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Presentation of ACS in women

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Chair for Research
Cardiovascular Division
Mayo Clinic, Rochester, MN

Conflict of interest:

Advisory board: Itamar Medical

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mayo

CP996233-30

- 50-year-old female c/o chest pain on exertion
- 58-year-old female developed acute onset of chest pain during a heated discussion with her boss
- 38-year-old female healthy, runner, no risk factors for atherosclerosis presents to ER with 1 hour heavy

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50-Year-Old Female With Chest Pain

- Previous history of NSTEMI
- C/O chest pain on exertion multiple ER presentations
- TTE: Normal
- TMET CP but no ECG changes
- Previous normal coronary angiograms

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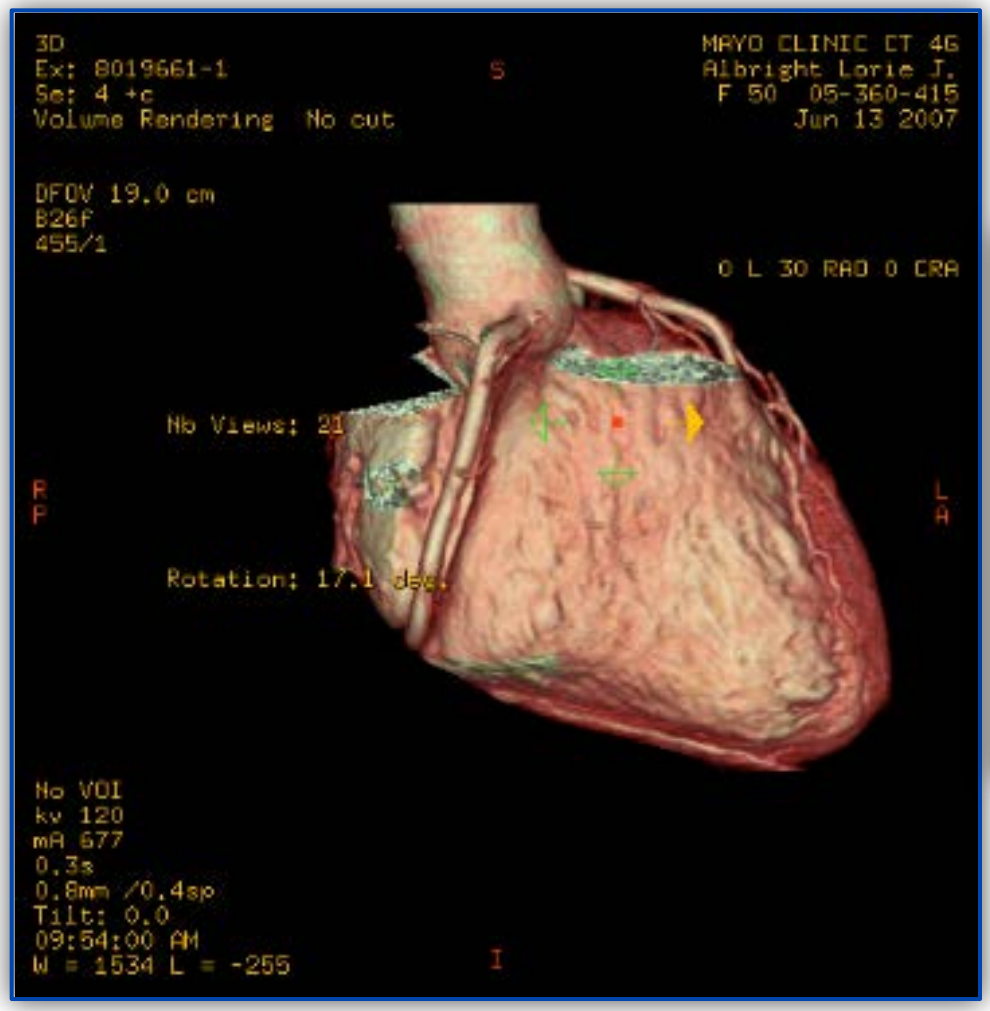
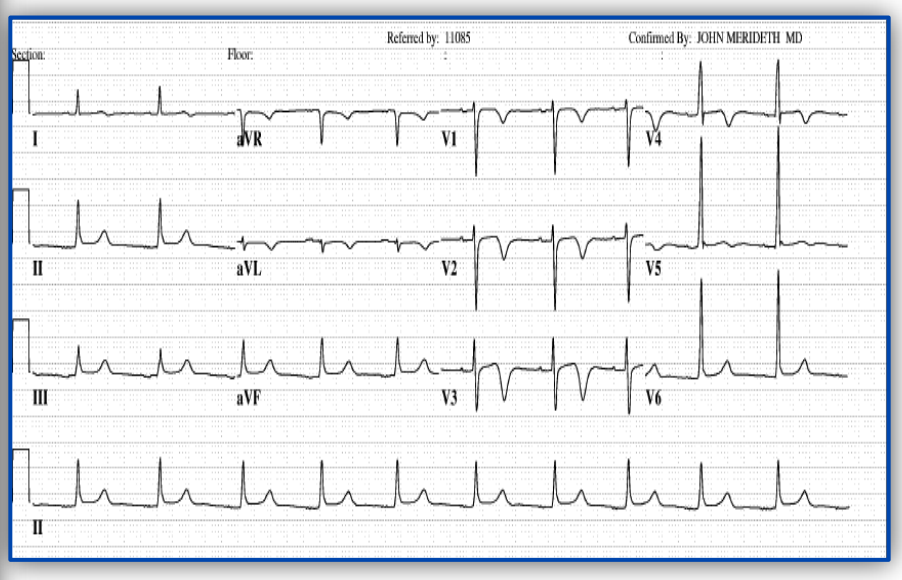
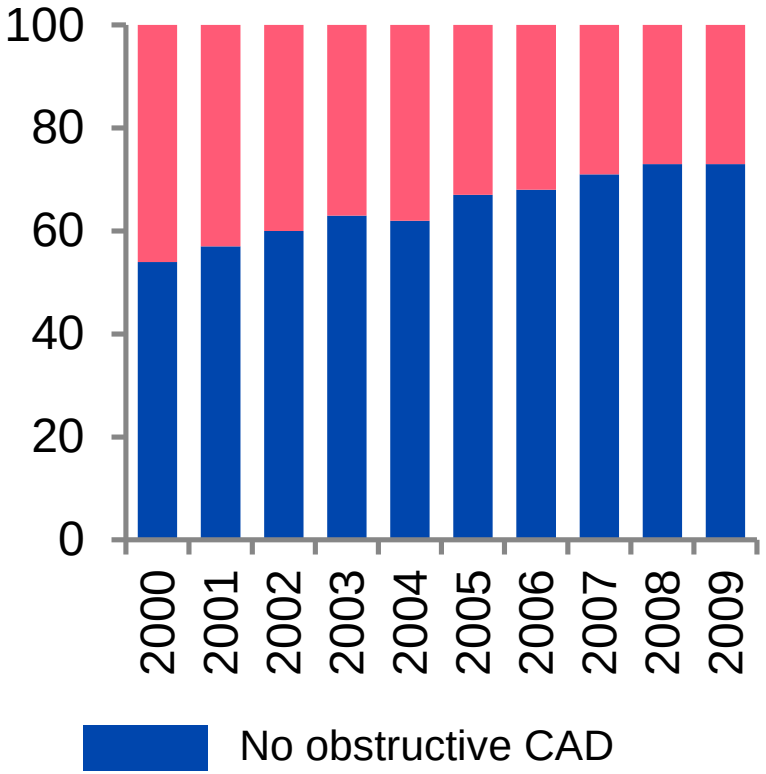
50-Year-Old Female With Chest Pain



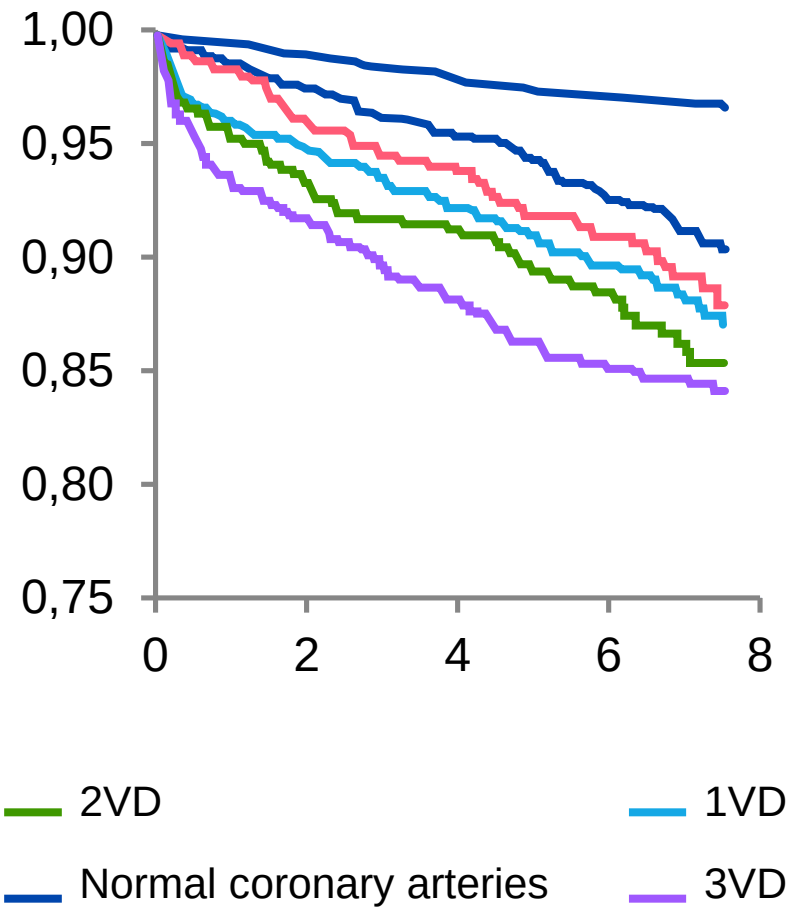


Major Adverse Cardiovascular Event-Free Survivor Functions Women

Degree of CAD
Change over time – Women



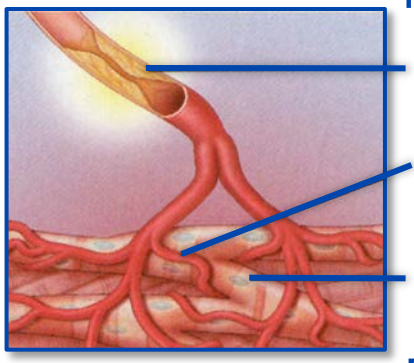
Survivor functions for women:
Age adjusted to 60 years



Jespersen: European Heart Journal (2012) 33, 734-744

Possible Mechanisms of Cardiac Pain

Mechanism in Coronary Artery Disease

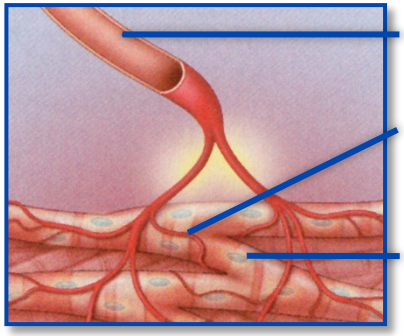


Luminal narrowing due to atherosclerotic plaque

Compensatory vasodilation of coronary microvessels

Normal nociception mediated through stimulation of pain receptors

Proposed Mechanism in Non-Obstructive CAD

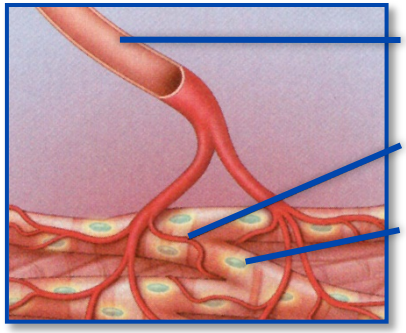


Normal epicardial coronary artery

Inappropriately increased vascular tone of coronary microvessels leading to myocardial ischemia

Appropriate stimulation of pain receptors

Proposed Mechanism in Non-Obstructive CAD



Normal epicardial coronary artery

Normal vascular tone of coronary microvessels

Abnormally enhanced sensitivity of myocardial pain receptors, leading to pain without myocardial ischemia

NEJM, 2002

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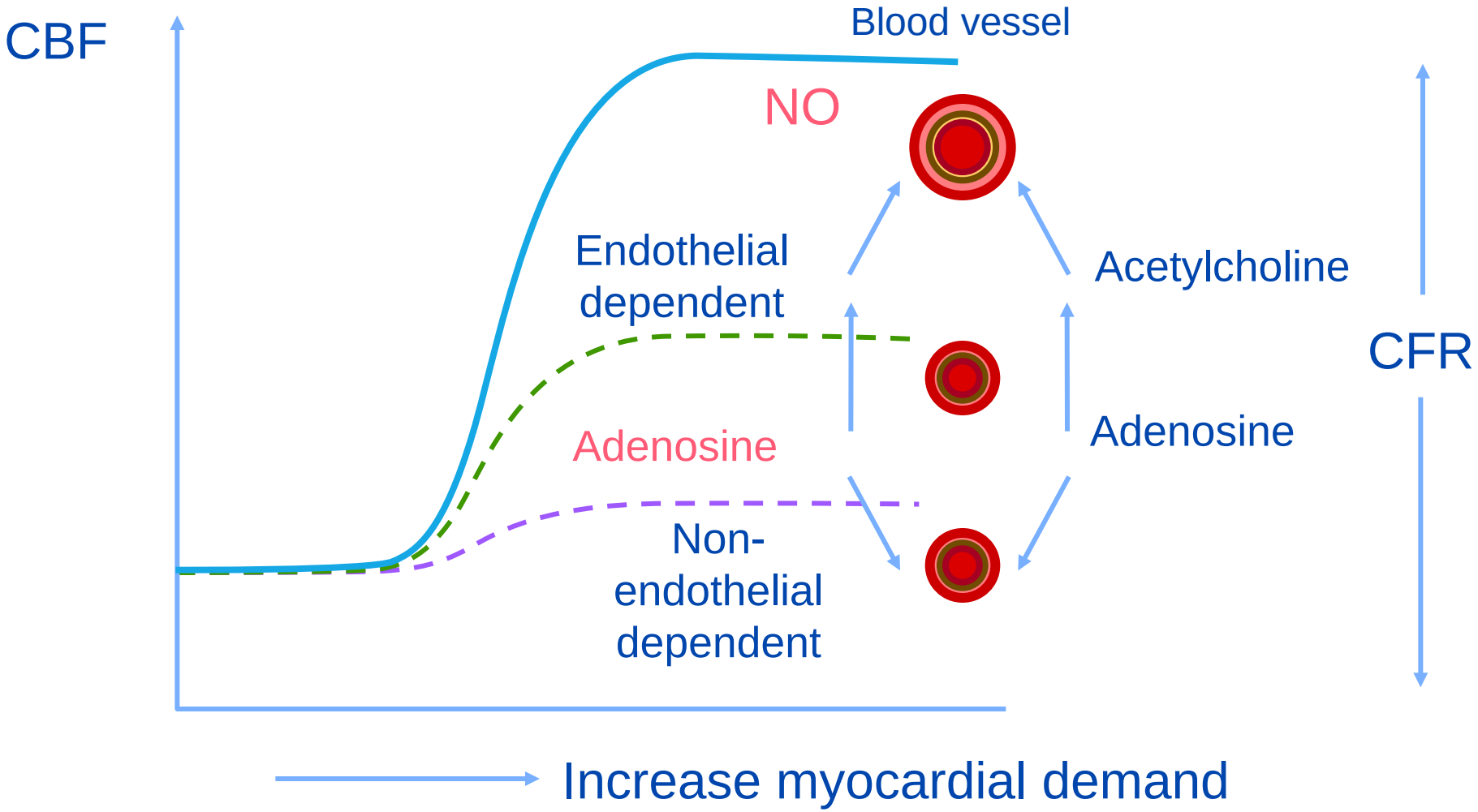
Coronary Blood Flow Response to Increase Myocardial Demand



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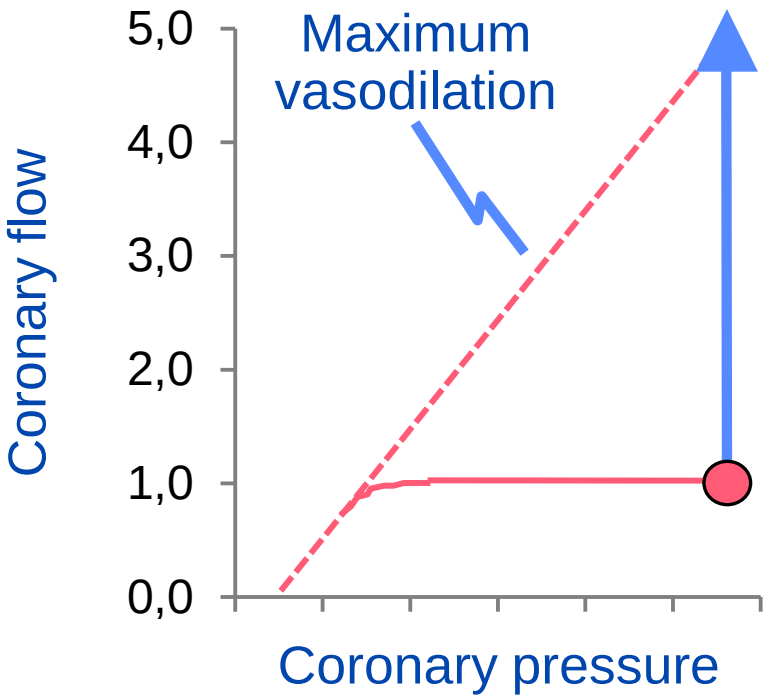
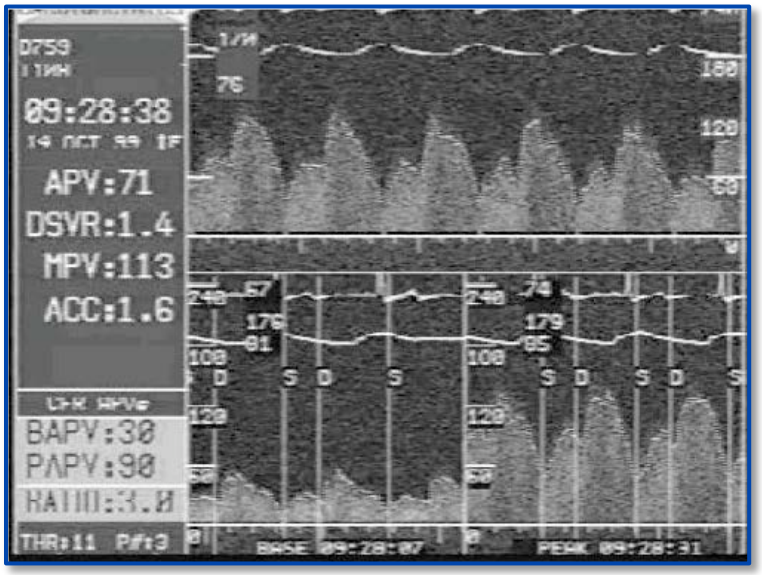
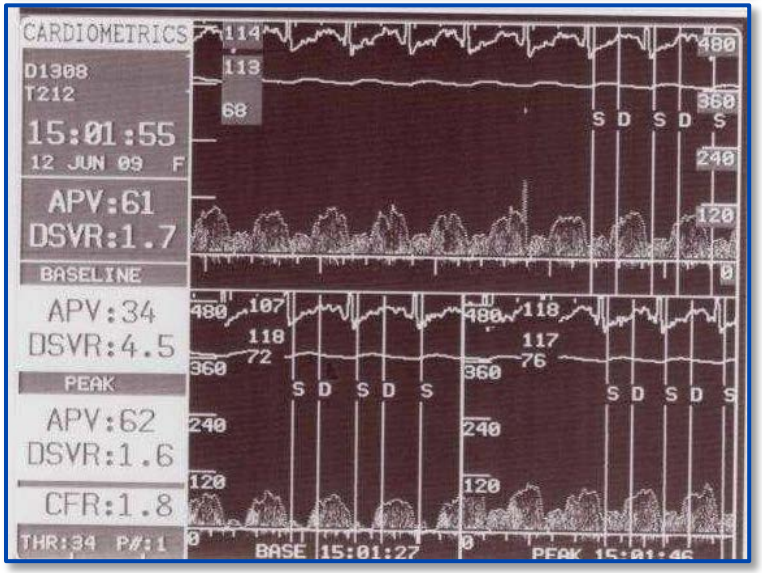
Coronary Flow Physiology







$$\text{Coronary reserve} = \frac{\text{Flow}_{\text{dilated}}}{\text{Flow}_{\text{initial}}}$$

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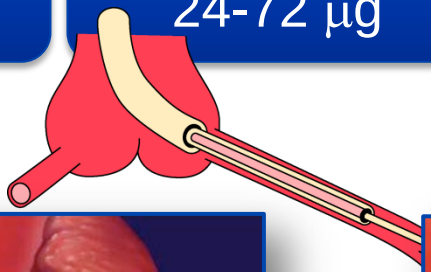
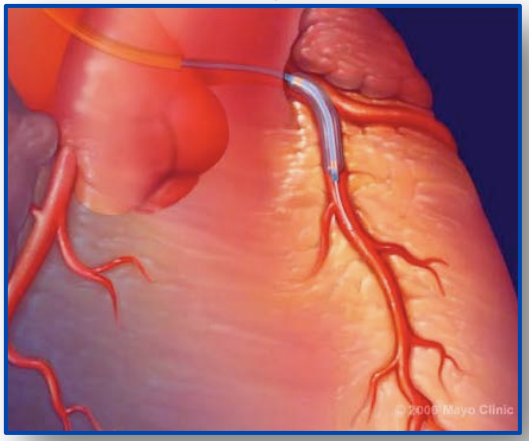
Functional Angioram Protocol

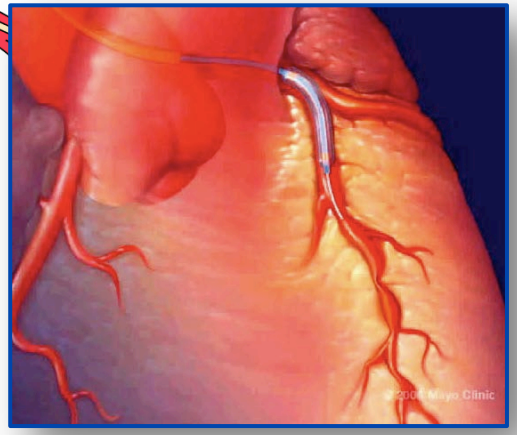
Diagnostic angiography

Adenosine IC 24-72 μg

CFR: Non endothelium **microcirculation**

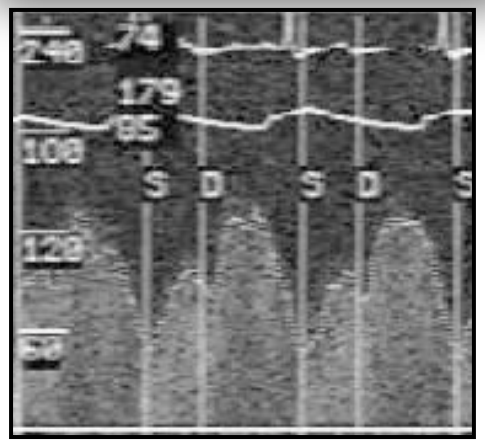




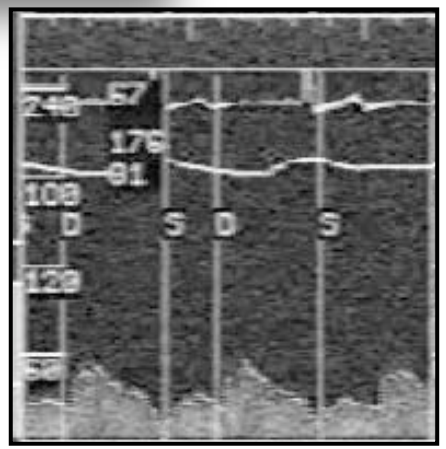


Acetylcholine (endothelium dependent vasodilator)

Epicardial



Microcirculation



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European Heart Journal Advance Access published August 30, 2013

European Heart Journal
doi:10.1093/eurheartj/eht296

2013 ESC guidelines on the management of stable coronary artery disease

The Task Force on the management of stable coronary artery disea of the European Society of Cardiology

It is necessary
to differentiate this pain from non-cardiac chest pain.

Diffuse coronary
artery spasm, pronounced in the distal epicardial coronary arteries
and probably extending into the microvasculature, may be
provoked by intracoronary injection of acetylcholine in a substantial proportion of patients with typical coronary microvascular
Disease.

Table 23 Investigation in patients with suspected coronary microvascular disease

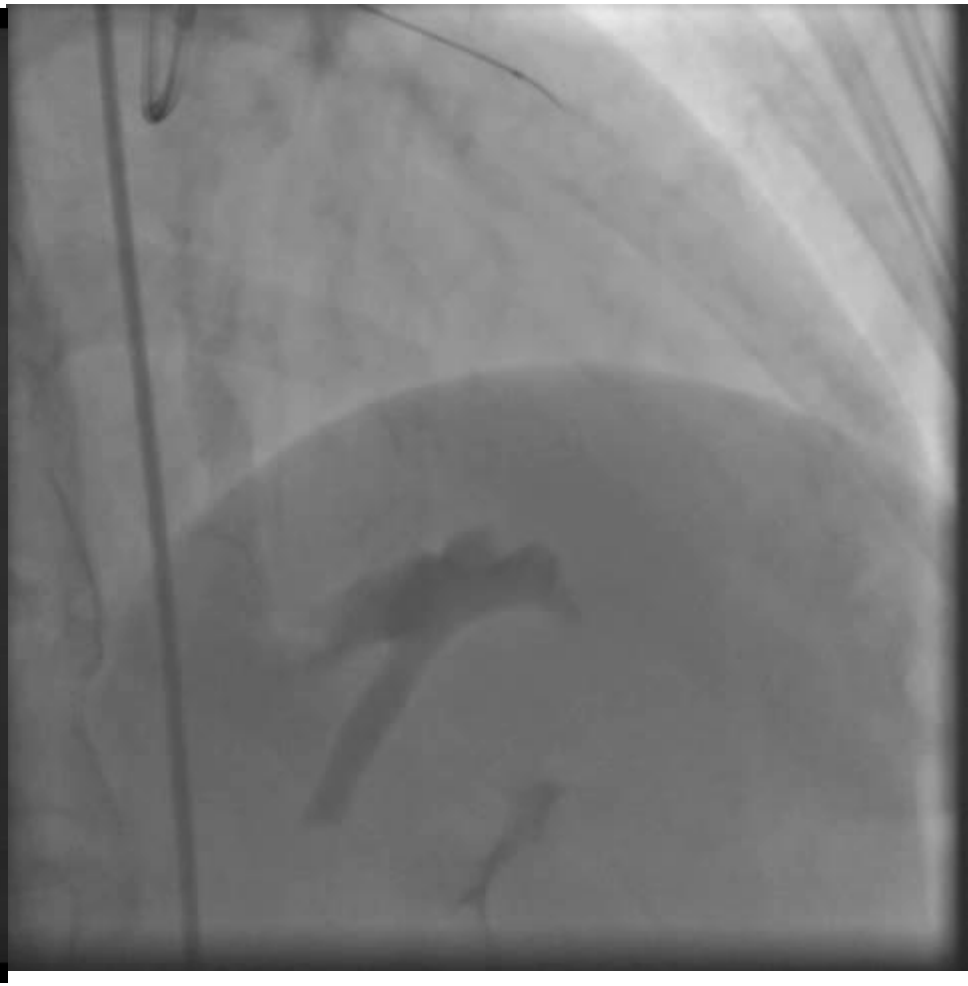
Recommendations	Class [a]	Level [b]
Exercise or dobutamine echocardiography should be considered in order to establish whether regional wall motion abnormalities occur in conjunction with angina and ST-changes.	IIa	C
Transthoracic doppler echocardiography of the LAD with measurement of diastolic coronary **blood flow following intravenous adenosine** and at rest may be considered for non invasive **measurement of coronary flow reserve.**	IIb	C
Intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram is visually normal, to assess endothelium dependent and non-endothelium **dependent coronary flow reserve, and detect** microvascular/epicardial vasospasm.	IIb	C

FFR = fractional flow reserve; LAD = left anterior descending.
[a] Class of recommendation.
[b] Level of evidence.

50-Year-Old Female With Chest Pain

Baseline

Acetylcholine 10-4M



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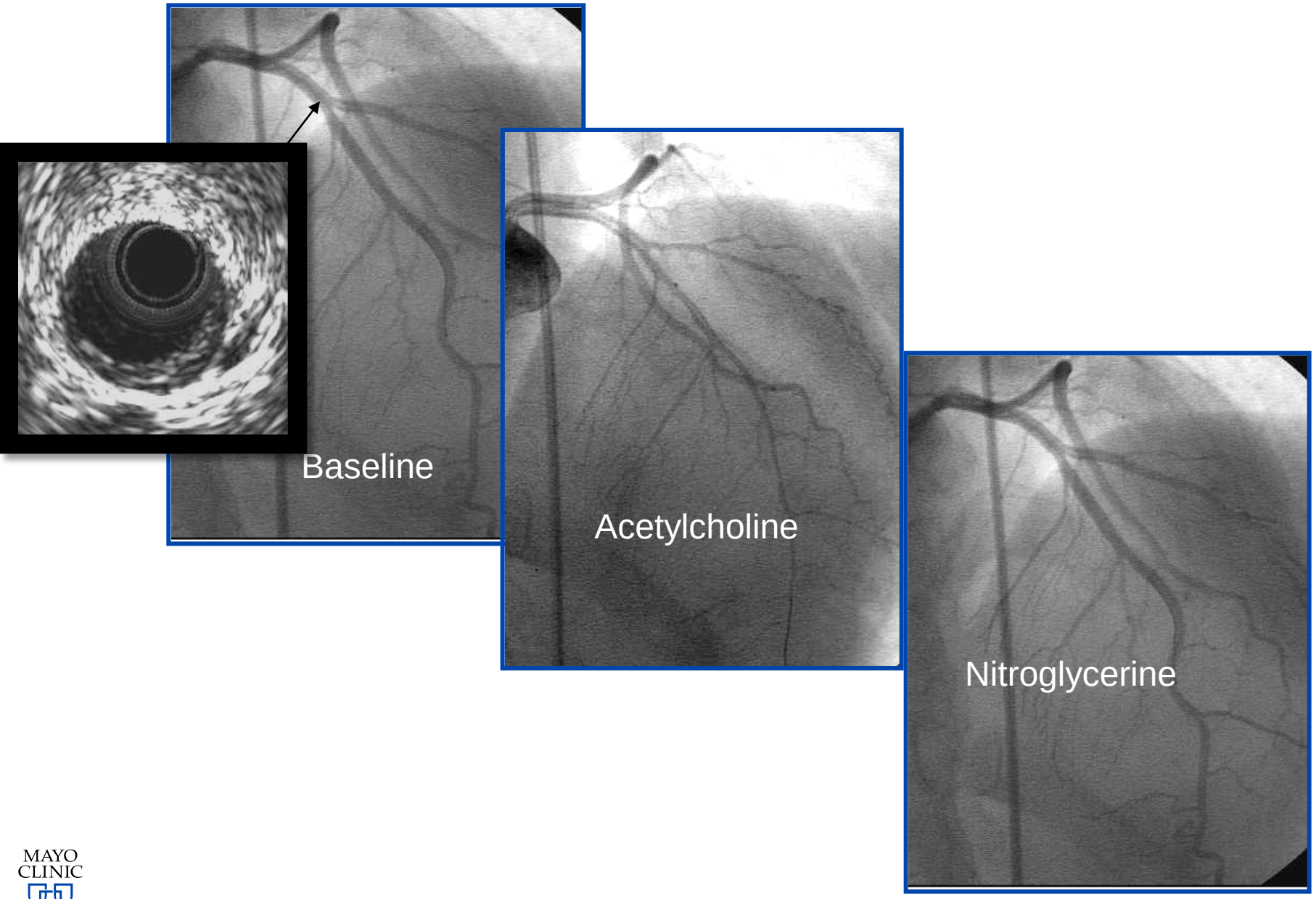
50-Year-Old Female With Chest Pain



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Coronary Endothelial Function: Prime ECG

European Heart Journal (2011) 32, 2758–2765
doi:10.1093/eurheartj/ehr221

CLINICAL RESEARCH
Coronary heart disease

Myocardial ischaemia in patients with coronary endothelial dysfunction: insights from body surface ECG mapping and implications for invasive evaluation of chronic chest pain

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Received 16 February 2011; revised 10 May 2011; accepted 15 June 2011; online publish-ahead-of-print 6 July 2011

Aims Coronary endothelial dysfunction (ED), by predisposing to abnormal vasomotion, may cause chest pain in individuals with non-obstructed coronary arteries. The aim of this study was to correlate the magnitude of coronary ED with the presence and extent of inducible myocardial ischaemia using body surface electrocardiogram (ECG) mapping in symptomatic patients.

Methods and results In 30 patients with chest pain and angiographically normal coronary arteries or mild atherosclerosis, we studied endothelium-dependent responses with acetylcholine (ACH) and endothelium-independent function with nitroglycerin and adenosine in the left anterior descending artery. Eighty-lead body surface ECG maps were collected at baseline and after each dose of ACH. There was a significant correlation between the maximal change in epicardial diameter with ACH and the magnitude of ST-segment shift [$r = -0.44$ (95% CI: -0.097 to -0.69), $P = 0.015$]. Patients with $\geq$0.05 mV ST-segment shift/lead had greater epicardial vasoconstriction (31.6 vs. 15.6%, $P = 0.019$), and lower coronary flow reserve (2.9 vs. 3.6, $P = 0.047$) compared with those with ST-segment shift $<$0.05 mV. Four patients had inducible ischaemia with ACH in the absence of abnormal epicardial or global microvascular vasomotion ($>$20% decrease in diameter or $<$50% increase in blood flow).

Conclusions This study demonstrates that abnormal vasomotion due to coronary ED is associated with myocardial ischaemia in patients with chest pain. The magnitude of ischaemia correlates with the extent of ED. A small subset of patients develop myocardial ischaemia during ACH infusion without significant abnormalities in epicardial or global microvascular endothelium-dependent blood flow responses.

Keywords Endothelial dysfunction • Vasospasm • Acetylcholine • Ischaemia • Electrocardiography

Introduction

Endothelial dysfunction (ED) is believed to play a key role in the pathophysiology of myocardial ischaemia and precipitating cardiovascular events.[1] In normal individuals, endothelial cells regulate coronary blood flow by responding to changes in shear stress, myogenic constriction, and vasoconstrictors such as acetylcholine (ACH) and endothelin, by releasing vasodilators such as nitric oxide.[2–4] Endothelial dysfunction develops in patients with cardiovascular risk factors and in turn predisposes to vasoconstriction and impaired homeostasis.[5–7] The presence and severity of ED can be measured invasively in the cardiac catheterization laboratory by evaluating coronary epicardial and microvascular blood flow responses to ACH.[8–10] The clinical utility of identifying coronary ED remains uncertain, in part, because it has been difficult to demonstrate that coronary ED is associated with

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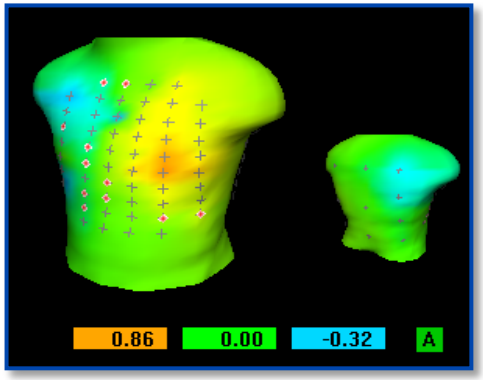
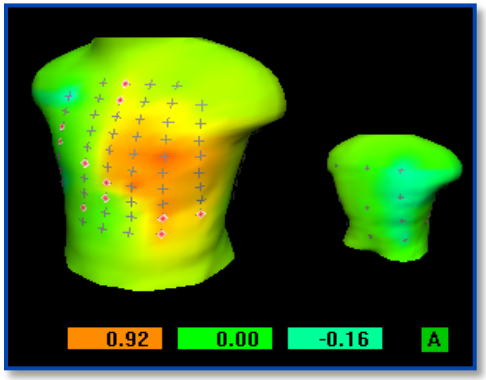
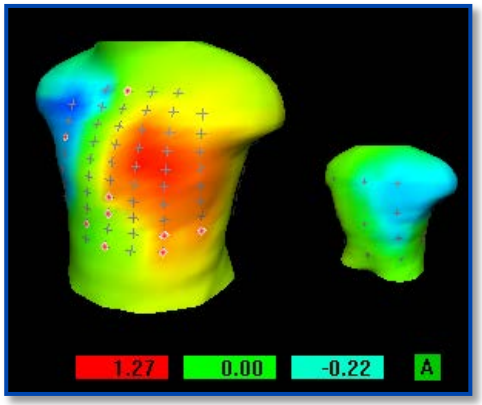
Baseline



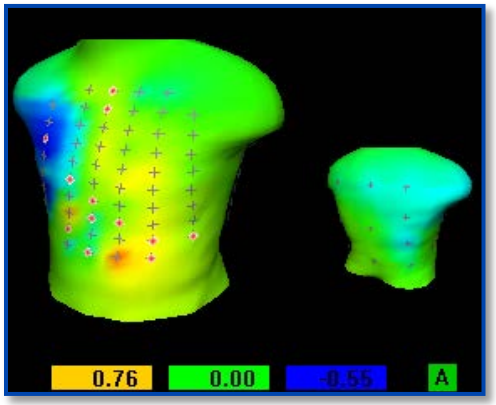
ACH 10^{-6}M



ACH 10^{-4}M



NTG



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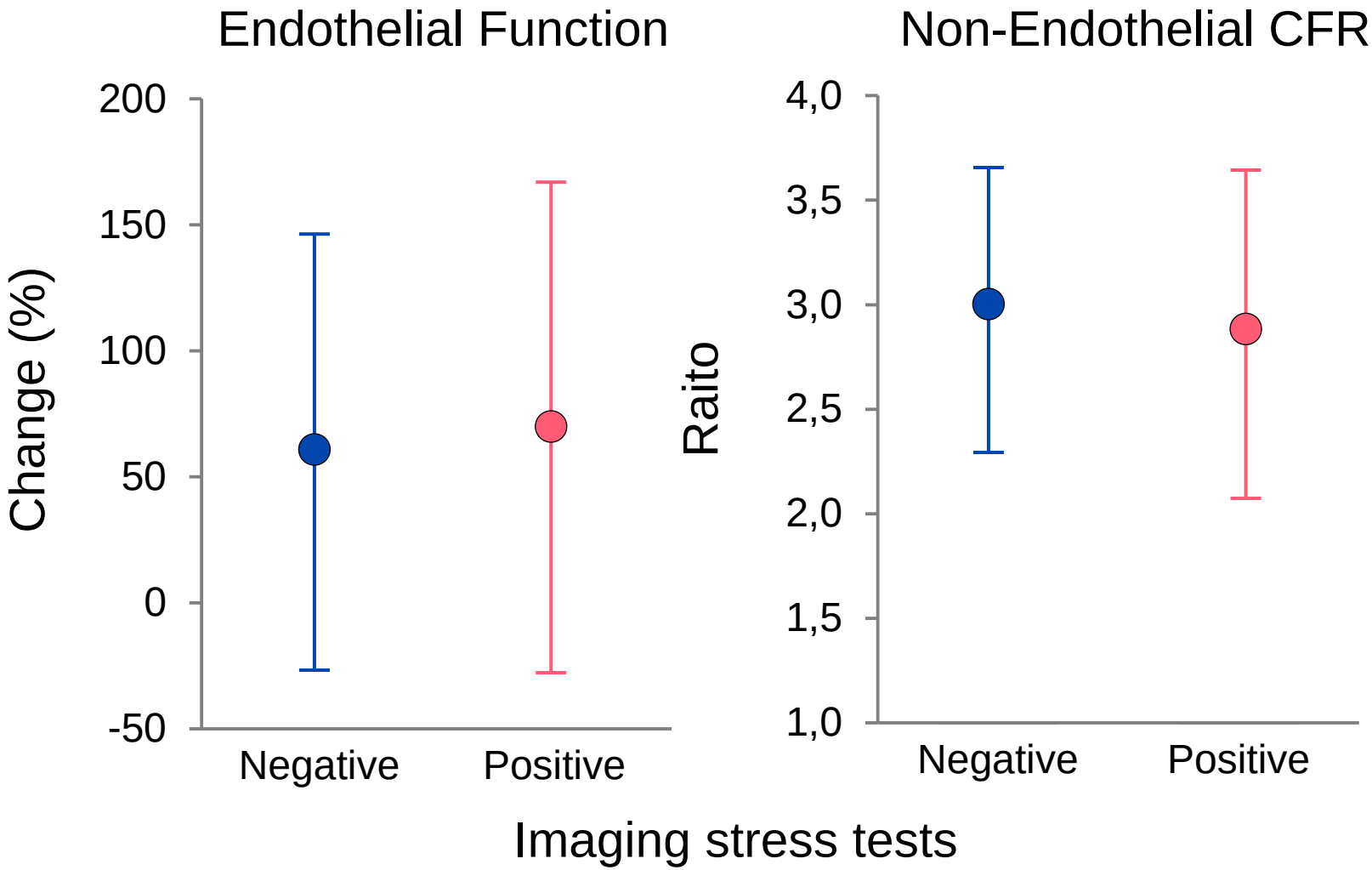
The Association Between Non-Invasive Tests and Coronary Flow Reserve



Cassar: Circ, 2009

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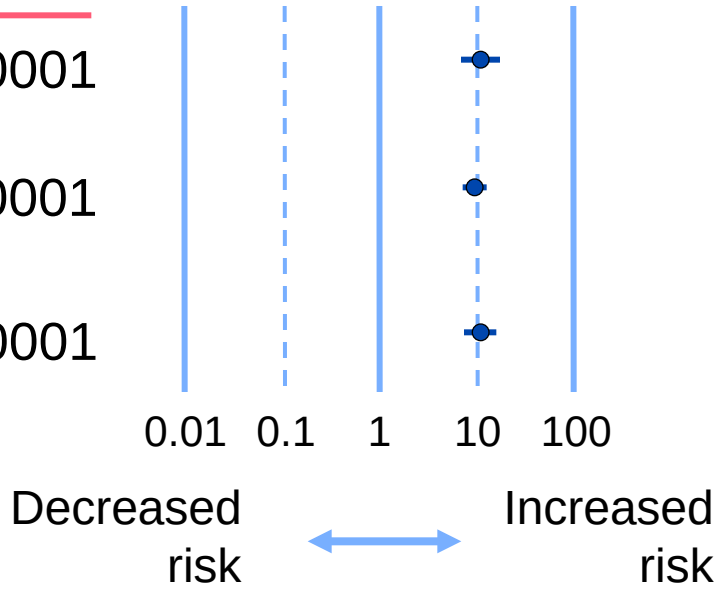
Summary Relative Risk for MACE in Women With Coronary or Peripheral Endothelial Dysfunction

	Summary RR	P
Coronary circulation	11.1 (6.9-17.8)	<0.0001
Peripheral circulation	9.6 (7.1-12.8)	<0.0001
Summary RR	10.0	<0.0001



Merz: JACC 47:S21, 2006

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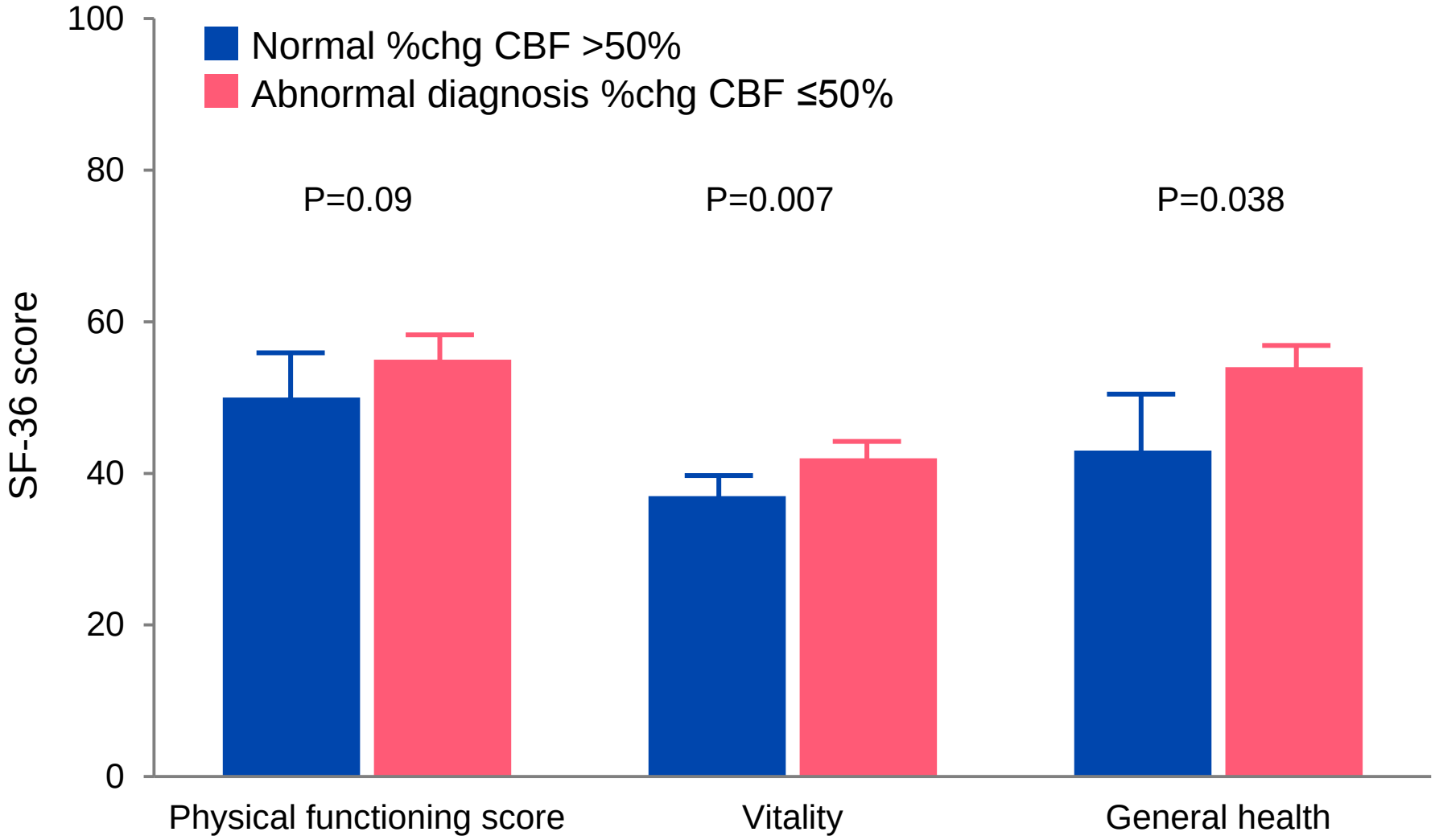
SF-36 in Patients With Microvascular Endothelial Dysfunction: Women



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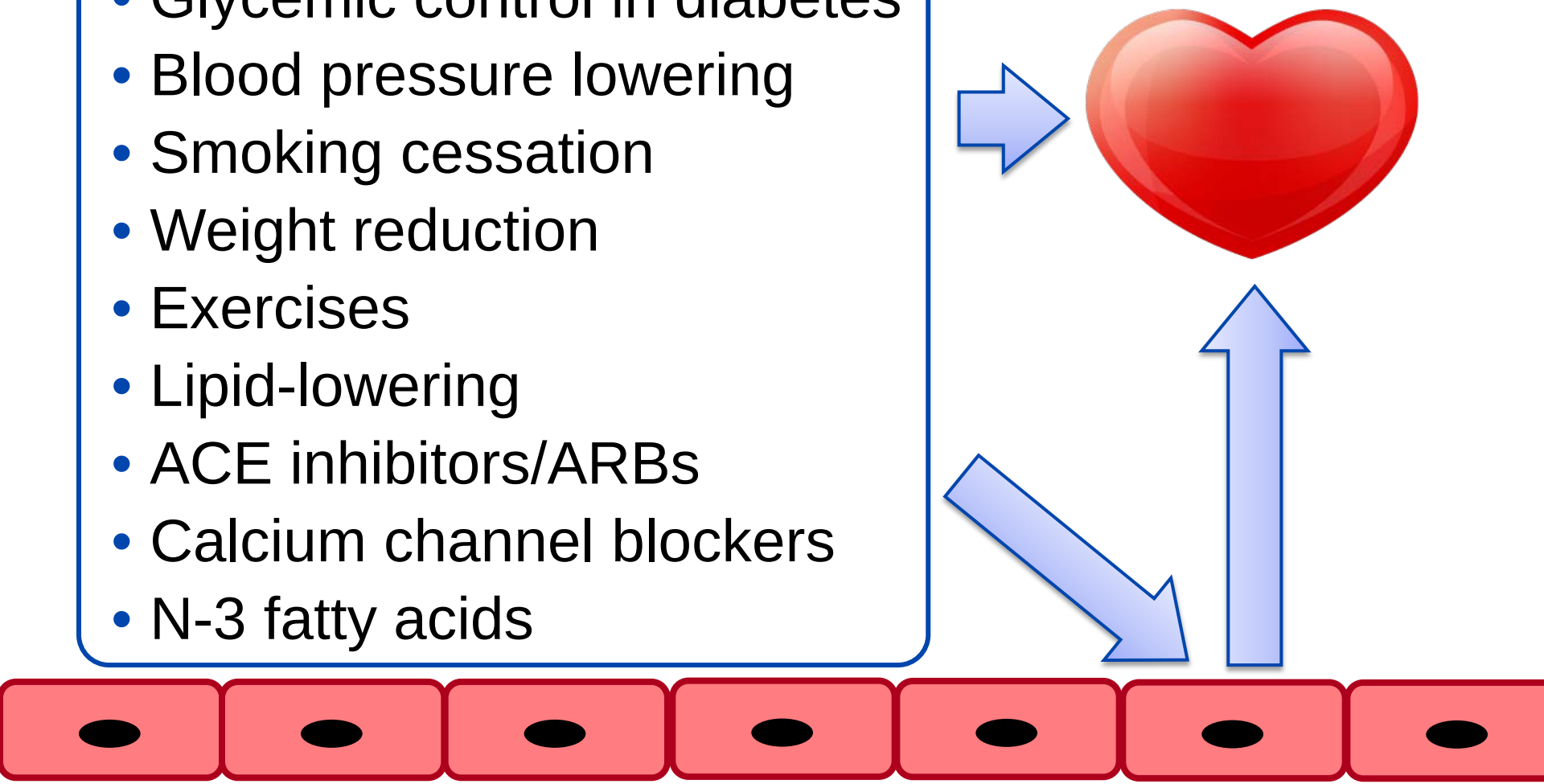
Interventions That Improve Endothelial Function and Clinical Outcome

- Glycemic control in diabetes
- Blood pressure lowering
- Smoking cessation
- Weight reduction
- Exercises
- Lipid-lowering
- ACE inhibitors/ARBs
- Calcium channel blockers
- N-3 fatty acids



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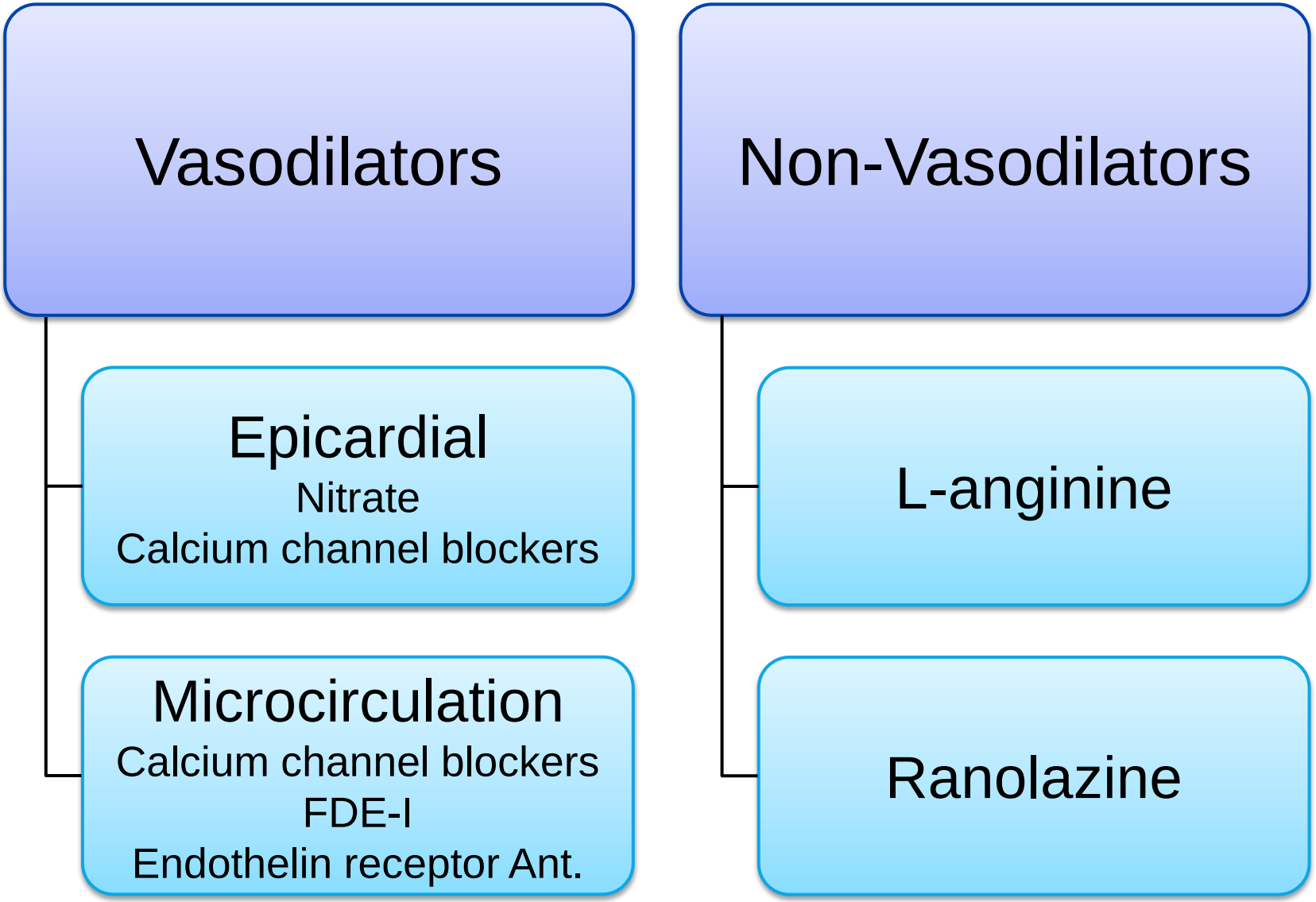

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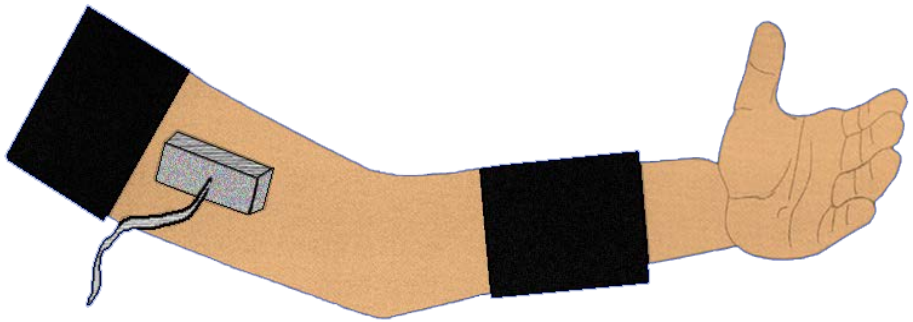
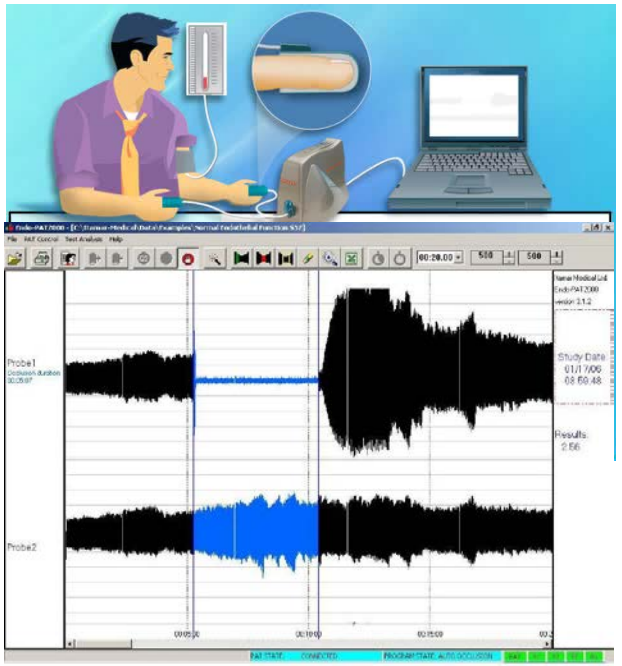
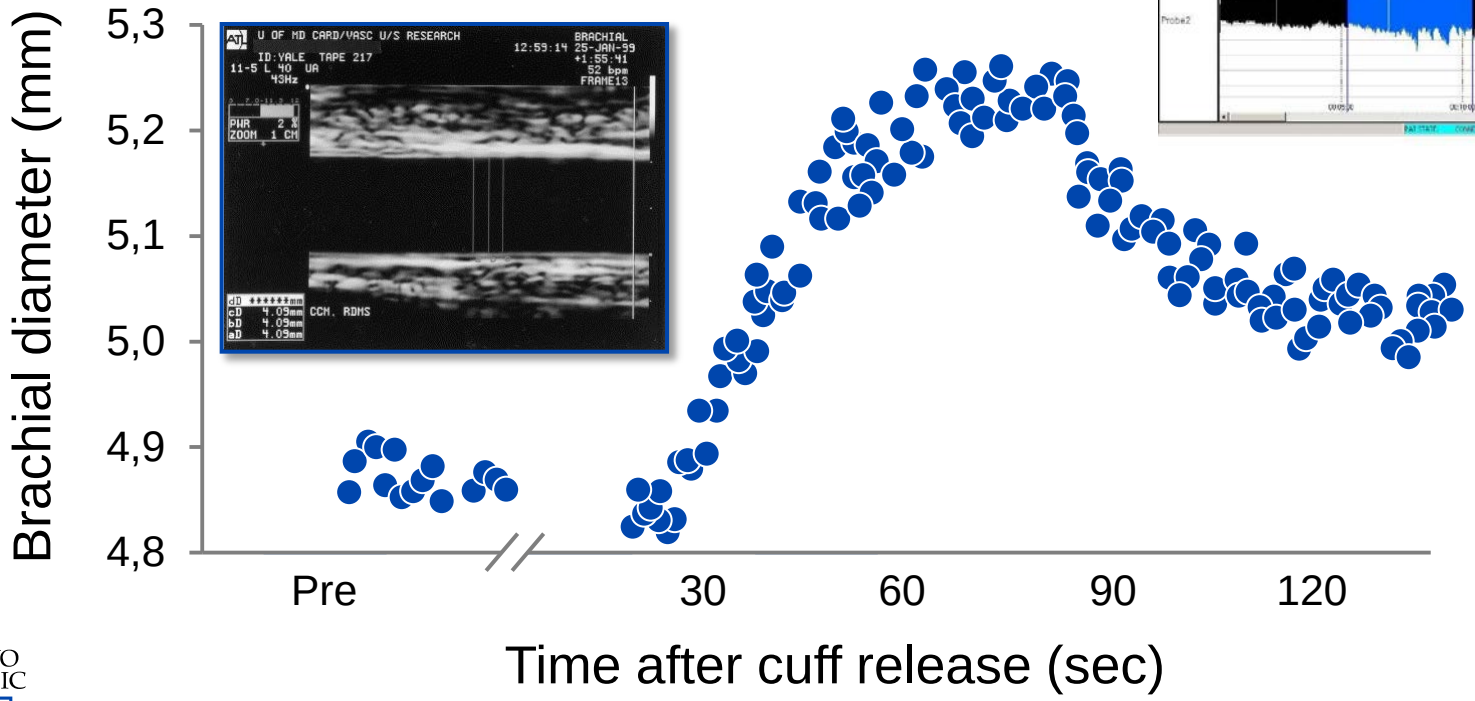
Reactive Hyperemia: Endothelium Dependent







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Can We use Endothelial Function to Individualize Therapy?

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Women and Cardiovascular Disease

Prognostic Role of Reversible Endothelial Dysfunction in Hypertensive Postmenopausal Women

Maria G. Modena, MD, FESC, FACC, Lorenzo Bonetti, MD, Francesca Coppi, MD, Francesca Bursi, MD, Rosario Rossi, MD

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Persistent Impairment of Endothelial Vasomotor Function Has a Negative Impact on Outcome in Patients With Coronary Artery Disease

Yoshinobu Kitta, MD, PHD, Jyun-ei Obata, MD, PHD, Takamitsu Nakamura, MD, Mitsumasa Hirano, MD, Yasushi Kodama, MD, Daisuke Fujioka, MD, PHD, Yukio Saito, MD, Ken-ichi Kawabata, MD, PHD, Keita Sano, MD, Tsuyoshi Kobayashi, MD, Toshiaki Yano, MD, Kazuto Nakamura, MD, PHD, Kiyotaka Kugiyama, MD, PHD

Yamanashi, Japan

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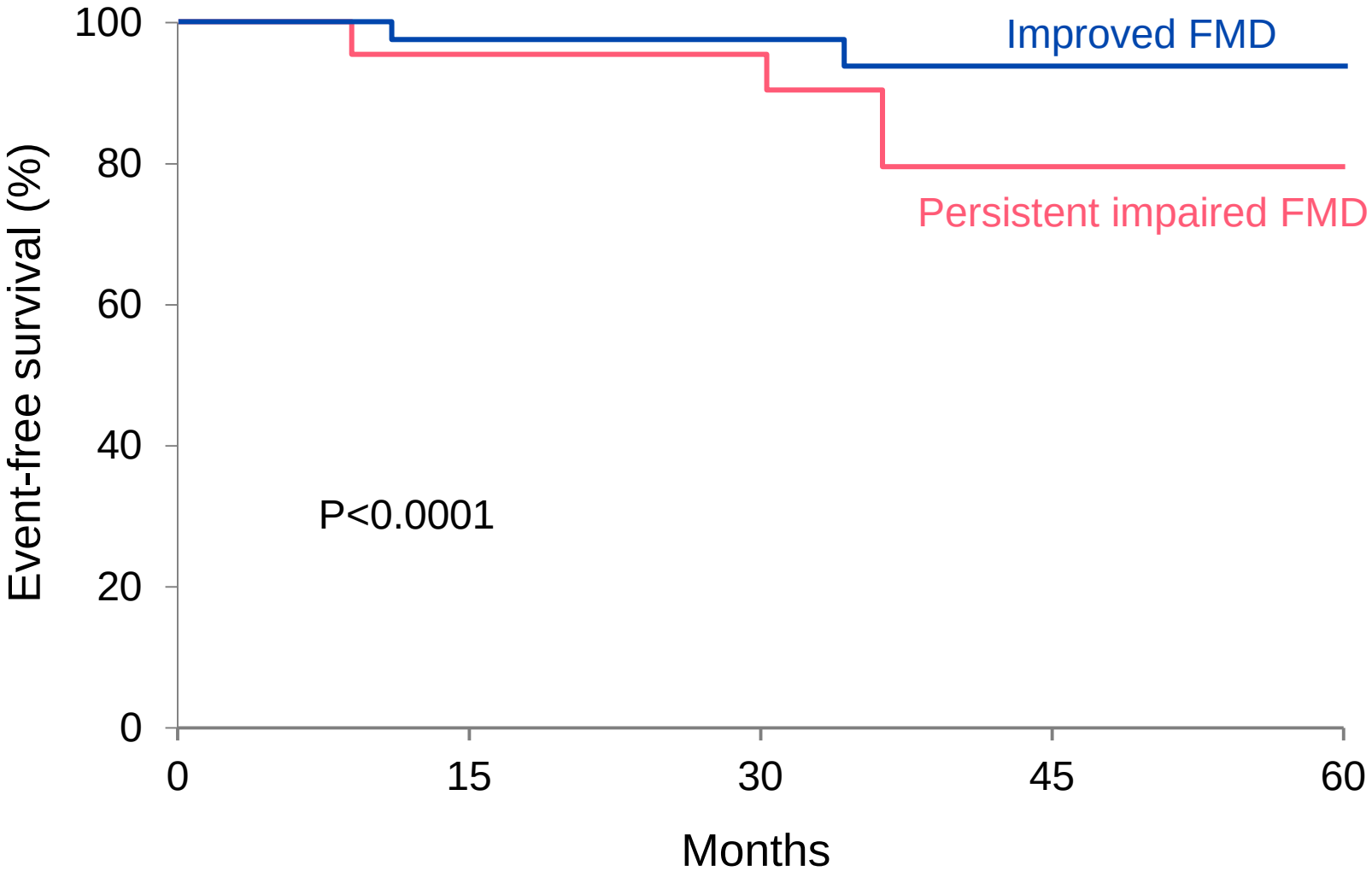
Event-Free Rate According to Persistent Endothelial Dysfunction in Patients With Mild CAD



Modena et al: JACC 40, 2002

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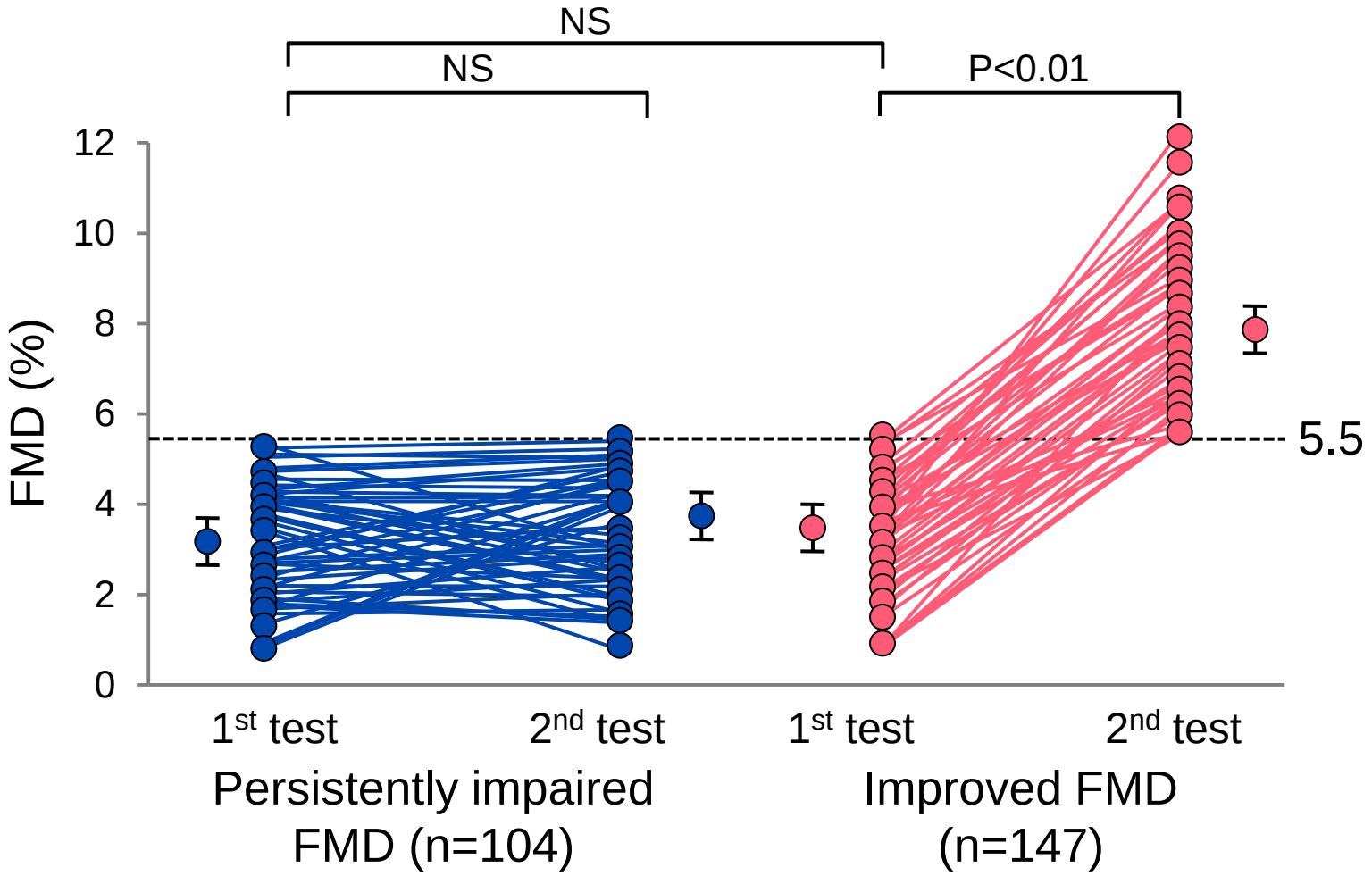
FMD Comparison Between First and Second Test in CAD Patients on OMT



Kitta Y et al: J Am Coll Cardiol 53:323, 2009

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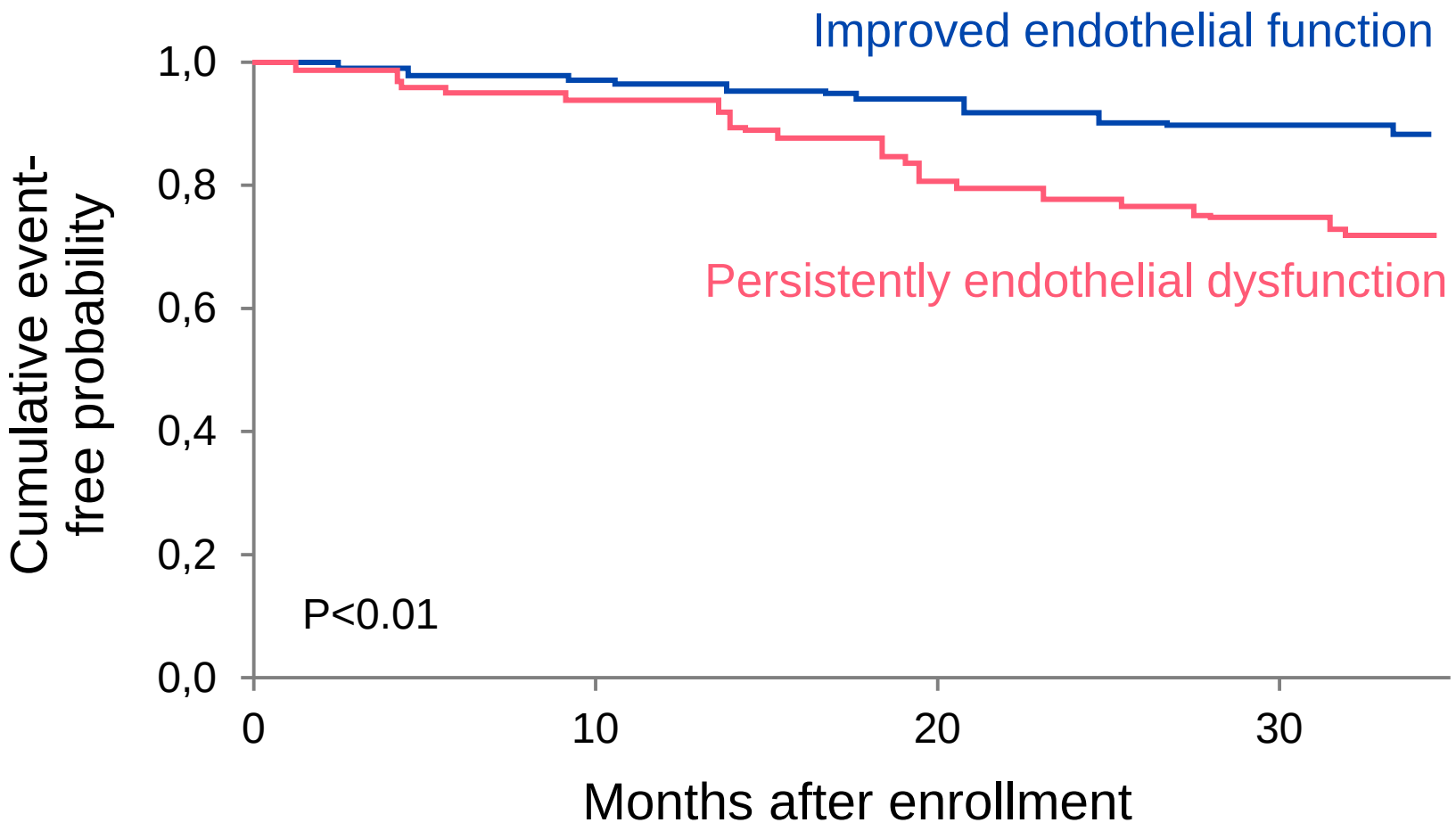
Event-Free Survival and Endothelial Function



Kitta Y et al: J Am Coll Cardiol 53:323, 2009

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Take Home Message

- Diagnosis
  - Severe epicardial and microcirculation endothelial dysfunction
- Treatment
  - Endothelial dysfunction
  - Symptoms
  - Prevent future events

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58-Year-Old Female Admitted With Chest Pain

- No previous cardiac history presents to ER
- Developed acute onset of chest pain during a heated discussion with her boss
- PMH: Nicotine abuse, anxiety disorder, history of hypertension
- Physical examination: Blood pressure 135/100 mm Hg otherwise normal
- Lab: Troponin T 0.08 mg/dL

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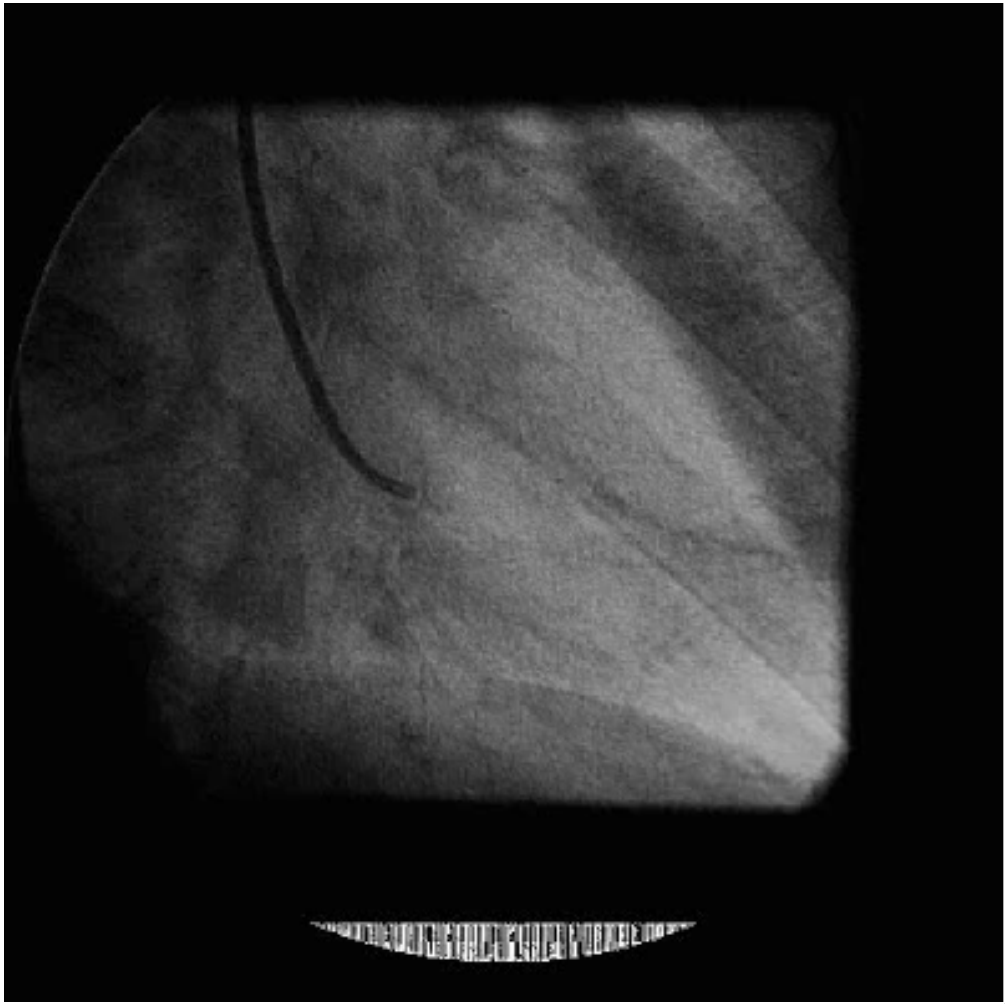

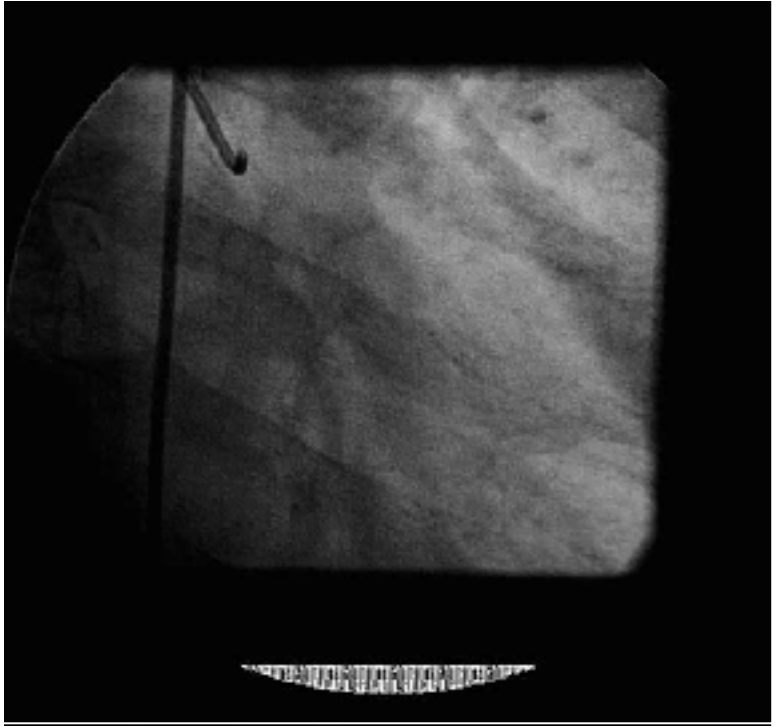

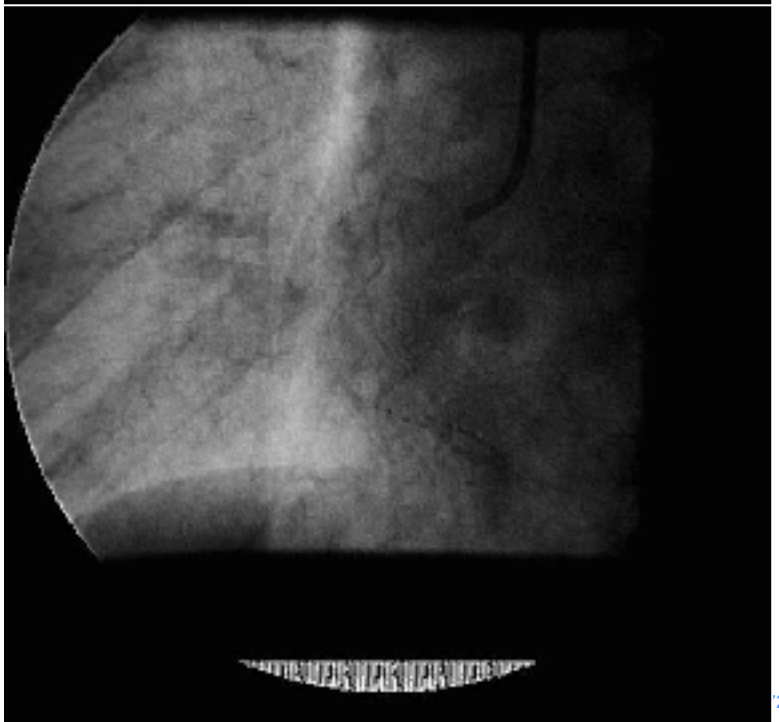

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Clinical Characteristics and Cardiovascular Magnetic Resonance Findings in Stress (Takotsubo) Cardiomyopathy

Ingo Eitel, MD
Florian von Knobelsdorff-Brenkenhoff, MD
Peter Bernhardt, MD

Context Stress cardiomyopathy (SC) is a transient form of acute heart failure triggered by stressful events and associated with a distinctive left ventricular (LV) contraction pattern. Various aspects of its clinical profile have been described in small single-center populations, but larger, multicenter data sets have been lacking so far. Furthermore, it remains difficult to quickly establish diagnosis on admission.

Apical ballooning

Midventricular ballooning with sparing of apical and basal region

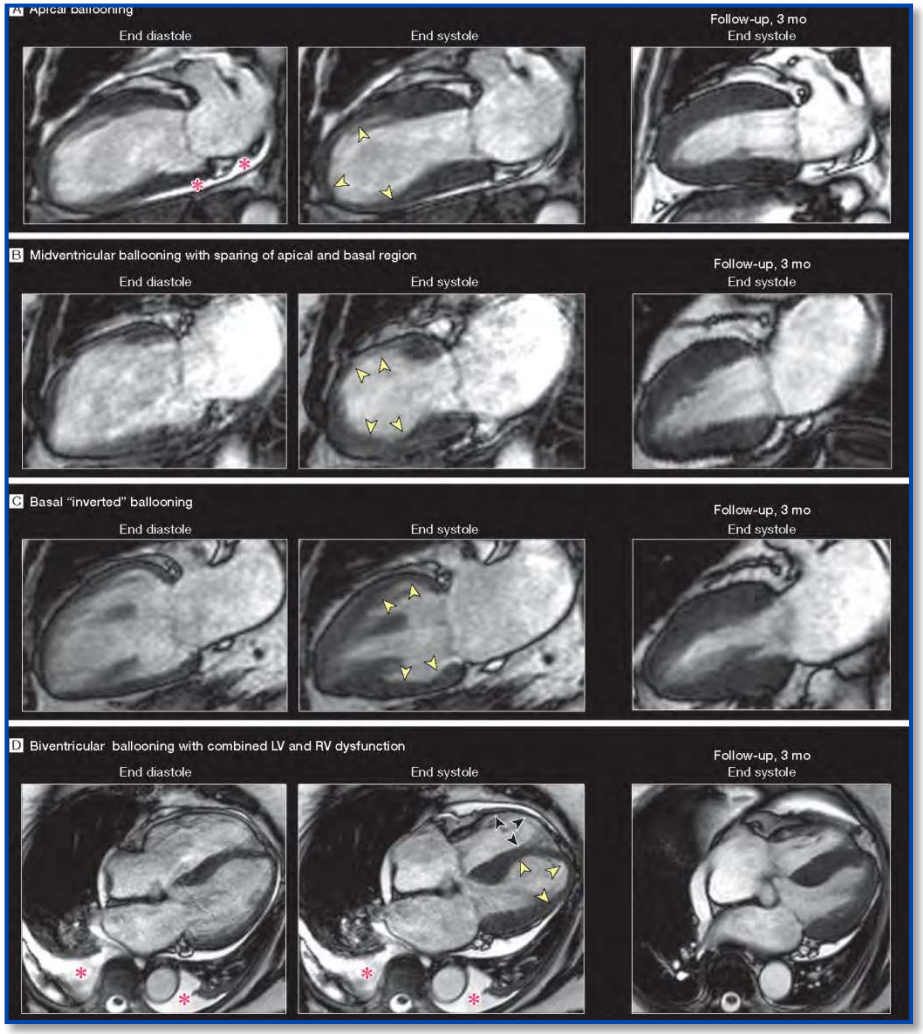
Basal “inverted” balloon

Biventricular ballooning with combined LV and RV dysfunction

End diastole

End systolic end systol

Follow-up 3 months



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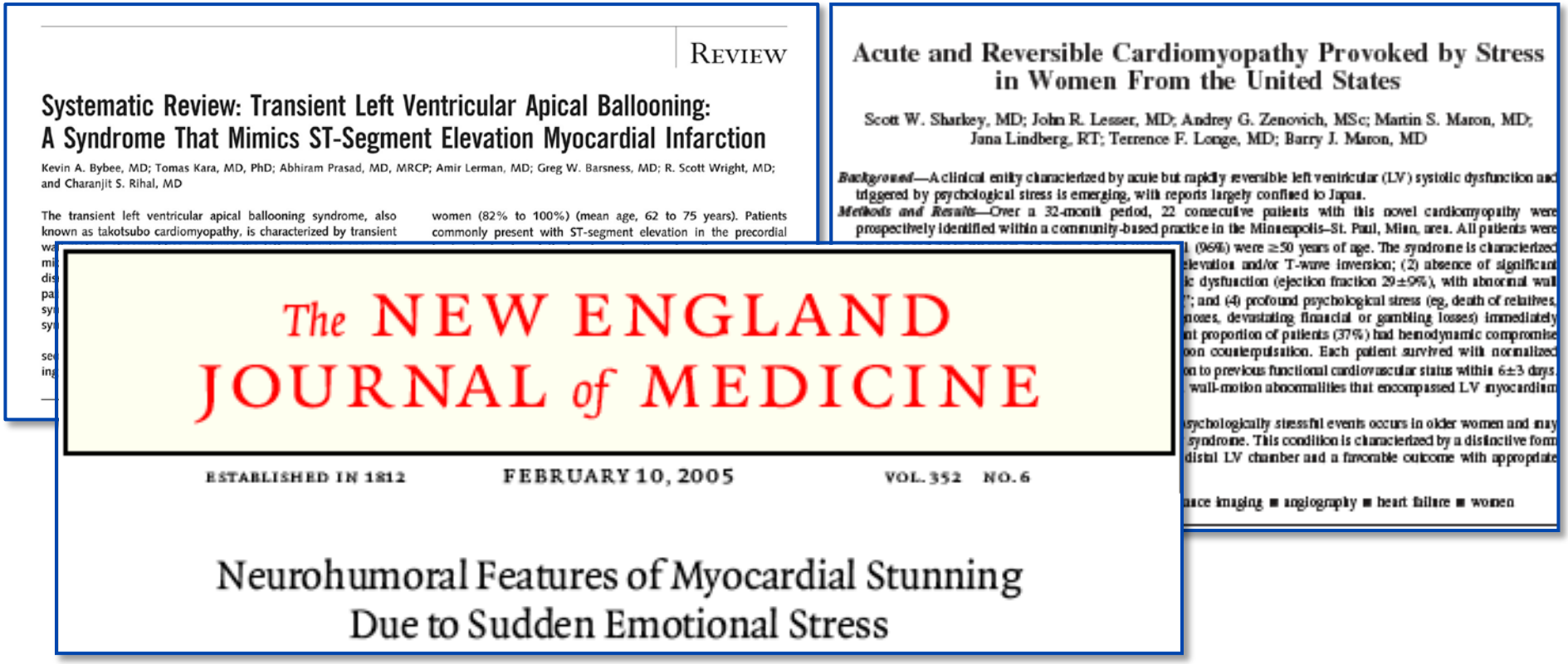

- Global wall motion abnormalities
- Women
- Post menopausal
- Mental stress

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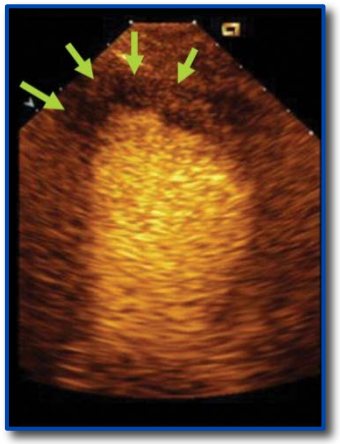


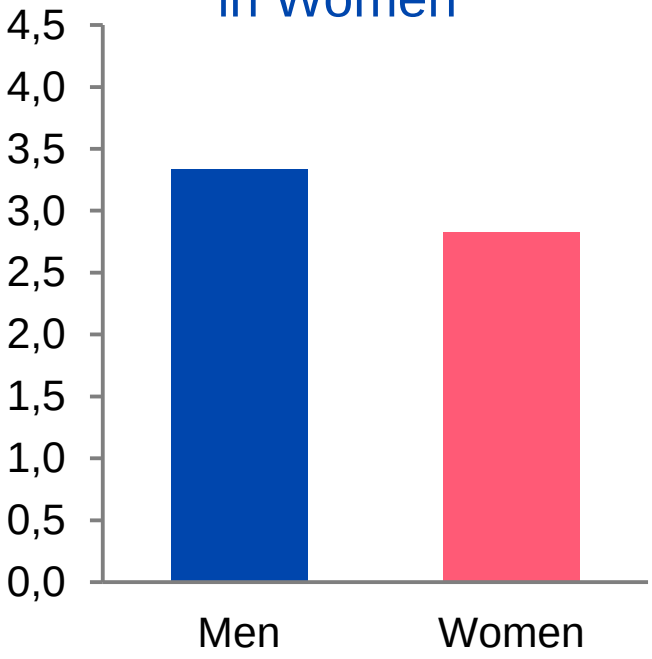
Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome

Leonarda Galiuto*, Alberto Ranieri De Caterina, Angelo Porfidia, Lazzaro Paraggio, Sabrina Barchetta, Gabriella Locorotondo, Antonio Giuseppe Rebuzzi, and Filippo Crea

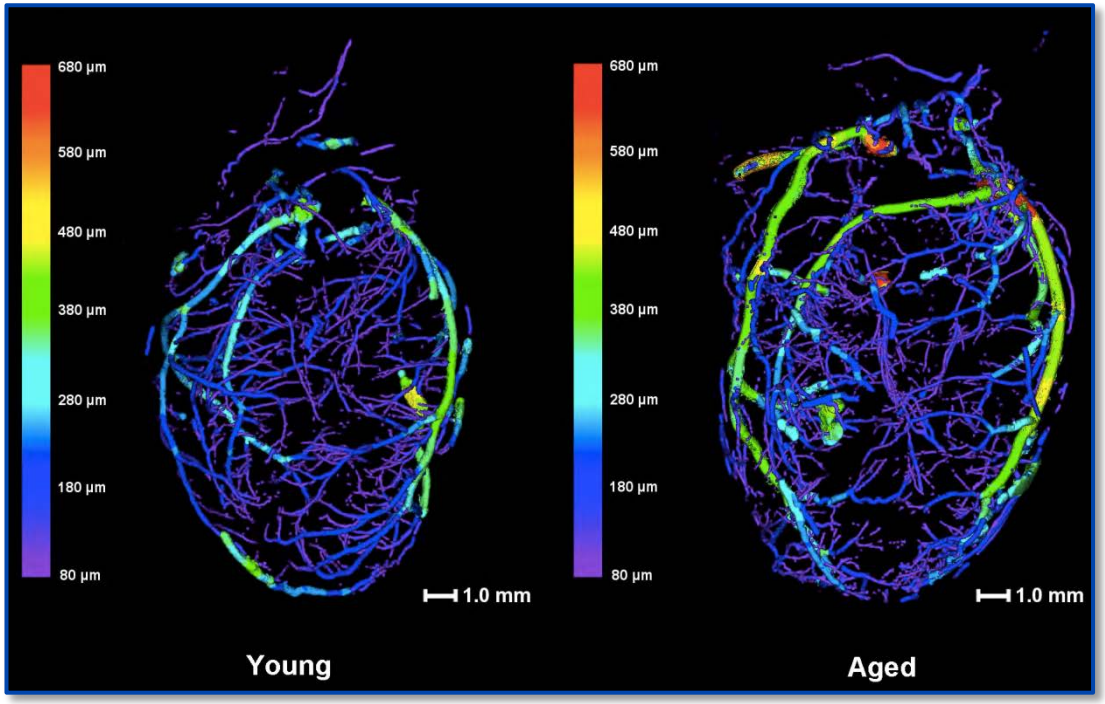
Institute of Cardiology, Catholic University of the Sacred Heart, Policlinico A. Gemelli, Largo A. Gemelli, 8,Rome 00168, Italy

Received 16 July 2009; revised 26 November 2009; accepted 10 December 2009; online publish-ahead-of-print 9 March 2010

CFR is Lower in Women



Lower Density of Microvessels With Aging



MAYO CLINIC

Clin Auton Res (2008)
DOI 10.1007/s10286-008-0497-5

RESEARCH ARTICLE

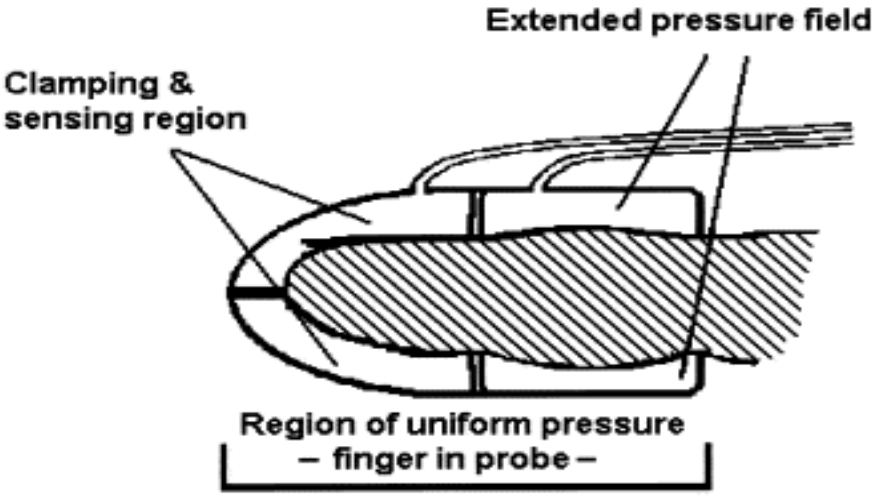
Elizabeth A. Martin
Shen-Li Tan
Leslie R. MacBride
Shahar Lavi
Lilach O. Lerman
Amir Lerman

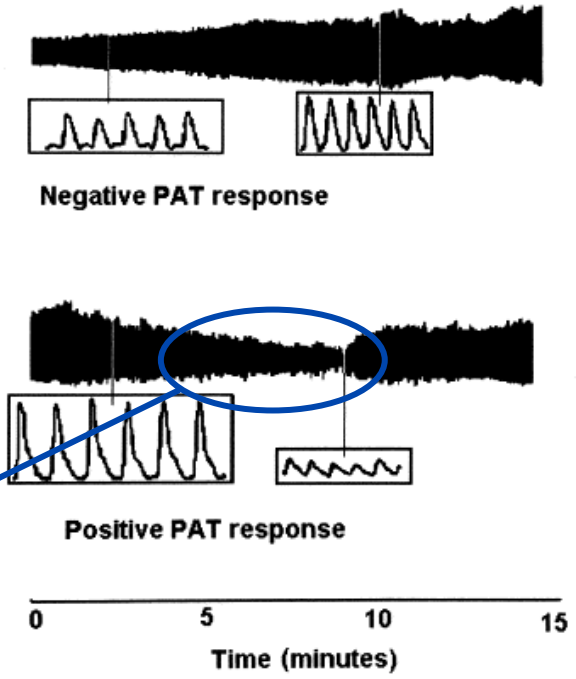
Sex differences in vascular and endothelial responses to acute mental stress

Tako

Endothelial Function and Vascular Response to Mental Stress Are Impaired in Patients With Apical Ballooning Syndrome

Elizabeth A. Martin, PHD,* Abhiram Prasad, MD,* Charanjit S. Rihal, MD,* Lilach O. Lerman, MD, PHD,† Amir Lerman, MD*
Rochester, Minnesota





≥ 20% decrease

PAT signal during mental stress

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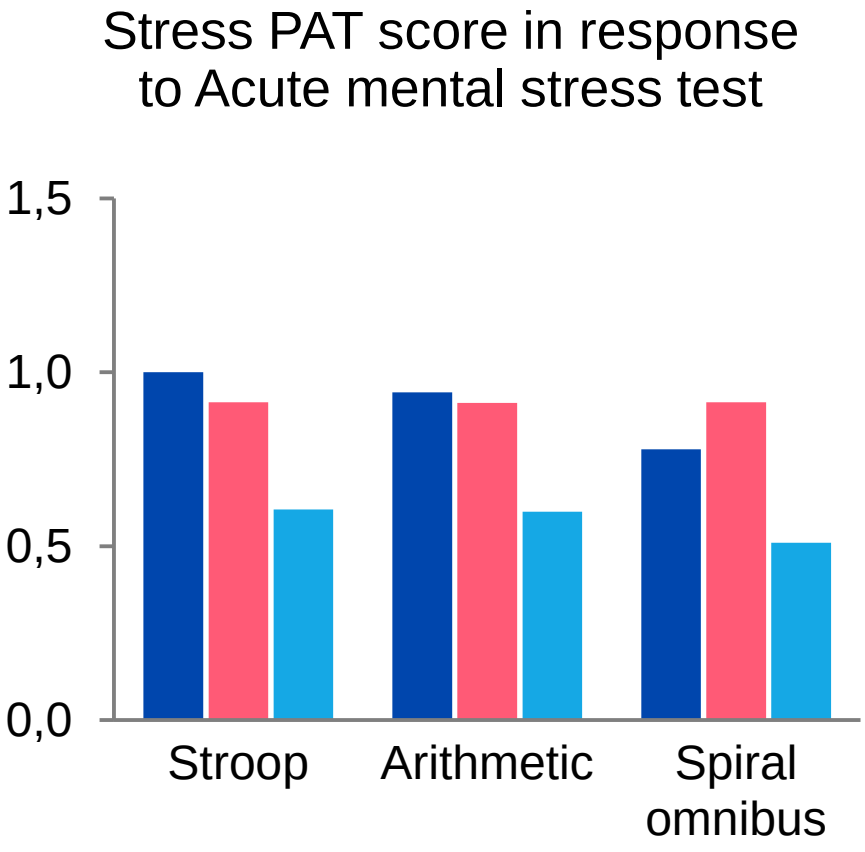
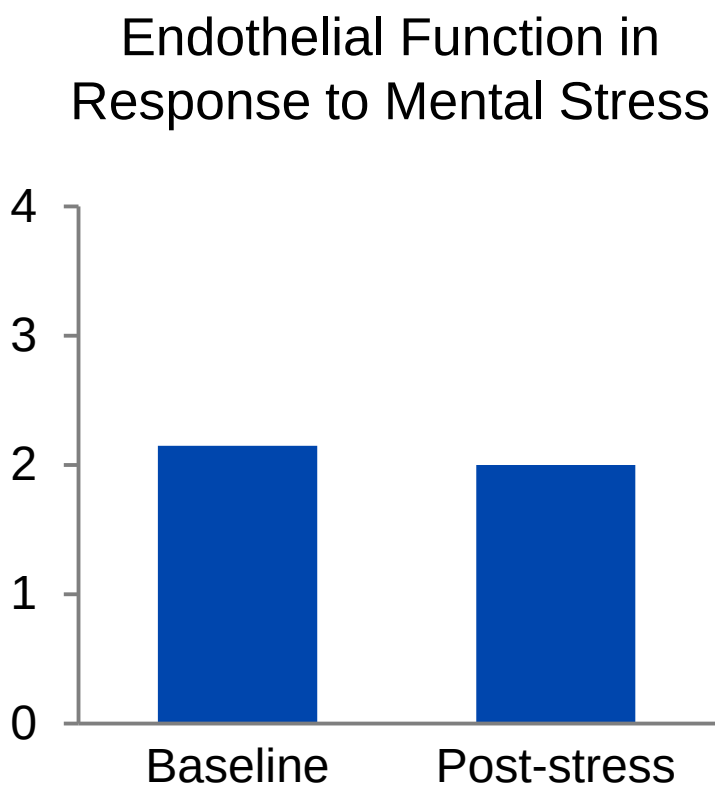
Vascular Responses to Mental Stress Tests





Postmenopausal controls MI patients ABS patients

Martin EA et al: JACC, 2010

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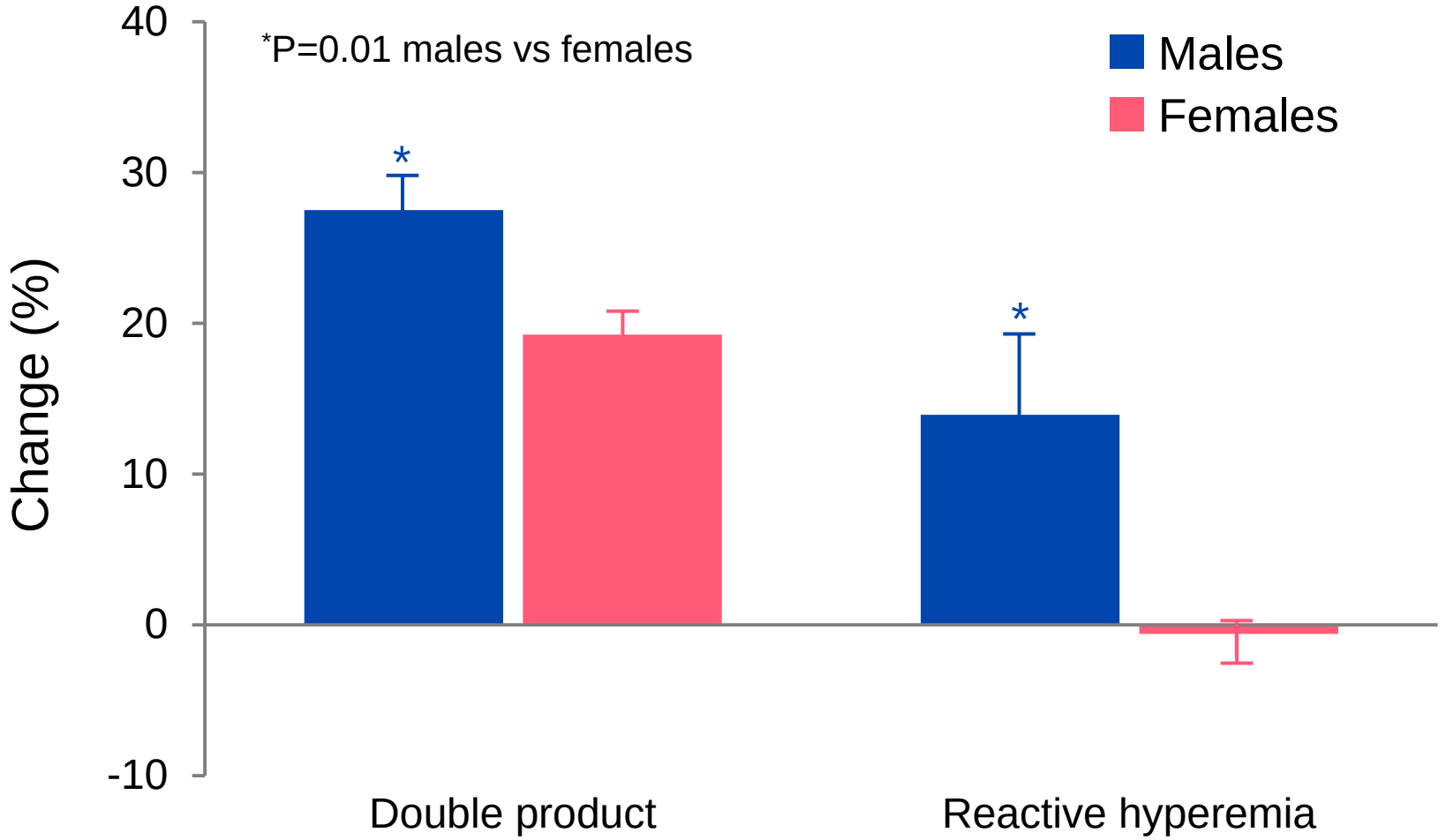
Sex Differences in Double Product and Reactive Hyperemia Response to Mental Stress



Martin EA et al: Clin Auton Res, 2008

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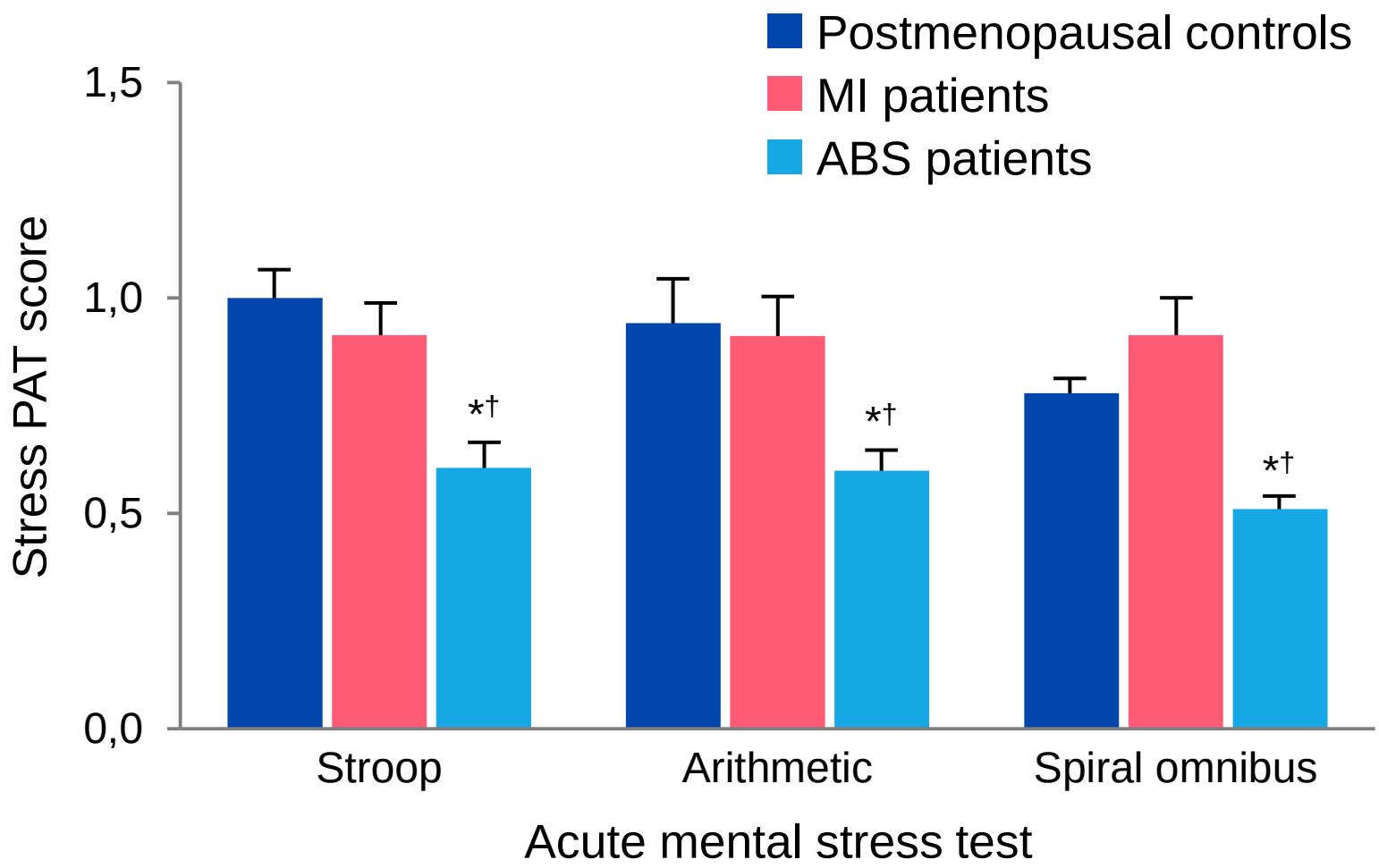
Vascular Responses to Mental Stress Tests



Martin EA et al: JACC, 2010

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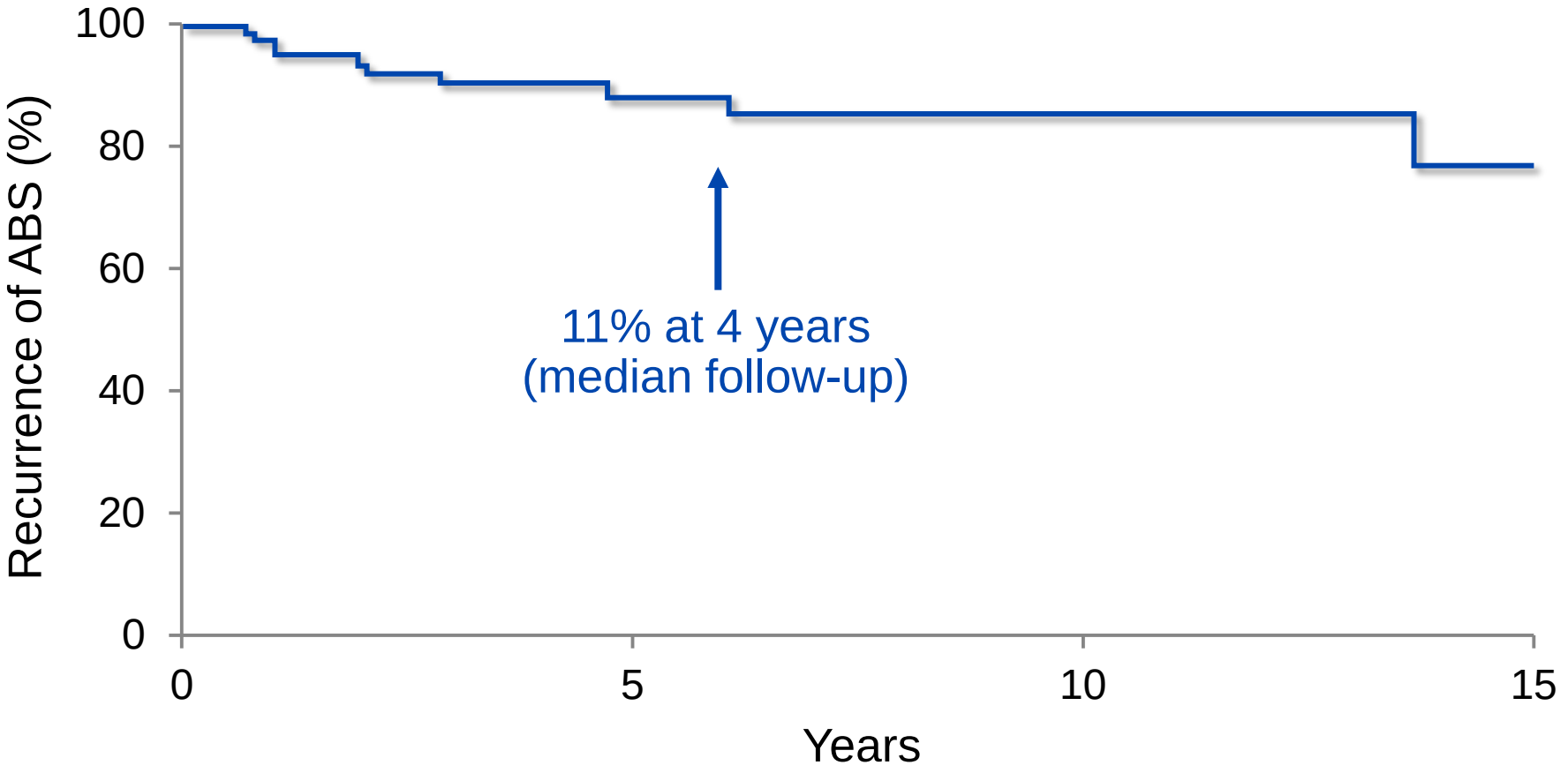
Four-Year Recurrence Rate and Prognosis of the Apical Ballooning Syndrome

Ahmad A. Elesber, MD,* Abhiram Prasad, MD, FACC,* Ryan J. Lennon, MS,†
R. Scott Wright, MD, FACC, FESC,* Amir Lerman, MD, FACC,* Charanjit S. Rihal, MD, FACC*



Eiesber & Lerman et al: JACC 50:448, 2007

MAYO CLINIC

Impaired Coronary Microvascular Reactivity in Women with Apical Ballooning Syndrome

European Heart Journal
Acute Cardiovascular Care
EUROPEAN SOCIETY OF CARDIOLOGY®

Original scientific paper

Impaired coronary microvascular reactivity in women with apical ballooning syndrome (Takotsubo/ stress cardiomyopathy)

European Heart Journal: Acute Cardiovascular Care
0(0) 1–6

DOI: 10.1177/2048872613475891
acc.sagepub.com
SAGE

A total of 228 cases of ABS were prospectively identified, and of these, 10 patients (median age 61 years (IQR 48-75); all females) who underwent coronary vasomotion testing were included in the study

(mean age 60 years) with normal microvascular responses to ACH. 103% (IQR 75, 149). Seven (70%) patients had <50% increase in coronary blood flow indicating abnormal microvascular response to ACH. 70% had either abnormal epicardial or microvascular response to ACH. Median coronary flow reserve was abnormal at 2.2% (IQR 2.0, 3.4; normal

70% had either abnormal epicardial or microvascular response to ACH

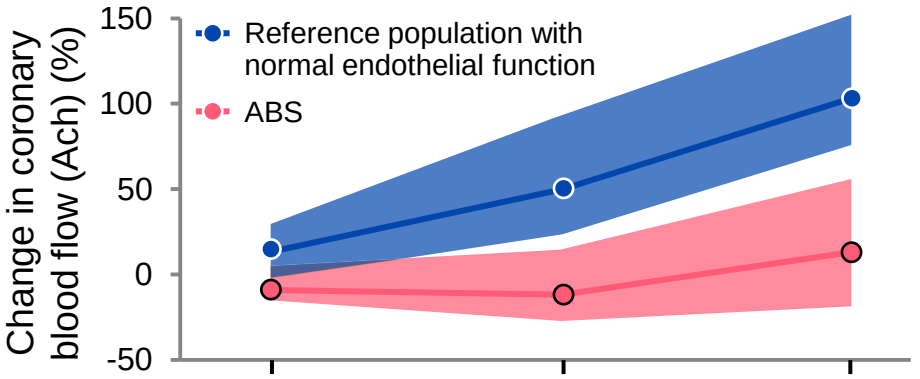
Apical ballooning syndrome, endothelium, microcirculation, stress cardiomyopathy, Takotsubo cardiomyopathy

Received: 13 December 2012; accepted: 6 January 2013

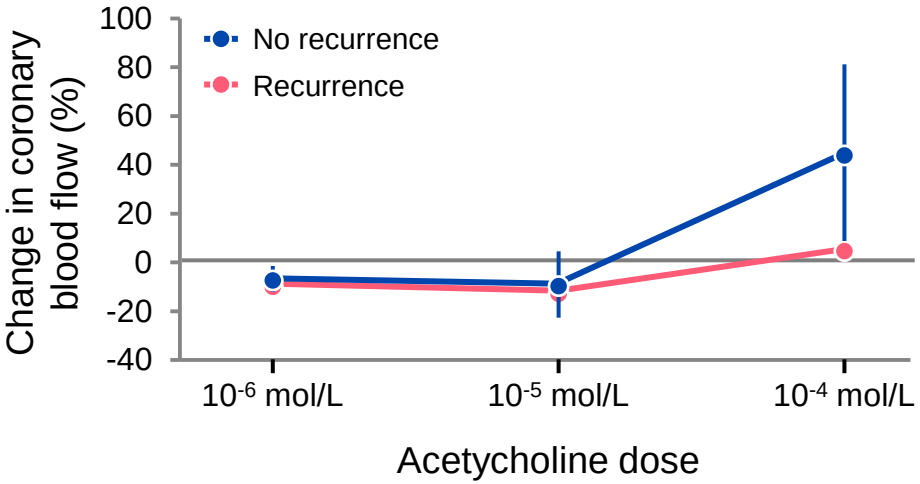
Conclusion: …coronary microvascular dysfunction is highly prevalent in patients with ABS..may be a central feature of the pathophysiology of ABS

motion abnormalities involving the apical and mid-ventricular segments which resolve spontaneously over time.

Minnesota 55905, USA.
Email: prasad.abhiram@mayo.edu



Coronary endothelial function in Patients With and Without Recurrence of ABS



Patel et al: EHJ ACC, 2013

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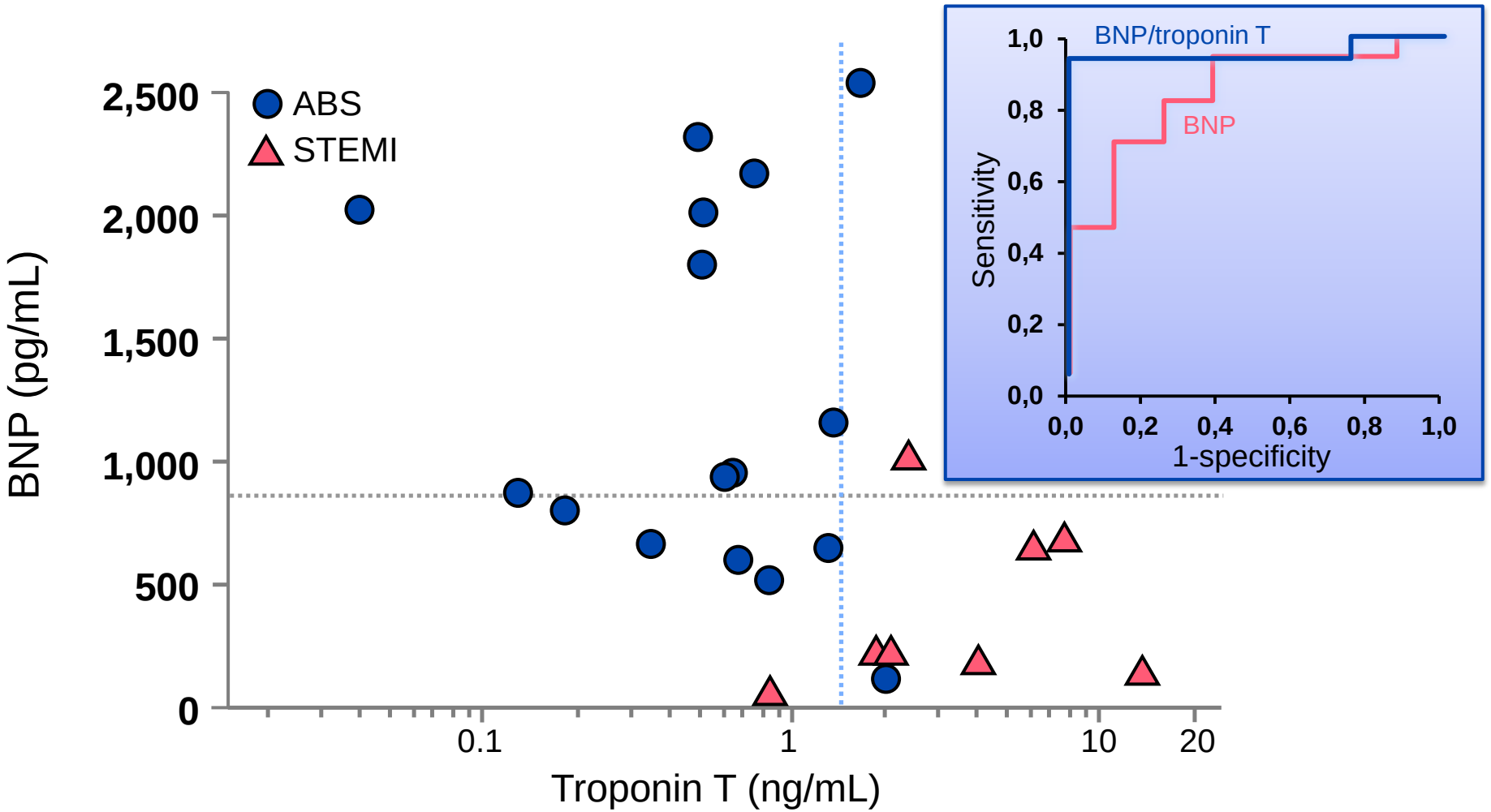
Troponin T and B-Type Natriuretic Peptide Levels in Patients With Apical Ballooning Syndrome and ST-Elevation Myocardial Infarction



Madhaven et al: Heart, 2009

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Take Home Message

- Need for LV gram in women with chest pain MI and normal angiogram
  - The need for proper diagnosis
- Treatment
  - Conservative: Medical therapy
  - Non-pharmacological therapy

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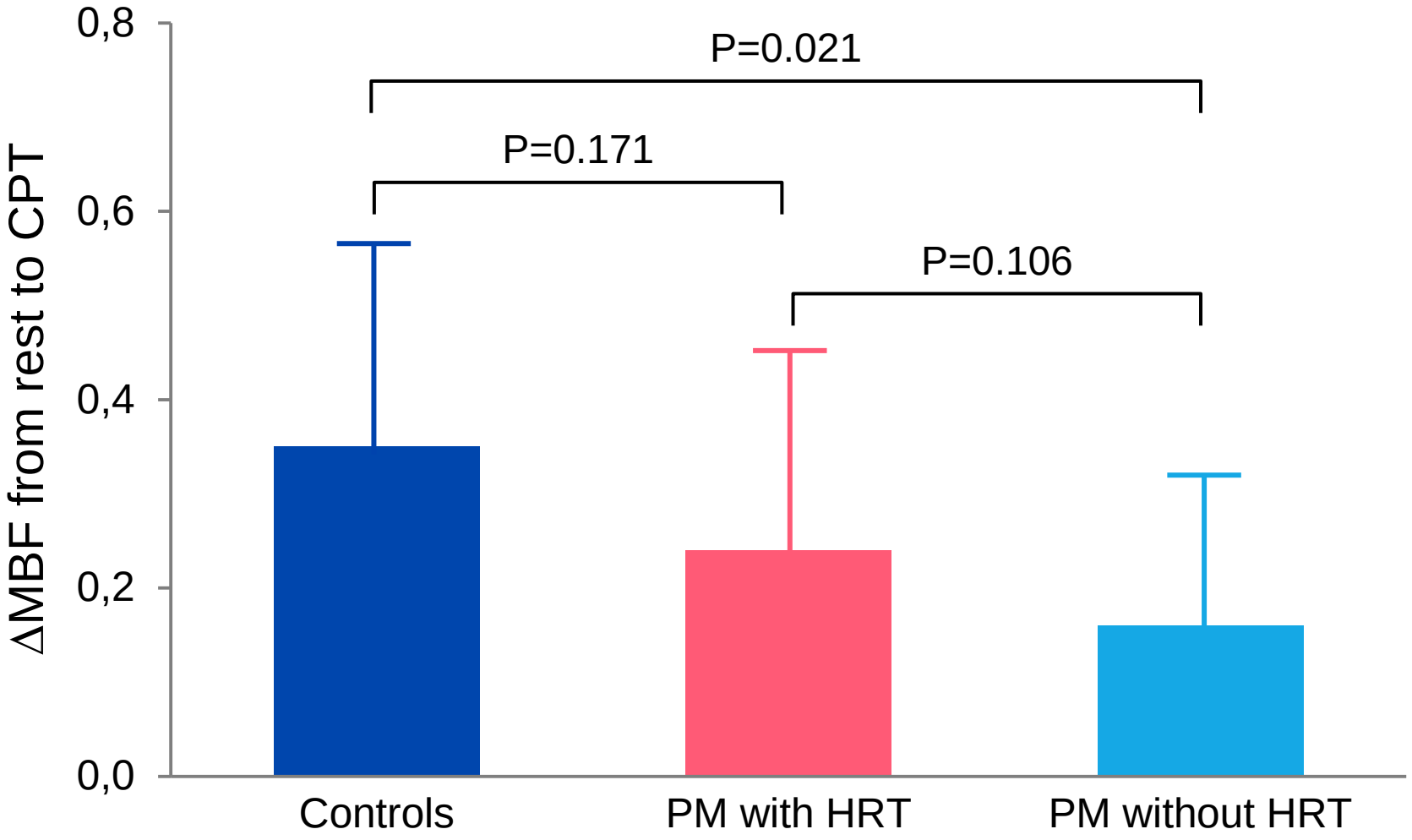
Change in Myocardial Blood Flow from Rest in Response to Cold Pressor Testing



Schindler et al: Euro Heart J 30:978, 2009

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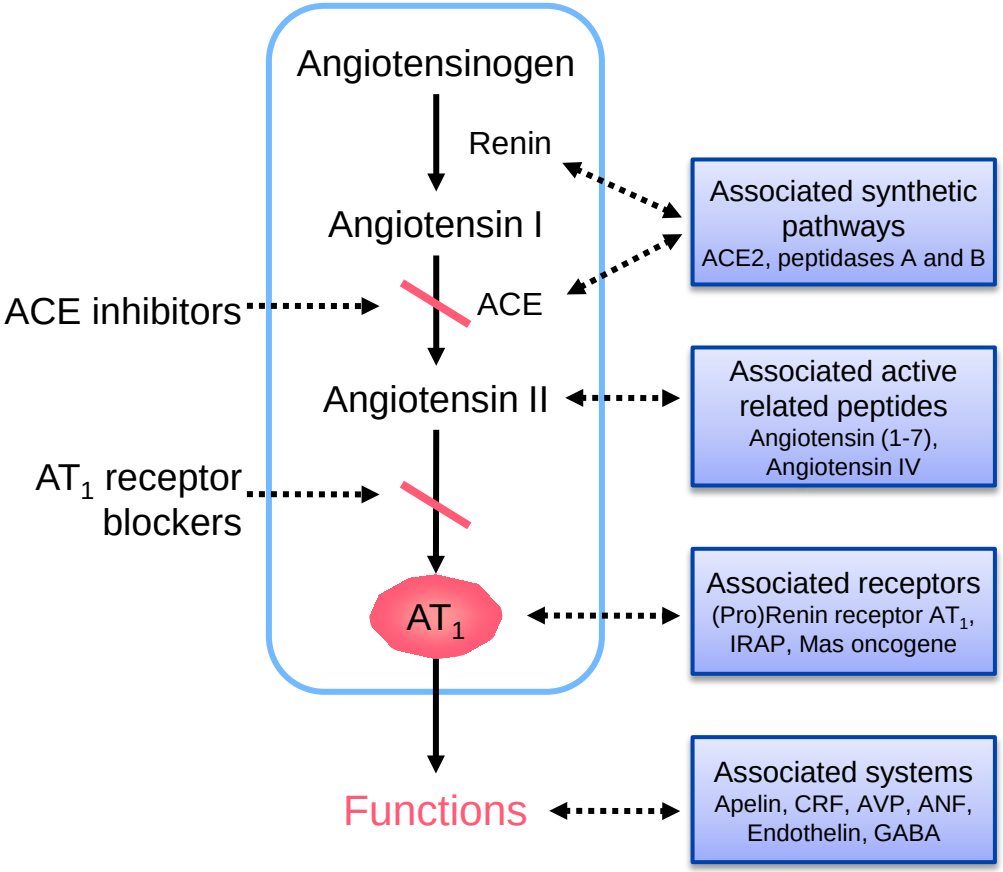

AT1 Receptor Functions

- Blood pressure and ion metabolism
- Blood brain barrier
- Brain circulation
- Innate immune response inflammation
- Brain development
- Sensory motor systems
- Stress
- Endocrine systems
- Autonomic systems
- Behavior and cognition

Saavedra et al: Psychoneuroendocinology 36:1, 2011

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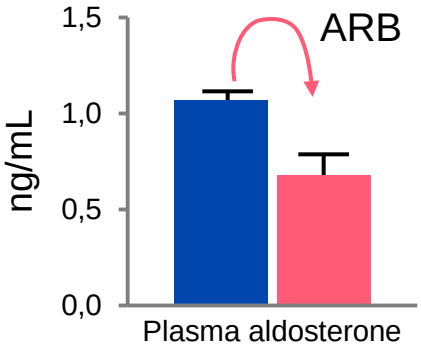
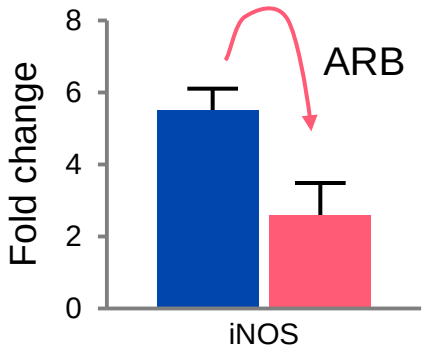
ARBs Decrease Peripheral and Brain Inflammation Produced by Systemic Administration of Bacterial Endotoxin

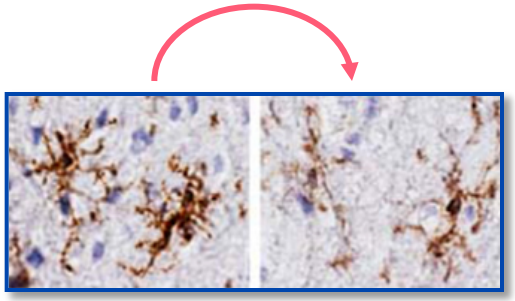
Decrease circulating inflammatory factors

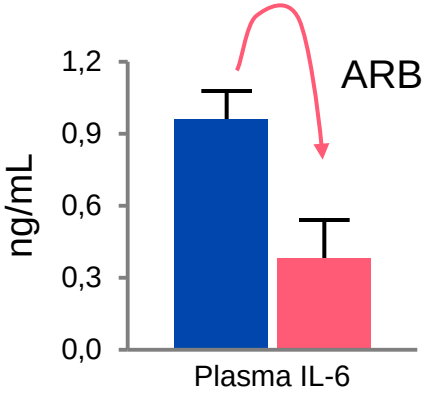
Decrease brain parenchymal inflammatory cascades

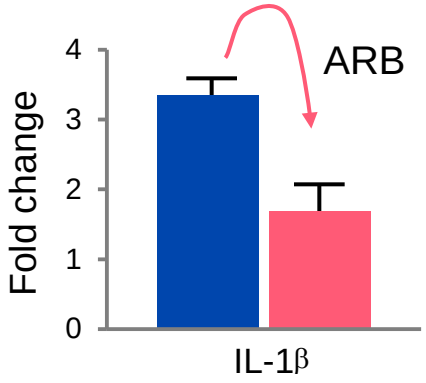
Decrease microglia activation











Saavedra et al: Psychoneuroendocinology 36:1, 2011

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Optimism, Cynical Hostility and Fully-Adjusted Hazard of Important Disease Outcomes in Women

CHD-related mortality

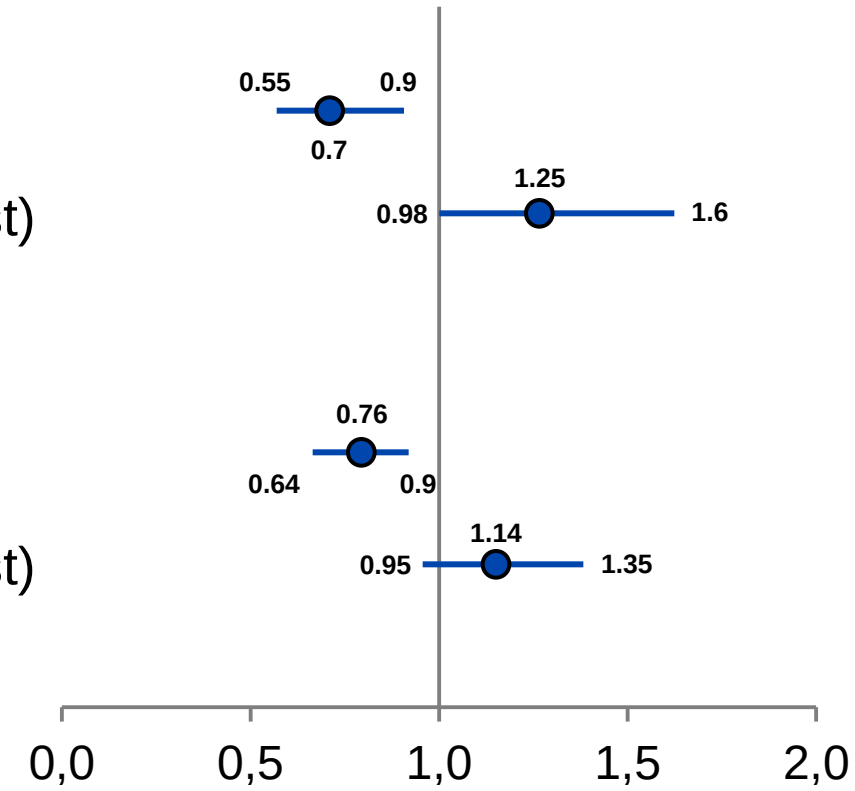
Optimism (most vs least)

Cynical hostility (most vs least)

CVD-related mortality

Optimism (most vs least)

Cynical hostility (most vs least)



Tindle et al: Circ 120:656, 2009

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Treatment

- Conservative: Medical therapy
  - Beta blockers
  - Preemptive with NTG
  - ASA
  - HRT
    ARB
- Mental stress assessment and modification
  - Yoga, meditation…

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38-Year-Old Female With Chest Pain

- 38-year-old female healthy, runner
- No risk factors for atherosclerosis
- Presents to ER with 1 hour heavy and central chest discomfort, diaphoresis
- Normal exam
- Normal ECG
- Troponin T 0.05, 0.09, 0.07 mg/dL

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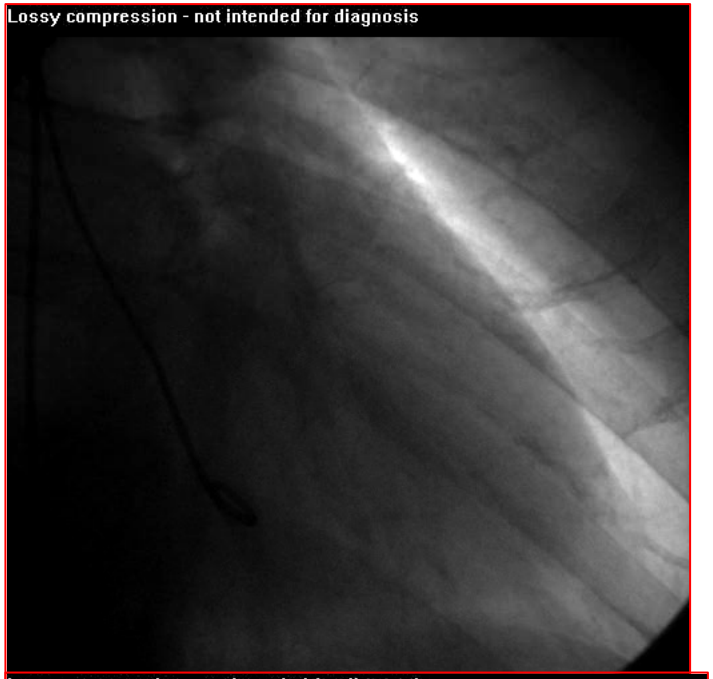
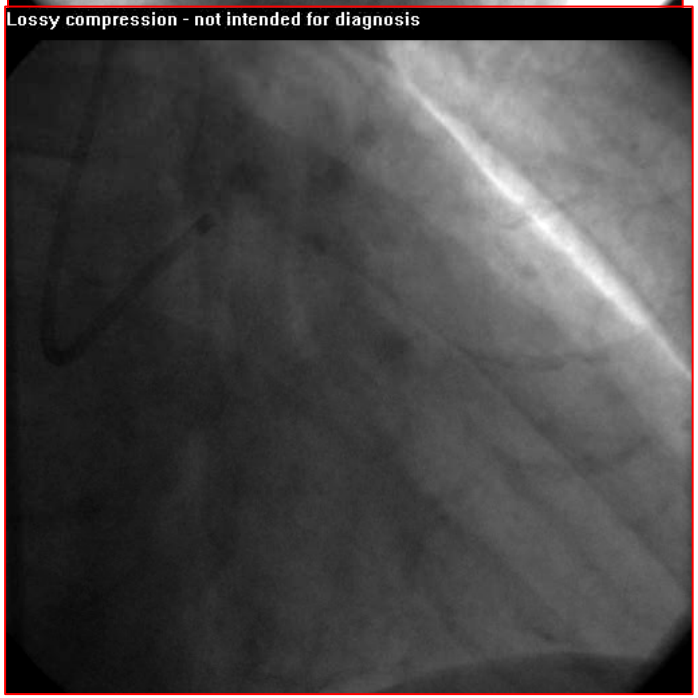
38-Year-Old Female With Chest Pain





38-Year-Old Female With Chest Pain

1. Another case of ABS?
2. Normal coronary arteries
3. Another case of microvascular disease and endothelial dysfunction?
4. Typical diffuse disease ?

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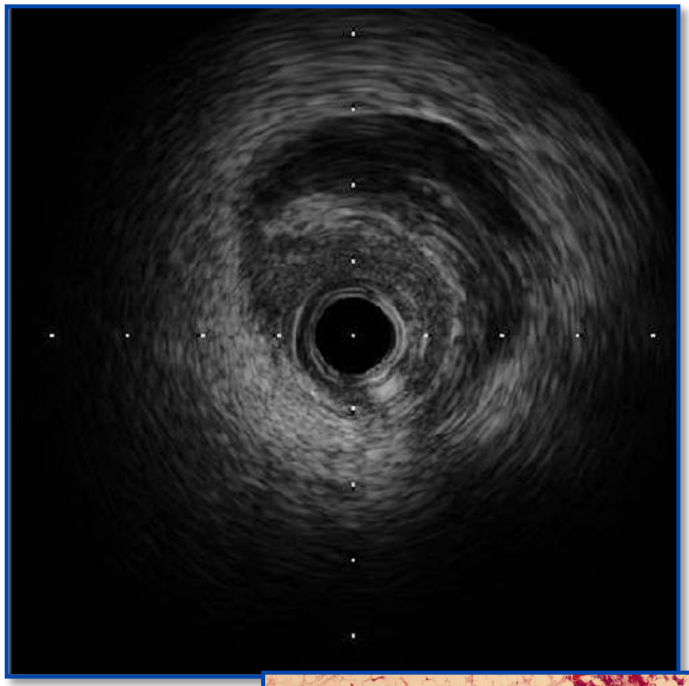
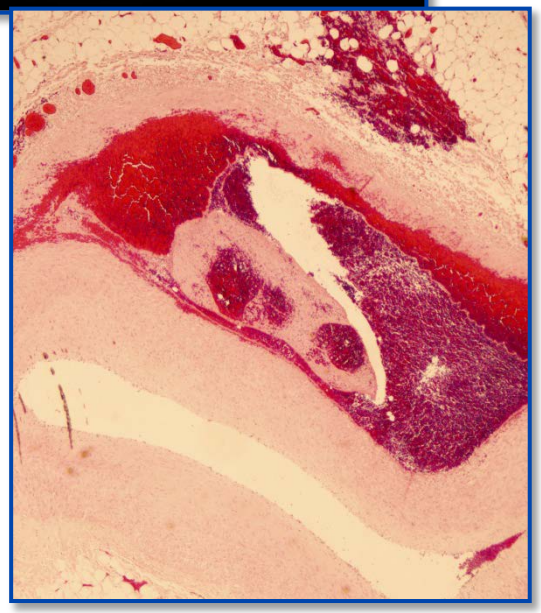
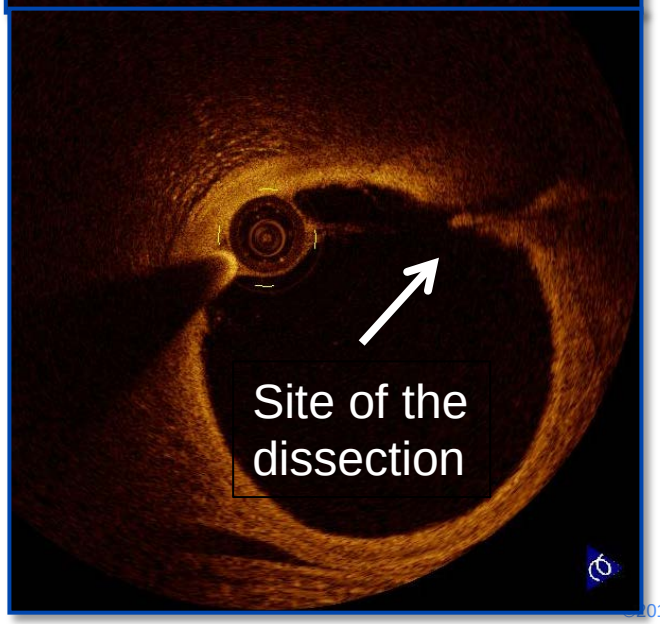
Imaging for Coronary Artery Dissection







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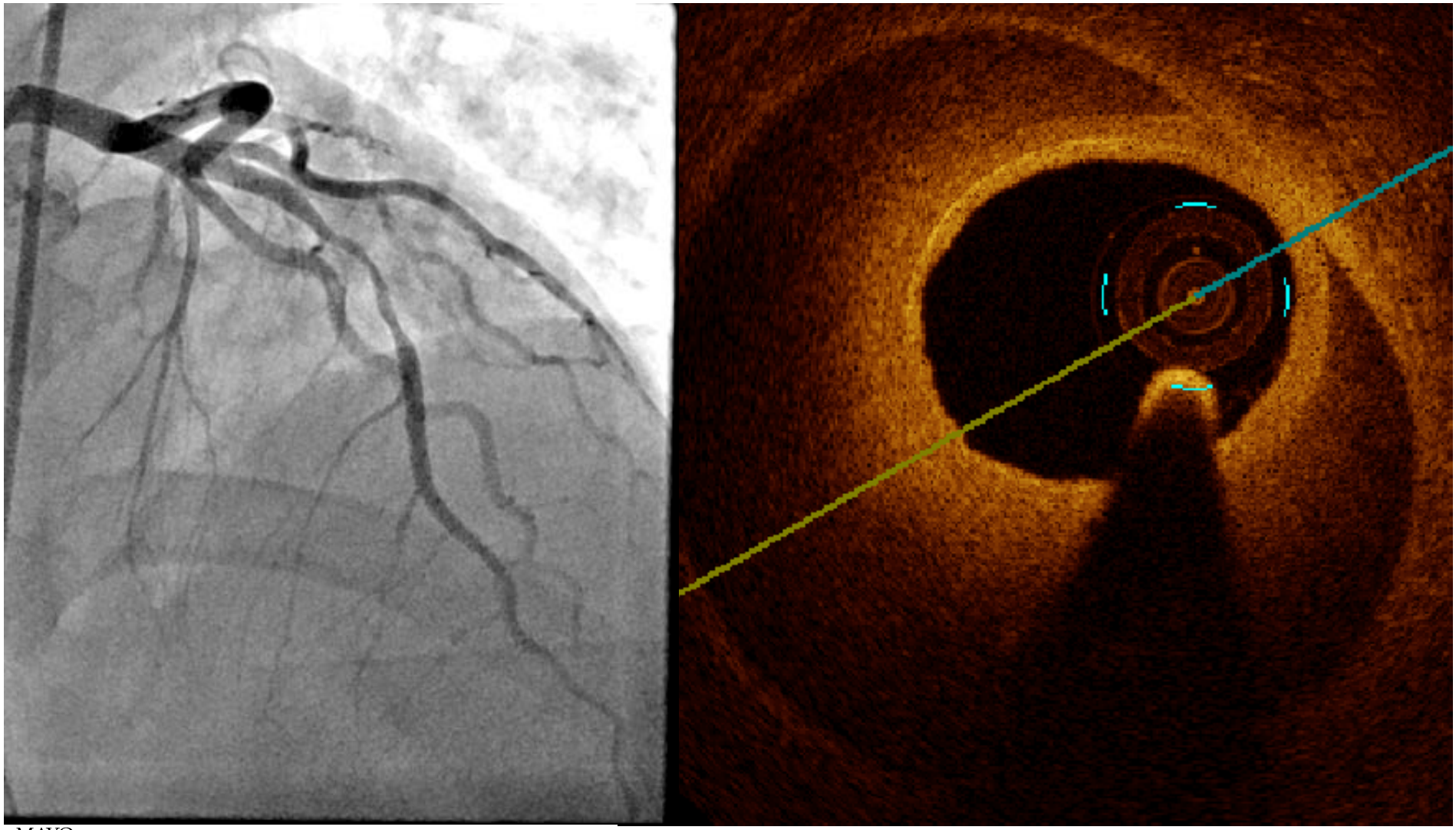
42 year old Female Out of hospital Ventricular Fibrillation

ACC/AHA/ESC Guidelines:

- Antiplatelets
- Stent
- Statin

42 year old Female Out of hospital Ventricular Fibrillation



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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Clinical Features, Management and Prognosis of Spontaneous Coronary Artery Dissection

Marysia S. Tweet, Sharonne N. Hayes, Sridevi R. Pitta, Robert D. Simari, Amir Lerman, Ryan J. Lennon, Bernard J. Gersh, Sherezade Khambatta, Patricia J.M. Best, Charanjit S. Rihal and Rajiv Gulati

- Infrequent cause of acute coronary syndrome
- Databases: 0.01-1.1% of all angiograms
- Dissection +/- intramural hematoma, although no formal diagnostic criteria
- Female >> Male
  - Postpartum 30%, low CAD risk profile
  - Incidence with FMD in women
  - Extreme exertion and smoking in male
  - Individual reports of vascular genetic associations

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Mayo Clinic SCAD Study

- Single center, keyword medical record search
- 508 records, angiograms to exclude non-SCAD
- n=87 (1984-2010)
- Non-atherosclerotic
  - Absence of atheroma on angio
  - No prior history of atherosclerotic disease
- Diagnosis is invasive
  - Dissection flap on angio or IVUS/OCT
  - Intramural hematoma of IVUS/OCT

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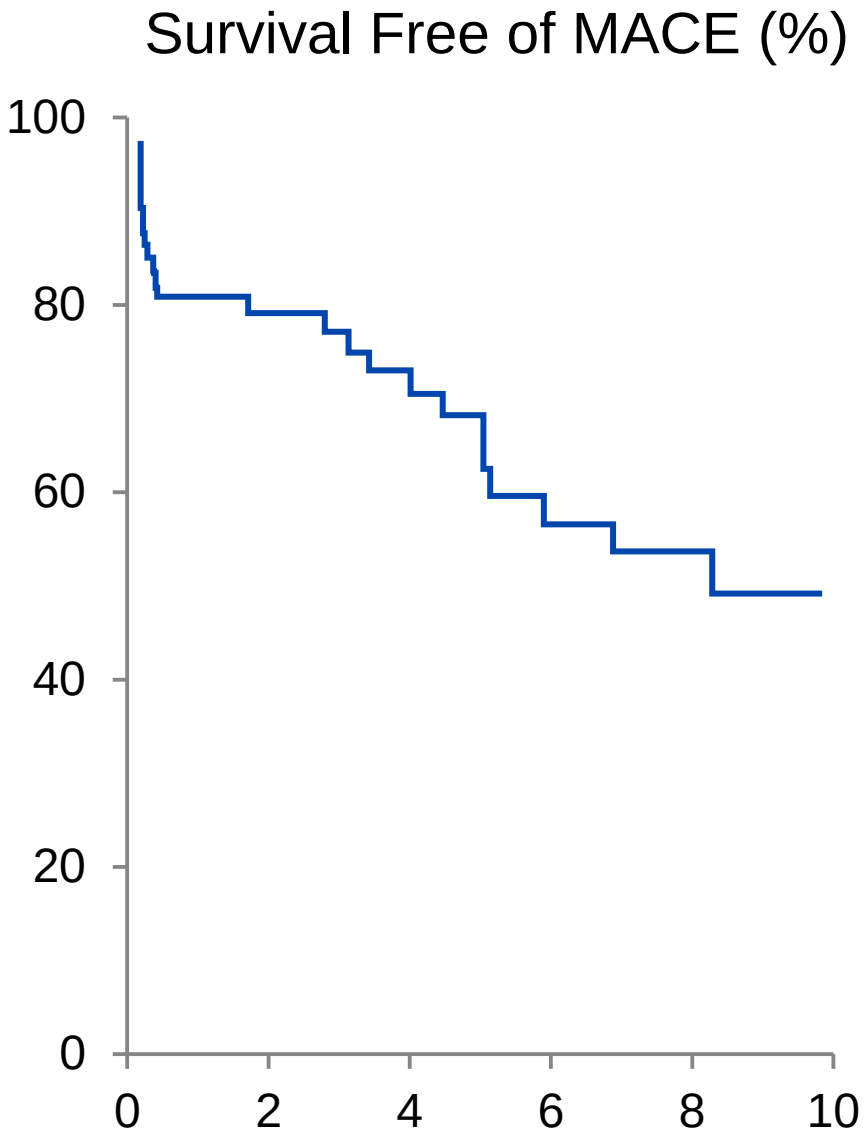
Long-Term Outcomes



- Recurrence rate 21% overall
- 15/71 females, 0/16 males (P=0.023)
- Median time to 2nd episode 2.8 years (3 days – 12 years)
- 4/10 patients with FMD experienced recurrence, including both carotid dissection patients

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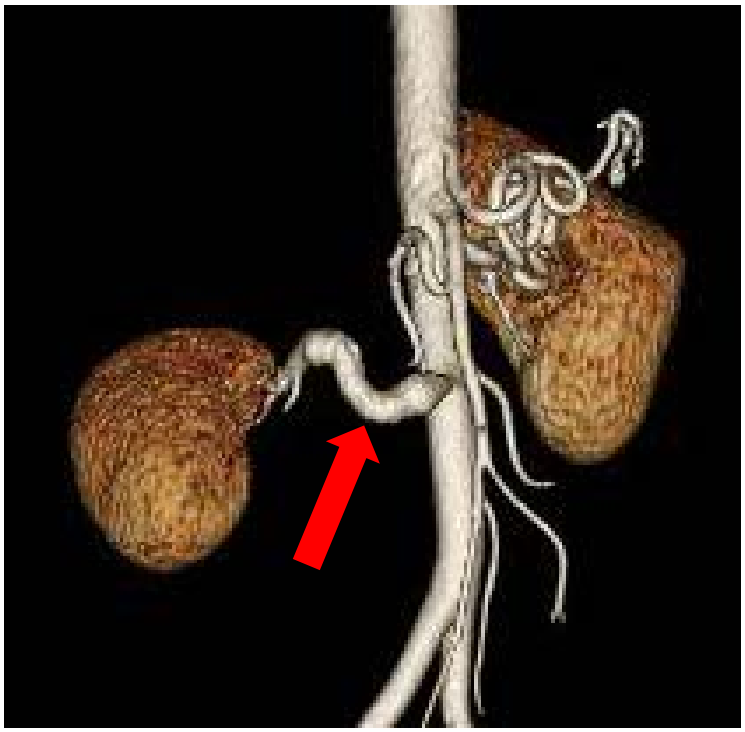
The Need for Extracoronary Vascular Imaging



Carotid FMD and Dissection

Spontaneous Coronary Artery Dissection

Spontaneous Coronary Artery Dissection

Prevalence of Predisposing Conditions Including Fibromuscular Dysplasia in a Tertiary Center Cohort

50 Patients, 98% women, all presented with MI

Objectives We sought to evaluate the prevalence of fibromuscular dysplasia (FMD) and other pre-

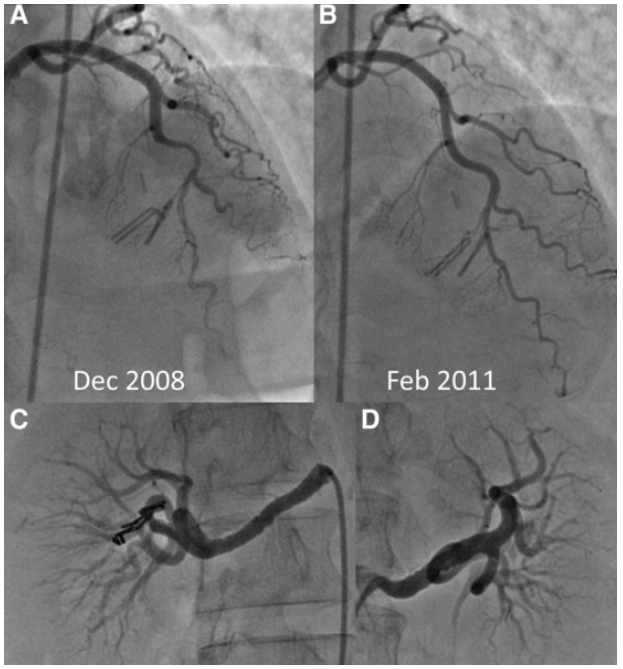
Emotional stress in 26%

FMD in 86%
- 58% renal
- 49% iliac
- 46% cerebrovascular

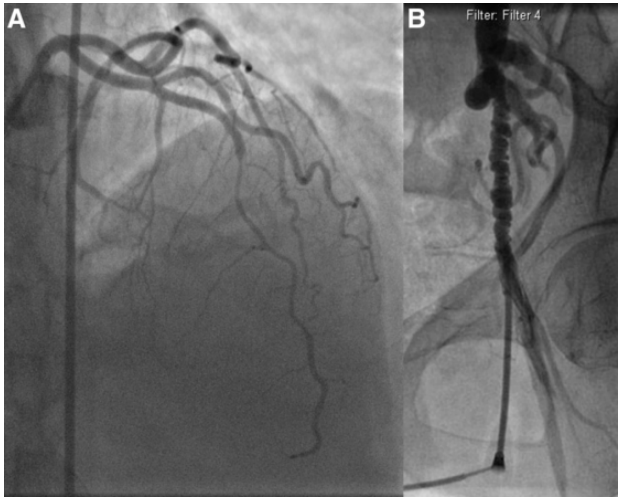
Was postpartum, and 2 were involved in intense isometric exercises. Emotional stress was reported

Conclusions: Nonatherosclerotic SCAD predominantly affect women, and most have concomitant FMD

Dissection of LAD and Subsequent Healing in Patients with FMD



Long Dissection of LAD in Patients with Severe Iliac FMD



Saw et al: JACC Intv, 2013

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SCAD Mayo Retrospective Study Conclusions

- Young females predominate, low burden of risk fx
- More than 50% present with STEMI or V Fib
- Males exercise; females post-partum
- FMD a novel association, likely underestimated, quite possibly a causative factor
- Conservative Rx associated with favorable in-hospital outcome; obvious caveat is selection bias
- PCI associated with high rates of procedural limitation
- Recurrence rate and MACE rates underscore need for close and long-term follow-up

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Treatment

- Be aware of the diagnosis.
- Use intravascular imaging
- Medical therapy
- Conservative
  - Beat blockers
  - ASA
  - ~~Statins~~
  - Screening

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Conflict of interest:

Advisory board: Itamar Medical

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mayo

CP996233-30

National Geographic Daily News

Egyptian Princess Mummy Had Oldest Known Heart Disease

- Known as Ahmose Meryet Amon, the princess lived some 3,500 years ago and died in her 40s
- She had blockages in 5 major arteries, including those that supply blood to the brain and heart
- She is now the earliest known sufferer of coronary atherosclerosis
- The princess was known to have arthritis and inflammation of the joints

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