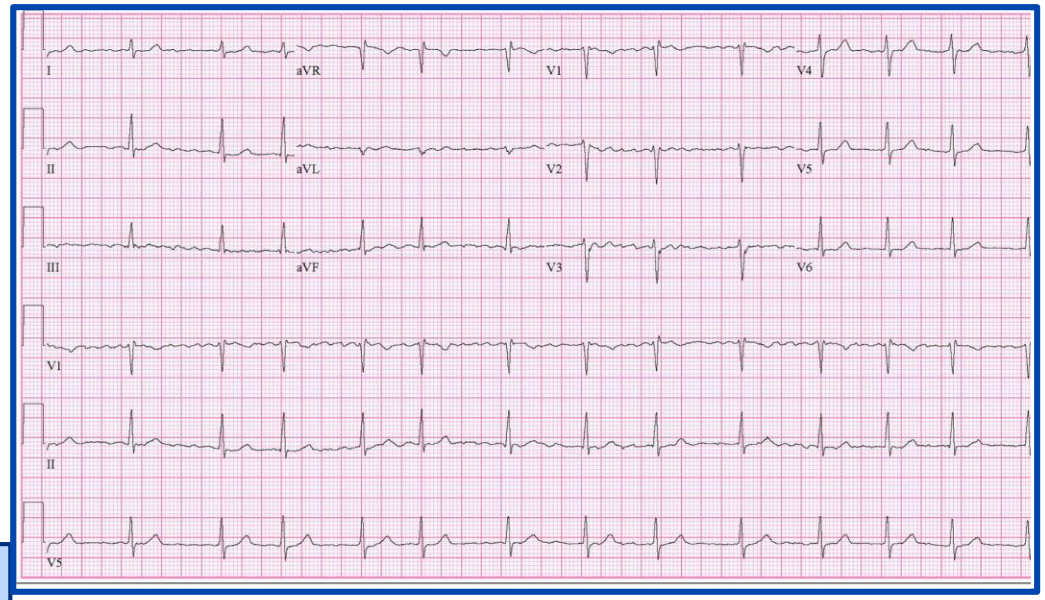
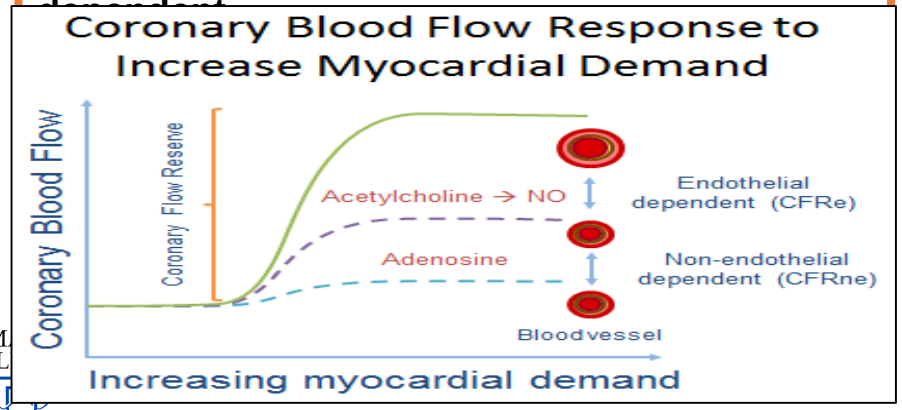
Atrial Fibrillation as a vascular disease





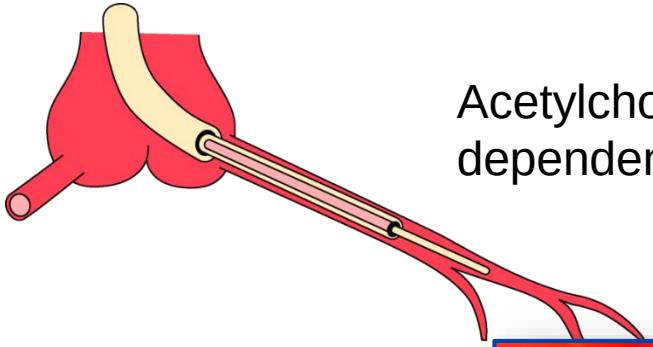


High oxygen extraction 60-80% vs. 20-30% in skeletal muscle: coronary perfusion is flow dependent

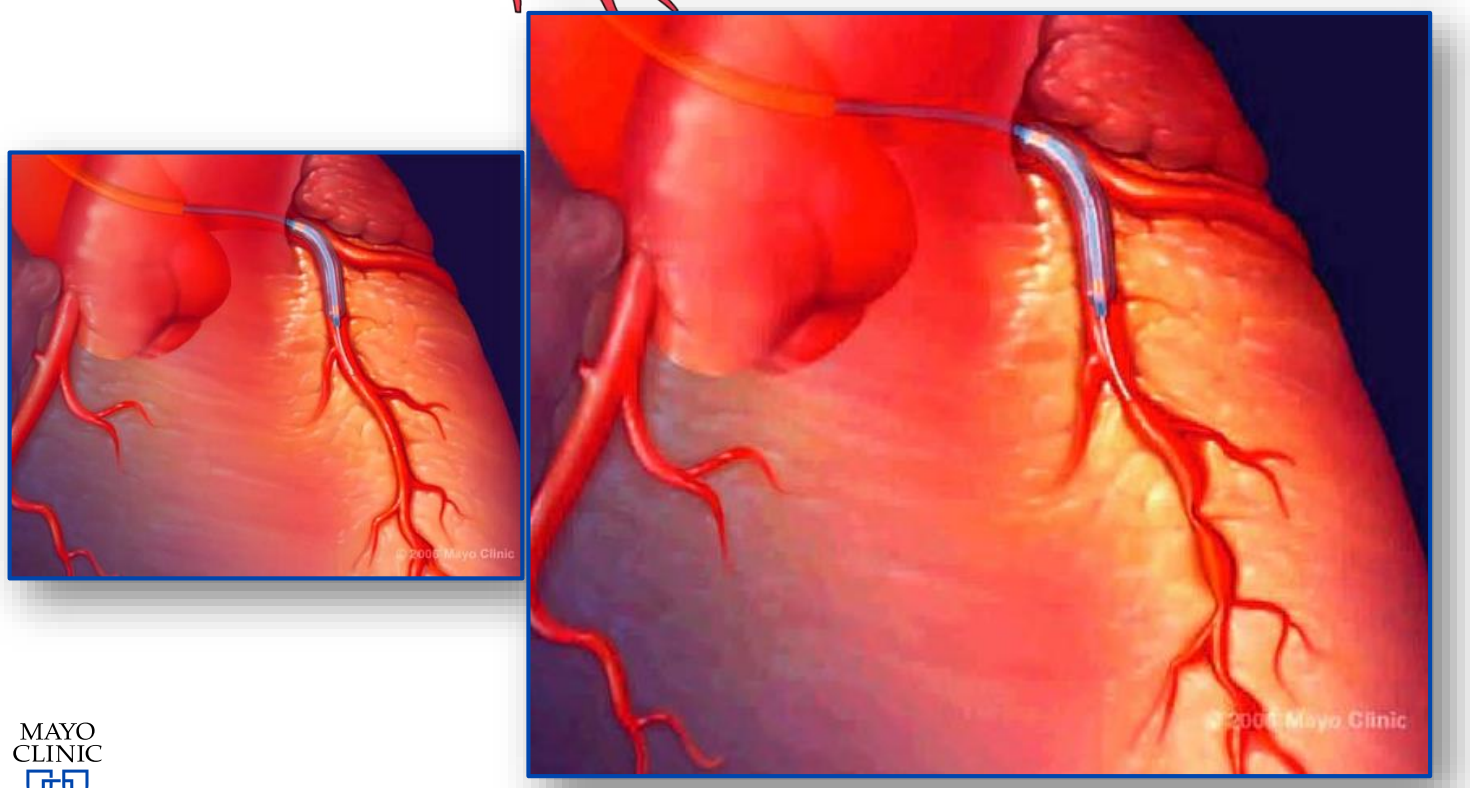


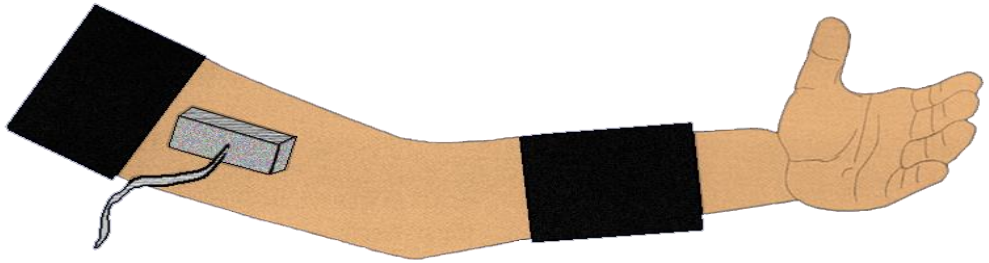
Precipitating factors

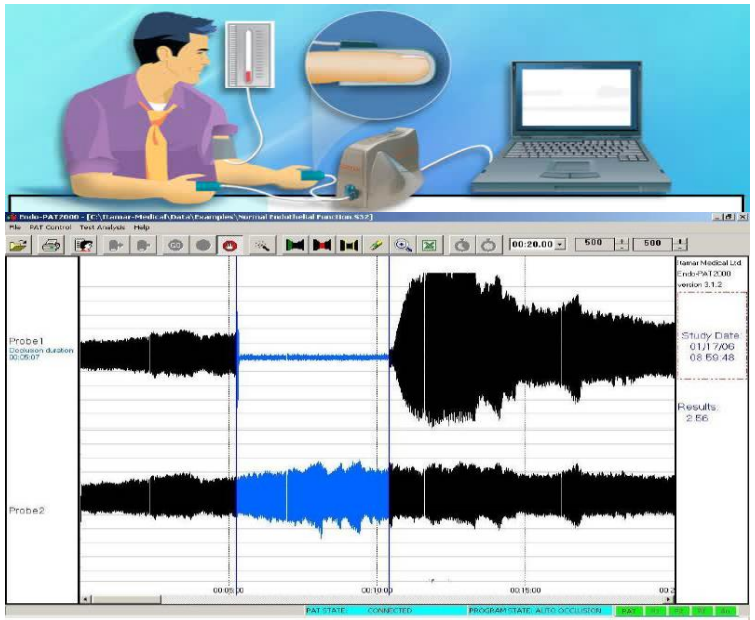
Assessment of Vascular Function:

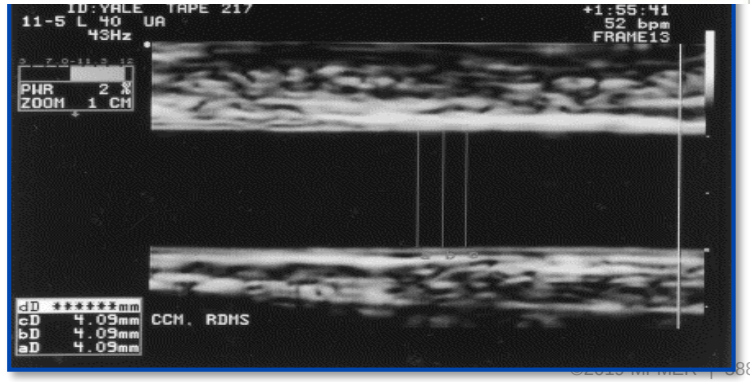


Acetylcholine (endothelium dependent vasodilator)









MAYO CLINIC

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis

Yasushi Matsuzawa, MD, PhD; Taek-Geun Kwon, MD, PhD; Ryan J. Lennon, MS; Lilach O. Lerman, MD, PhD; Amir Lerman, MD

Background—Endothelial dysfunction plays a pivotal role in cardiovascular disease progression, and is associated with adverse events. The purpose of this systematic review and meta-analysis was to investigate the prognostic magnitude of noninvasive peripheral endothelial function tests, brachial artery flow-mediated dilation (FMD), and reactive hyperemia—peripheral arterial tonometry (RH-PAT) for future cardiovascular events.

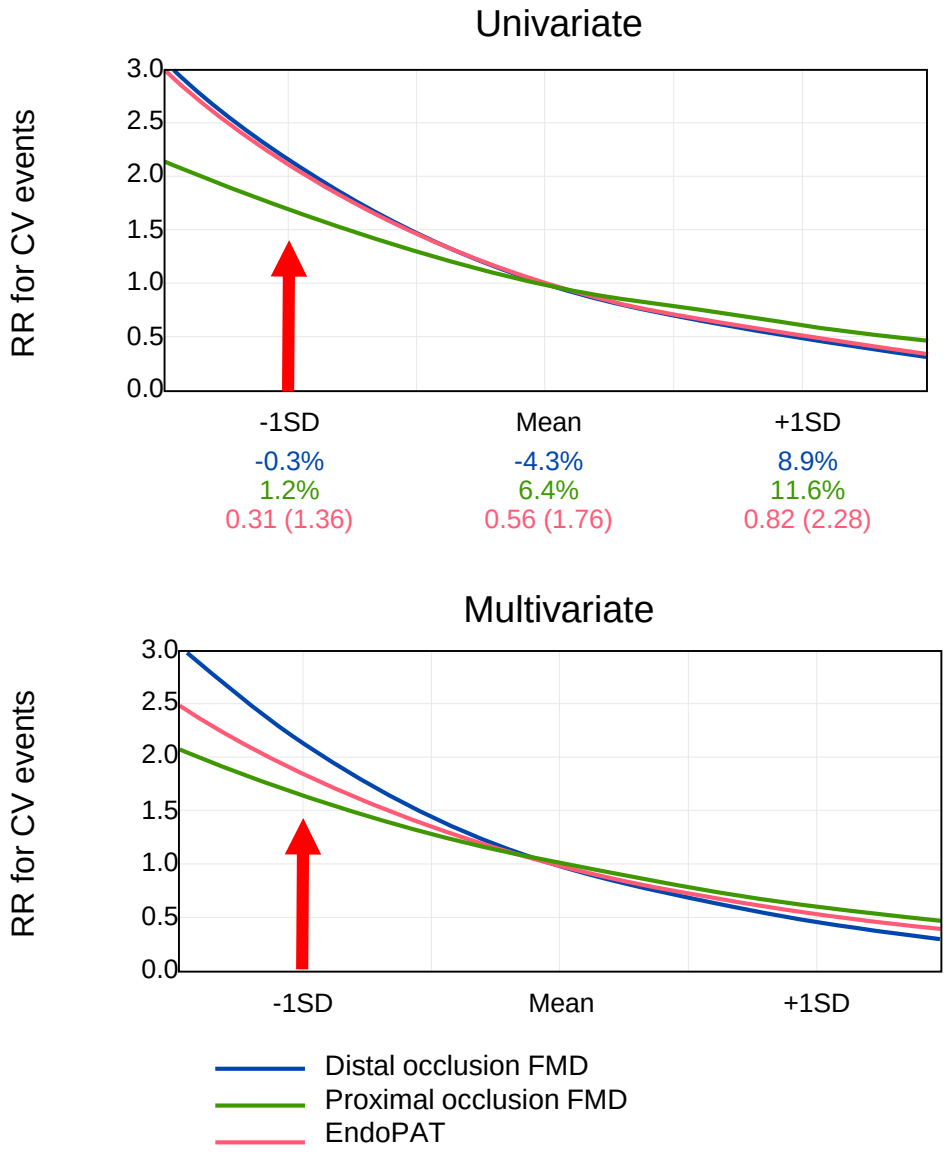
- Thirty-five FMD studies of 17 280 participants and 6 RH-PAT studies of 602 participants were included in the meta-analysis.
- The magnitude of the prognostic value in cardiovascular disease subjects was comparable between these 2 methods

Mayo Clinic, Rochester, MN.

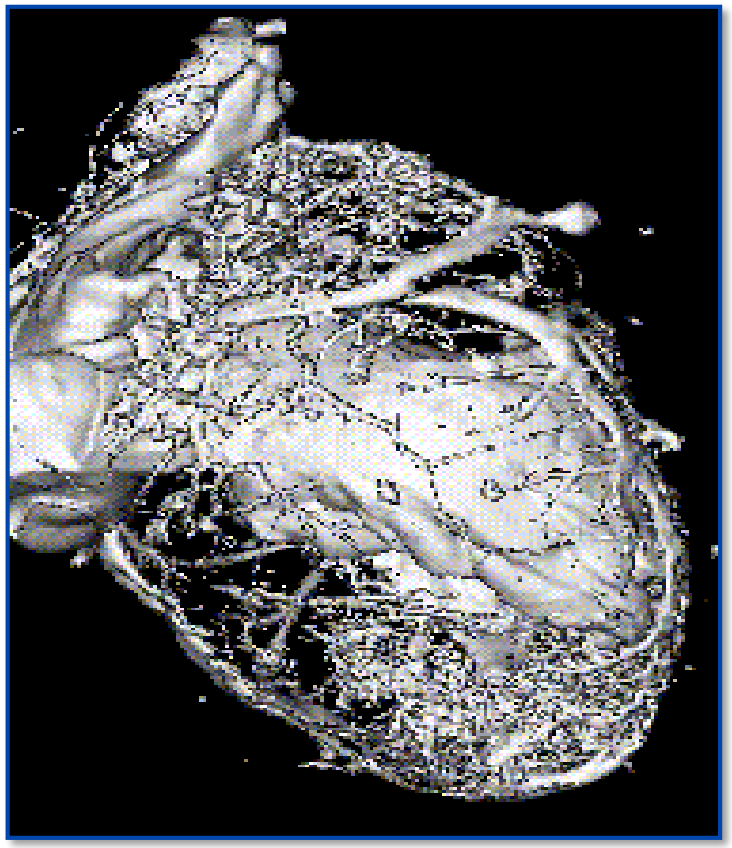
during cardiac catheterization. More recently, several nonin-

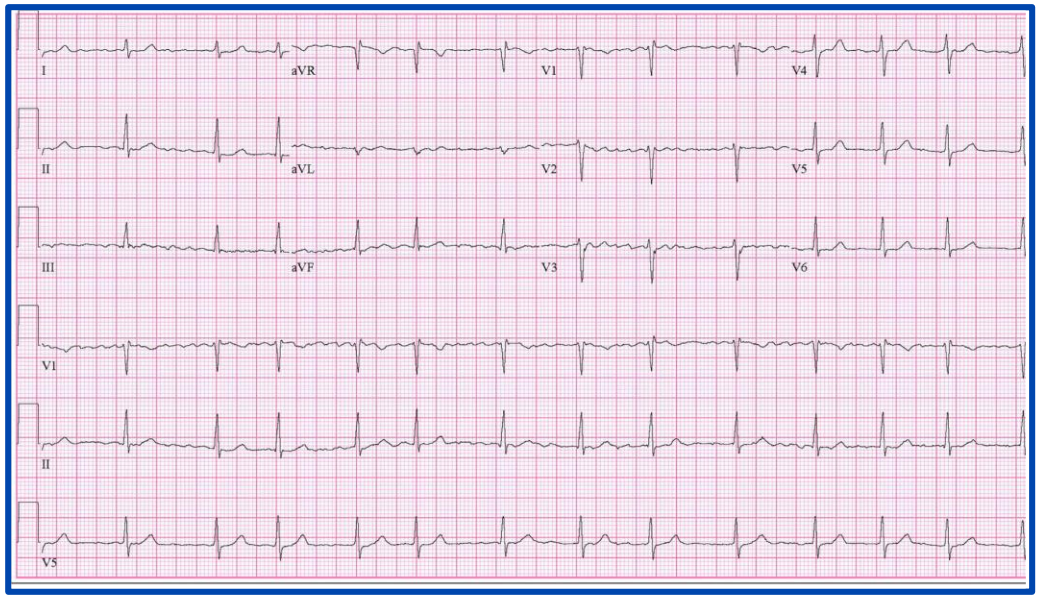
A 1 SD worsening in endothelial function was associated with double cardiovascular risk.

Relative Risk for FMD and Endo PAT



Atrial Fibrillation as a vascular disease





Precipitating factors

Downregulation of Endocardial Nitric Oxide Synthase Expression and Nitric Oxide Production in Atrial Fibrillation

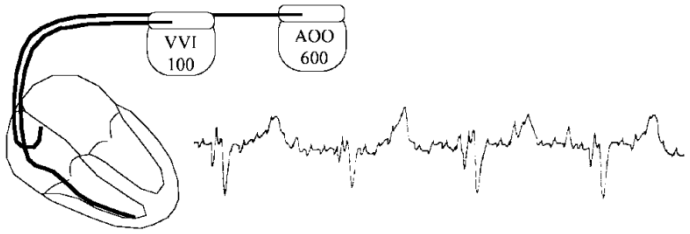
Potential Mechanisms for Atrial Thrombosis and Stroke

Hua Cai, MD, PhD; Zongming Li, MD; Andreas Goette, MD; Fernando Mera, MD; Clegg Honeycutt, MS; Kristian Feterik, MD; Josiah N. Wilcox, PhD; Samuel C. Dudley, Jr, MD, PhD; David G. Harrison, MD; Jonathan J. Langberg, MD

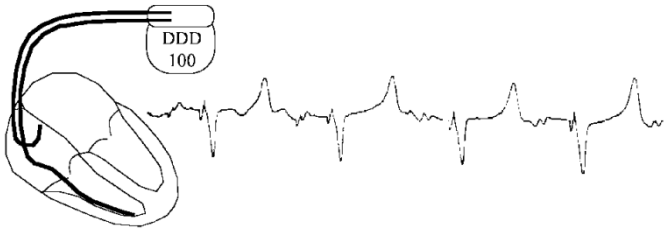
In the arterial endothelium laminar flow and cyclical stretch induce expression of NO synthase (NOS); we hypothesized that atrial fibrillation (AF) causes a downregulation of atrial endocardial NOS expression and NO production

Diagram of pacing methods used in experimental and control groups

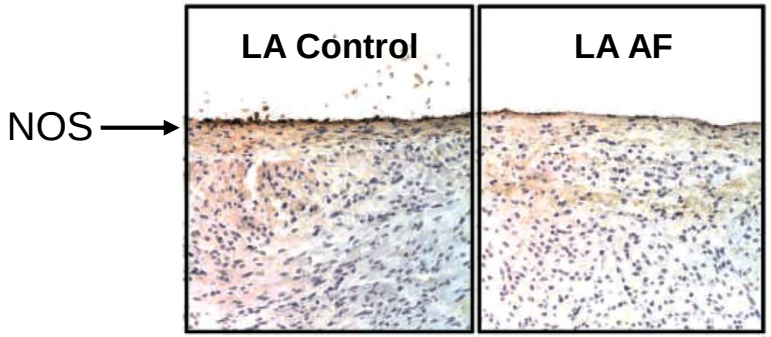
Experimental Group – AV block, rapid atrial pacing, ventricular pacing at 100 BPM



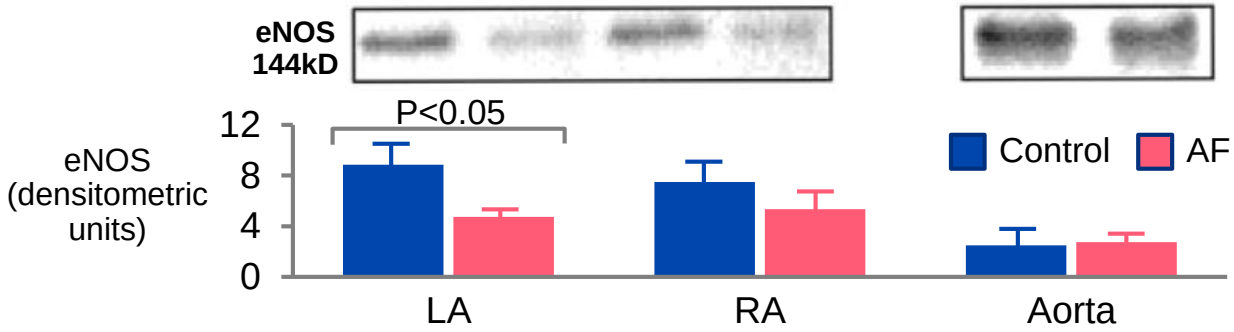
Control Group – AV block, dual chamber pacing at 100 BPM



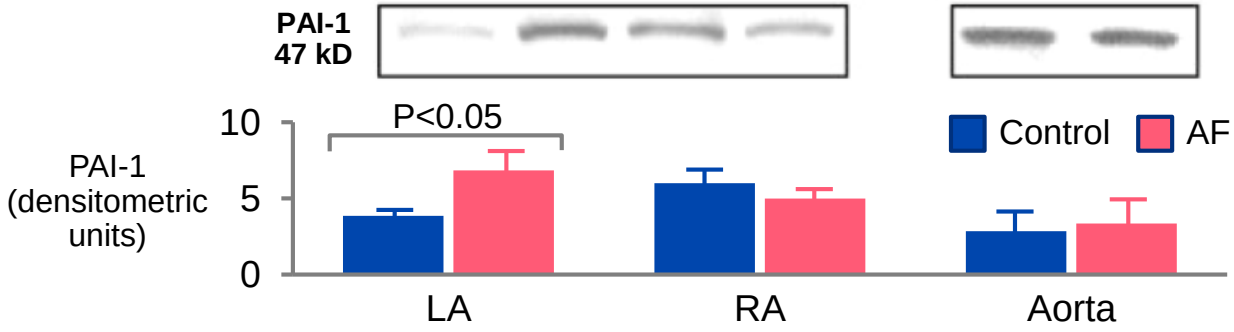
NOS Protein Expression in Left Atria Isolated from Control and AF Animals Determined by Immunohistochemical Staining



NOS Protein Expression in Atrial and Aortic Tissues Isolated from Control and AF animals Determined by Western Analysis



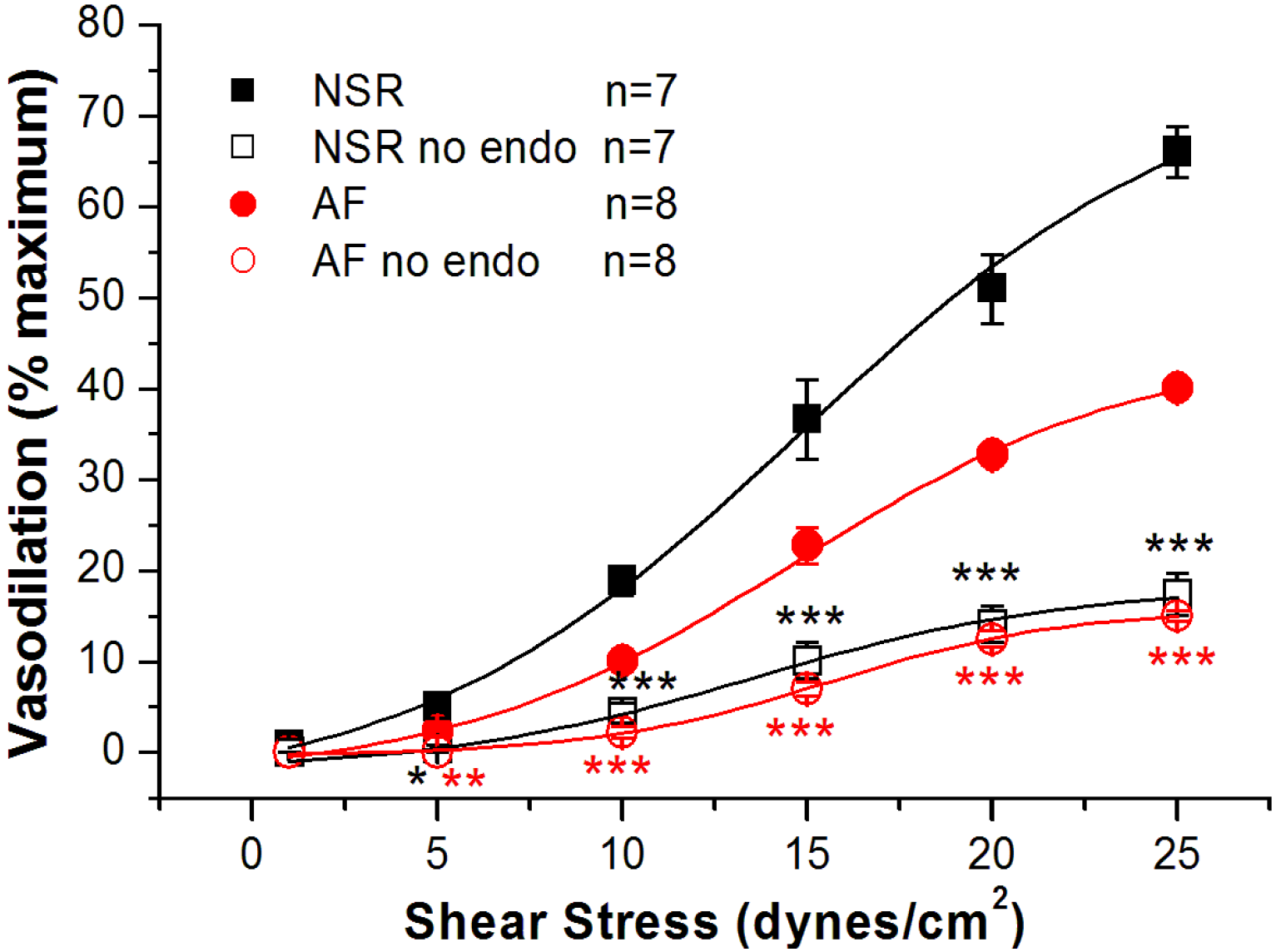
PAI-1 Protein Expression in LA Isolated from Control and AF Animals Determined by Western Analysis



Cai H et al: Circulation 106:2854-2858, 2002

MAYO CLINIC

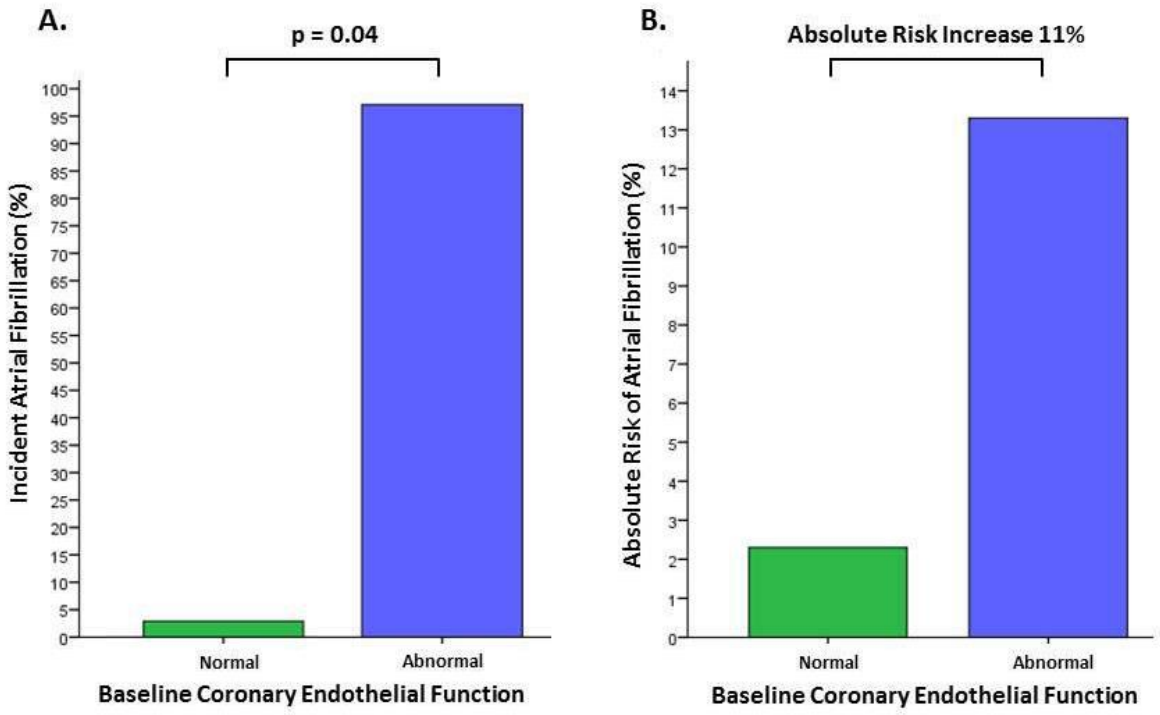
Attenuated Atrial Microvascular Function in Patents with AFib



Curtesy of Dr. HC Li

Coronary Endothelial Dysfunction and Incidence of AFib

300 patients, and no history of AF underwent coronary endothelial function assessment incident AF over a mean follow-up period of 10.5 ±5.5 years.

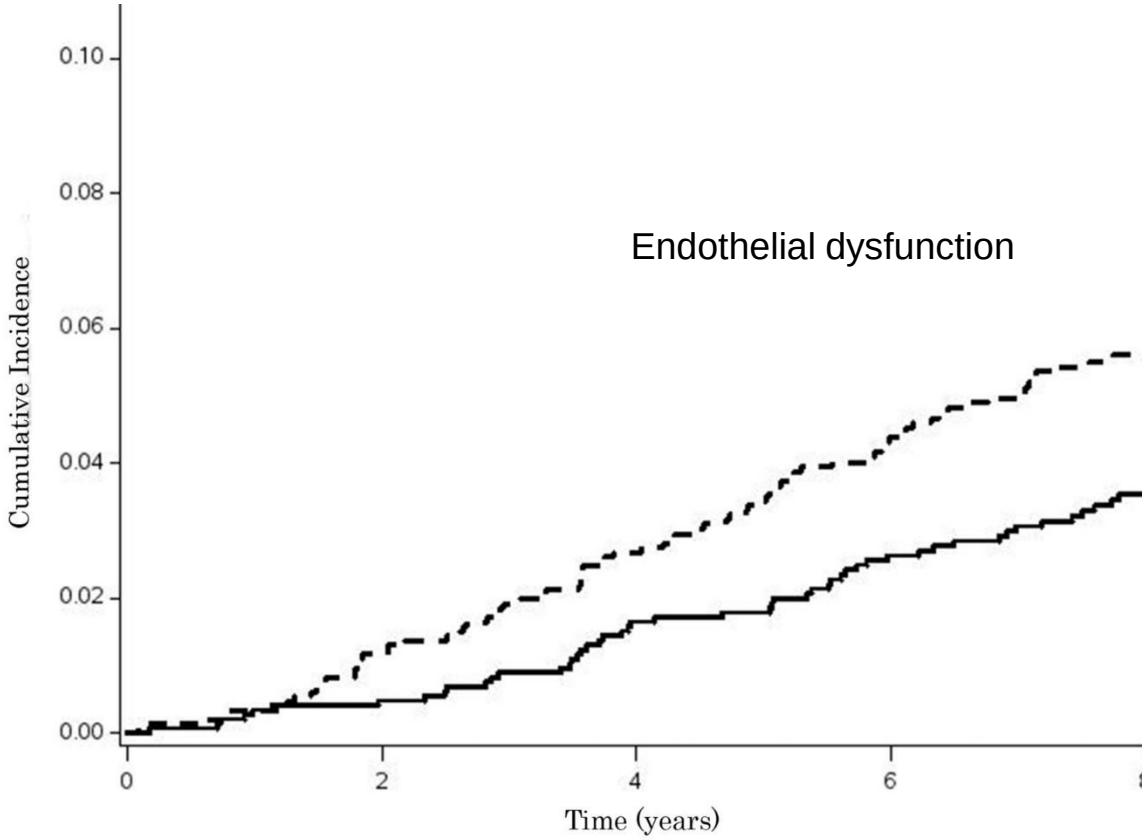


CED was associated with 11% increased absolute risk and 5.8-fold increased relative risk of incident AF

Published in final edited form as:
Arterioscler Thromb Vasc Biol. 2014 December ; 34(12): 2717–2720. doi:10.1161/ATVBAHA.114.304560.

Brachial Flow-Mediated Dilation and Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

A total of 2,936 participants (rom the Multi-Ethnic Study of *Atherosclerosis* with available ultrasound brachial FMD measurements who were free of baseline AF, median follow-up of 8.5 years



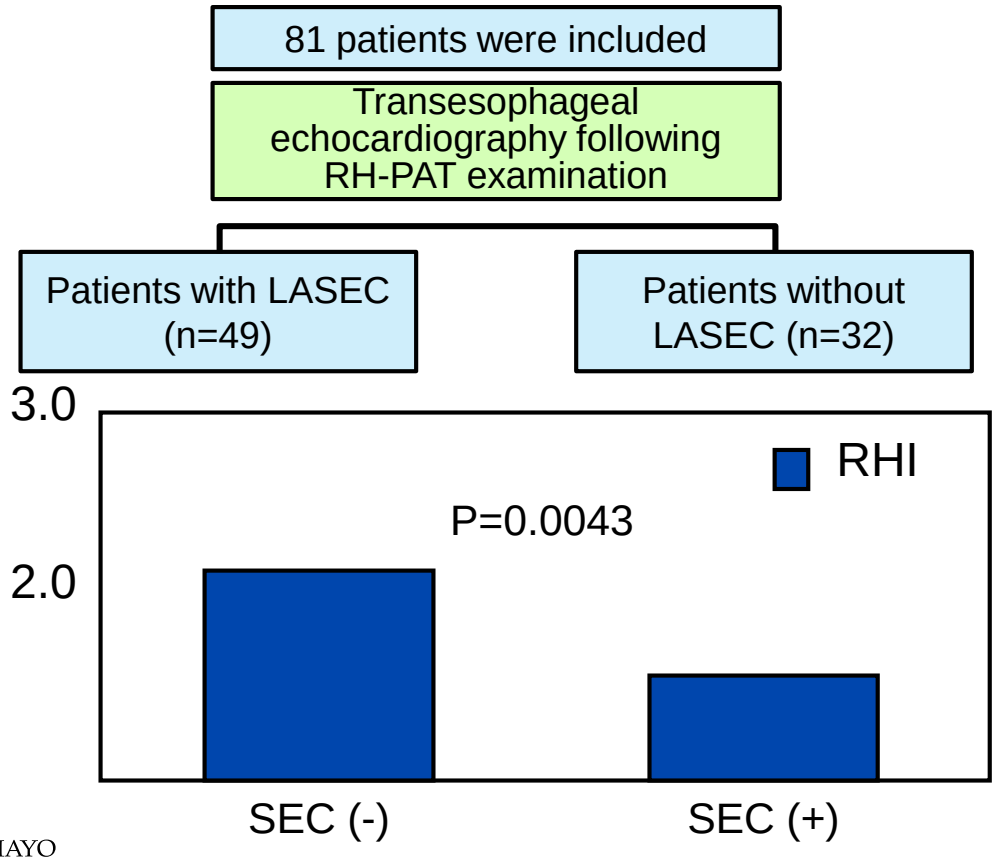
MAYO CLINIC

Corban & Lerman (in review)

Clinical Significance of Peripheral Endothelial Function for Left Atrial Blood Stagnation in Nonvalvular Atrial Fibrillation Patients With Low-to-Intermediate Stroke Risk

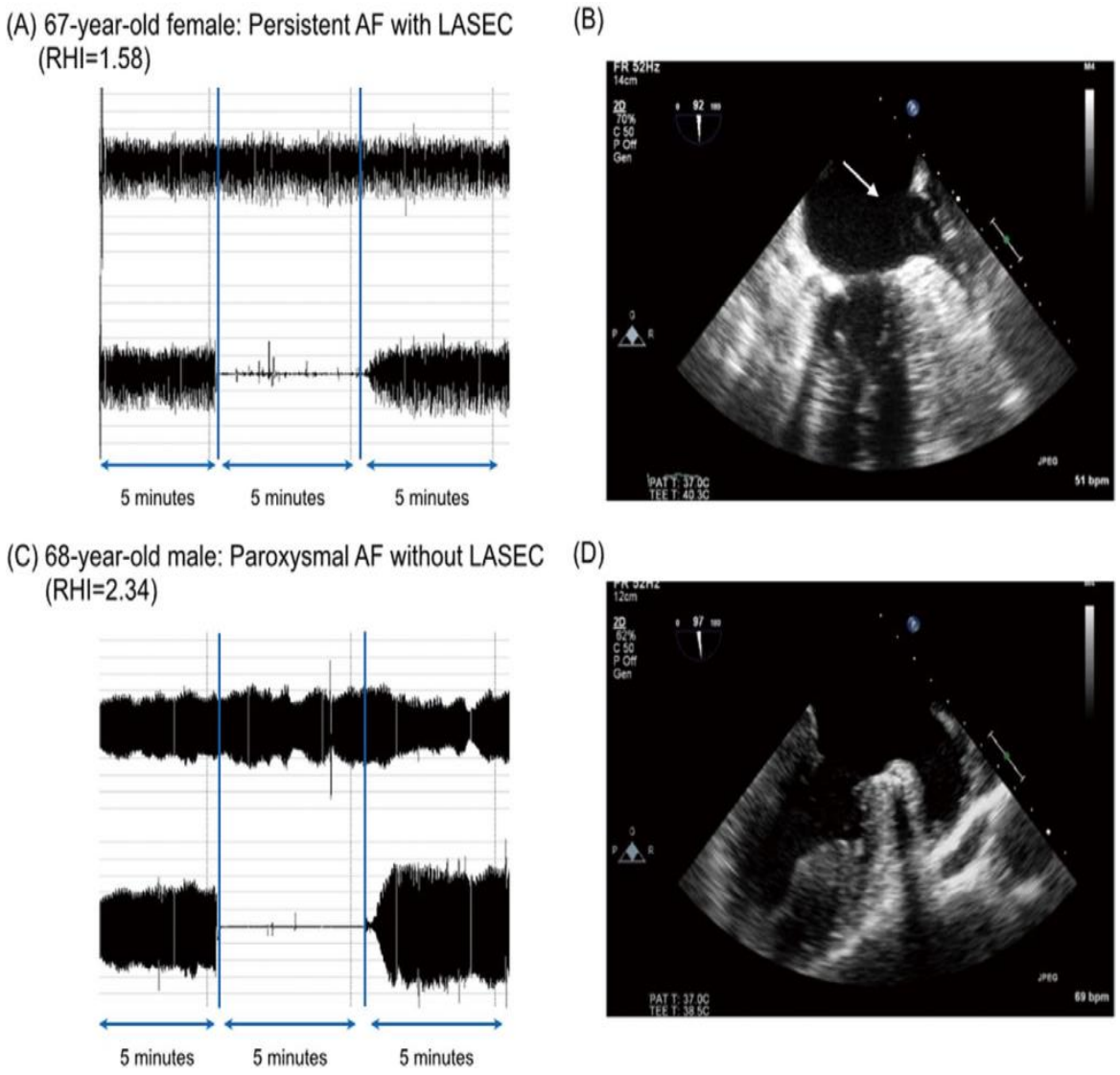
Akira Fujii, MD; Katsuji Inoue, MD; Takayuki Nagai, MD; Teruyoshi Uetani, MD; Kazuhisa Nishimura, MD; Jun Suzuki, MD; Jun-ichi Funada, MD; Takafumi Okura, MD; Jitsuo Higaki, MD; Akiyoshi Ogimoto, MD

This study aimed to determine whether impaired endothelial function assessed by reactive hyperemia-peripheral arterial tonometry (RH-PAT) predicted left atrial blood stagnation in these patients



; LASEC, left atrial spontaneous echo contrast; LVEF, left ventricular ejection fraction; RH-PAT, reactive hyperemia-peripheral arterial tonometry.

RH-PAT Examination and TEE in Patients with and Without , left atrial spontaneous echo contrast



Fujii et al: *Circ J* 2016; **80:** 2117-2123, 2016

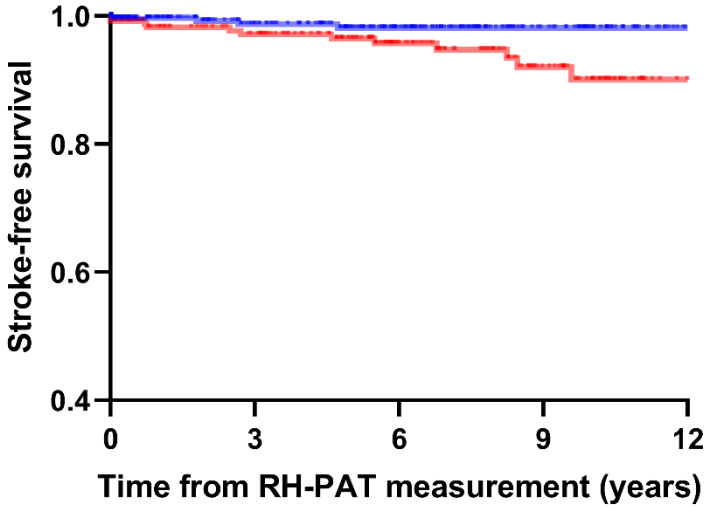
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

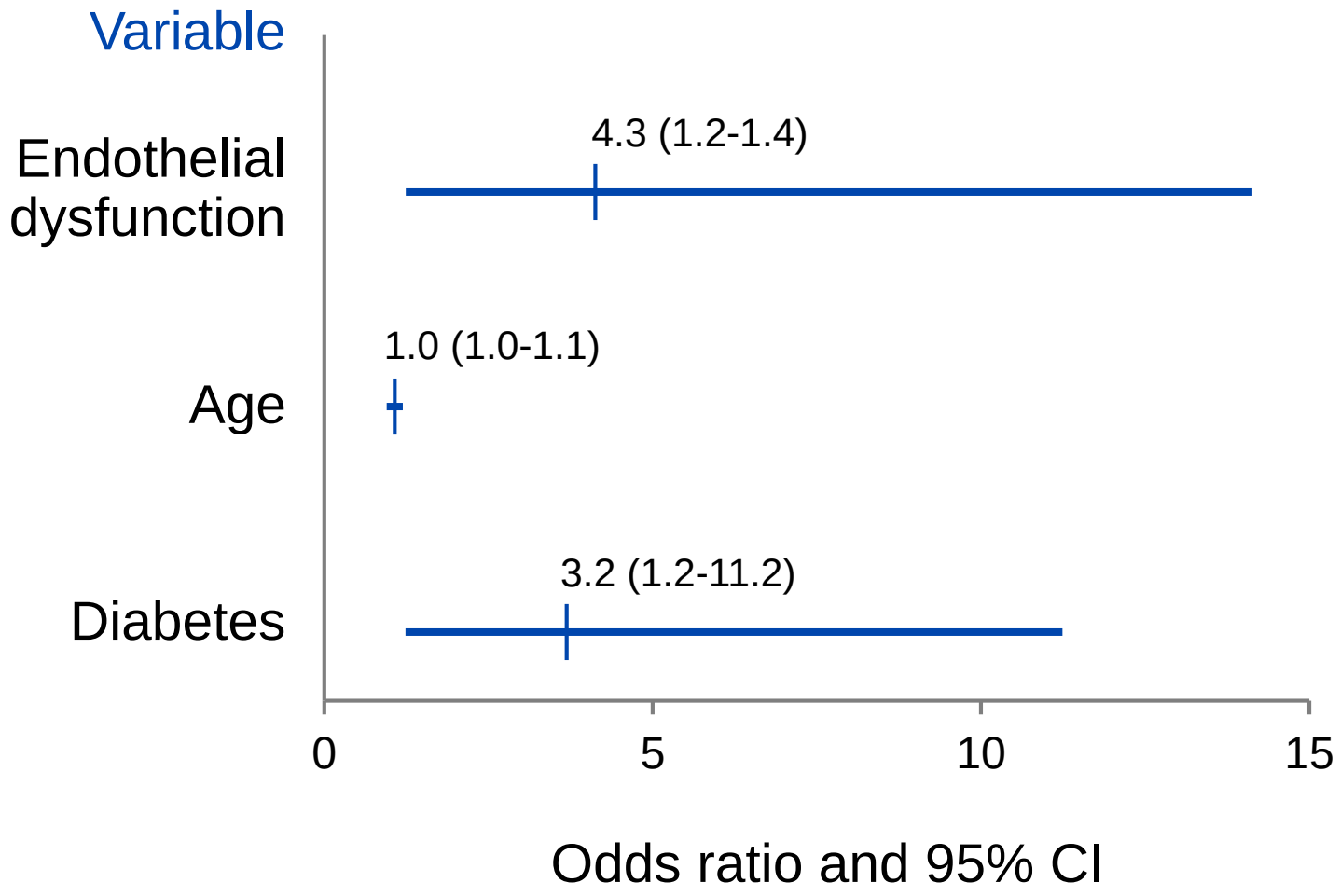
Coronary Endothelial Dysfunction Is Associated With an Increased Risk of Cerebrovascular Events

Paul V. Targonski, Piero O. Bonetti, Geralyn M. Pumper, Stuart T. Higano, David R. Holmes, Jr and Amir Lerman

503 patients, mean age of 52 years old without obstructive coronary artery disease who underwent coronary endothelial function testing by intracoronary acetylcholine infusion.

Peripheral endothelia function and stroke





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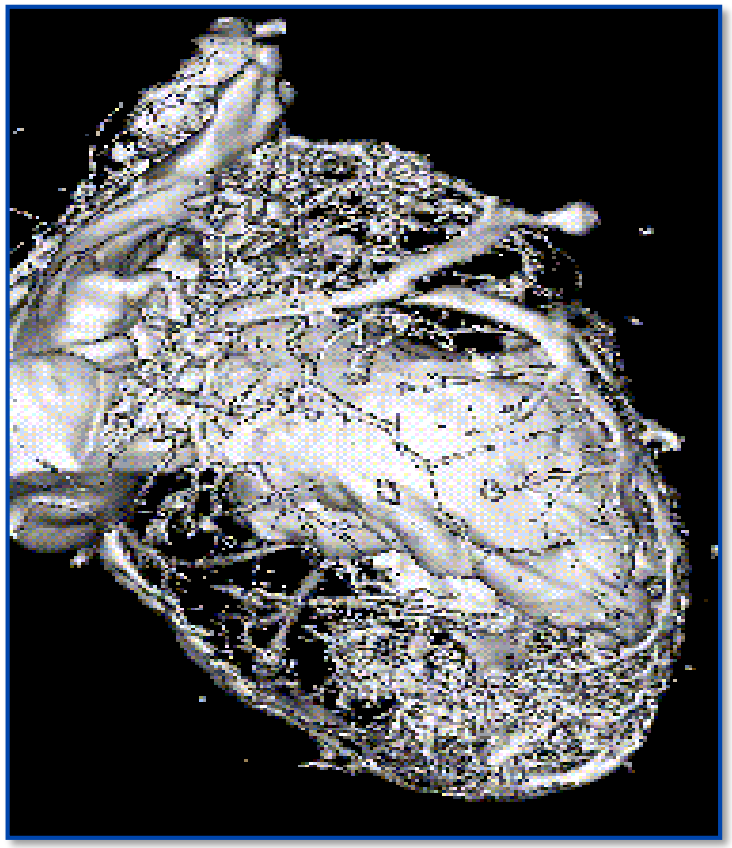
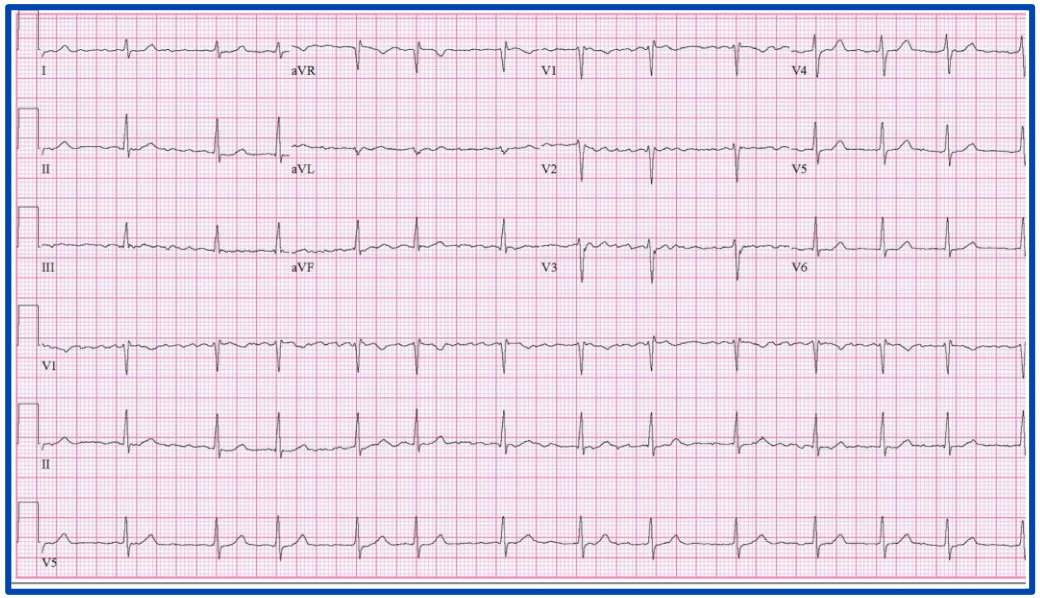
Targonski and Lerman: Circulation 107, 2003

Atrial Fibrillation as a vascular disease





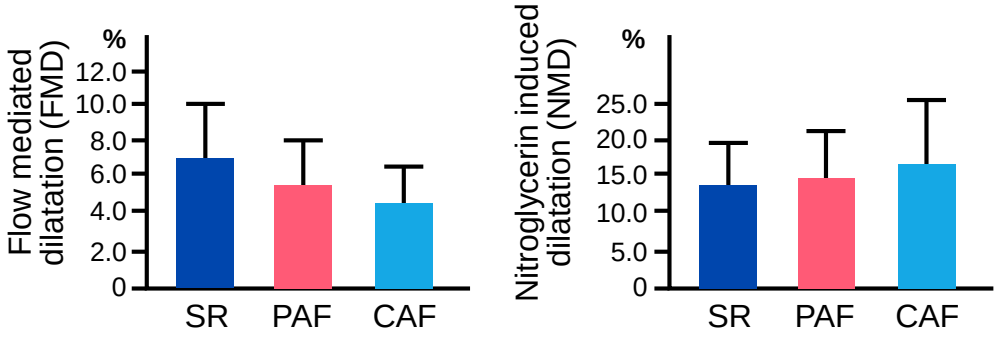
Precipitating factors

MAYO CLINIC

Relationship between Impairment of the Vascular Endothelial Function and the CHA_2DS_2-VASc Score in Patients with Sinus Rhythm and Non-valvular Atrial Fibrillation

A study was designed to assess the influence of the heart rhythm on the vascular endothelial function in patients with non-valvular atrial fibrillation (AF) compared with studies concerning sinus rhythm (SR).

Relationship Between the Heart Rhythm Status and Flow-Mediated Dilatation/Nitroglycerin-Induced Dilatation. SR: Sinus Rhythm, PAF=Paroxysmal Atrial Fibrillation, CAF: Chronic Atrial Fibrillation



Forearm Blood Flow) Responses to Exercise During Control Conditions and After NO Synthesis Inhibition with L-NMMA Before and After Cardioversion (DC) in Patients with Chronic Atrial Fibrillation

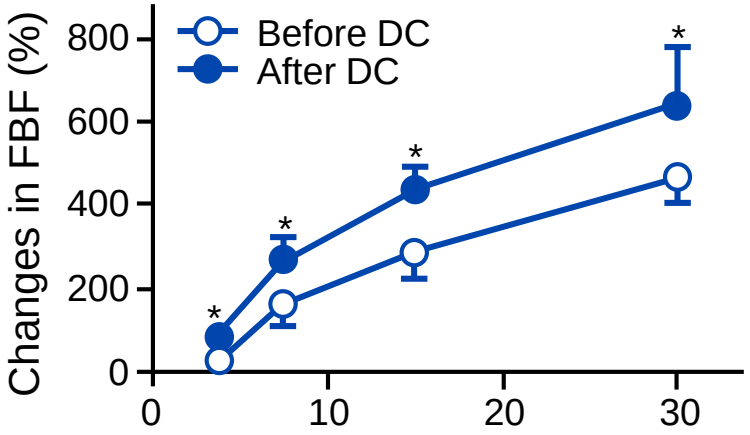
Conclusion In comparison with SR, the frequency and duration of AF episodes appear to cause deterioration of the vascular endothelial function.

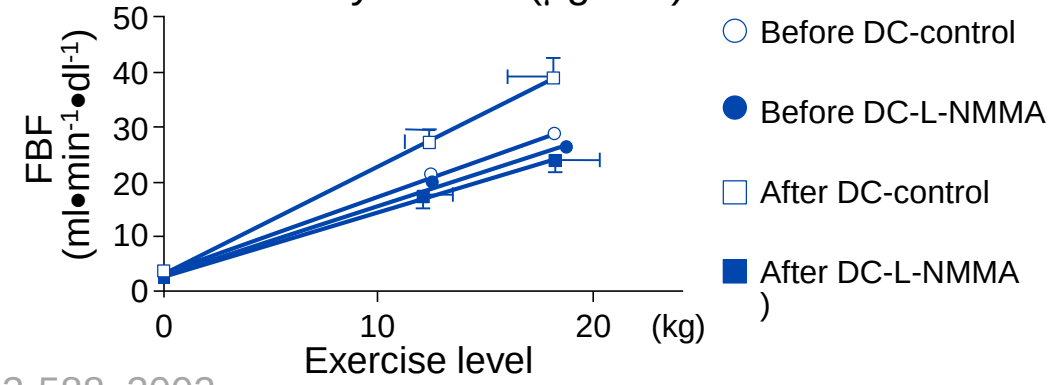
Impaired Exercise-Induced Vasodilatation in Chronic Atrial Fibrillation

— Role of Endothelium-Derived Nitric Oxide —

The present study was designed to investigate whether nitric oxide (NO)-mediated vasodilatation is attenuated during exercise in patients with AF by measuring forearm blood flow (FBF)

Effects of Cardioversion (DC) on the Percent Changes in Forearm Blood Flow at baseline and exercise





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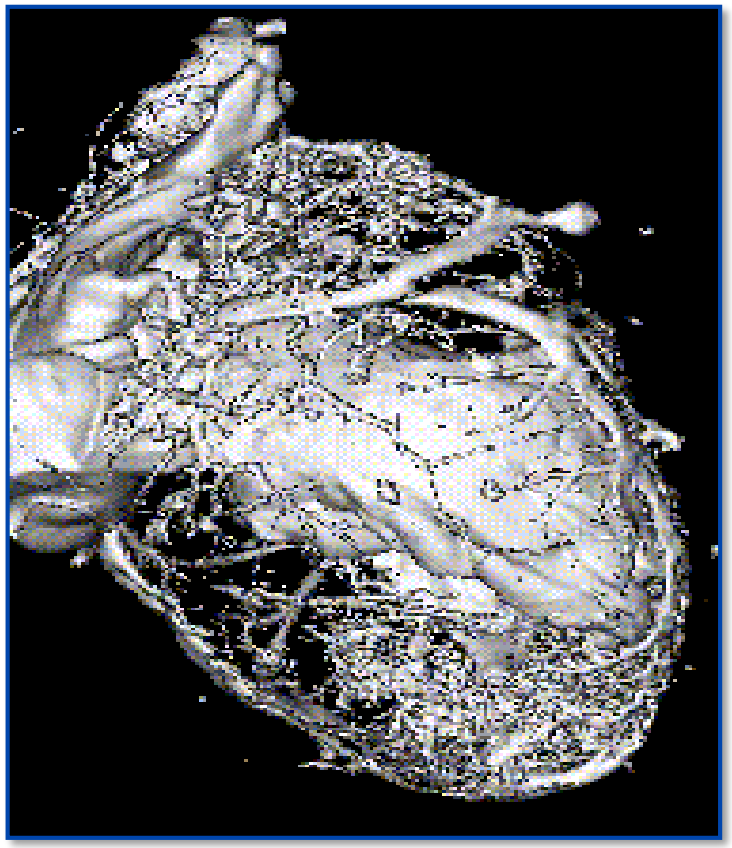
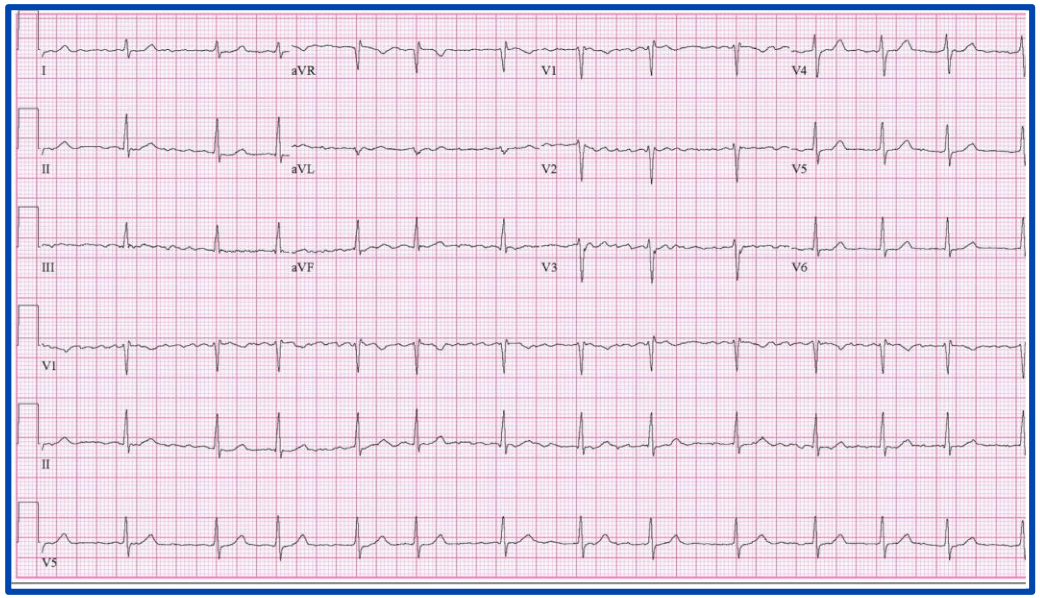
Komatsu et al: *Intern Med* 57;2131-2139, 2018Takahashi et al: *Circ J* 66:583-588, 2002

Atrial Fibrillation as a vascular disease





Precipitating factors

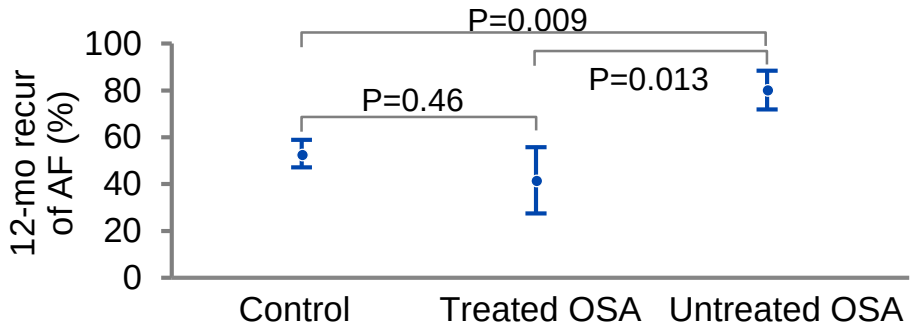
MAYO CLINIC

Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation

Ravi Kanagala, MD; Narayana S. Murali, MD; Paul A. Friedman, MD; Naser M. Ammash, MD;
Bernard J. Gersh, MB ChB, DPhil; Karla V. Ballman, PhD;
Abu S.M. Shamsuzzaman, MD, PhD; Virend K. Somers, MD, PhD

We tested the hypothesis that patients with untreated OSA would be at increased risk for recurrence of AF after cardioversion

Recurrence of AF at 12 Months Comparing Patients Who Did Not Have Sleep Studies (Controls) with Treated OSA Patients and with Untreated



- Pts with untreated OSA have a higher recurrence of AF after cardioversion than patients without poly-somnographic diagnosis of sleep apnea
- Appropriate treatment with CPAP in OSA pts is associated with lower recurrence of AF

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ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.08.060

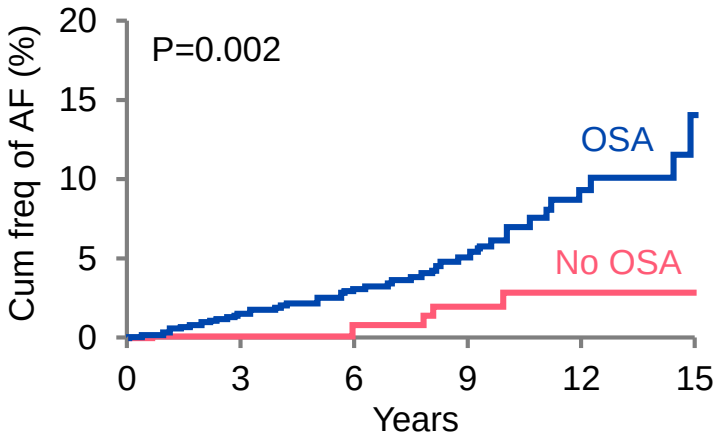
Atrial Fibrillation

Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation

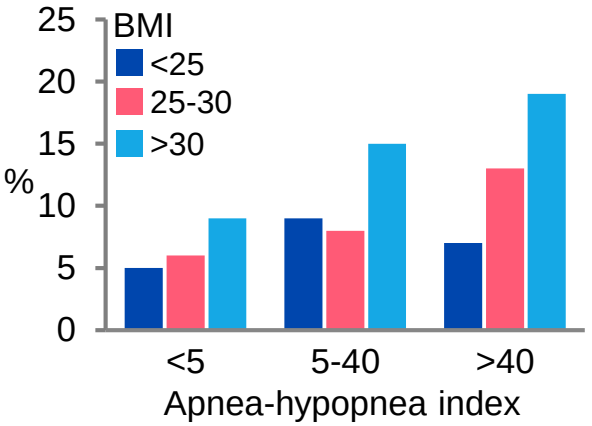
Apoor S. Gami, MD,*† Dave O. Hodge, MS,‡ Regina M. Herges, BS,‡ Eric J. Olson, MD,†§
Jiri Nykodym, BS,*† Tomas Kara, MD,*† Virend K. Somers, MD, PhD, FACC*†‖
Rochester, Minnesota

- Retrospective cohort study of 3,542 Olmsted County adults without past or current AF who were referred for initial diagnostic polysomnogram
- New onset AF was assessed and confirmed by electrocardiography during mean F-U of 4.7 years

Incidence of AF Based on Presence or Absence of OSA



Incidence of AF Based on Severity of OSA & Obesity



MAYO CLINIC

Age-Dependent Predictive Value of Endothelial Dysfunction for Arrhythmia Recurrence Following Pulmonary Vein Isolation

Yasushi Matsuzawa, MD, PhD; Mahmoud Suleiman, MD; Raviteja R. Guddeti, MD; Taek-Geun Kwon, MD, PhD; Kristi H. Monahan, RN; Lilach O. Lerman, MD, PhD; Paul A. Friedman, MD; Amir Lerman, MD

- Tested hypothesis that impact of endothelial dysfunction on arrhythmia recurrence following catheter ablation is age dependent
- Participants were divided into 2 age groups at a threshold of 60 yrs

Study Design

847 pts screened

567 had exclusion criteria

280 met entry critieria

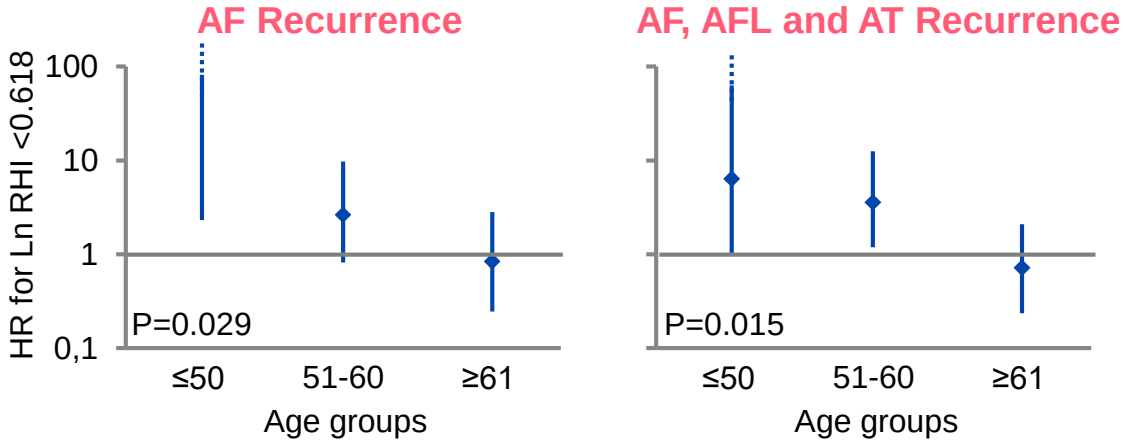
155 not willing to participate

Baseline RH-PAT exam (n=92)

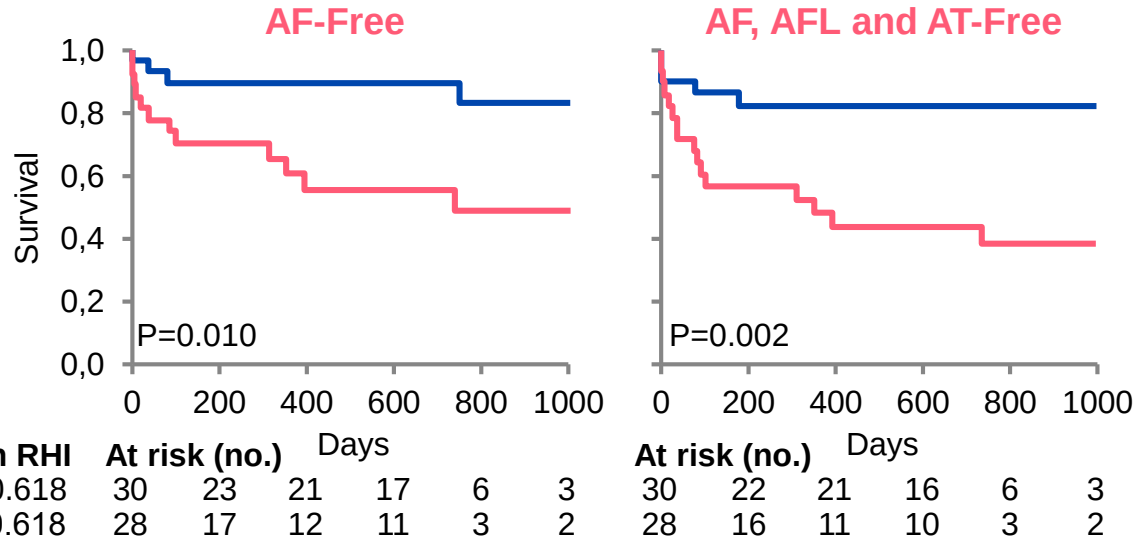
Left atrium ablation

Followed for AF, AFL and AT
Median 14 mo (IQR 3-26 mo)
AF recurrence in 27 pts
AF, AFL and AT recurrence in 36 pts

Hazard Ratios of Endothelial Dysfunction for Incident AF and Atrial Arrhythmia Recurrence



Analysis for Probability of AF and Atrial Arrhythmia Recurrence According to Baseline Endothelial Function in Participants Aged ≤60 yrs

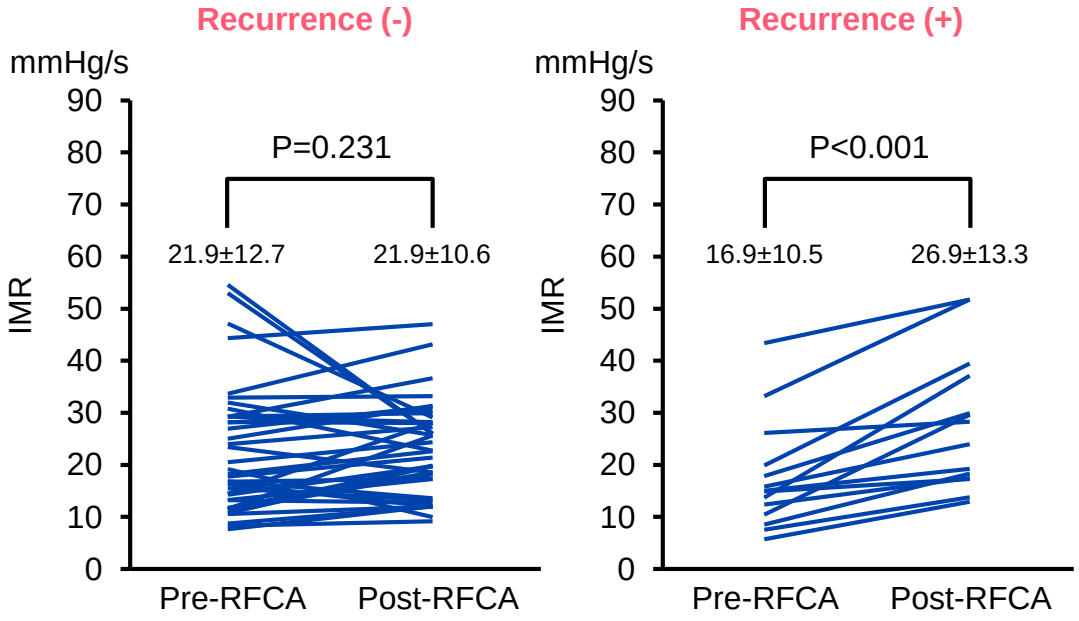


Effects of Iatrogenic Myocardial Injury on Coronary Microvascular Function in Patients Undergoing Radiofrequency Catheter Ablation of Atrial Fibrillation

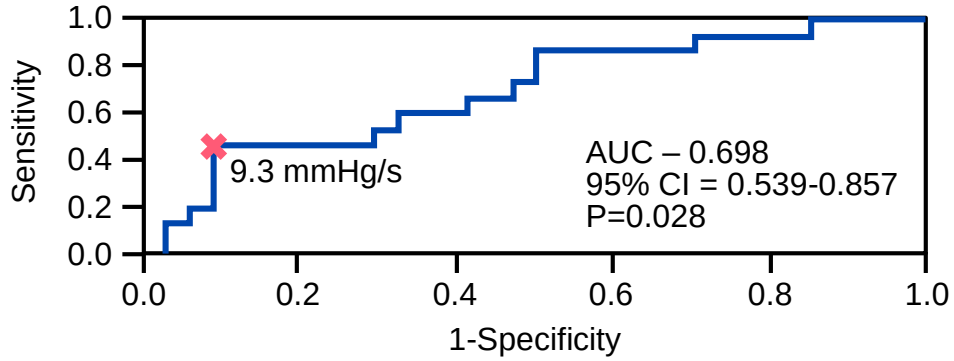
Hong Euy Lim, MD; Cheol Ung Choi, MD; Jin Oh Na, MD; Jong-Il Choi, MD; Seong Hwan Kim, MD; Jin Won Kim, MD; Eung Ju Kim, MD; Seong Woo Han, MD; Sang Weon Park, MD; Seung-Woon Rha, MD; Chang Gyu Park, MD; Hong Seog Seo, MD; Dong Joo Oh, MD; Chun Hwang, MD; Young-Hoon Kim, MD

The aim of this study is to evaluate the effect of nonischemic myocardial damage on coronary microvascular function in patients undergoing atrial fibrillation (AF) ablation

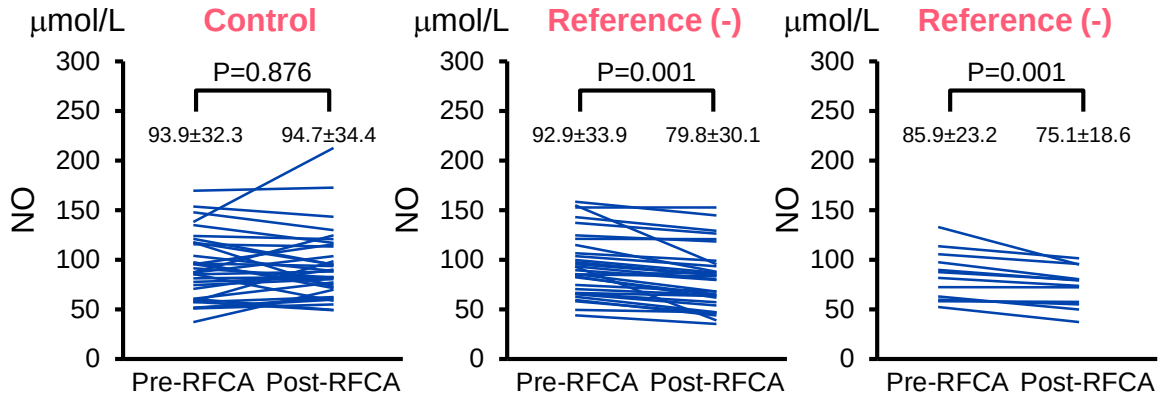
Differences in Index of Microvascular Resistance (IMR) Values Before and After Radiofrequency Catheter Ablation (RFCA) for Atrial Fibrillation



Receiver-Operator characteristic Curves for the Change In Index or Microvascular Resistance Were Used to identify Subjects with Early Recurrence During the First 3 Months after Radiofrequency Catheter Ablation



Difference in Nitric Oxide (NO)



CONCLUSIONS: Myocardial damage by RFCA provoked coronary microvascular dysfunction through systemic proinflammatory reaction that may contribute to transient diastolic dysfunction. This phenomenon may represent a mechanism for early recurrence of arrhythmia after RFCA.

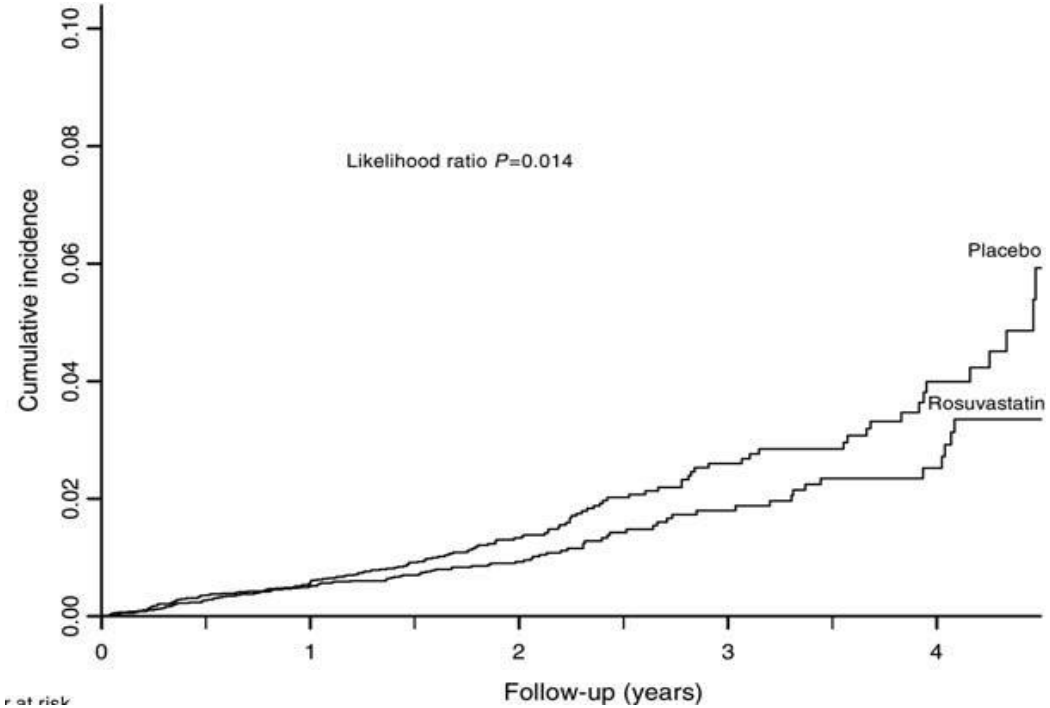
Lim et al: Circ Arrhythm Electrophysiol; 6:318-326, 2013

MAYO CLINIC

European Heart Journal (2012) 33, 531–537
doi:10.1093/eurheartj/ehr460

CLINICAL RESEARCH
Prevention

High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial

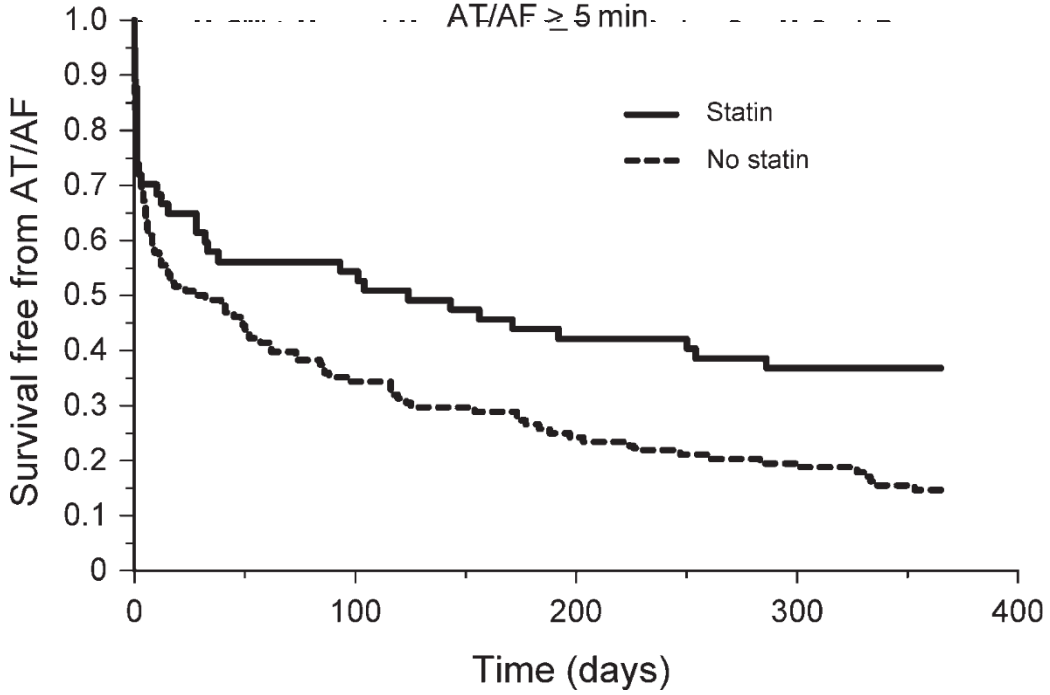


Men and women with LDL cholesterol ,130 mg/dL and high-sensitivity C-reactive protein ≥2 mg/L to receive either rosuvastatin 20 mg daily or placebo. 17 120 participants without prior history of arrhythmia, each increasing tertile of baseline high- sensitivity C-reactive protein was associated with a 36% increase in the risk of developing

European Heart Journal (2009) 29, 1873–1880
doi:10.1093/eurheartj/ehn192

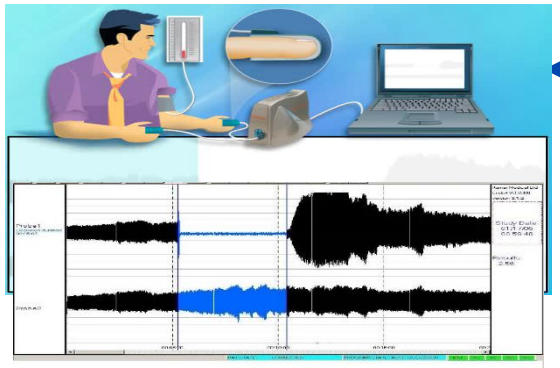
CLINICAL RESEARCH
Arrhythmia/electrophysiology

Beneficial effects of statin therapy for prevention of atrial fibrillation following DDDR pacemaker implantation



At 1 year of follow-up, patients without recurrence were more likely to be on statin therapy (54%) when compared with patients without statin therapy (25%)
Statin therapy was the only significant predictor of AT/AF recurrence in a multivariate logistic regression model (adjusted odds ratio 0.33, 0.14–0.74,).

CV risk factors



A Fibrillation

Sleep studies

Sleep Apnea

CPAP

Sleep studies?

Inflammation

Endothelial Dysfunction

Modify current management

Normal endothelial Function

Medical Treatment
Ablation

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