Χ.ΠΑΠΑΜΙΧΑΗΛ

ΔΙΕΥΘΥΝΤΗΣ ΕΣΥ

ΑΓΓΕΙΟΛΟΓΙΚΟ ΕΡΓΑΣΤΗΡΙΟ ΘΕΡΑΠΕΥΤΙΚΗ ΚΛΙΝΙΚΗ

ΕΝΔΟΘΗΛΙΑΚΗ ΛΕΙΤΟΥΡΓΙΑ ΚΑΙ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

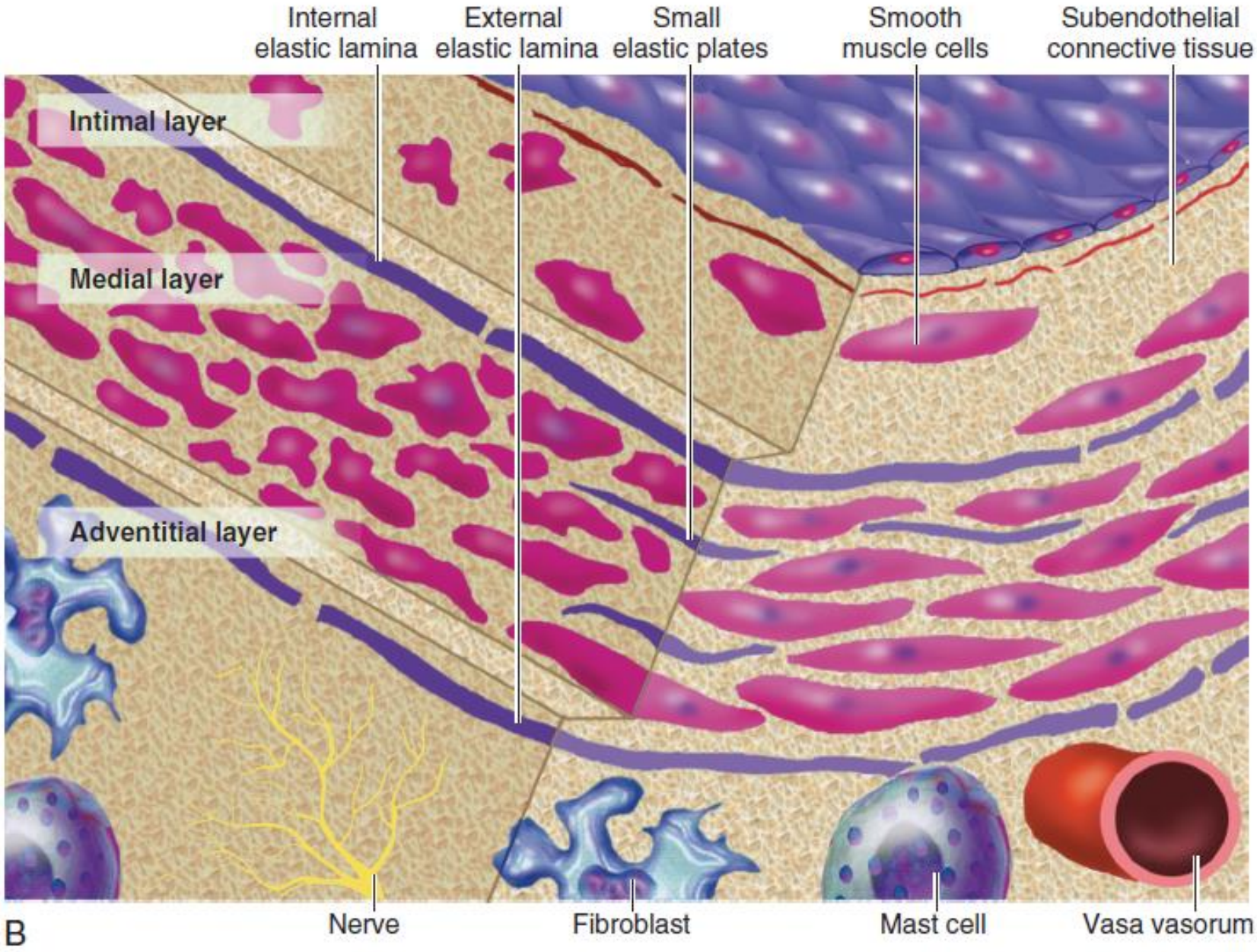


FIGURE 41-4 The structures of normal arteries. **A,** Elastic artery. Note the concentric laminae of elastic tissue that form sandwiches with successive layers of SMCs. Each level of the elastic arterial tree has a characteristic number of elastic laminae. **B,** Muscular artery. In the muscular artery, the SMCs are surrounded by a collagenous matrix but lack the concentric rings of the well-organized elastic tissue characteristic of larger arteries.

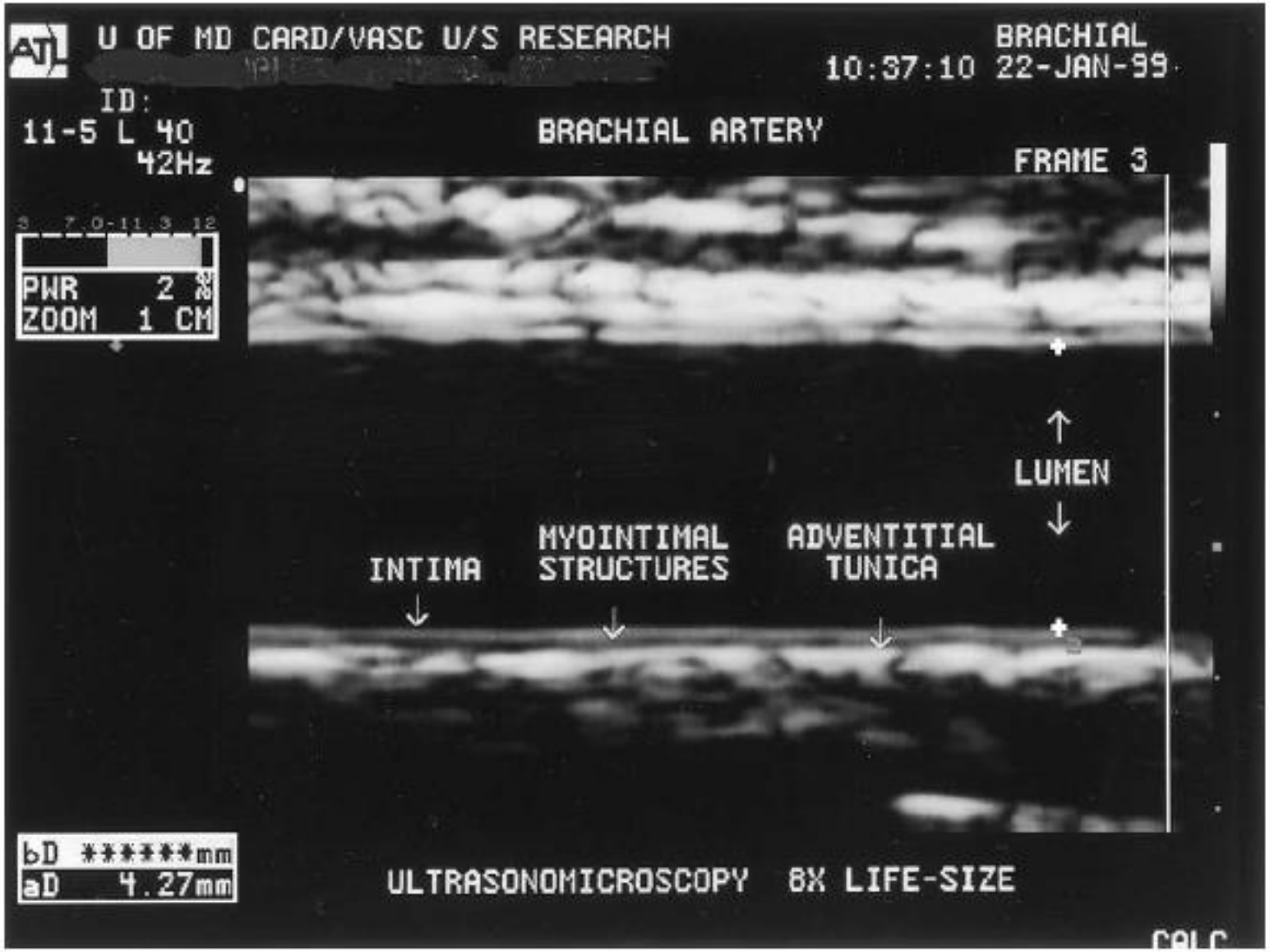


Figure 1. Ultrasound image of the brachial artery (longitudinally) at 8× magnification, 11-MHz transducer frequency annotated for anatomic landmarks.

VASCULAR ENDOTHELIUM VASOACTIVE SUBSTANCES

- Represents a surface area of about 4000 to 7000m². The endothelium controls vascular permeability and actively regulates the exchange of molecules

- Healthy endothelial cells are crucial in the prevention of thrombotic events and they express **antiplatelets** and **anticoagulant** molecules whereas dysfunctional cells make the vessel **prone to thrombotic events**.

Flammer AJ Pflugers Arch –Eur J Physiol 2010

Steffel J Circulation 2006

VASOACTIVE SUBSTANCES

- **EDRF-NO** The substance has **vasodilatory properties**. It also prevents platelets **adhesion** and aggregation as well as **leukocyte adhesion** and migration and **inhibits smooth muscle cell proliferation all key events in the development of atherosclerosis.** NO is synthesized from L-arginine. It is released by endothelial cells in response to shear stress but also by many other molecules such as acetylocholine, bradykinin,thrombin,ADP leading to relaxation of vascular smooth cells.

- **PGI2** It is synthesized from **arachidonic acid**. It has **vasodilatory and anti platelet properties**.

Furchgott R Nature 1980

Pohl U Hypertension 1986

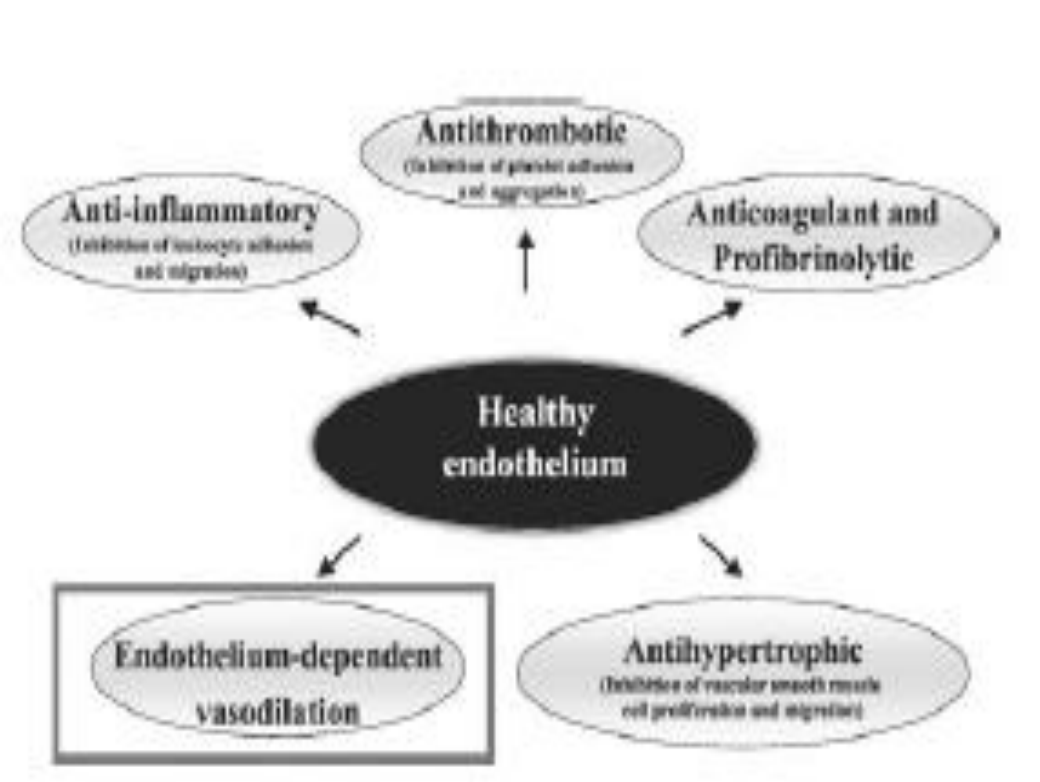
VASOACTIVE SUBSTANCES

- **Endothelin-ET**

Some years after the detection of NO the **vasoconstrictor peptide endothelin(ET)** was discovered. It is also synthesized by vascular endothelial cells . Three isoforms of the peptide(ET-1,ET-2,ET-3) exist. There are several factors modulating ET-1 production and release, among them **shear stress angiotensin II, thrombin, adrenaline, oxidized LDL and inflammatory cytokines. In humans ET raises BP, induces vascular and myocardial hypertrophy.**

Yalagisawa Nature 1988

HEALTHY ENDOTHELIAL FUNCTIONS



Landmesser U Circulation 2004

METHODS FOR CLINICAL ASSESSMENT OF ENDOTHELIAL FUNCTION

Methods for Clinical Assessment of Endothelial Function

Technique (Outcome Measure)	Noninvasive	Repeatable	Reproducible*	Reflects Biology	Reversible	Predicts Outcome†
Cardiac catheterization (change in diameter, change in coronary blood flow)	−	−	+/−	+	+	+
Venous occlusion plethysmography (change in forearm blood flow)	−	+/−	+/−	+	+	+
Ultrasound FMD (change in brachial artery diameter)	+	+	+/−	+	+	+‡
PWA (change in augmentation index)	+	+	+/−	+	−	−
PCA (change in reflective index)	+	+	+/−	+	−	−
PAT (change in pulse amplitude)	+	+	+/−	+	−	−

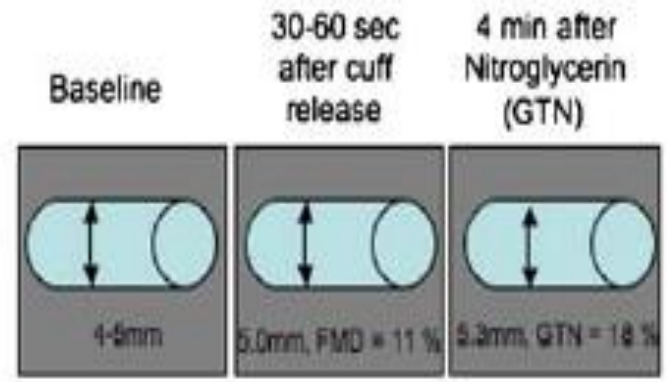
+ indicates supportive evidence in literature; −, insufficient evidence; FMD, flow-mediated dilatation; PWA, pulse wave analysis; PCA, pulse contour analysis; and PAT, pulse amplitude tonometry.

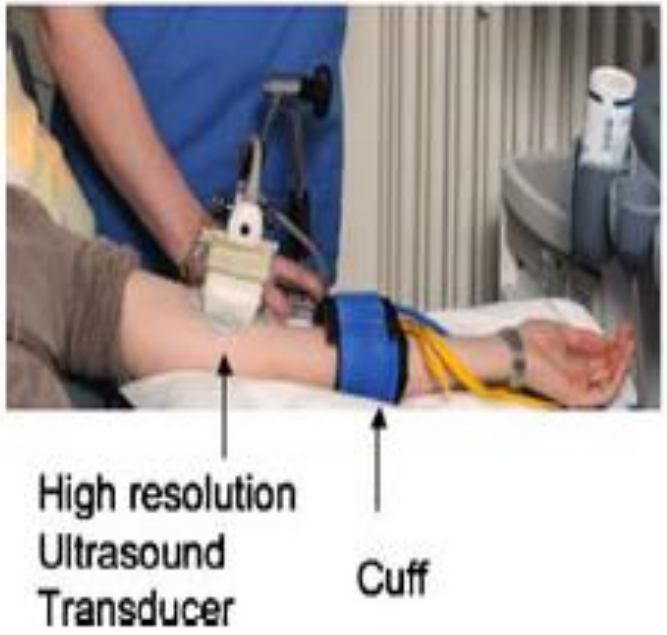
*Reproducibility of PWA, PCA, and PAT has been less extensively investigated than FMD.

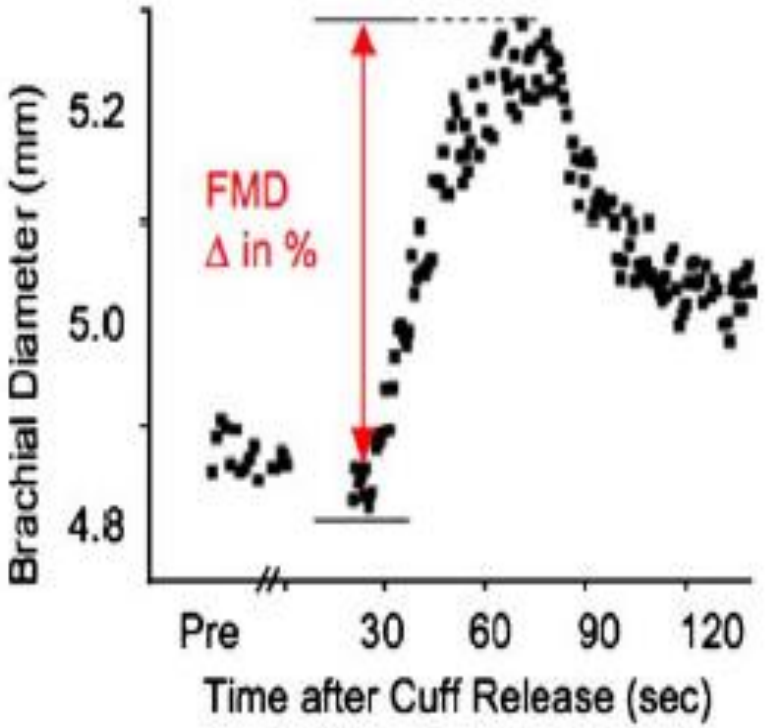
†Studies that link PWA, PCA, and PAT to outcome have not yet been reported.

‡FMD is currently the standard for noninvasive assessment of conduit artery endothelial function because there is considerable clinical trial experience, validation, a firm link to biology, and association with cardiovascular events.

Fig. 2 Flow-mediated vasodilatation. Schematic ultrasound images of the brachial artery at baseline, after reactive hyperemia induced flow-mediated vasodilatation and after nitroglycerin (*GTN*) application, are shown. Blood pressure cuffs can be placed on the *upper or the lower side* of the transducer in the antecubital fossa; however, the latter is the preferred method. On the *left hand side*, the time course of an FMD measurement is shown [20]. See text for further explanation







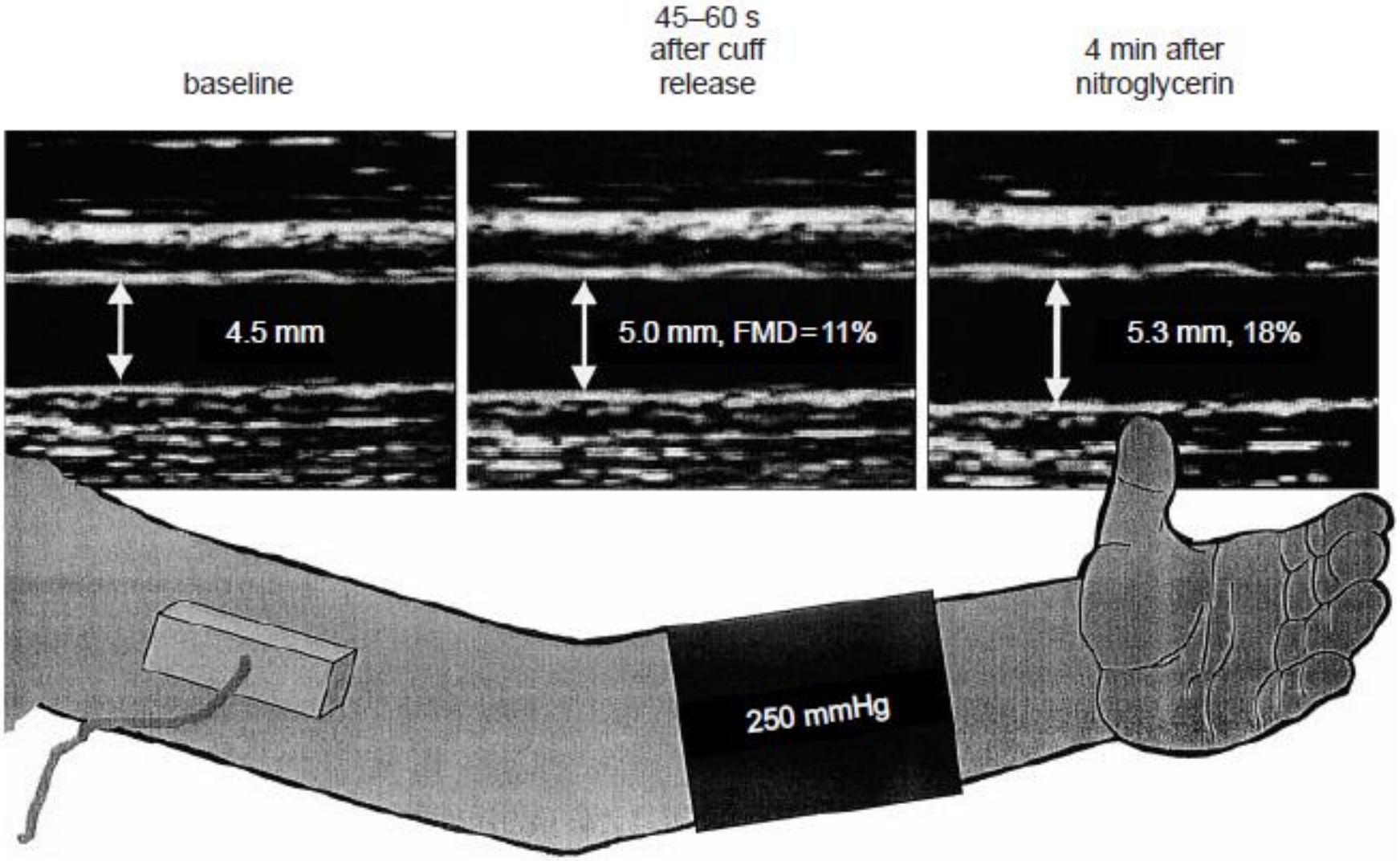


Figure 1 Brachial artery diameter is measured during three conditions; baseline (after at least 10 min supine rest), during reactive hyperaemia (induced by inflation to 250 mmHg and then deflation of a sphygmomanometer cuff around the forearm) and finally after the administration of sublingual nitroglycerin. A linear array, high resolution ultrasound transducer is used to provide B-mode images of the target vessel, proximal to the forearm cuff. FMD = flow-mediated dilatation.

ENDOTHELIAL DYSFUNCTION

- It is characterized by an **impaired NO bioavailability** due to reduced production of NO or increased breakdown by reactive oxygen species.

- ED has been documented in almost every condition associated with atherosclerosis and cardiovascular disease. ED has been observed in patients with hypertension,in smokers,in dyslipidemia,diabetes mellitus,obesity,hyperhomocysteinemia,in CHF,in aging and in patients with inflammatory diseases.

- Therapeutic interventions which influence the cardiovascular risk profile of individuals impact beneficially on endothelial function.

Panza JA NEJM 1990

ENDOTHELIAL DYSFUNCTION IN HEART FAILURE

- The failing heart is characterized by an altered redox state with overproduction of reactive oxygen species. There is neurohumoral activation increased oxidative stress and reduced production of NO. The resulting endothelial dysfunction triggers an increase in the production of cytokines, down-regulation or uncoupling of eNOS , and further increases in oxidative stress .

- These processes culminate in reduced NO bioavailability and worsening endothelial dysfunction, which in turn propagates development and progression of HF.

Marti CN JACC 2012

CHRONIC HEART FAILURE

- There is increased afterload due **to systemic and pulmonary vascular** constriction.
- Decreased coronary endothelium-dependent vasodilation reduces **coronary flow** and impairs ventricular function.
- The dysfunctional endothelium contributes to increased **vascular stiffness** and impaired arterial distensibility, augmenting myocardial damage.
- Reduced NO in HF affects endothelial **progenitor cells**, disabling endothelial repair and regeneration.
- Furthermore, serum from patients with HF has been shown to induce **endothelial cell apoptosis**.

Ramsey MW Circulation 1995

Table 2

Pathophysiological mechanisms contributing to endothelial dysfunction in chronic heart failure

↓ shear stress (↓cNOS–↓NO)
↑ catecholamines (↓cNOS–↓NO)
↑ angiotensin II (↓cNOS–↓NO, ↑endothelin-1, ↓bradykinin)
↑ endothelin-1 (↓cNOS–↓NO, vascular remodeling)
↓ bradykinin (↓cNOS–↓NO)
↑ proinflammatory cytokines (↓cNOS+inactivation of NO+↑iNOS of macrophages, ↑oxidative stress)
↑ endothelial cell apoptosis (↓NO)
↓ intracellular availability of L-arginine (↓NO)
↑ microvessel structural remodeling (↓shear stress, ↓NO)
↑ adhesive properties of endothelial cells to circulating macrophages (↑iNOS, ↑oxidative stress)

Adamopoulos S Europ J Inter Med 2002

RENAL DYSFUNCTION

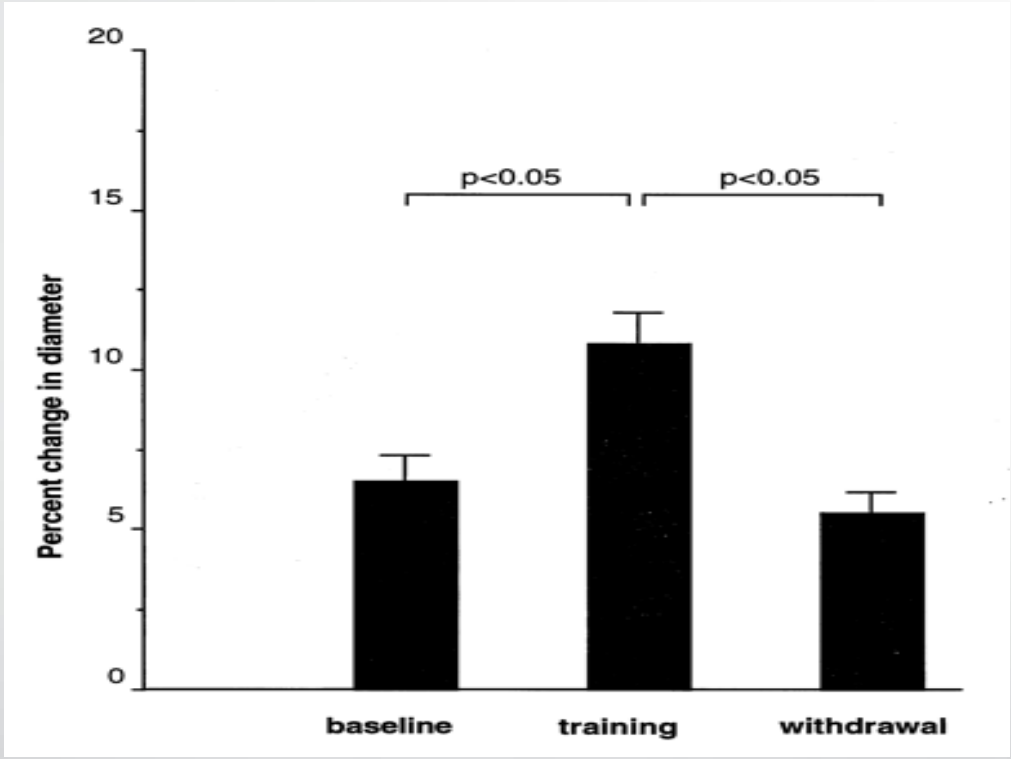
- NO imbalance underlies acute renal damage and the cardiorenal syndrome. This action is in part due to reduced renal flow from inappropriate arteriolar vasoconstriction superimposed on baseline low cardiac output.

- The net result of NO action on renal function is increased renal and gromerular perfusion, natriuresis and diuresis. Thus NO imbalance affects renal function, worsening HF.

Fonarow GC JAMA 2005

STRATEGIES TO IMPROVE ENDOTHELIAL FUNCTION IN HEART FAILURE

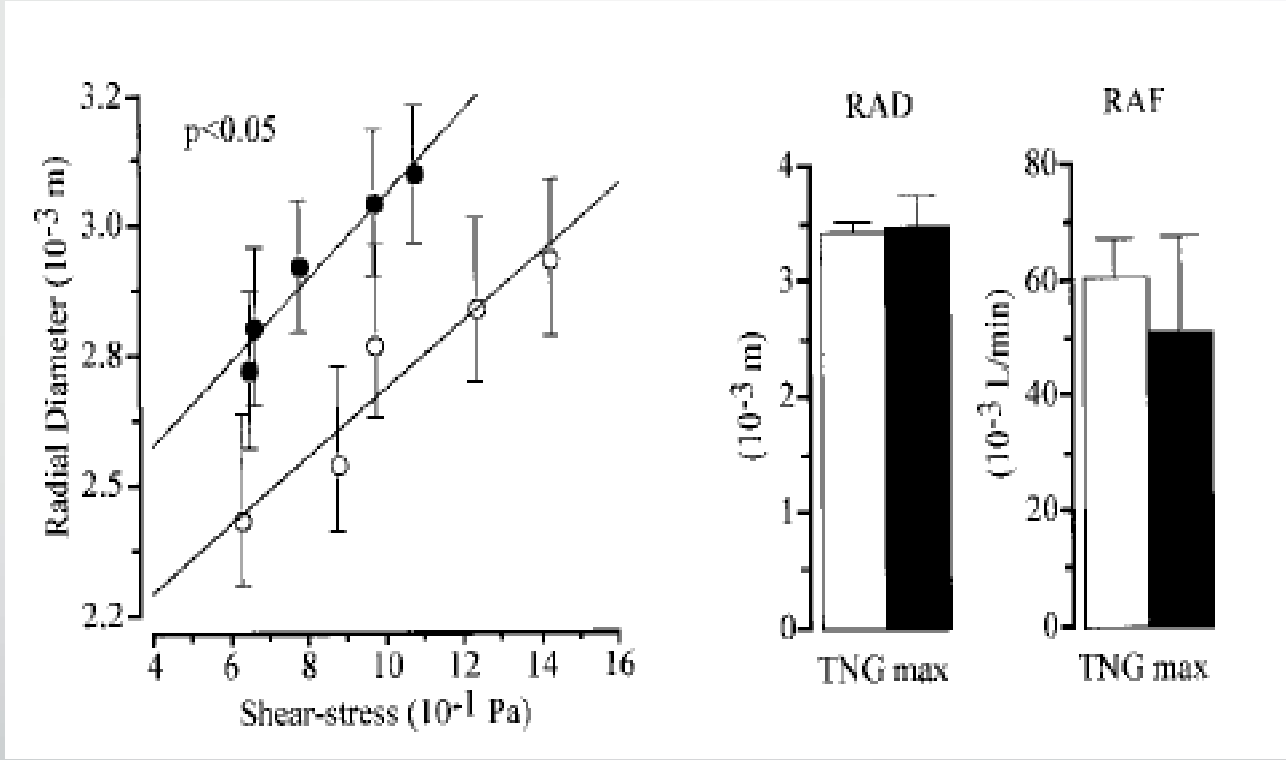
PHYSICAL TRAINING AND ENDOTHELIAL FUNCTION IN HEART FAILURE



Bar graph shows percentage change in diameter during reactive hyperemia (FMD) in the nondominant forearm after 4 minutes of upper-arm occlusion at baseline, after 4 weeks of training, and 6 weeks after the end of the training (n=12).

Hornig B Circulation 1996

Chronic ACE Inhibition Enhances the Endothelial Control of Arterial Mechanics and Flow-Dependent Vasodilatation in Heart Failure



The study demostrates that the chronic administration of the ACE inhibitor perindropril increases the magnitude of the FMD and restores the flow-dependent increase in compliance and distensibility of the radial artery.

Ioannides R Hypertension 2001

Effects of High Doses Versus Standard Doses of *Enalapril* on Endothelial Cell Function in Patients With Chronic Congestive Heart Failure Secondary to Idiopathic Dilated or Ischemic Cardiomyopathy

Stavros G. Drakos, MD, Christos M. Papamichael, MD, George P. Alexopoulos, MD, Maria I. Anastasiou-Nana, MD, John V. Stathopoulos, MD, and John N. Nanas, MD, PhD

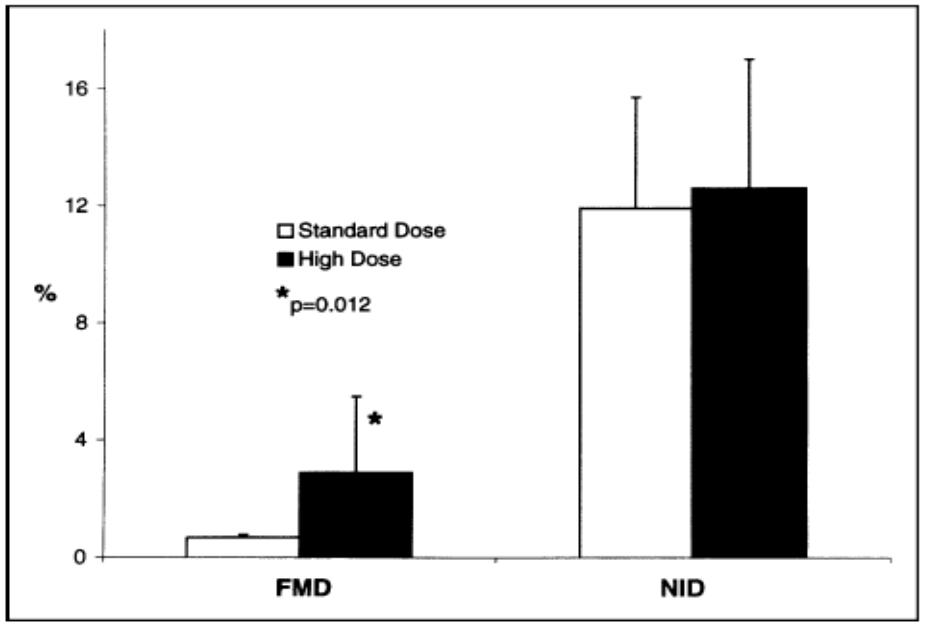
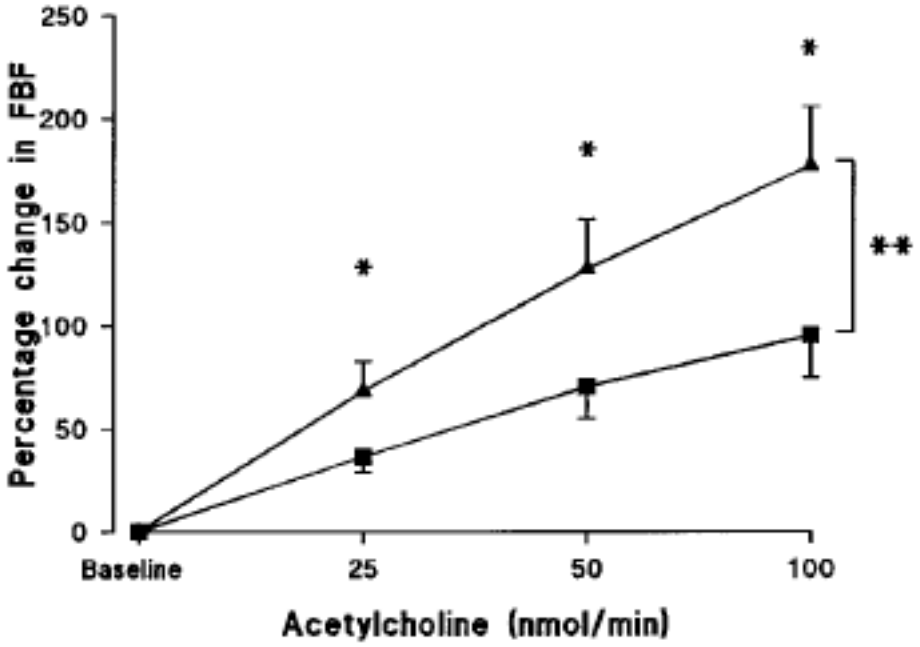
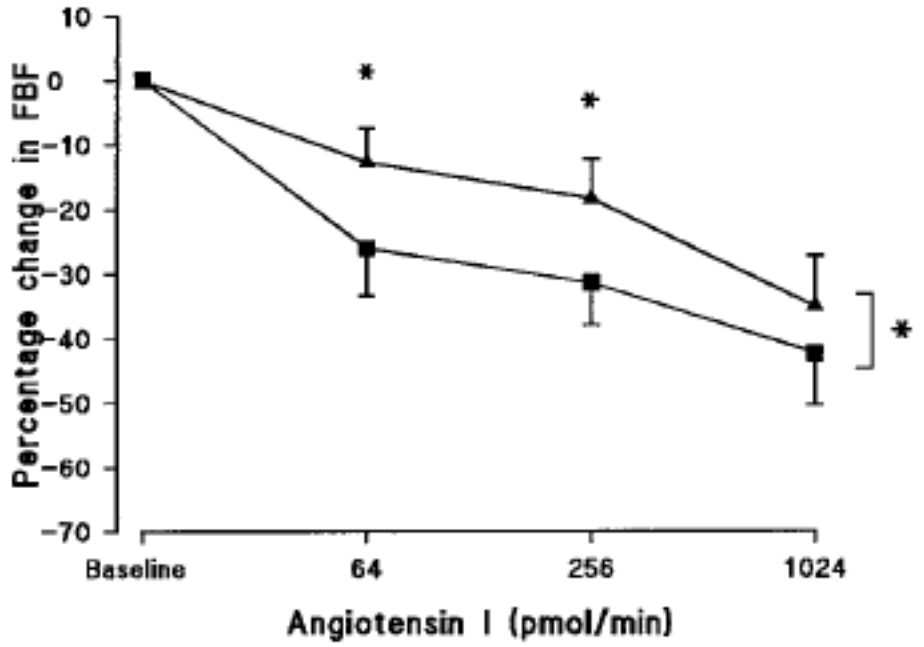


FIGURE 1. FMD and nitrate-induced dilation (NID) in the standard- and high-dose enalapril groups.

Am J Card 2003

Spironolactone Increases Nitric Oxide Bioactivity, Improves Endothelial Vasodilator Dysfunction, and Suppresses Vascular Angiotensin I/Angiotensin II Conversion in Patients With Chronic Heart Failure





Farguharson CA Circulation 2000.

Congestive Heart Failure Induces Endothelial Cell Apoptosis: Protective Role of Carvedilol

- Congestive heart failure is associated with impaired endothelial function in the peripheral systemic vasculature and with systemic release of inflammatory cytokines.
- The serum of patients with CHF revealed a significantly enhanced pro-apoptotic activity. Carvedilol completely suppressed the increase in apoptosis induced by the serum of patients with CHF.
- The suppression of apoptosis by carvedilol was due to its antioxidative rather than beta-blocking effects.
- **Inhibition of endothelial cell apoptosis by carvedilol may contribute to the beneficial effects of carvedilol in patients with heart failure.**

Rossig L JACC 2000

Acute Type 5 Phosphodiesterase Inhibition With Sildenafil Enhances Flow-Mediated Vasodilation in Patients With Chronic Heart Failure

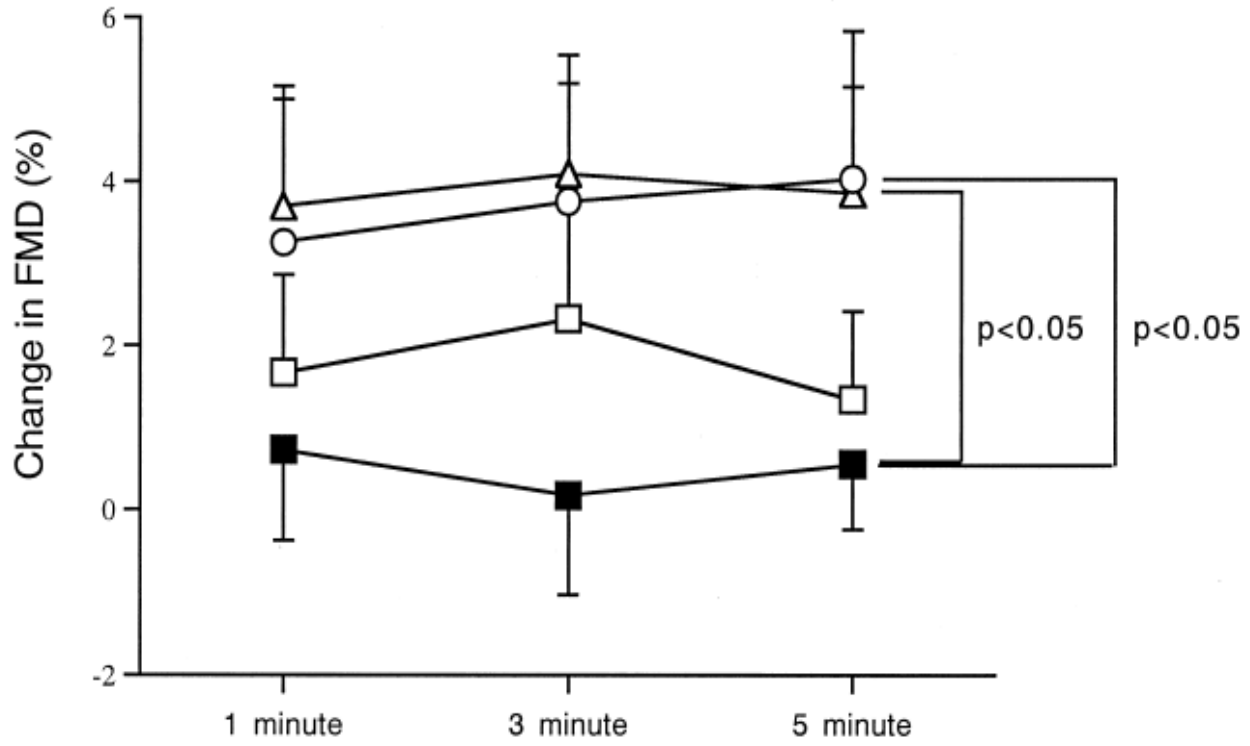


Figure 1. Change (means ± SEM) in flow-mediated dilation (FMD, %) from pretreatment values after release of 1, 3 and 5 min of arterial occlusion in patients treated with placebo **(closed squares)**, sildenafil 12.5 mg **(open squares)**, sildenafil 25 mg **(open circles)** and sildenafil 50 mg **(open triangles)**.

Katz SD JACC 2000

Vitamin C Improves Endothelial Function of Conduit Arteries in Patients With Chronic Heart Failure

- ***Background***—Chronic heart failure (CHF) is associated with endothelial dysfunction including impaired endothelium mediated, flow-dependent dilation (FMD). There is evidence for increased radical formation in CHF, raising the **possibility that nitric oxide is inactivated by radicals**, thereby impairing endothelial function.

- ***Methods and Results*** In **15 patients with CHF and 8 healthy** volunteers. Vascular effects of vitamin **C (25 mg/min IA**) and and after ***4 weeks (2 gr/d*)** of oral therapy . Vitamin C restored FMD in patients with heart failure after acute intra-arterial administration (13.261.7% versus 8.261.0%; *P*<01) and after 4 weeks of oral therapy (11.960.9% versus 8.261.0%; *P*,<05).

- Therefore, our results support the concept that the impaired NO-mediated FMD in CHF is, at least in part, due to **increased inactivation** of endothelium derived NO by radicals and that vitamin C exerts its antioxidant properties within the vasculature by directly scavenging.

Horing B Circulation 1996

Dietary Supplementation With L-Arginine Fails to Restore Endothelial Function in Forearm Resistance Arteries of Patients With Severe Heart Failure

- Objectives. We sought to examine the efficacy of dietary supplementation of L-arginine on endothelium-dependent vasodilation in patients with congestive heart failure.
- Methods. Twenty patients with heart failure (New York Heart Association functional class III/IV and seven healthy control subjects were studied. All patients continued taking their usual treatment. Patients with heart failure received either **L-arginine (20 g/day every day for 28 days) or placebo**.
- Conclusions. Endothelial dysfunction was apparent in patients with heart failure despite rigorous vasoactive treatment. **Oral administration with L-arginine was ineffective in influencing endothelial function in these patients**.

Chin-Dusting JPF JACC 1996

Vascular Endothelial Dysfunction and Mortality Risk in Patients With Chronic Heart Failure

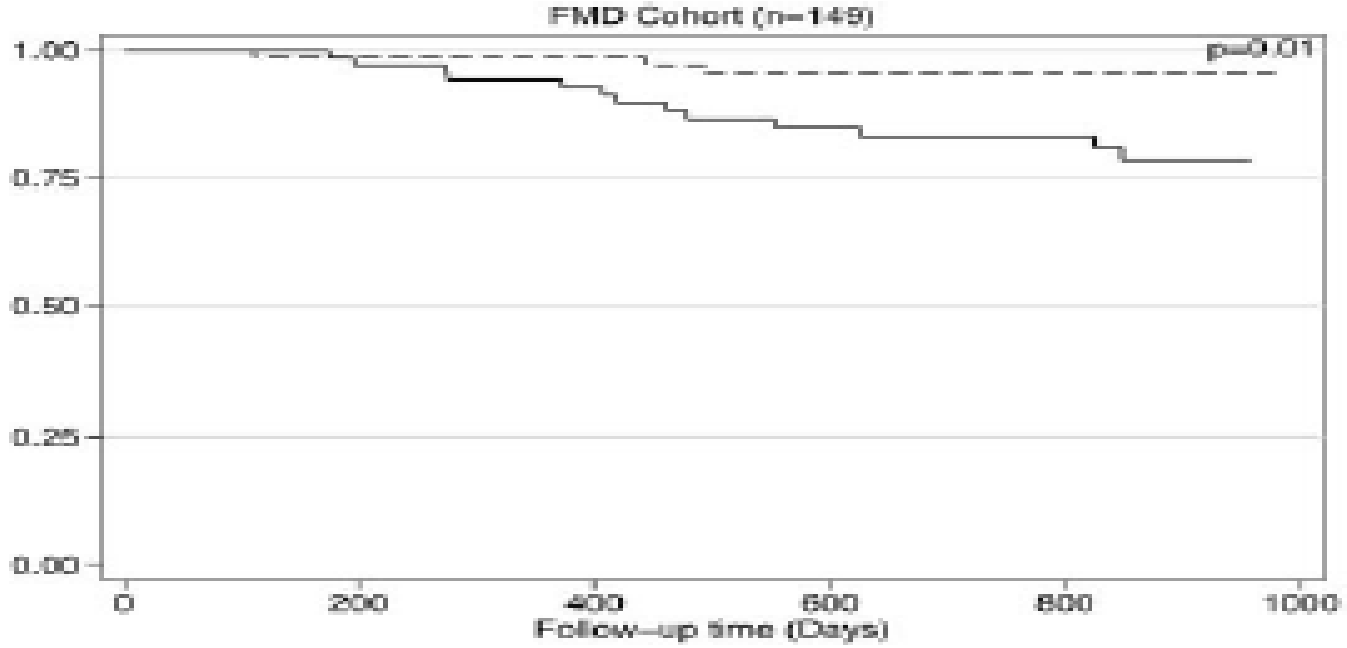


Figure 1. Kaplan-Meier plot showing proportion of survivors over time in subjects with FMD above (dashed line) and below (solid line) median value of 1.79%. Subjects with lower FMD values had more events (n=13) than did subjects with higher FMD values (n=4; *P*=0.01, by log-rank test). Abbreviations are as defined in text.

Katz SD Circulation 2005

Vascular Endothelial Dysfunction and Mortality Risk in Patients With Chronic Heart Failure

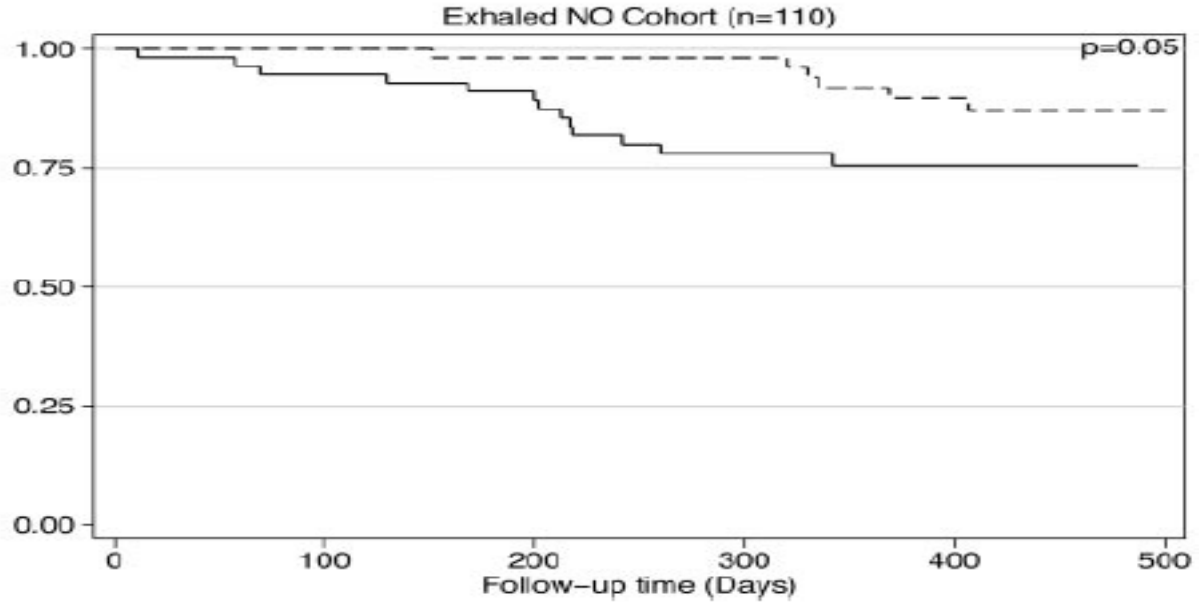


Figure 2. Kaplan-Meier plot showing proportion of survivors over time in subjects with exhaled NO production above (dashed line) and below (solid line) median value of 4.1 ppb/min. Subjects with lower values of NO production had more events (n=13) than did subjects with higher values of NO production (n=6; *P*=0.05, by log-rank test). Abbreviations are as defined in text.

Katz SD Circulation 2005

Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death

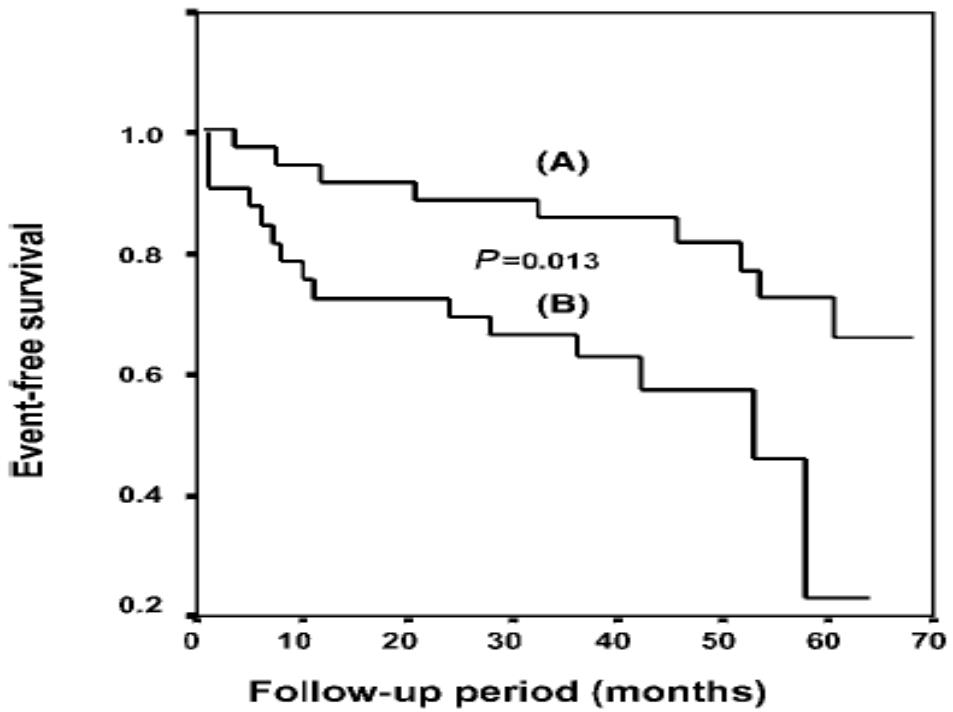


Figure 1 Relationship between endothelium-dependent vasodilation and cardiovascular events in the follow-up of patients with chronic heart failure. Kaplan–Meier analyses demonstrating proportion of patients surviving free from heart failure events during long-term follow-up. Study cohort is divided into those with flow-dependent vasodilation (FDD) >median (6.2%) and < median. (*A*) shows patients with FDD above median, (*B*) shows patients with FDD below median.

Fischer D Eur H J 2005

ΣΑΣ ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ

ΠΡΟΣΟΧΗ ΣΑΣ

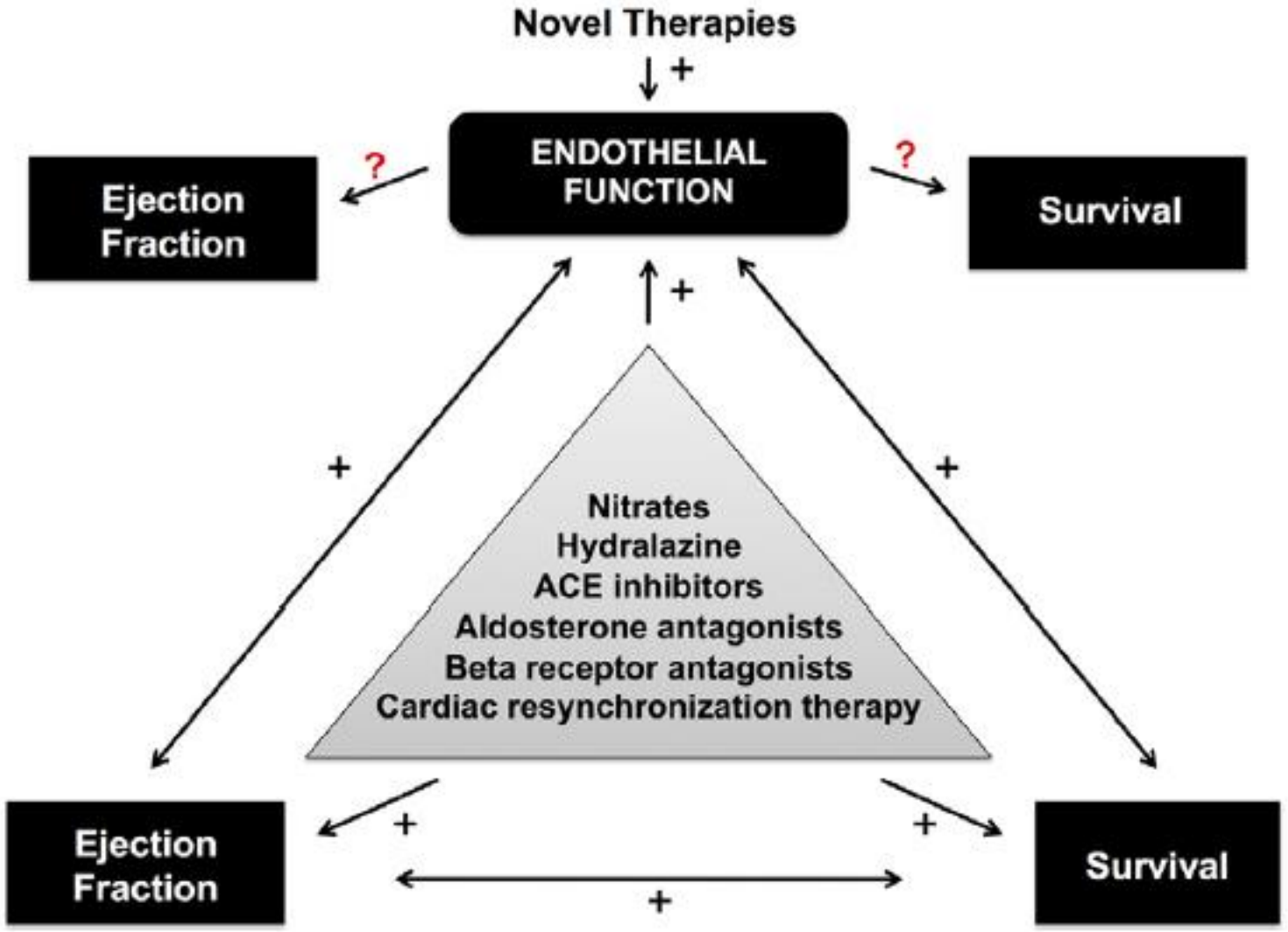


Figure 4 **Effect of Approved Heart Failure Therapies on Ejection Fraction, Endothelial Function, and Survival**

All currently approved therapies for heart failure that have been shown to improve survival and ejection fraction also favorably impact endothelial function. This raises the possibility of assessing endothelial function as a potential early drug development surrogate marker. ACE = angiotensin-converting enzyme.

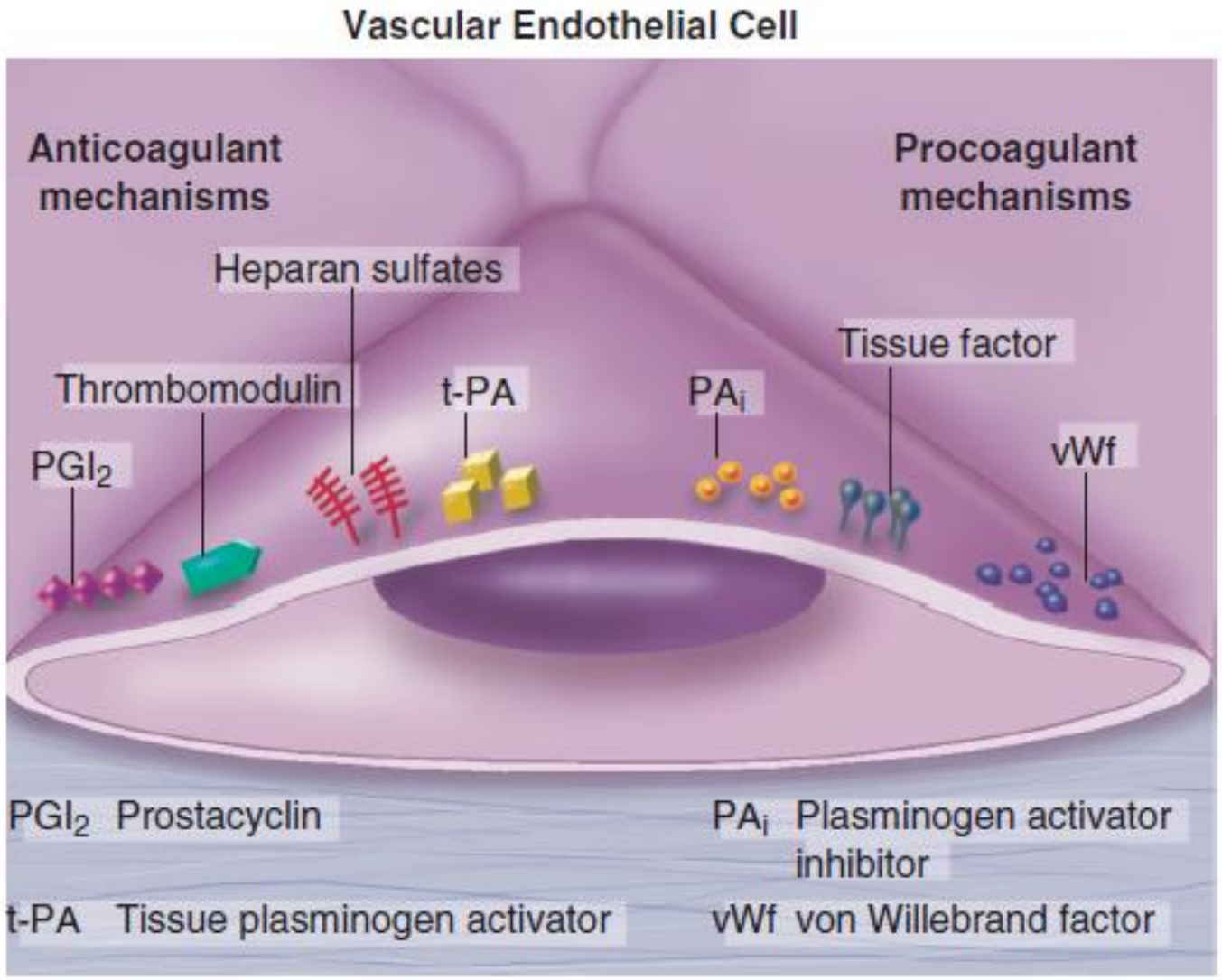


FIGURE 41-2 The endothelial thrombotic balance. This diagram depicts the anticoagulant profibrinolytic functions of the endothelial cell (*left*) and certain procoagulant and antifibrinolytic functions (*right*).

CHRONIC HEART FAILURE

- Endothelial dysfunction is also related to exercise capacity . In HF, reduced blood flow and sheer stress results
- in impaired exercise-induced NO release, affecting muscle function, exercise capacity, and ventilation .
- Down-regulation of eNOS shifts catabolism from free fatty acids to lactate, worsening exercise tolerance.
- Endothelial dysfunction also affects autonomic balance, decreasing vagal and increasing adrenergic activity, thus further worsening chronic HF.
- Increased endothelin-1 in HF causes increased vascular resistance, smooth muscle cell growth, and matrix production, resulting in vascular remodeling, endothelial dysfunction,and HF progression.

MEYER B JACC 2005