What Interventional Cardiology Has Taught Us About Physiology and Pathophysiology

47th Annual Carl J. Wiggers Memorial Lecture
Cleveland, OH

David R. Holmes, MD
Mayo Clinic
Rochester, MN

Presenter Disclosure Information

David R. Holmes, Jr., M.D.

"What Interventional Cardiology Has Taught Us About Physiology and Pathophysiology"

The following relationships exist related to this presentation:

None

Interventional Cardiology
Physiology and Pathophysiology

- **Acute ischemic syndromes**
- **Coronary flow**
- **Role of platelets in health and disease**
- **Vascular healing**

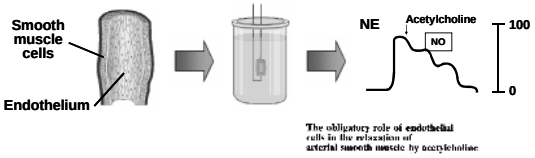
Endothelial Function
Basic Science to Clinical Practice

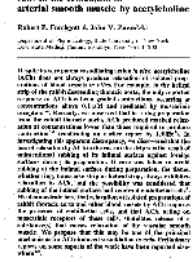
Discovery of NO and the role of the endothelium

1980

Basic science → **Clinical practice**

CP1240167-10





The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine

Robert F. Furchgott & John V. Zawadzki

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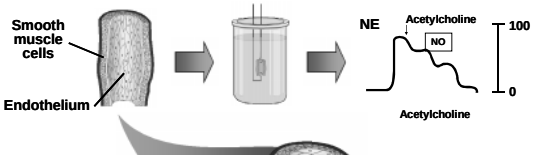

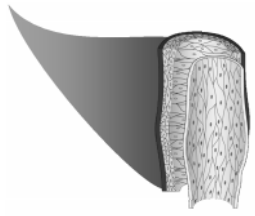

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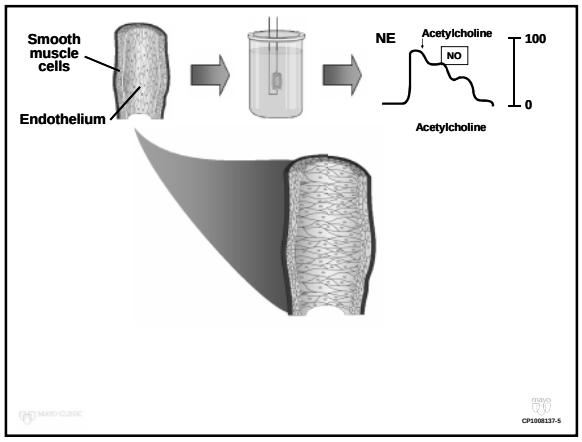
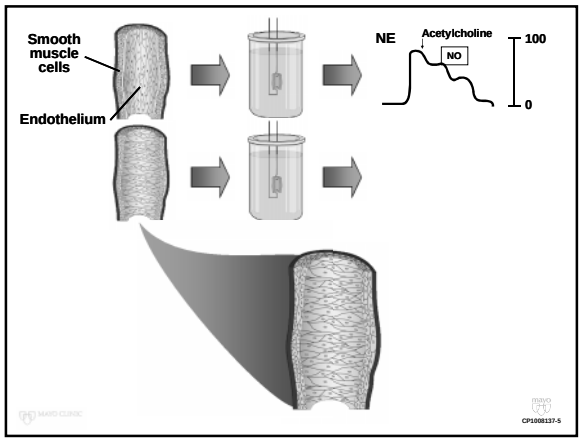

Smooth muscle cells
Endothelium
NE
Acetylcholine
NO
100
0
Acetylcholine
CP1008137-5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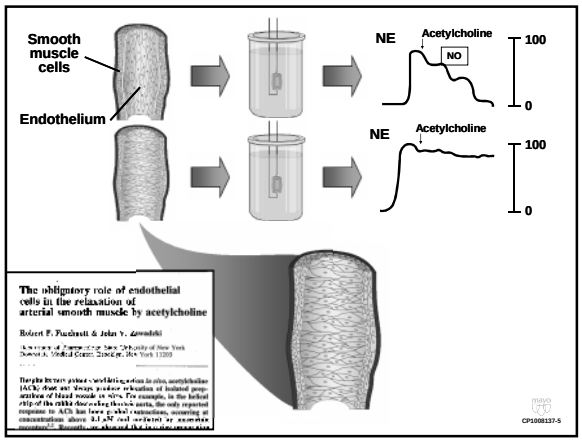
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The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine
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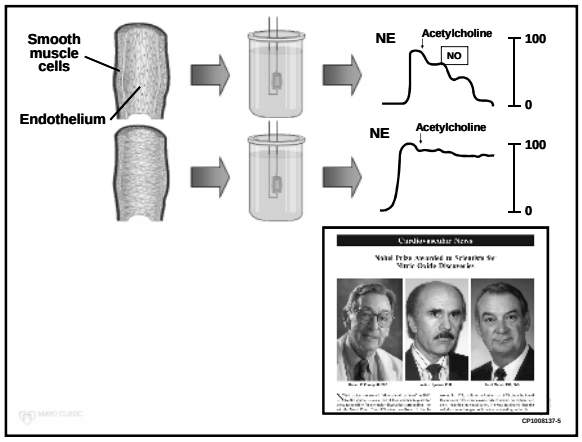
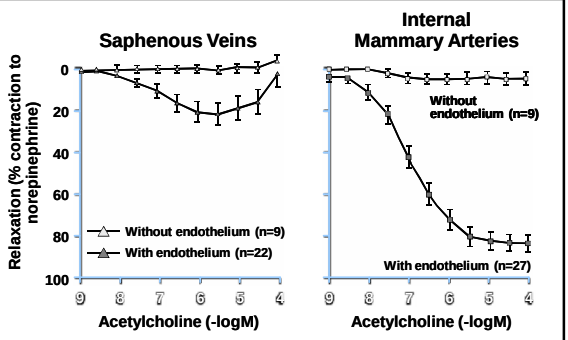
CP1008137-5



Endothelium-Dependent Relaxation Responses



Lüscher et al: NEJM 319:462, 1988

CP1298208-11

Endothelial Function
Basic Science to Clinical Practice

PARADOXICAL VASOCONSTRICTION INDUCED BY ACETYLCHOLINE IN ATHEROSCLEROTIC CORONARY ARTERIES

PAUL L. LUDMER, M.D., ANDREW P. SELWYN, M.D., THOMAS L. SHOOK, M.D., RICHARD R. WAYNE, B.S., GILBERT H. MUDGE, M.D., R. WAYNE ALEXANDER, M.D., PH.D., AND PETER GANZ, M.D.

Abstract Acetylcholine is believed to dilate normal blood vessels by promoting the release of a vasorelaxant substance from the endothelium (endothelium-derived relaxing factor). By contrast, if the endothelium is removed experimentally, acetylcholine constricts blood vessels. We tested the hypothesis that muscarinic cholinergic vasodilaties. acetylcholine caused a dose-dependent dilation from a control diameter of 1.94±0.16 mm to 2.16±0.15 mm with the maximal acetylcholine dose (P<0.01). In contrast, all eight of the arteries with advanced stenoses showed dose-dependent constriction, from 1.05±0.05 to 0.32±0.16 mm at the highest concentration of acetylcho-

New England Journal of medicine 315 (17) 1986

CP990350-1

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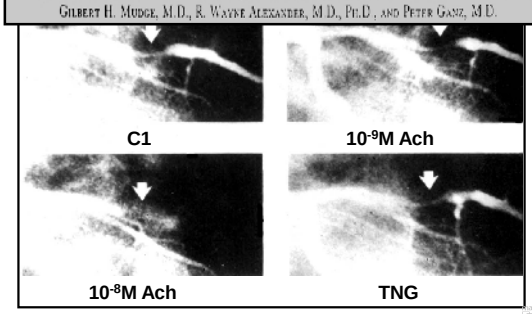

New England Journal of medicine 315 (17) 1986

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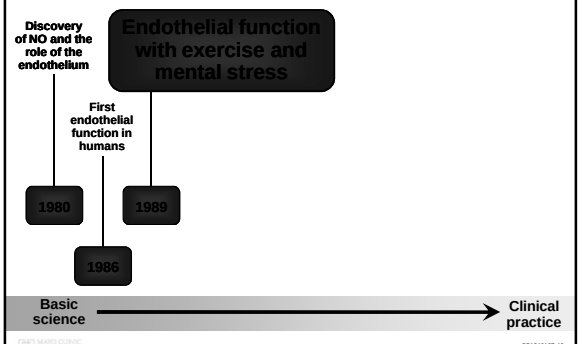
Endothelial Function
Basic Science to Clinical Practice



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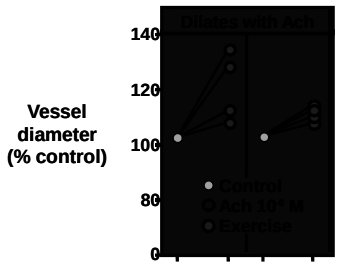
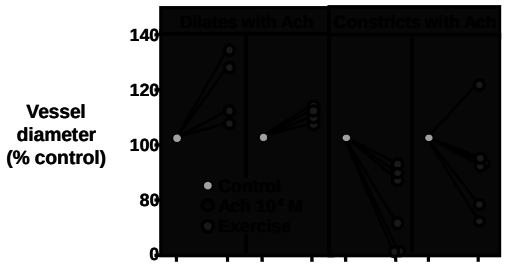
Exercise and Coronary Endothelial Function



Gordon, 1989

CP990291-9

Exercise and Coronary Endothelial Function



Gordon, 1989

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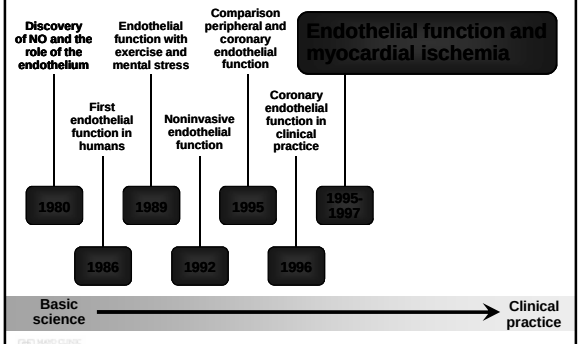
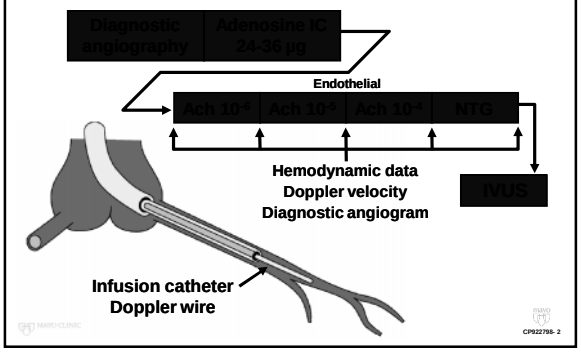
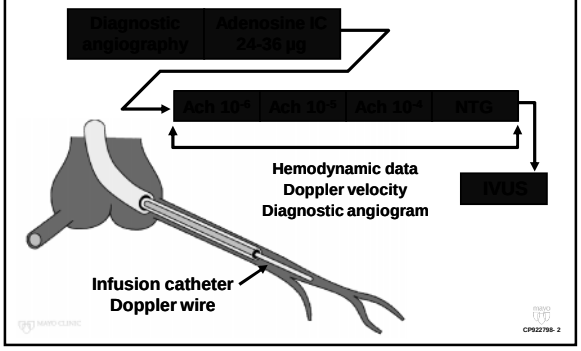
Endothelial Function
Basic Science to Clinical Practice



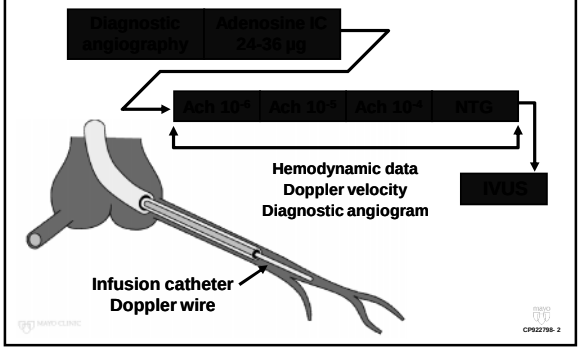
Coronary Blood Flow Function Protocol



Functional Coronary Angiogram



Functional Coronary Angiogram



Coronary Endothelial Dysfunction in Humans Is Associated With Myocardial Perfusion Defects

David Hasdai, MD; Raymond J. Gibbons, MD; David R. Holmes, Jr, MD; Stuart T. Higano, MD; Amir Lerman, MD

Background Coronary endothelial dysfunction may occur in patients with minimally obstructive coronary artery disease and angina, and potentially may cause myocardial ischemia.

Methods and Results Coronary endothelium-dependent vasodilation was examined in patients with angina and <50% coronary artery diameter (CAD) stenosis by selectively infusing acetylcholine (10^{-4} mol/L to 10^{-1} mol/L) into the left anterior descending coronary artery (LAD). Percent change in CAD (%ΔCAD) was measured by quantitative coronary angiography, and percent change in coronary blood flow (%ΔCBF) was calculated using intracoronary flow Doppler. Coronary endothelium-independent vasodilation was examined using intracoronary adenosine and nitroglycerin. ^{99m}Tc sestamibi was injected intravenously just prior to the infusion of the highest dose of acetylcholine. Patients were divided blindly into three groups: Perfusion defects in non-LAD territory (group 1, n=6), no perfusion defects (group 2, n=7), and perfusion defects in the LAD territory (group 3, n=7). All patients had intact endothelium-independent vasodilation. In group 1, perfusion defects outside the LAD territory reflected an increase in %ΔCAD and %ΔCBF by 24±5% and 241±45% in the LAD. In group 2, %ΔCAD decreased by 26±5%, but %ΔCBF increased by 34±17%. In group 3, perfusion defects were within the LAD territory, reflecting a decrease in %ΔCAD and %ΔCBF by 35±5% and 51±14%, respectively.

Conclusions This study demonstrates that coronary endothelial dysfunction in humans may be temporally associated with myocardial perfusion defects and supports a role for the coronary epicardial and microcirculation endothelium in regulating myocardial perfusion. Myocardial ischemia may occur in humans with impaired endothelium-dependent coronary flow reserve of the coronary epicardial and microcirculation.
(*Circulation*. 1997;96:3390-3395.)

Key Words • coronary disease • angina • vasodilation • microcirculation • perfusion

CP990323-2

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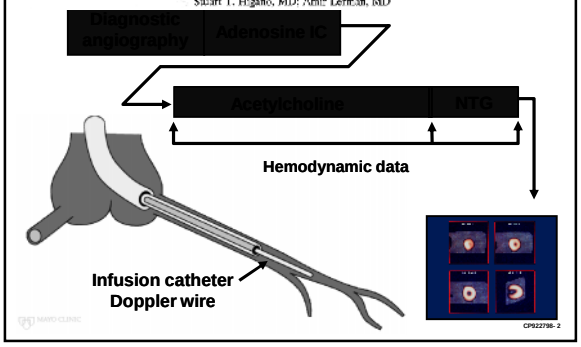
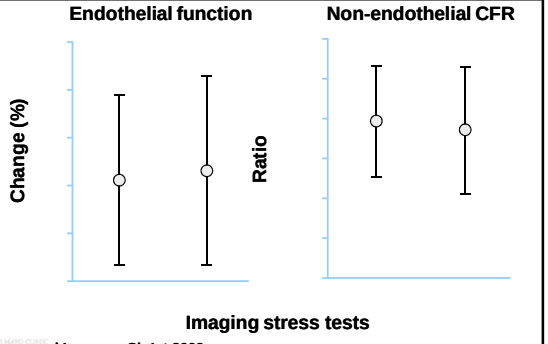


CP022798- 2

The Association Between Non-invasive Tests and Coronary Flow Reserve



Cessar and Lerman: Cir Int 2009

CP1349028-3

Abnormal coronary microvascular endothelial function in humans with asymptomatic left ventricular dysfunction

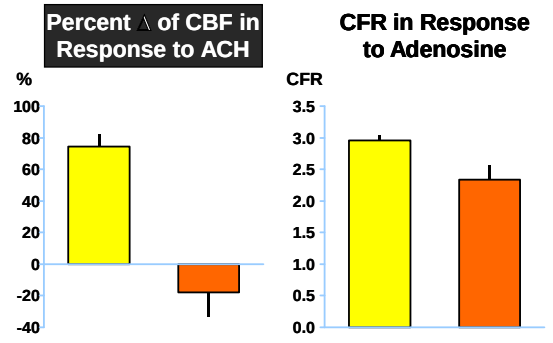
Abhiram Prasad, MBBS, MD, MRCP,* Stuart T. Higano, MD, FACC,* Jassim Al Suwaidi, MB, ChB,* David R. Holmes Jr, MD, FACC,* Verghese Mathew, MD, FACC,* Gerald Pumper, RN,* Ryan J. Lennon, MS,† and Amir Lerman, MD, FACC* Rochester, Minn

Background Coronary endothelial dysfunction may potentially lead to myocardial ischemia and to the progression of heart failure. Though endothelial dysfunction is associated with advanced heart failure in humans, no study to date is known regarding their temporal relationship. Thus, the current study was designed to test the hypothesis that coronary endothelial dysfunction is present in patients with asymptomatic left ventricular dysfunction.

Methods and Results Three hundred patients without symptoms of heart failure with normal or mildly diseased coronary arteries at angiography underwent coronary vascular reactivity evaluation using intracoronary adenosine, acetylcholine (ACh), and nitroglycerin. Patients were divided into 2 groups based on the left ventricular ejection fraction (EF): patients with asymptomatic left ventricular dysfunction (AVD, EF ≤45% [n = 11]) and patients with EF >45% (n = 289, controls). Except for a lower high-density lipoprotein level in patients with AVD, there were no significant differences between the groups in regards to conventional cardiovascular risk factors. There was no difference in the change (mean ± SE) in epicardial diameter in response to ACh (−21.2% ± 7.2% vs −13.8% ± 1.5%, $P = .3$). The change in coronary blood flow in response to ACh was significantly attenuated in the patients with AVD when compared to the controls (−18.5% ± 14.5% vs 74.0% ± 7.2%, $P = .012$). By multivariate analysis, EF was an independent predictor of coronary microvascular dilation with ACh ($P < .001$).

Conclusion The current study demonstrates that coronary microvascular endothelial dysfunction is present in AVD. Thus, coronary endothelial dysfunction may be an early event in the pathophysiology of heart failure. (Am Heart J 2003; 146:000.)

CP1119632-1



Prasad and Lerman et al: AHJ, 2003

CP1119632-2

Coronary endothelial dysfunction and hyperlipidemia are independently associated with diastolic dysfunction in humans

Ahmed A. Elkayam, MD,* Margaret W. Sheffield, MD,* Chermaine S. Bibal, MD,* Abhiram Prasad, MD,* Shahar Lavi, MD,* Brian Lennon, MS,* Verghese Mathew, MD,* Ulrich O. Sorajman, MD, PhD,* and Amir Lerman, MD* Rochester, MN

Background Coronary endothelial dysfunction (CED) and DHF are both associated with myocardial ischemia and CAD risk factors. The objective of the this study was to determine if CED and CAD factors are associated with diastolic dysfunction before the development of occlusive CAD or clinical heart failure.

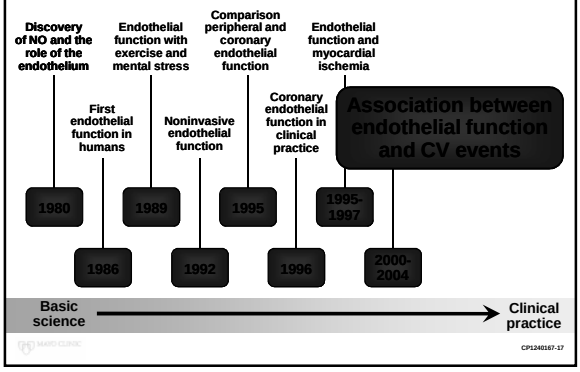
Methods Patients with normal ejection fraction and nonocclusive CAD who underwent coronary endothelial function studies were identified. Left ventricular relaxation was assessed by tissue Doppler assessment of early diastolic excursion of the septal mitral annulus (Ea). Multiple linear regression was used to investigate whether coronary risk factors influenced diastolic function after adjusting for the presence of CED.

Results A total of 160 patients had adequate assessment of diastolic relaxation. With multiple linear regression models, %ACBF ($P = .018$) was associated with a higher Ea; in contrast, older age ($P < .001$), female sex ($P = .003$), higher left ventricular mass index ($P = .016$), and higher low-density lipoprotein cholesterol ($P = .022$) were associated with a lower Ea.

Conclusion Coronary endothelial dysfunction and hyperlipidemia are independently associated with impaired relaxation in patients with normal ejection fraction in the absence of occlusive CAD and heart failure. The current study suggests a new potential mechanism for the development of endothelial and diastolic dysfunction in humans. (Am Heart J 2007;153:1081-7.)

CP1345773-20

Endothelial Function
Basic Science to Clinical Practice



CP1240167-17

Endothelial Dysfunction, Oxidative Stress, and Risk of Cardiovascular Events in Patients With Coronary Artery Disease

Thomas Heitzer, MD; Titus Schlinzig, BS; Karoline Krohn, BS; Thomas Meinertz, MD; Thomas Münzel, MD

Background—Endothelial function is impaired at coronary artery disease and may contribute to its clinical manifestations. Increased oxidative stress has been linked to impaired endothelial function in atherosclerosis and may play a role in the pathogenesis of cardiovascular events. This study was designed to determine whether endothelial dysfunction and vascular oxidative stress have prognostic impact on cardiovascular event rates in patients with coronary artery disease.

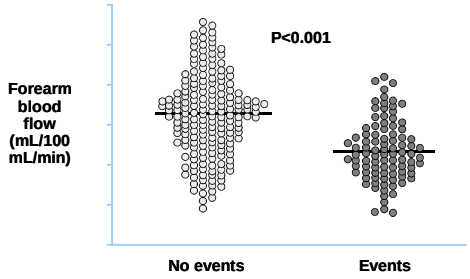
Methods and Results—Endothelium dependent and -independent vasodilation was determined in 281 patients with documented coronary artery disease by measuring forearm blood flow responses to acetylcholine and sodium nitroprusside using venous occlusion plethysmography. The effect of the coadministration of vitamin C (24 mg/min) was assessed in a subgroup of 179 patients. Cardiovascular events, including death from cardiovascular causes, myocardial infarction, ischemic stroke, coronary angioplasty, and coronary or peripheral bypass operation, were studied during a mean follow-up period of 4.5 years. Patients experiencing cardiovascular events (n=91) had lower vasodilator responses to acetylcholine ($P<0.001$) and sodium nitroprusside ($P<0.05$), but greater benefit from vitamin C ($P<0.01$). The Cox proportional regression analysis for conventional risk factors demonstrated that blunted acetylcholine-induced vasodilation ($P=0.001$), the effect of vitamin C ($P=0.001$), and age ($P=0.016$) remained independent predictors of cardiovascular events.

Conclusions—Endothelial dysfunction and increased vascular oxidative stress predict the risk of cardiovascular events in patients with coronary artery disease. These data support the concept that oxidative stress may contribute not only to endothelial dysfunction but also to coronary artery disease activity. (**Circulation. 2001;104:2673-2678.**)

Key Words: antioxidants ■ coronary disease ■ endothelium ■ free radicals ■ prognosis

CP1045482-20

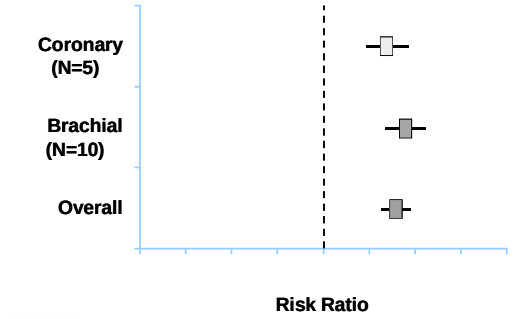
CV Events During Follow-Up (53 Months)



Heitzer et al: Circulation 104, 2001

CP1045482-5

Endothelial Dysfunction and CV Events: Meta-analysis of 15 Studies



Lerman and Zeiher Circulation 2004

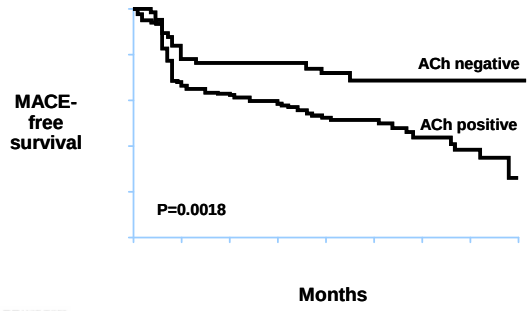
CP1137788-3

Provoked Coronary Spasm Predicts Adverse Outcome in Patients With Acute Myocardial Infarction

…the relationship between endothelial dysfunction and clinical course after AMI…

CP1325082-4

Kaplan-Meier Curves for MACE-Free Survival



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