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Saturday, June 10, 2017

(Room 6)

14:00 - 14:55 WS #141: Erectile Dysfunction is Endothelial Dysfunction

15:05 - 16:00 WS #153: Erectile Dysfunction is Endothelial Dysfunction (Repeated)

Erectile Dysfunction is Endothelial Dysfunction: Understanding the Symptoms that Lead to Heart Disease

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General Practice Conference and Medical Education
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Financial Disclosures

Founder and Shareholder of HumanN (www.humann.com)

Shareholder and advisor for SAJE Pharma

Receive royalties on patents from University of Texas Health
Science Center at Houston

Functional and Integrative Medicine (FxMed) is exclusive
distributor for UT patented NO products in
New Zealand and Australia (Booth 16)

Structure of Presentation

- What is Endothelial Dysfunction
- Role of NO in Sexual and Cardiovascular Function
- Risk Factors for ED
- Therapies and Strategies to Restore NO and Combat Disease

***“A man is as old as his
arteries.”***

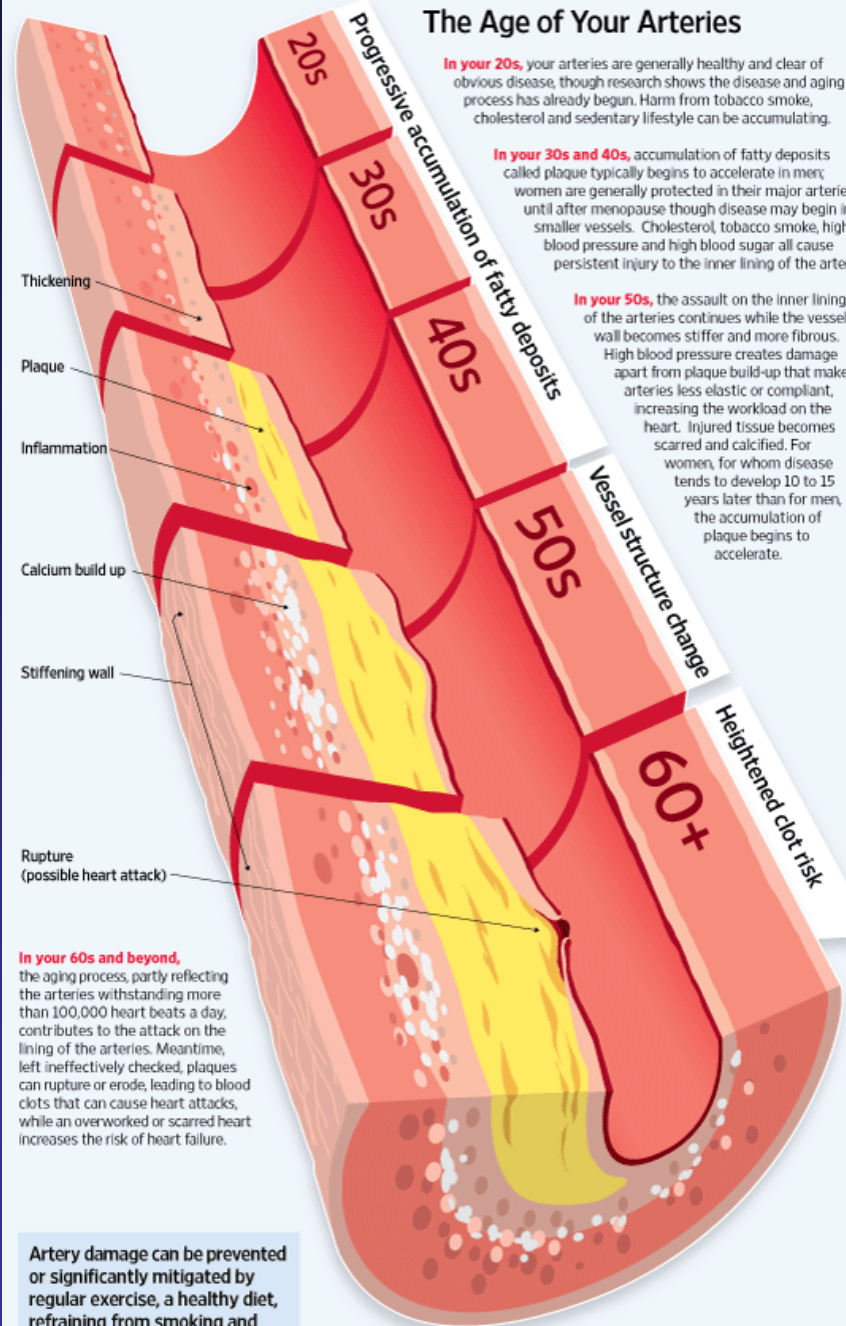
*~ Thomas Sydenham, English physician,
1624-1689*

The Age of Your Arteries

In your 20s, your arteries are generally healthy and clear of obvious disease, though research shows the disease and aging process has already begun. Harm from tobacco smoke, cholesterol and sedentary lifestyle can be accumulating.

In your 30s and 40s, accumulation of fatty deposits called plaque typically begins to accelerate in men; women are generally protected in their major arteries until after menopause though disease may begin in smaller vessels. Cholesterol, tobacco smoke, high blood pressure and high blood sugar all cause persistent injury to the inner lining of the artery.

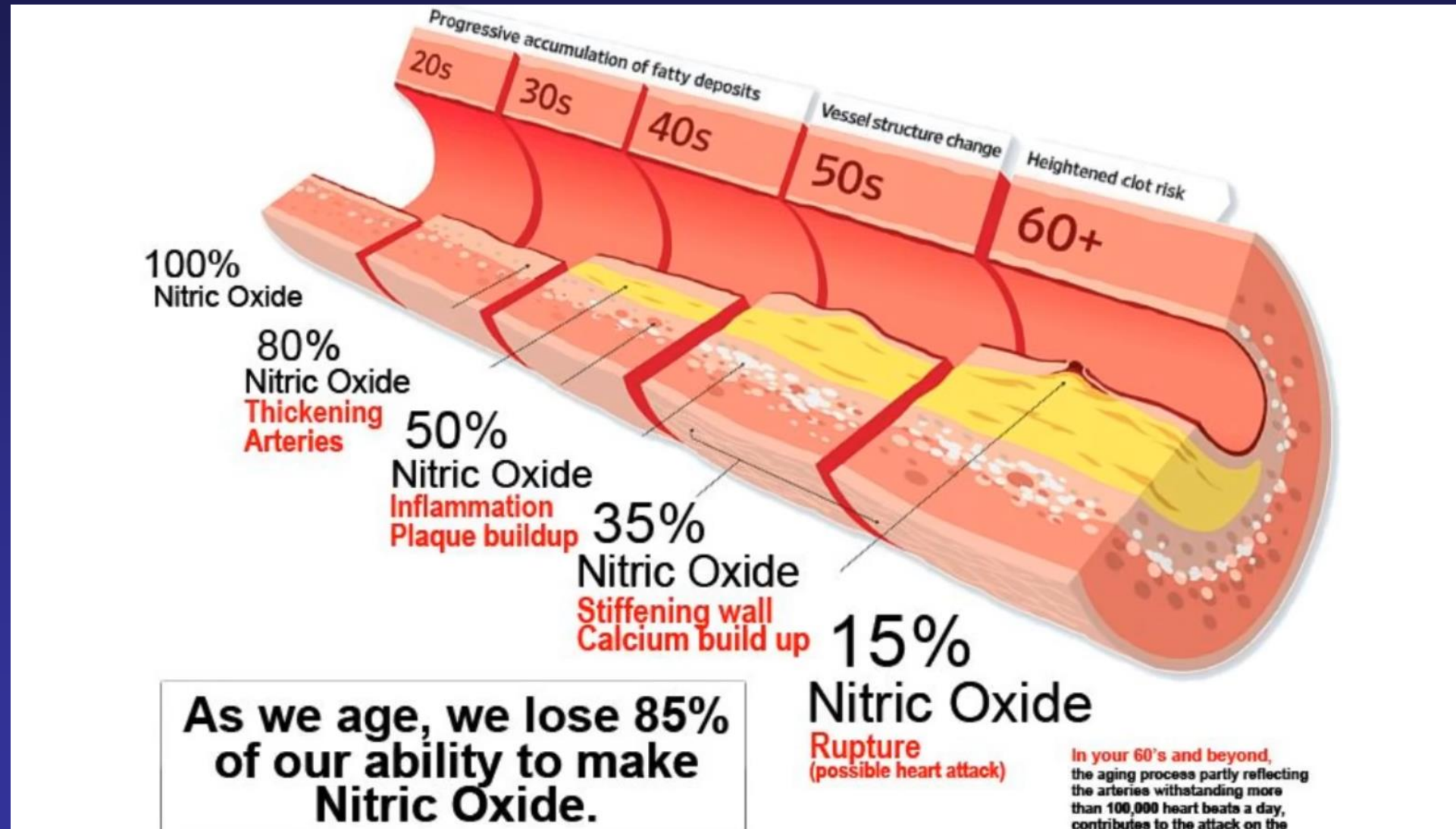
In your 50s, the assault on the inner lining of the arteries continues while the vessel wall becomes stiffer and more fibrous. High blood pressure creates damage apart from plaque build-up that makes arteries less elastic or compliant, increasing the workload on the heart. Injured tissue becomes scarred and calcified. For women, for whom disease tends to develop 10 to 15 years later than for men, the accumulation of plaque begins to accelerate.



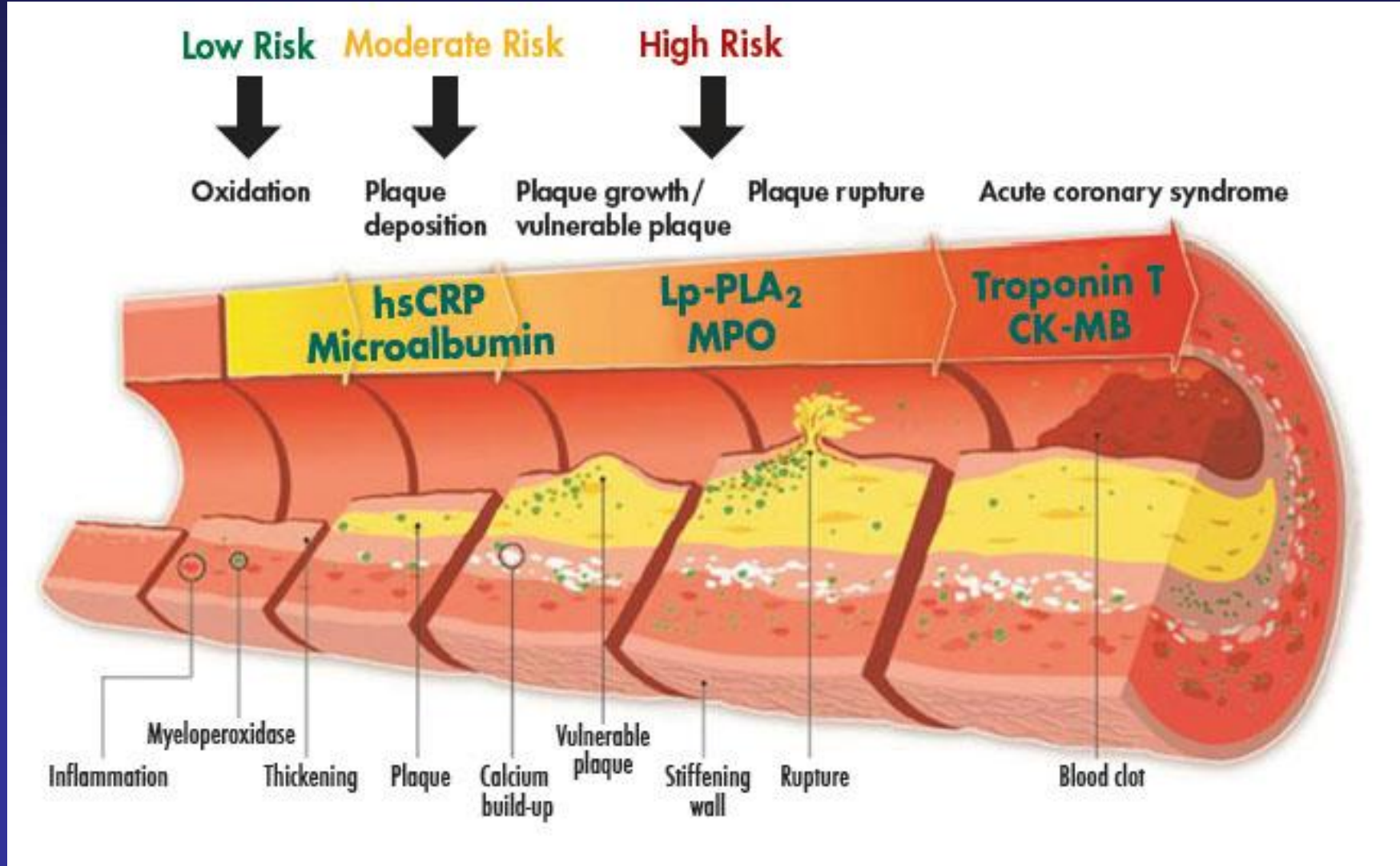
In your 60s and beyond, the aging process, partly reflecting the arteries withstanding more than 100,000 heart beats a day, contributes to the attack on the lining of the arteries. Meantime, left ineffectively checked, plaques can rupture or erode, leading to blood clots that can cause heart attacks, while an overworked or scarred heart increases the risk of heart failure.

Artery damage can be prevented or significantly mitigated by regular exercise, a healthy diet, refraining from smoking and adherence to heart medicines.

Loss of NO is Associated with Atherosclerosis



Inflammatory Biomarkers Diagnostic For Different Stages of Vascular Disease



Endothelial Dysfunction

In vascular diseases, endothelial dysfunction is a systemic pathological state of the endothelium (the inner lining of blood vessels) and can be broadly defined as an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) the endothelium. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function and control of volume and electrolyte content of the intravascular and extravascular spaces.

What is Nitric Oxide?

The chemical compound **nitric oxide** is a gas with chemical formula NO .

It is one of the most important signaling molecules in the body of mammals including humans, one of the few gaseous signaling molecules known.

It is also a toxic air pollutant produced by automobile engines and power plants.

NO should not be confused with nitrous oxide (N_2O), a general anesthetic, or with nitrogen dioxide (NO_2) which is another poisonous air pollutant.

The nitric oxide molecule is a free radical, which is relevant to understanding its high reactivity. It reacts with the oxygen in air to form nitrogen dioxide, signaled by the appearance of the reddish-brown color.

Half-Life of NO

water (10^{-1} μ M, 37°C, pO₂ 150mmHg, pH 7.4): 1-3 min

blood (5×10^9 erythrocytes): 0.5 - 2 ms

in presence of HbO₂ (15g/dL): 2 μ s

Nitric Oxide Plays a Key Role in the Regulation of Numerous Vital Biological Functions

Immunology

Unspecific Immunity
Inhibition of Viral Replication
Transplant Rejection

Gastrointestinal/ Urogenital

Penile
Pre-ejaculation

Respiratory - Bronchodilation Asthma, Atherosclerosis

Cell Proliferation

Apoptosis
Angiogenesis
Tumor Cell Growth

Central Nervous System

Learning and Memory
Pain Sensitization
Epilepsy
Neurodegeneration
Central BP Control

Regeneration

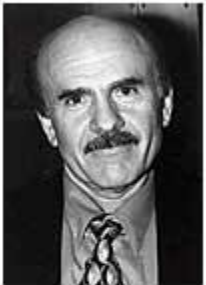
Mobilization of resident stem cells
Targeted differentiation

Cardiovascular System

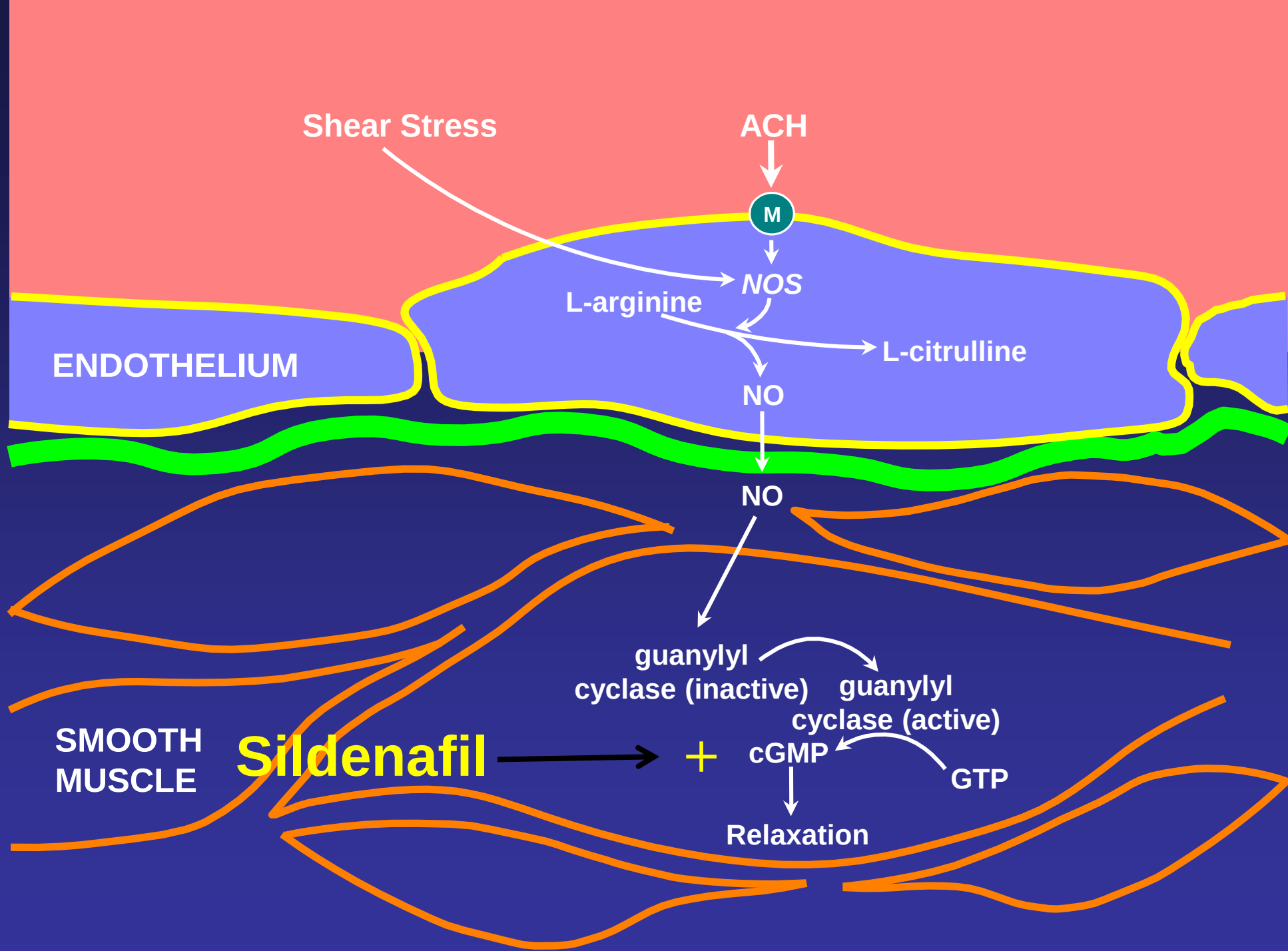
Regulation of
Contractility
Vascular Permeability

Endocrine System

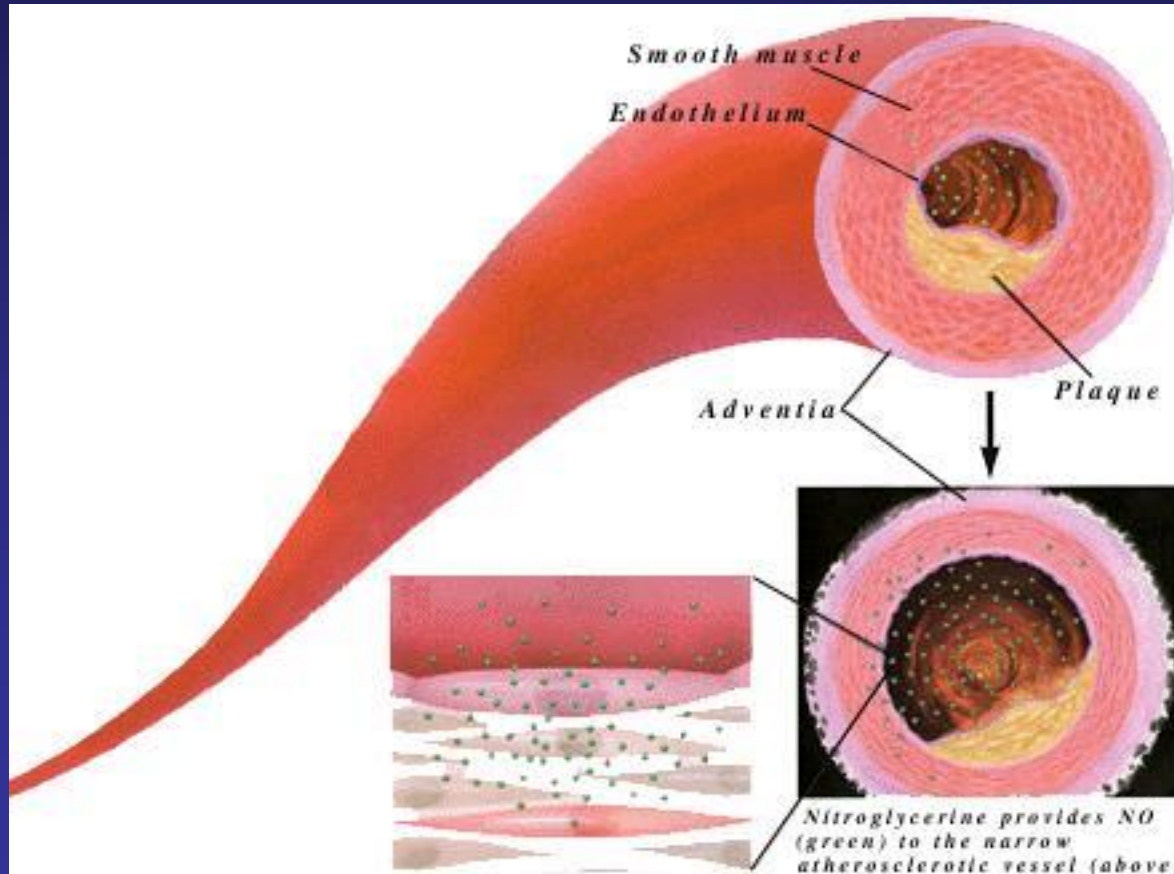
Nerve-mediated
hormone release

			
Robert F. Furchgott	Louis J. Ignarro	Ferid Murad	The Nobel Prize in Physiology or Medicine 1998
🕒 1/3 of the prize USA	🕒 1/3 of the prize USA	🕒 1/3 of the prize USA	“For their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system”
SUNY Health Science Center Brooklyn, NY, USA	University of California School of Medicine Los Angeles, CA, USA	University of Texas Medical School at Houston Houston, TX, USA	
b. 1916	b. 1941	b. 1936	

Source: Nobel e-Museum
www.nobel.se



Nitroglycerine, a 100 year old explosive and heart medicine



In atherosclerosis, plaques reduce blood flow in the arteries. This decreases oxygen supply to the heart muscle causing chest pain (angina pectoris) and sometimes even myocardial infarction.

Treatment with nitroglycerine provides NO, dilates the vessels, and increases blood flow.

Thanks to the 1998 Nobel Laureates we now understand how nitroglycerine, an important heart medicine, works.

It acts as a NO donor, causes dilation of the blood vessels, increases oxygen supply and protects the heart from damage and cell death.

Erectile Dysfunction

Erectile dysfunction, or ED, is the inability to achieve or sustain an erection suitable for sexual intercourse. Causes include medications, chronic illnesses, poor blood flow to the penis, drinking too much alcohol, or being too tired.

More than 18 million men in the United States over age 20 are affected by erectile dysfunction, according to a study by researchers from the Johns Hopkins Bloomberg School of Public Health. The prevalence of erectile dysfunction was strongly linked with age, cardiovascular disease, diabetes and a lack of physical activity. The findings also indicate that lifestyle changes, such as increased physical activity and measures to prevent cardiovascular disease and diabetes, may also prevent decreased erectile function.

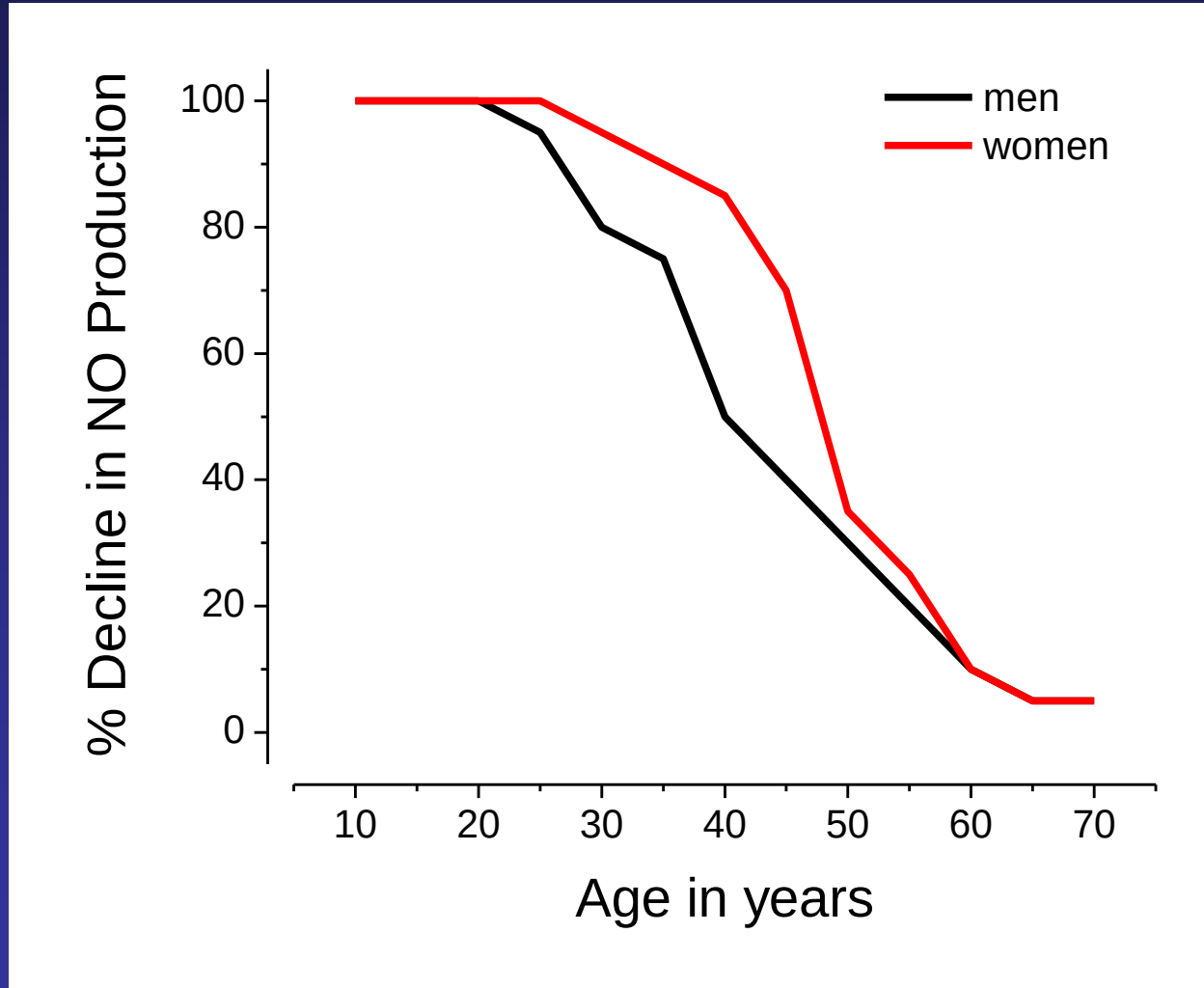
Erectile Dysfunction with Age



20% UNDER 40
50% OVER 40
66% OVER 70

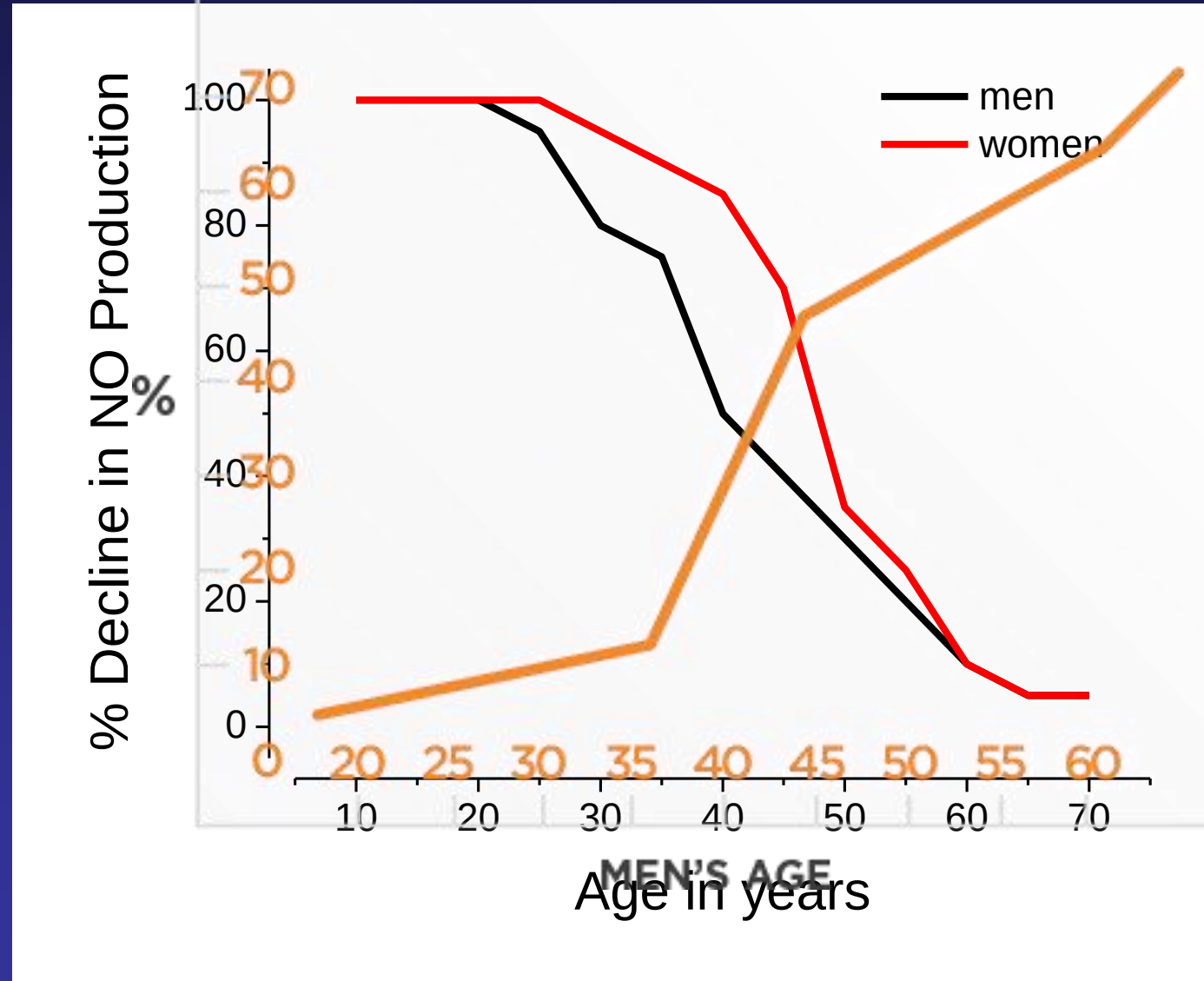
Erectile dysfunction is present in about 50% of men by age 40 with about a 10% increase for each decade thereafter.

NOS Derived NO Declines With Age

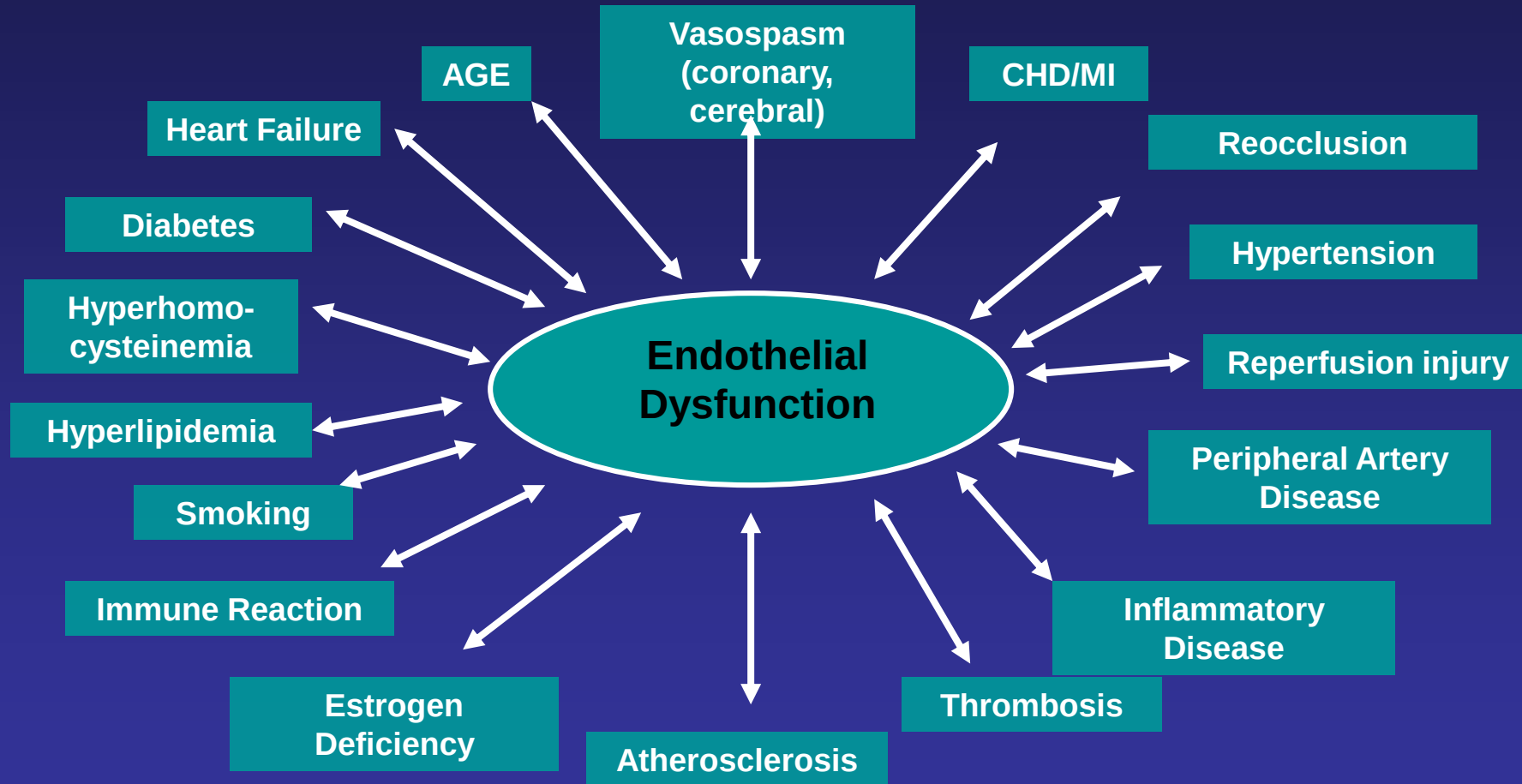


Gerhard et al Hypertension 1996
Celermajer et al JACC 1994
Taddei et al Hypertension 2001
Egashira et al Circulation 1993

Direct Negative Correlation Between Endothelial NO Production and ED



Causes and Consequences of Endothelial Dysfunction



Factors that cause endothelial dysfunction.

- **Atherosclerotic risk factors**
 - Hypertension
 - Cigarette smoking
 - Hypercholesterolemia
 - Diabetes mellitus
 - Male gender
 - Increased age
 - Family history of atherosclerosis
 - Metabolic Syndrome
- **Chronic infections**
 - Herpes viruses
 - Cytomegalovirus
 - Respiratory syncytial virus
 - Helicobacter pylori
 - C. pneumoniae
- **Environmental factors**
 - Hypoxia
 - Turbulent flow
 - Oxidants
- **Genetic factors**
 - Homocysteine
 - Lipoprotein (a)
 - Familial hypercholesterolemia
 - Hypertriglyceridemia

Consequences of NO insufficiency

Hypertension

Lack of energy

Atherosclerosis

Thrombosis

Alzheimers

Sexual Dysfunction

Peripheral Artery Disease

Immune Dysfunction – Chronic Infections

Uncontrolled Cell Proliferation – Cancer

Chronic Inflammation

Pain

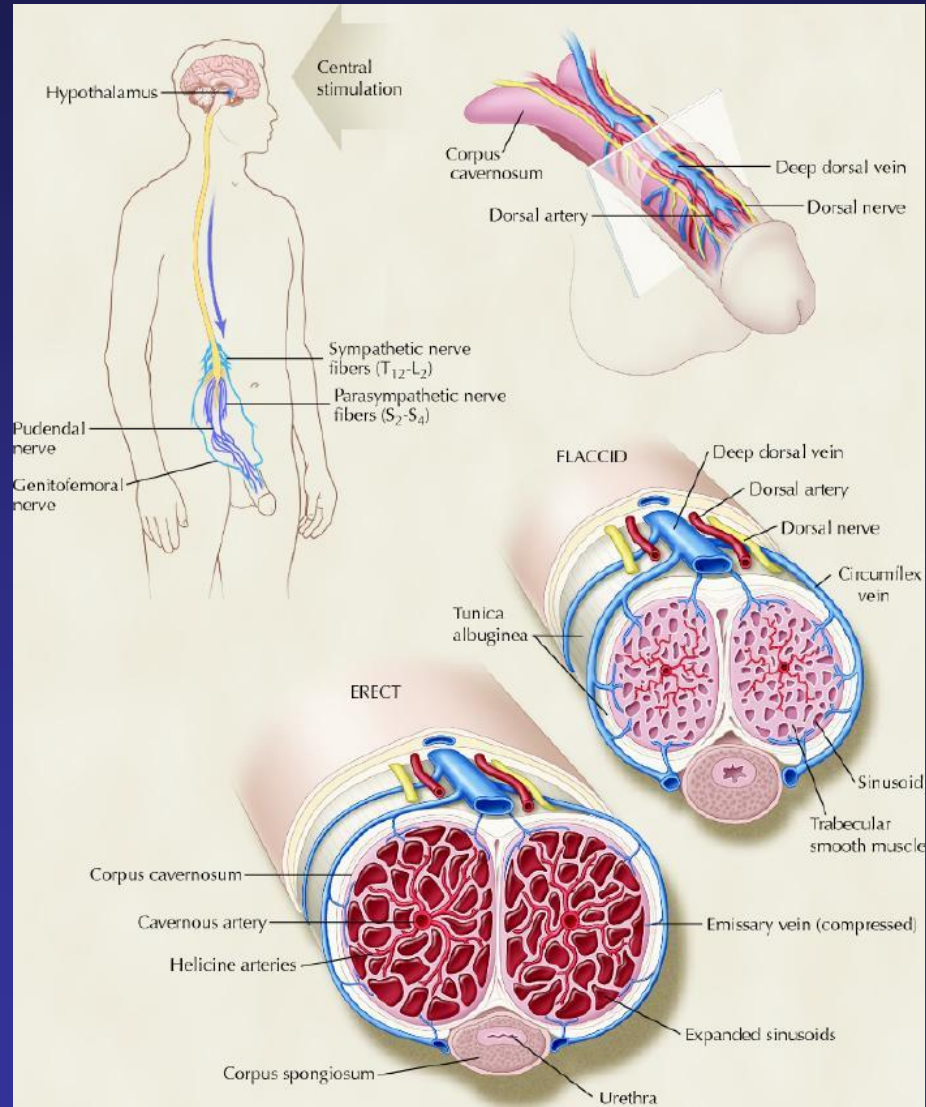
Mitochondrial Dysfunction

Sexual Function - Complex neurovascular process that is controlled by psychological and hormonal inputs

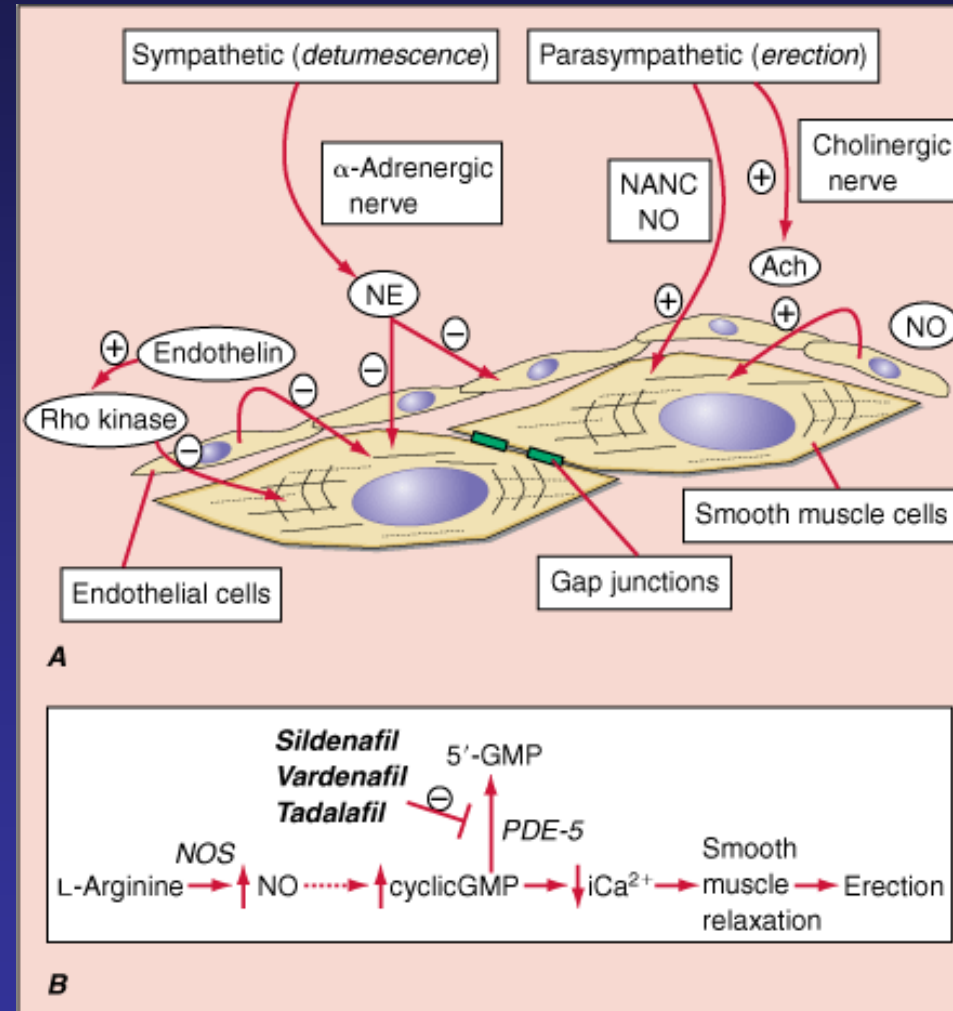
Optimal Sexual Function is multi-factorial

- Anatomical
- Hormonal
- Neurological
- Psychological
- Physiological
- Social-interpersonal

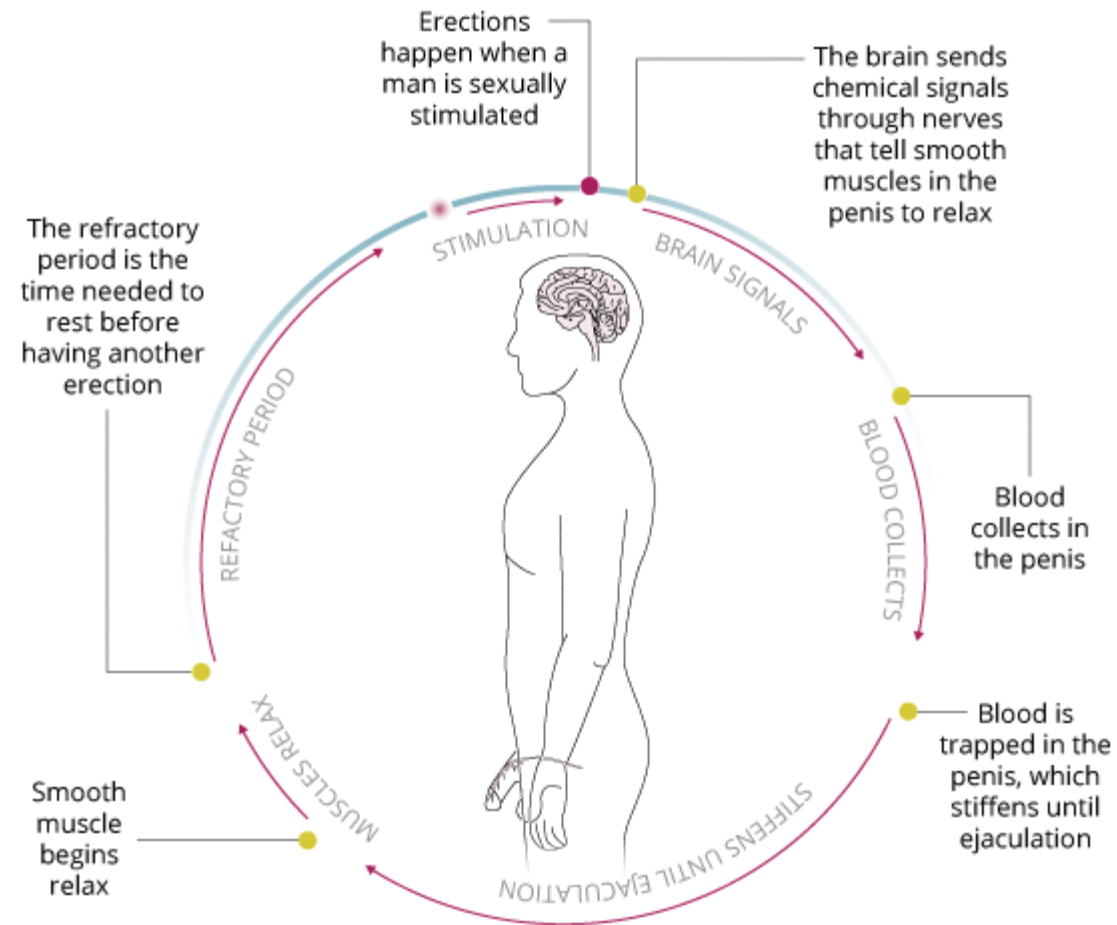
Erectile Function in Men



Neuronal, Endocrine and Physiological Control of Genital Bloodflow



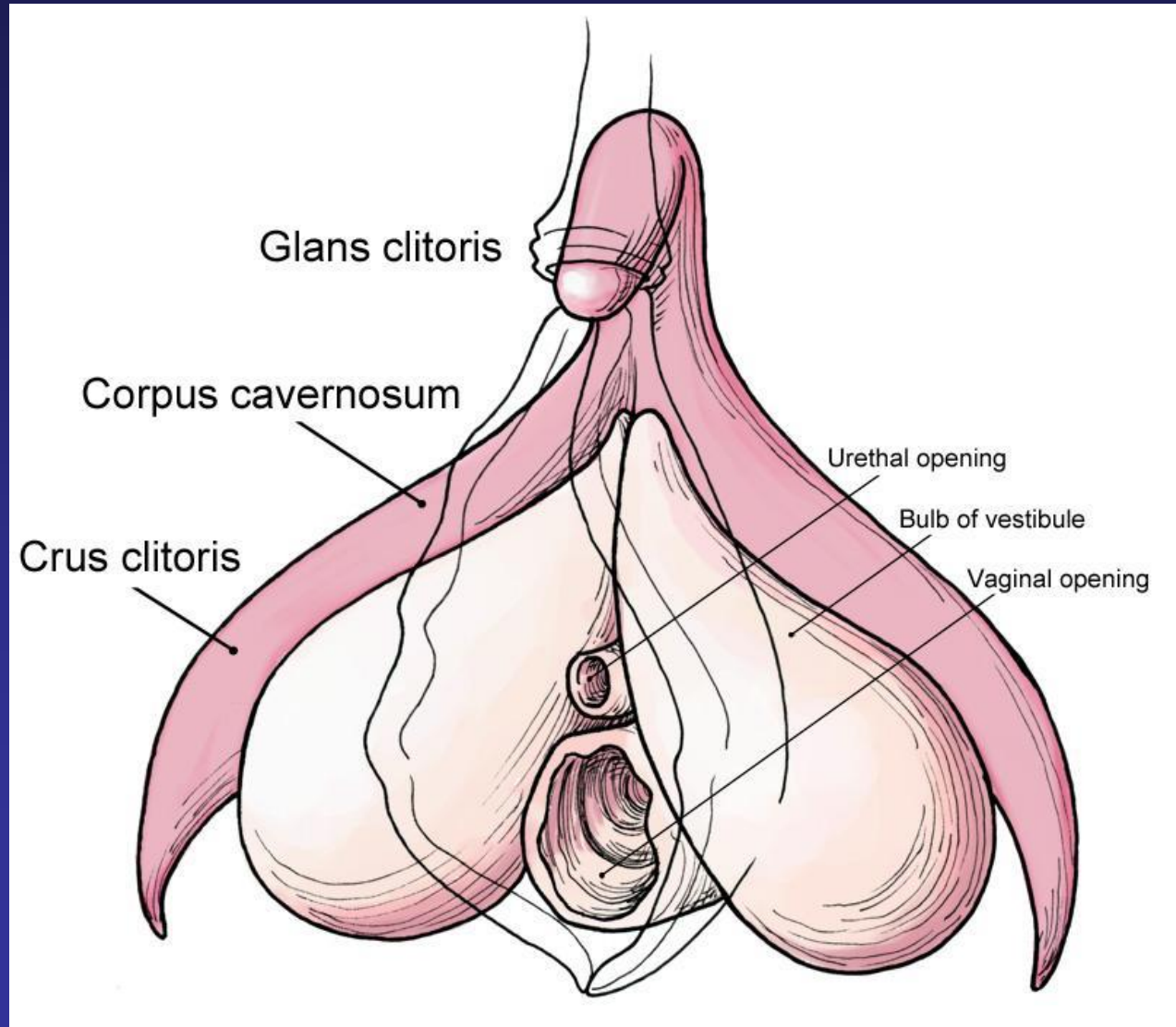
How An Erection Works



Source: Dr. Jacob Rajfer of UCLA, WebMD

THE HUFFINGTON POST

Erectile Function in Women



Sexual Dysfunction Linked to CVD in both men and women

Atherosclerosis

PAD

Hypertension

Hatzimouratidis & Hatzichristiou J Sex Med 2007

Jackson G Int J Clin Pract 2009

Treatment of FSD or ED as purely a lifestyle disorder may severely underestimate the seriousness of disorder

Neurological

Psychological

NANC

Dopamine

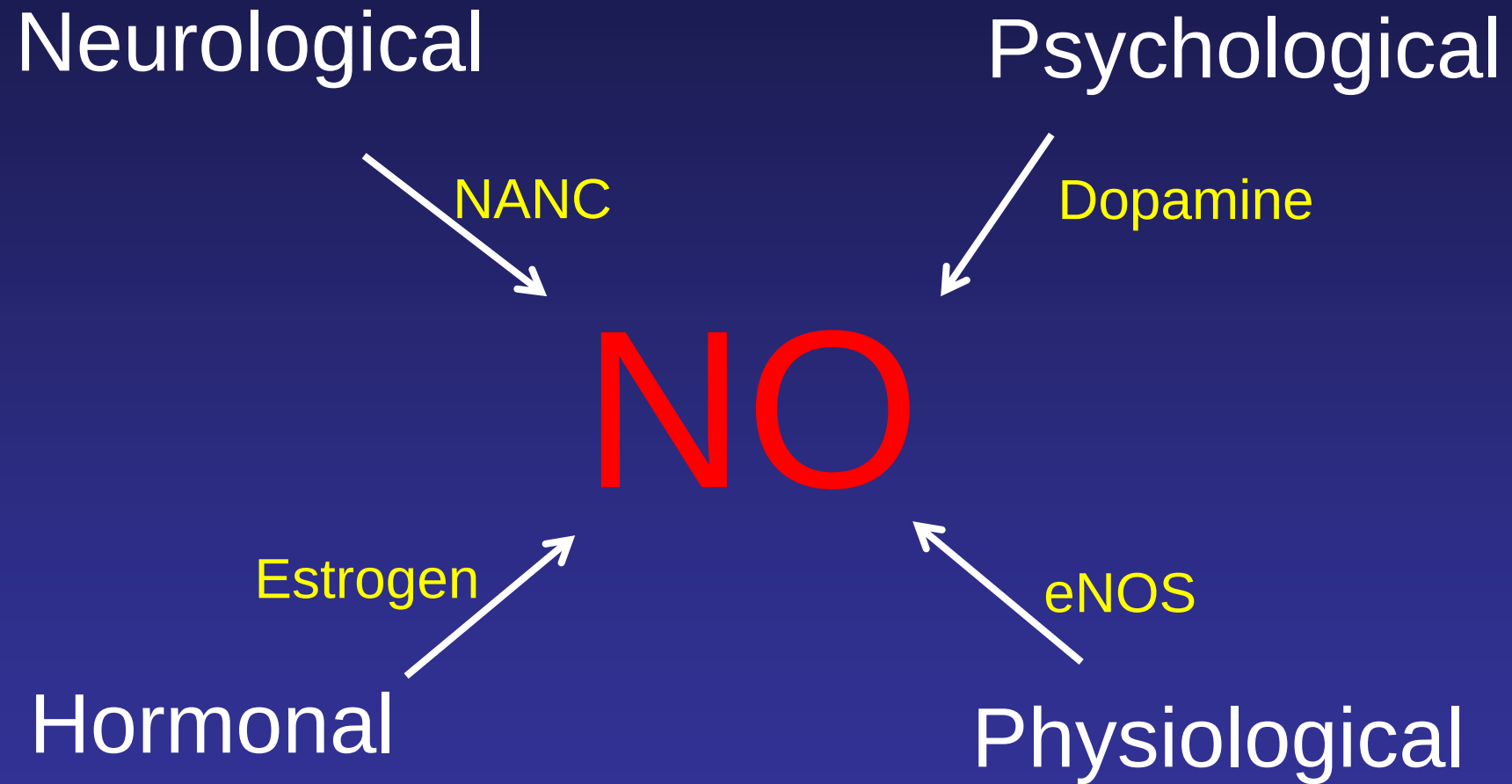
NO

Estrogen

eNOS

Hormonal

Physiological



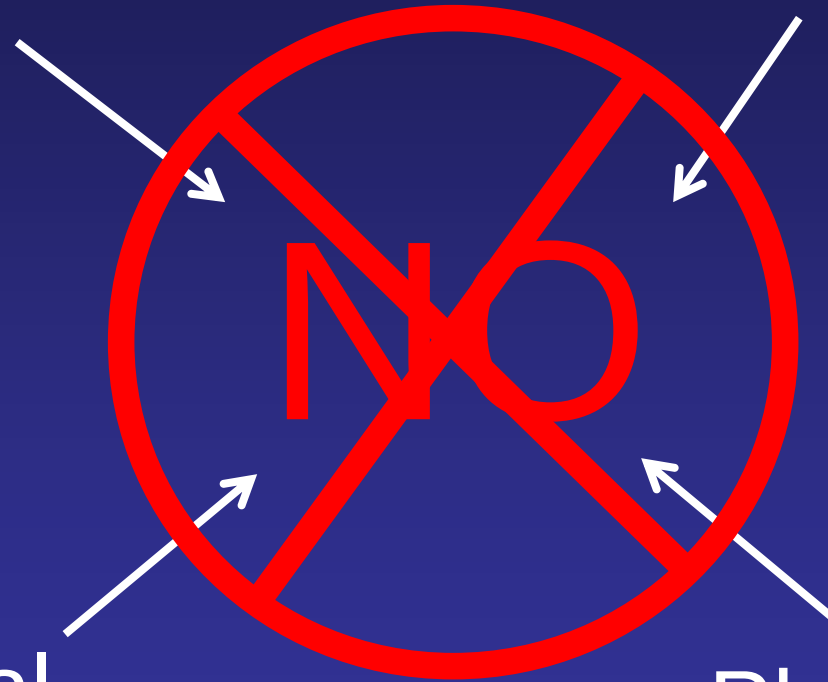
Sexual Dysfunction

Neurological

Psychological

Hormonal

Physiological



Sexual Dysfunction is now considered
an early marker/risk factor for
cardiovascular disease and consequently
a life-threatening condition

It is the canary in the coal mines!!!

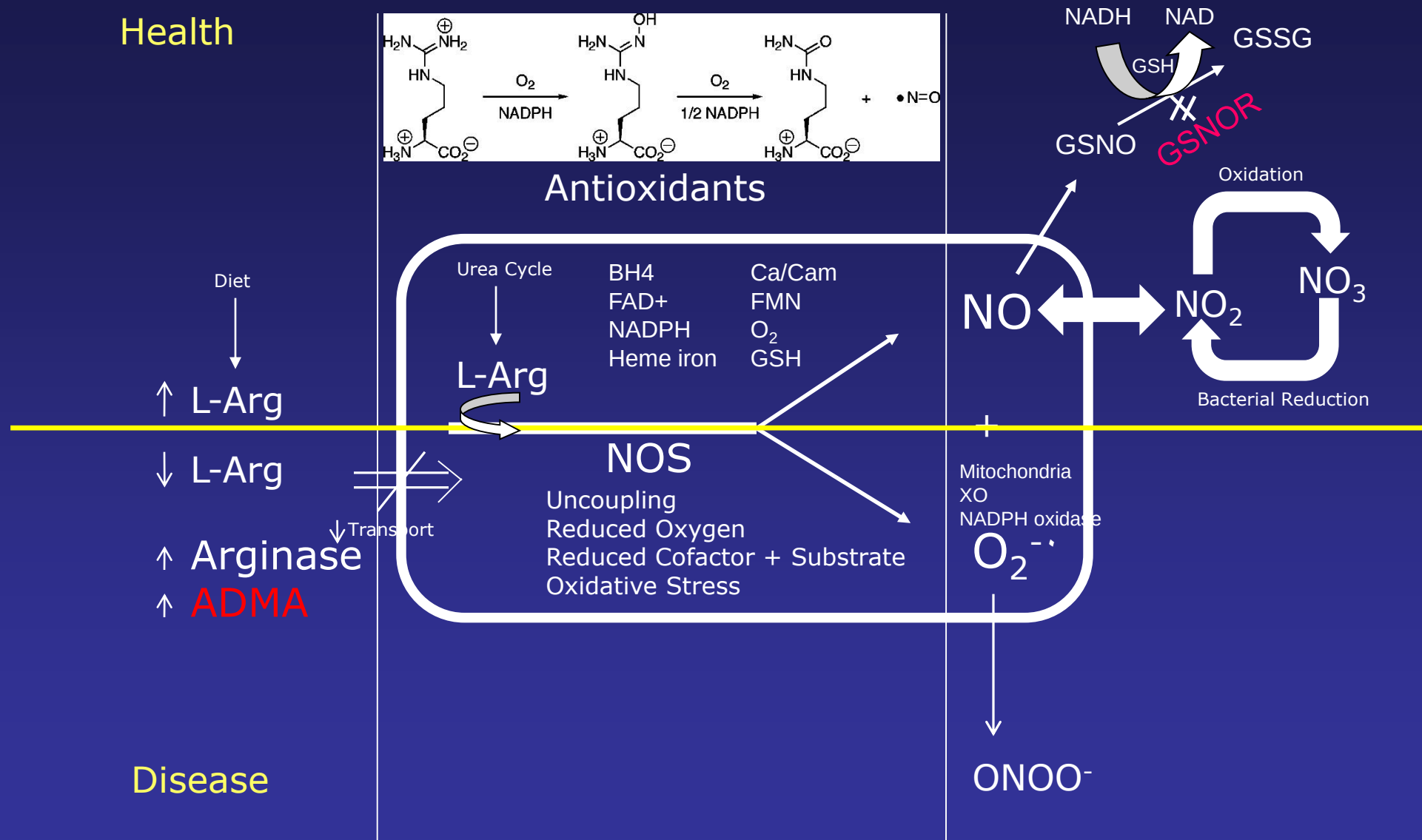
Reduced NO availability is a hallmark of a number of cardiovascular disorders.

- **Endothelial dysfunction** is a physiological dysfunction of normal biochemical processes carried out by the endothelium, the cells that line the inner surface of all blood vessels including arteries and veins (as well as the innermost lining of the heart and lymphatics).
- Loss of endothelial NO function is associated with several cardiovascular disorders, including atherosclerosis, which is due either to decreased production or to increased degradation of NO (Davignon and Ganz 2004).
- Experimental and clinical studies provide evidence that defects of endothelial NO function, referred to as endothelial dysfunction, is not only associated with all major cardiovascular risk factors, such as hyperlipidemia, diabetes, hypertension, smoking and severity of atherosclerosis, but also has a profound predictive value for the future atherosclerotic disease progression (Schachinger, Britten et al. 2000; Halcox, Schenke et al. 2002; Bugiardini, Manfrini et al. 2004; Lerman and Zeiher 2005).
- The dysfunctional eNOS/NO pathway is considered as an early marker or a common mechanism for various cardiovascular disorders. Over the last two decades, it has become evident that decreased bioavailability of endothelial NO, produced from endothelial NO synthase (eNOS), plays a crucial role in the development and progression of atherosclerosis.

How do we control and regulate
NO production?

The L-Arginine-Nitric Oxide Pathway

Health

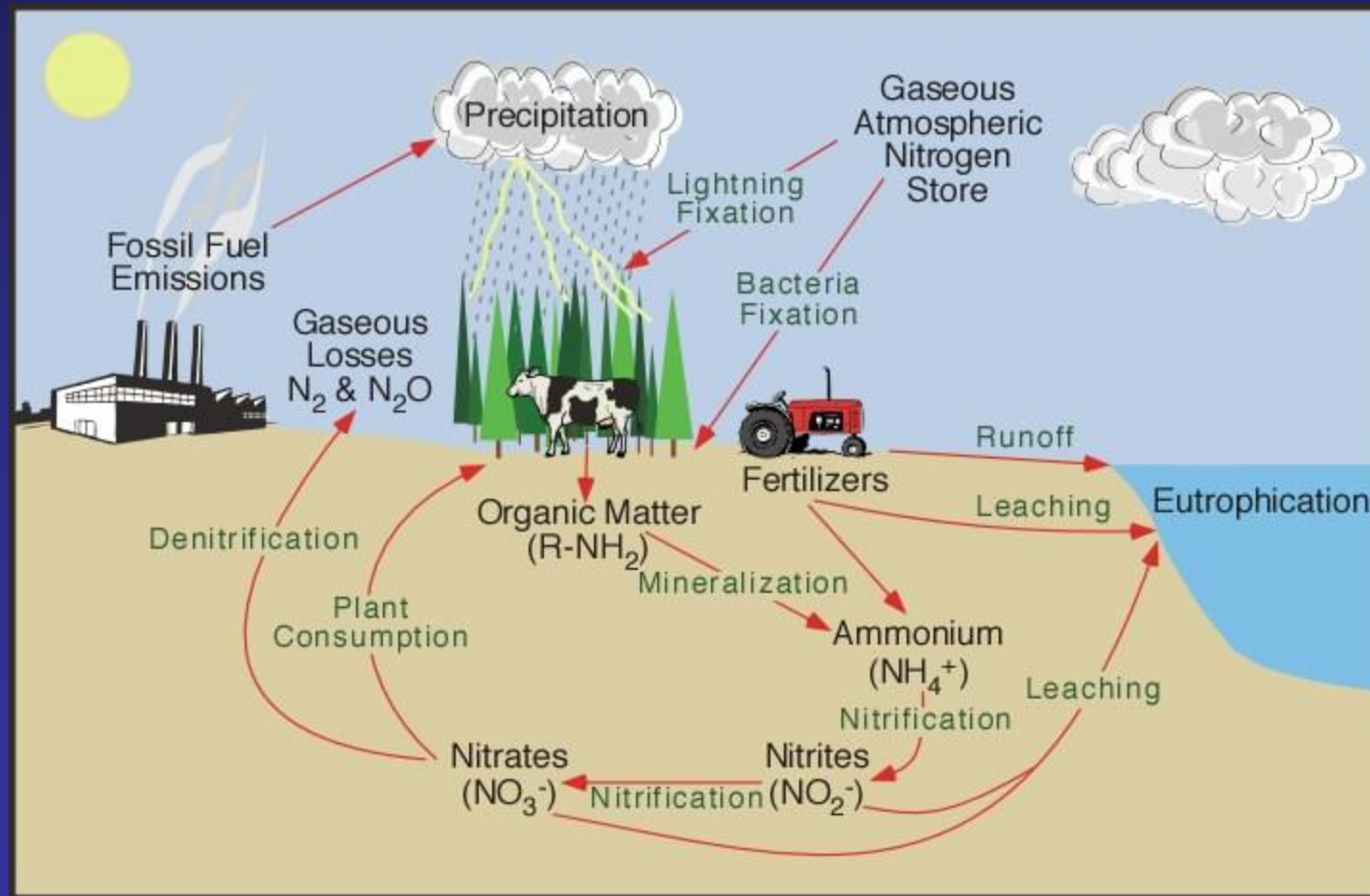


Disease

What if 50% or more of NO
bioactivity was determined and
dictated by foods and diets containing
nitrite and nitrate and oral bacteria?

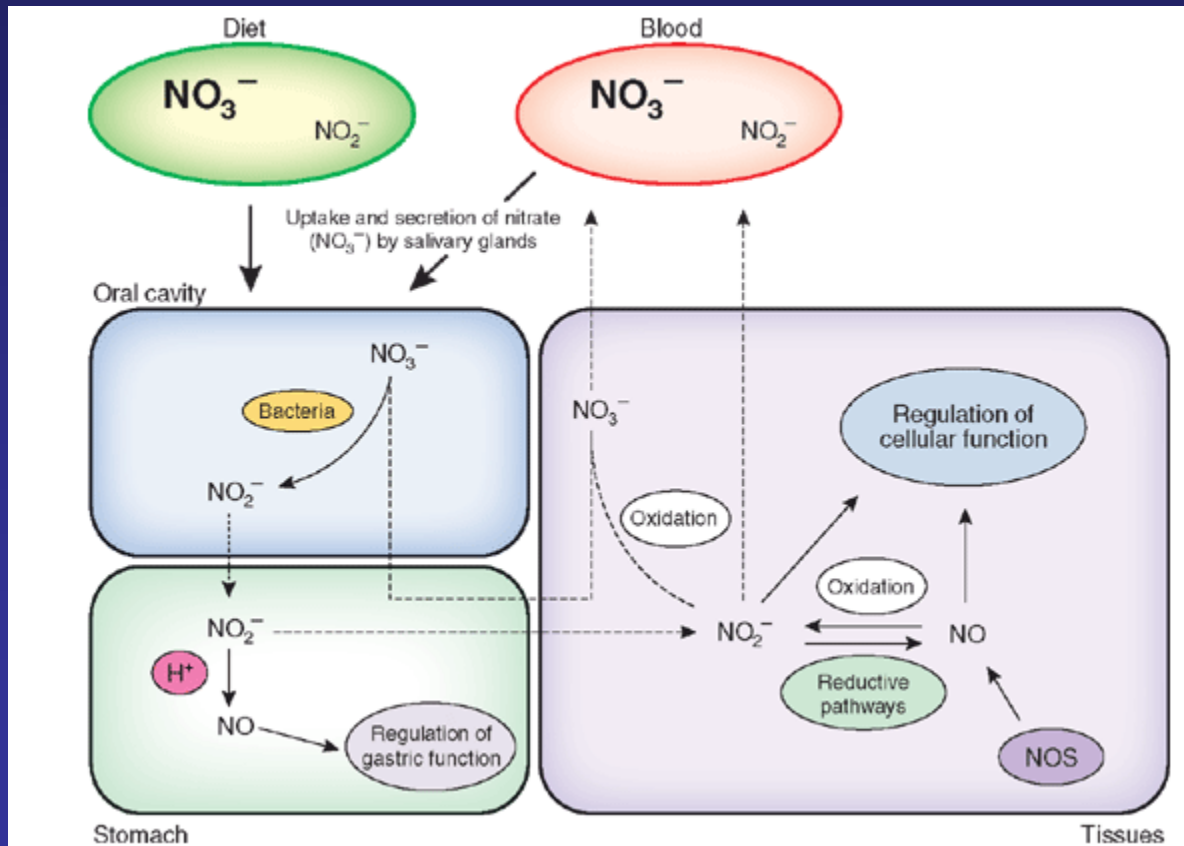
Atmospheric Nitrogen Cycle

The store of nitrogen found in the atmosphere, where it exists as a gas (mainly N_2), plays an important role for life. Most plants can only take up nitrogen in two solid forms: ammonium ion (NH_4^+) and the nitrate ion (NO_3^-). Most plants obtain the nitrogen they need as nitrate from the soil. When released, most of the ammonium is often chemically altered by a specific type of bacteria (genus *Nitrosomonas*) into nitrite (NO_2^-). Further modification by another type of bacteria (genus *Nitrobacter*) converts the nitrite to nitrate. All nitrogen obtained by animals can be traced back to the eating of plants at some stage of the food chain.



New Paradigm - Human Nitrogen Cycle

One-electron reduction is favorable to five-electron oxidation



Dietary nitrate is rapidly absorbed into the bloodstream, where it mixes with endogenous nitrate from the NOS/NO pathway. A large portion of nitrate is taken up by the salivary glands, secreted with saliva and reduced to nitrite by symbiotic bacteria in the oral cavity. Salivary-derived nitrite is further reduced to NO and other biologically active nitrogen oxides in the acidic stomach. Remaining nitrite is rapidly absorbed and accumulates in tissues, where it serves to regulate cellular functions via reduction to NO or possibly by direct reactions with protein and lipids. NO and nitrite are ultimately oxidized to nitrate, which again enters the enterosalivary circulation or is excreted in urine.

Dietary Nitrate Can Be Metabolized to Nitrite and NO

Nitrate, bacteria and human health

Lundberg JO, Weitzberg E, Cole JA, Benjamin N.
Nat Rev Microbiol. 2004 Jul;2(7):593-602

Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite.

Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, Rashid R, Miall P, Deanfield J, Benjamin N, MacAllister R, Hobbs AJ, Ahluwalia A.
Hypertension. 2008 Mar;51(3):784-90.

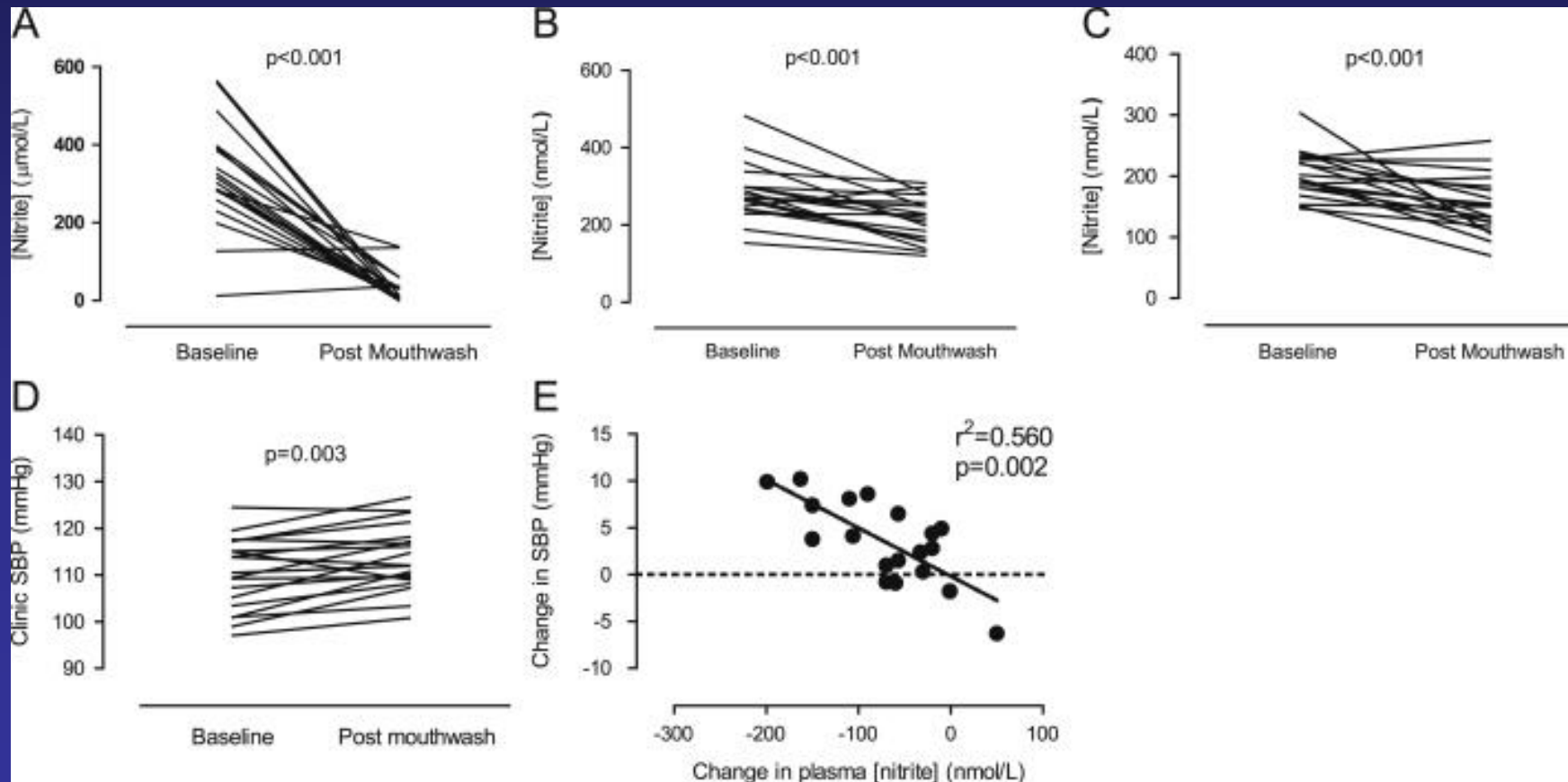
Dietary nitrate supplementation reduces the O₂ cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans.

Bailey SJ, Winyard P, Vanhatalo A, Blackwell JR, Dimenna FJ, Wilkerson DP, Tarr J, Benjamin N, Jones AM.
J Appl Physiol. 2009 Oct;107(4):1144-55.

Physiological role for nitrate-reducing oral bacteria in blood pressure control

Kapil V, Haydar SM, Pearl V, Lundberg JO, Weitzberg E, Ahluwalia A.
Free Radic Biol Med. 2013 Feb;55:93-100.

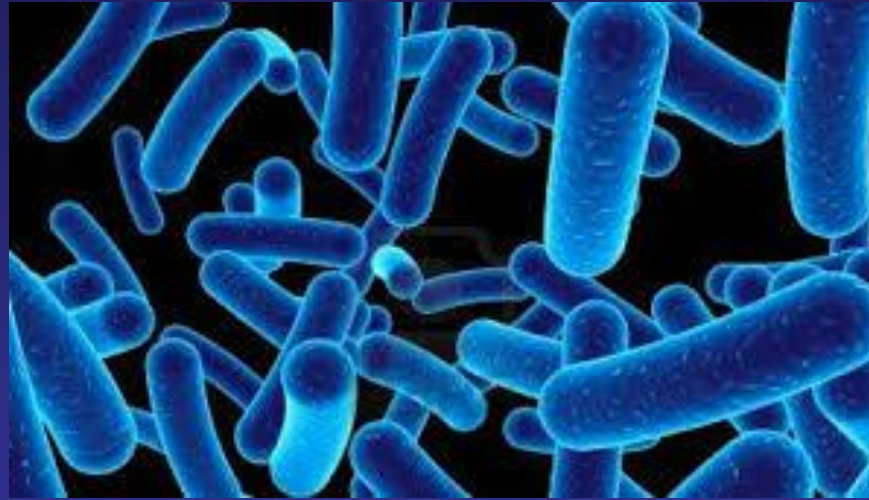
Physiological Role for Nitrate-Reducing Oral Bacteria in Blood Pressure Control



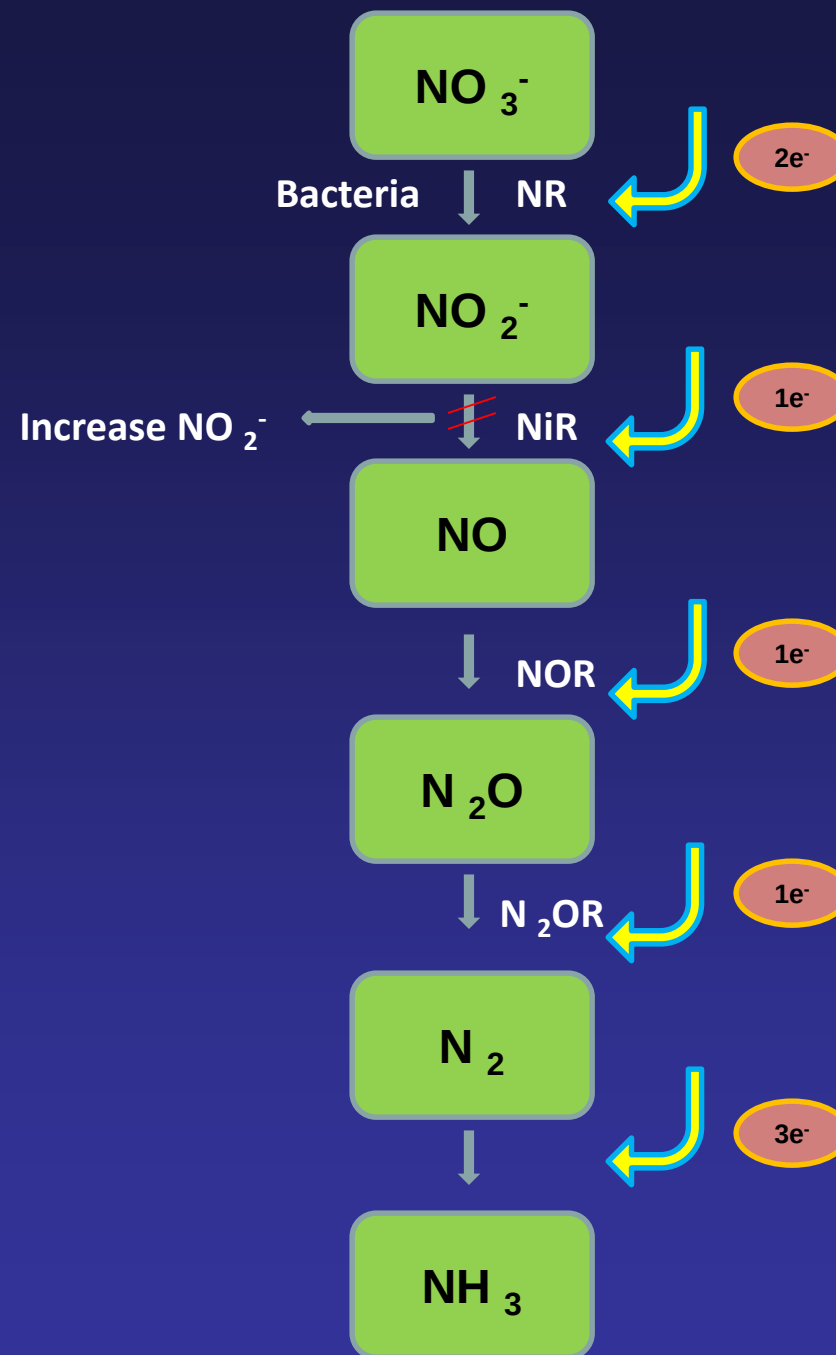
Genetic Diversity



23,000 genes



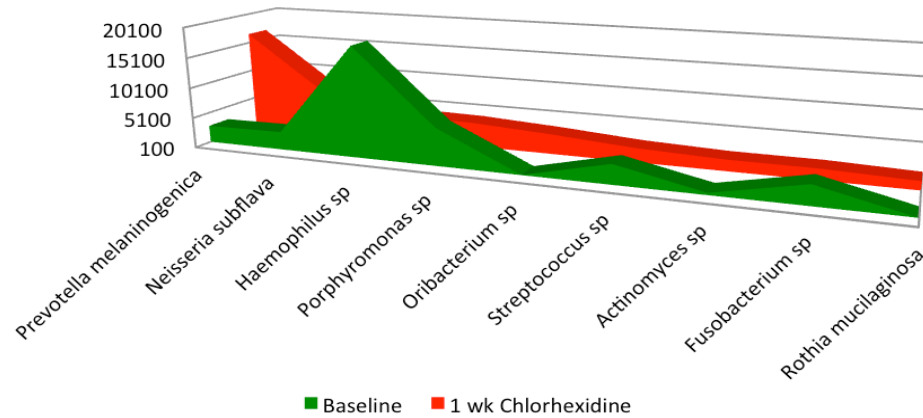
3,000,000 genes



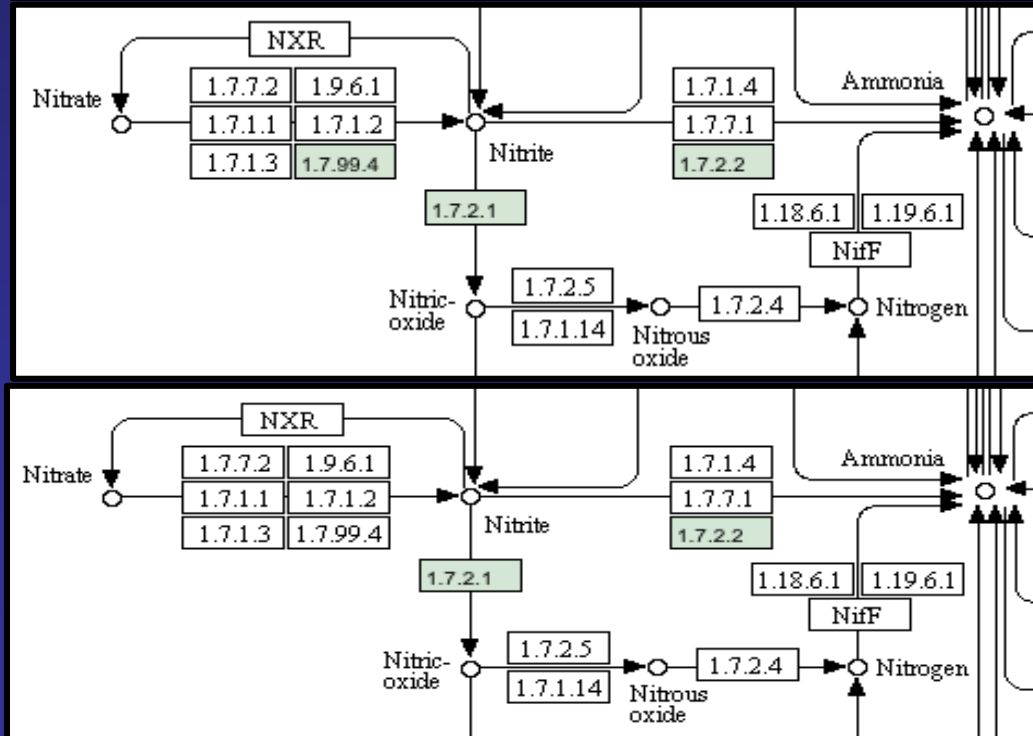
Ideal Community:

- Higher Nitrate reduction efficacy
- No NiR enzyme; Nitrite can accumulate, enrich saliva to form NO when swallowed.

Subject #29 Blood Pressure Increase

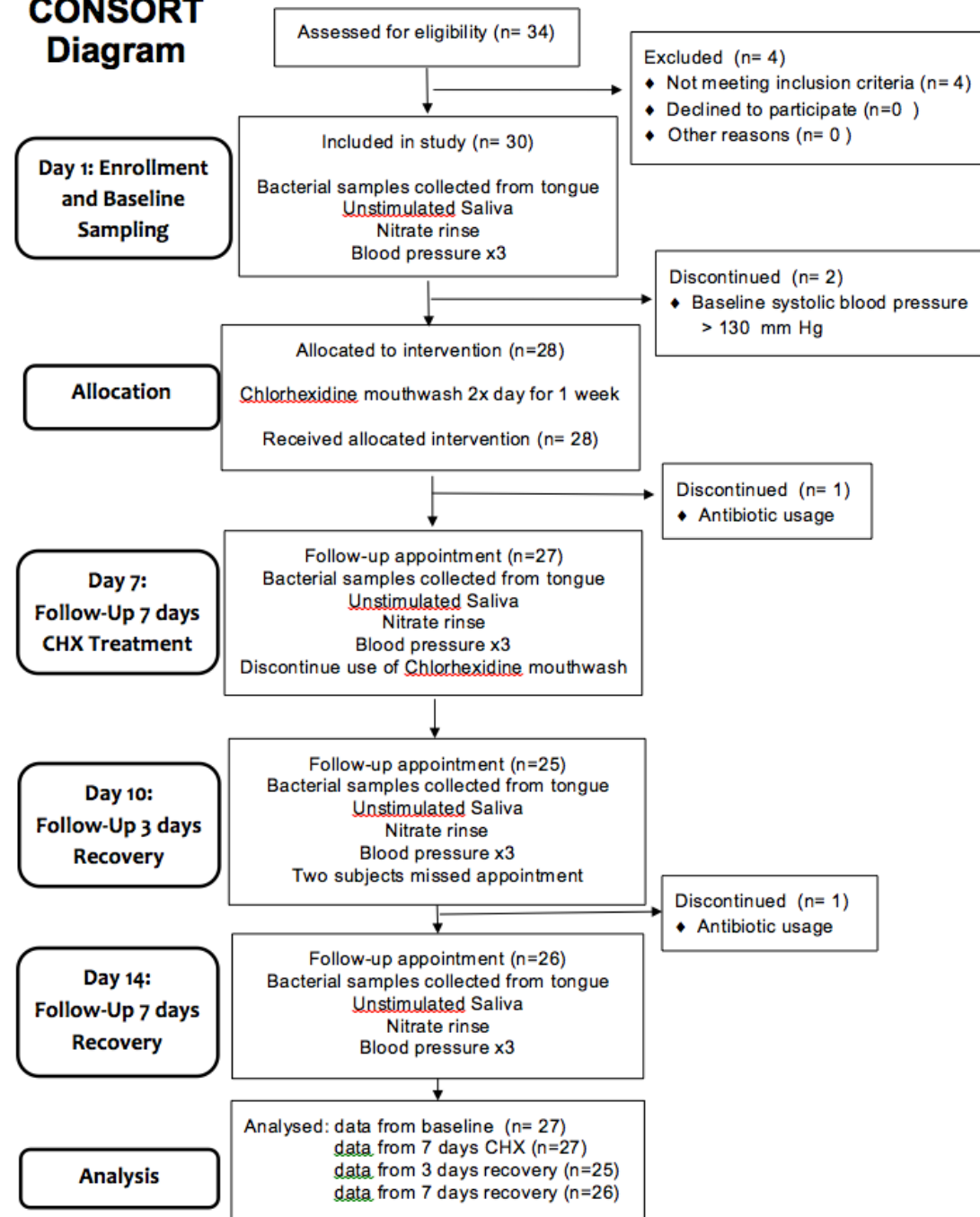


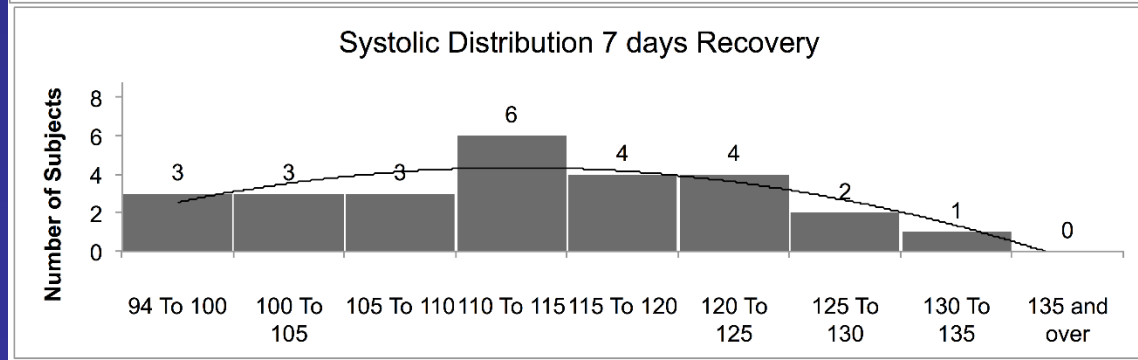
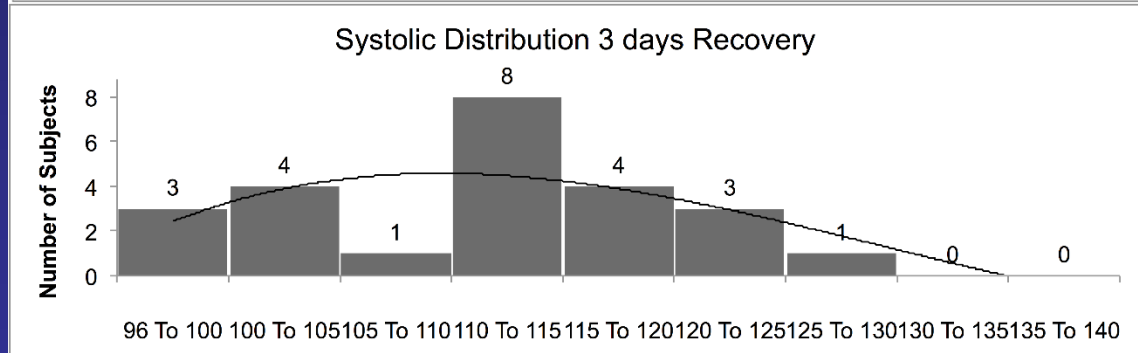
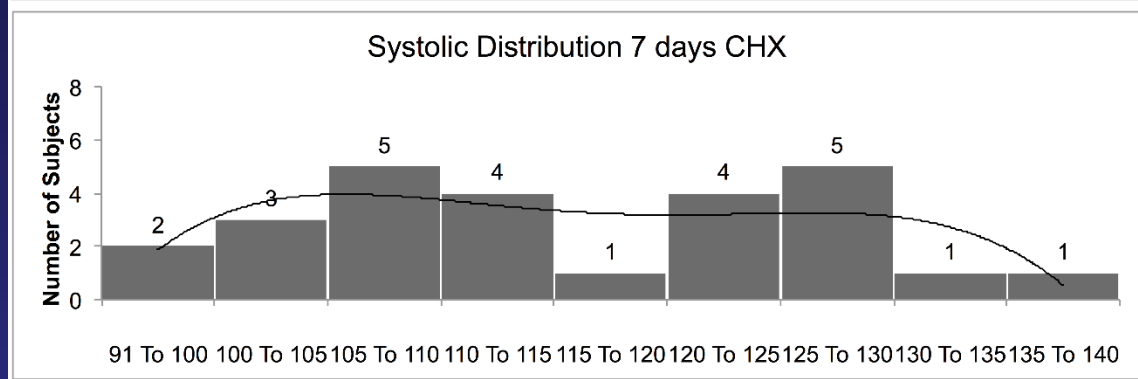
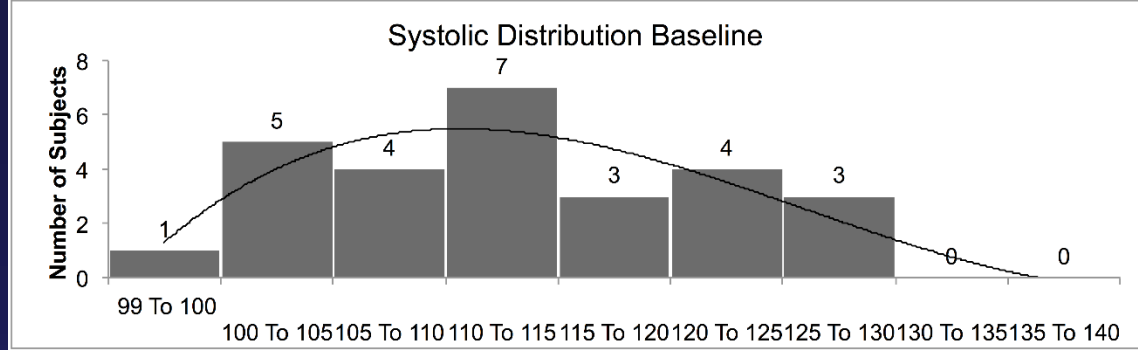
One week Chlorhexidine treatment caused 26 mmHg increase in systemic blood pressure. This was associated with change in bacterial communities that disrupted nitrate reduction and NO production



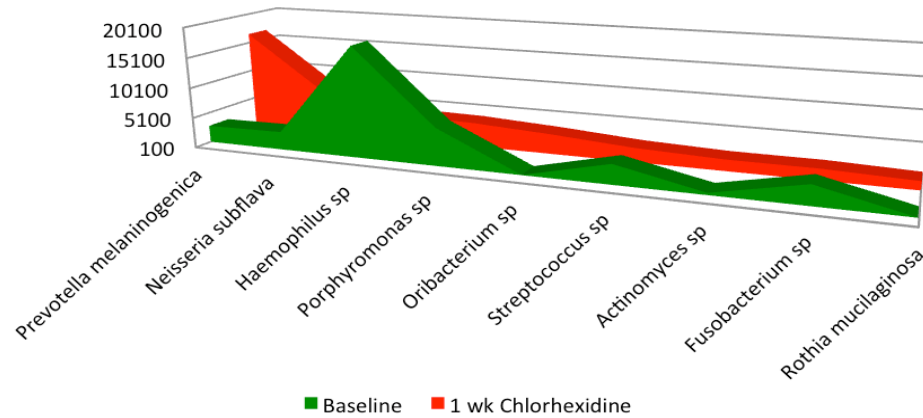
How Does Chlorhexidine Treatment
Affect Diversity of Oral Microbiome
And Nitrate Reduction in Healthy
Subjects and what Effect
Does this have on Systemic Blood
Pressure?

CONSORT Diagram

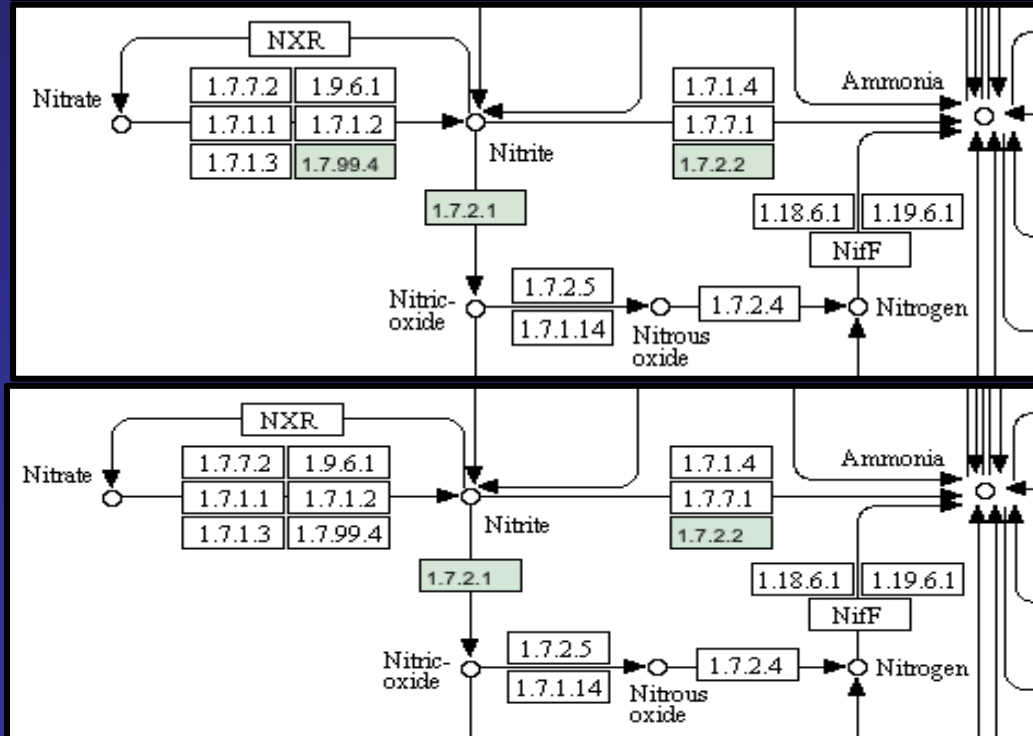




Subject #29 Blood Pressure Increase



One week Chlorhexidine treatment caused 26 mmHg increase in systemic blood pressure. This was associated with change in bacterial communities that disrupted nitrate reduction and NO production



Oral Hygeine Survey

Brush teeth	<i>Count</i>	<i>Percent</i>
<i>twice a day</i>	22	81%
<i>three times a day</i>	5	19%

Floss	<i>Count</i>	<i>Percent</i>
<i>several times per month</i>	1	4%
<i>several times per week</i>	8	30%
<i>once a day</i>	16	67%
<i>twice a day</i>	2	7%

Clean tongue	<i>Count</i>	<i>Percent</i>
<i>Less than once a week</i>	4	15%
<i>Once a day</i>	13	48%
<i>Twice a day or more</i>	10	37%

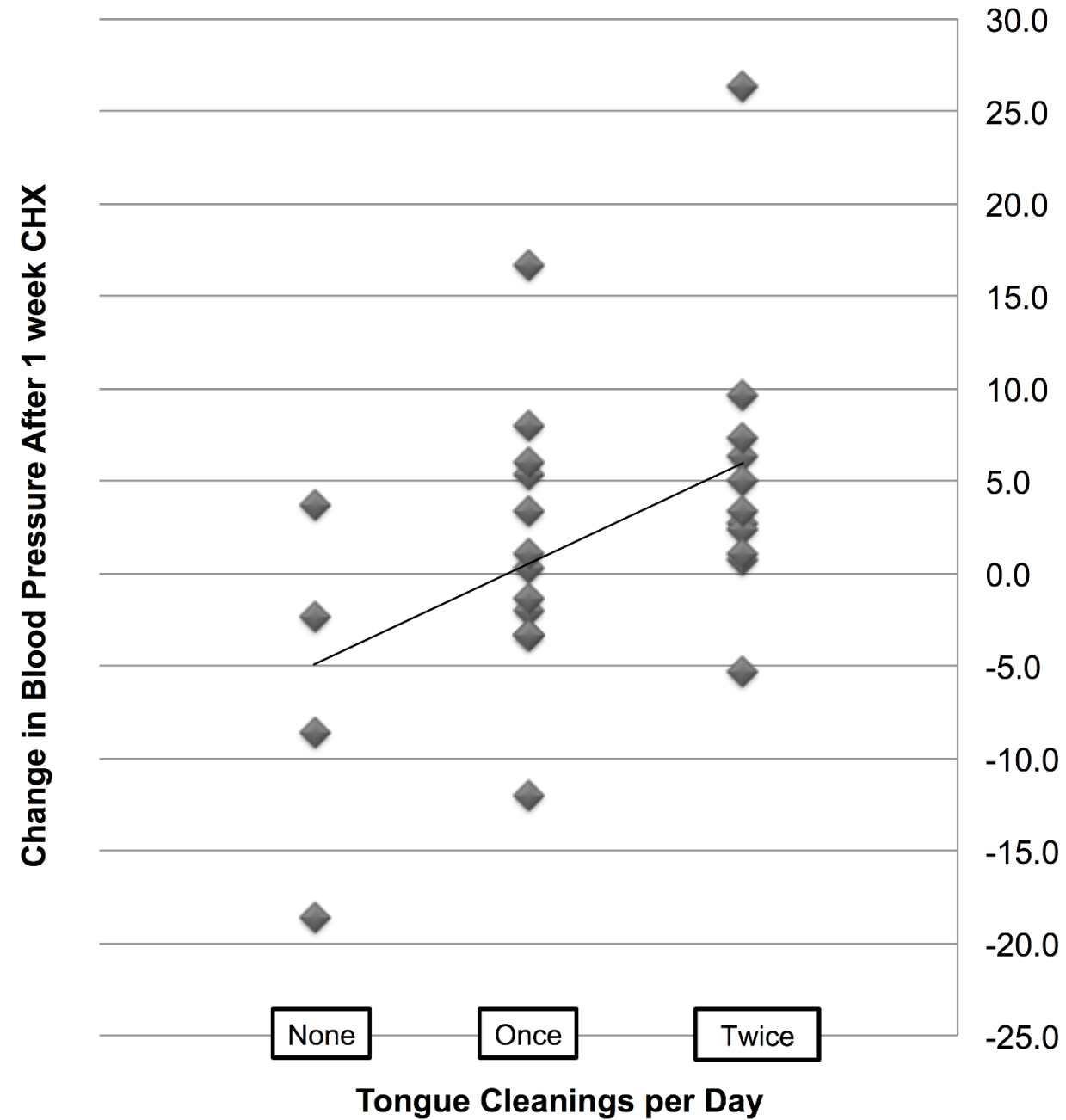
Mouthwash use	<i>Count</i>	<i>Percent</i>
<i>As needed</i>	5	19%
<i>Once a day</i>	16	59%
<i>Twice a day</i>	6	22%

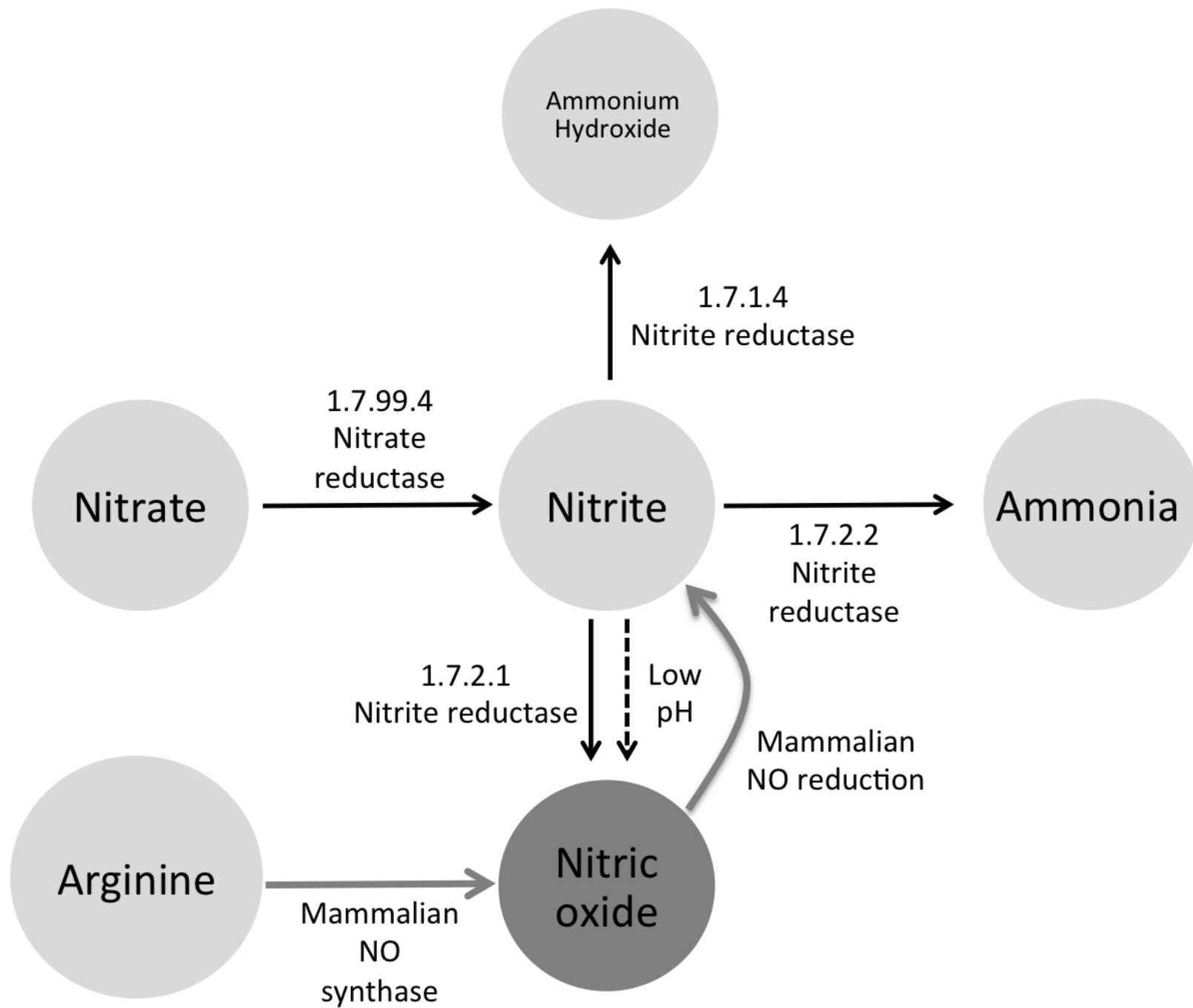
Mouthwash ingredient	<i>Count</i>	<i>Percent</i>
<i>Essential oils</i>	11	41%
<i>Cetylpyridinium chloride</i>	10	37%
<i>No response</i>	6	22%

Type of Toothbrush	<i>Count</i>	<i>Percent</i>
<i>Manual</i>	10	37%
<i>Electric</i>	12	44%
<i>Both manual and electric</i>	5	19%

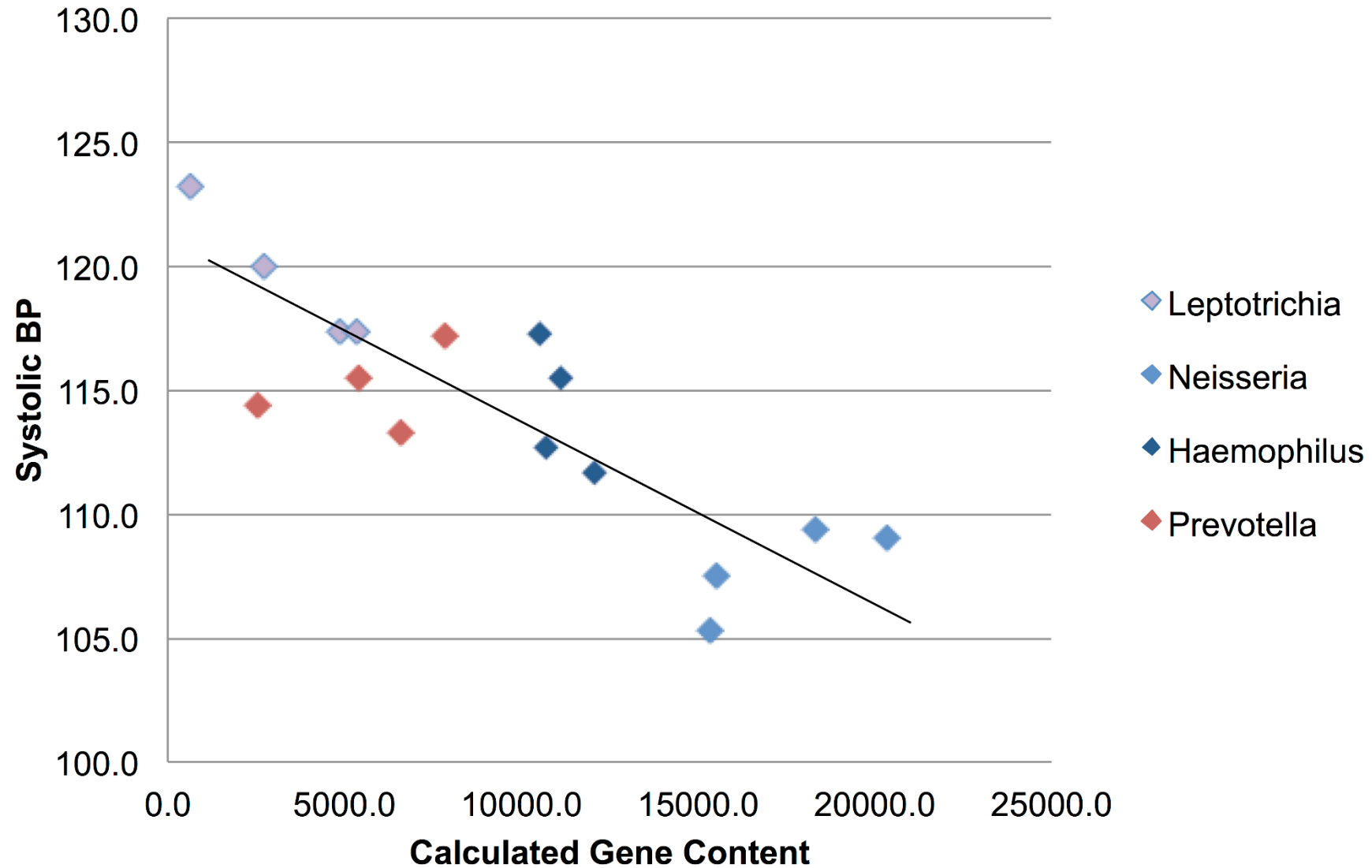
Visits to dentist per year	<i>Count</i>	<i>Percent</i>
<i>None</i>	1	4%
<i>Once</i>	12	44%
<i>Twice or more</i>	14	52%

Δ Systolic BP Correlates with Tongue Hygiene





Nitrite Reductase (NO-forming) Correlates with Systolic BP



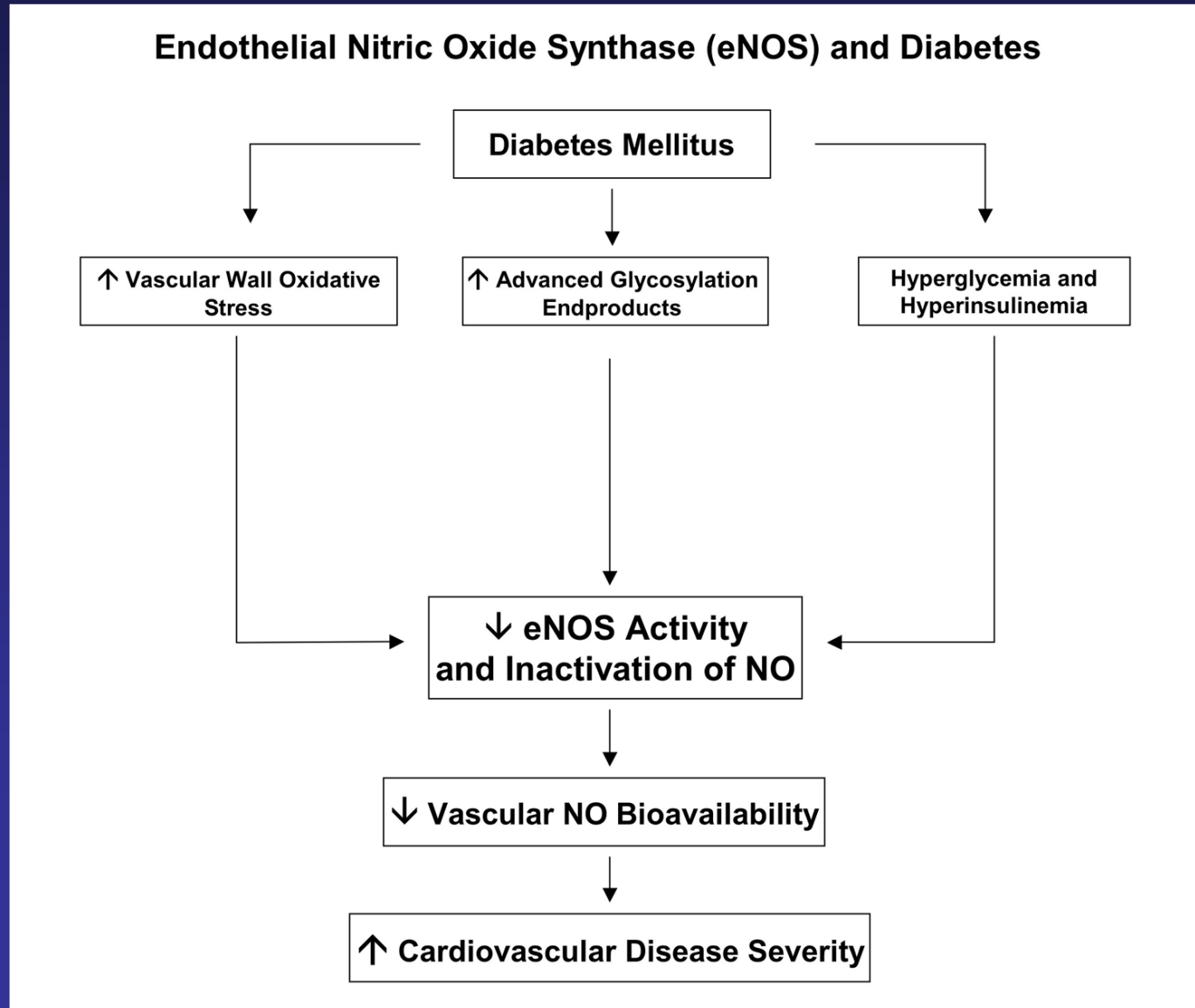
Acid Reflux Drug May Cause Heart Disease

The Wall Street Journal
July 10, 2013

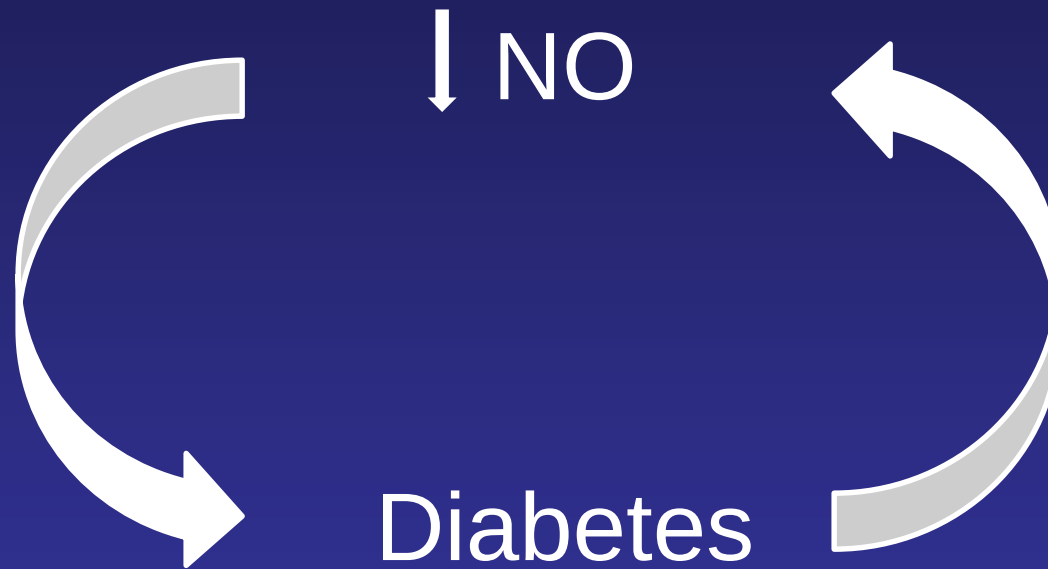
ED and Diabetes

- At any given time an estimated 30 million American men experience impotence (erectile dysfunction). **Sexual difficulties in people with diabetes are not always related to their disease.**
- Impotence can occur in men of any age, but it most often affects older men.
A recent study* of 1,300 males found some degree of erection difficulty in 52 percent of participants ages 40 to 70.
- Over 50 percent of the estimated 10 million men with diagnosed type 2 diabetes experience impotence.
- In men whose diabetes is well controlled, the rate of impotence is about 30 percent.
- Approximately 35 percent of women with diabetes may experience some form of
- sexual dysfunction related to their disease.
- Of people with complications from diabetes, 50 to 70 percent of men and 40 to 50
- percent of women may have sexual difficulties because of nerve damage

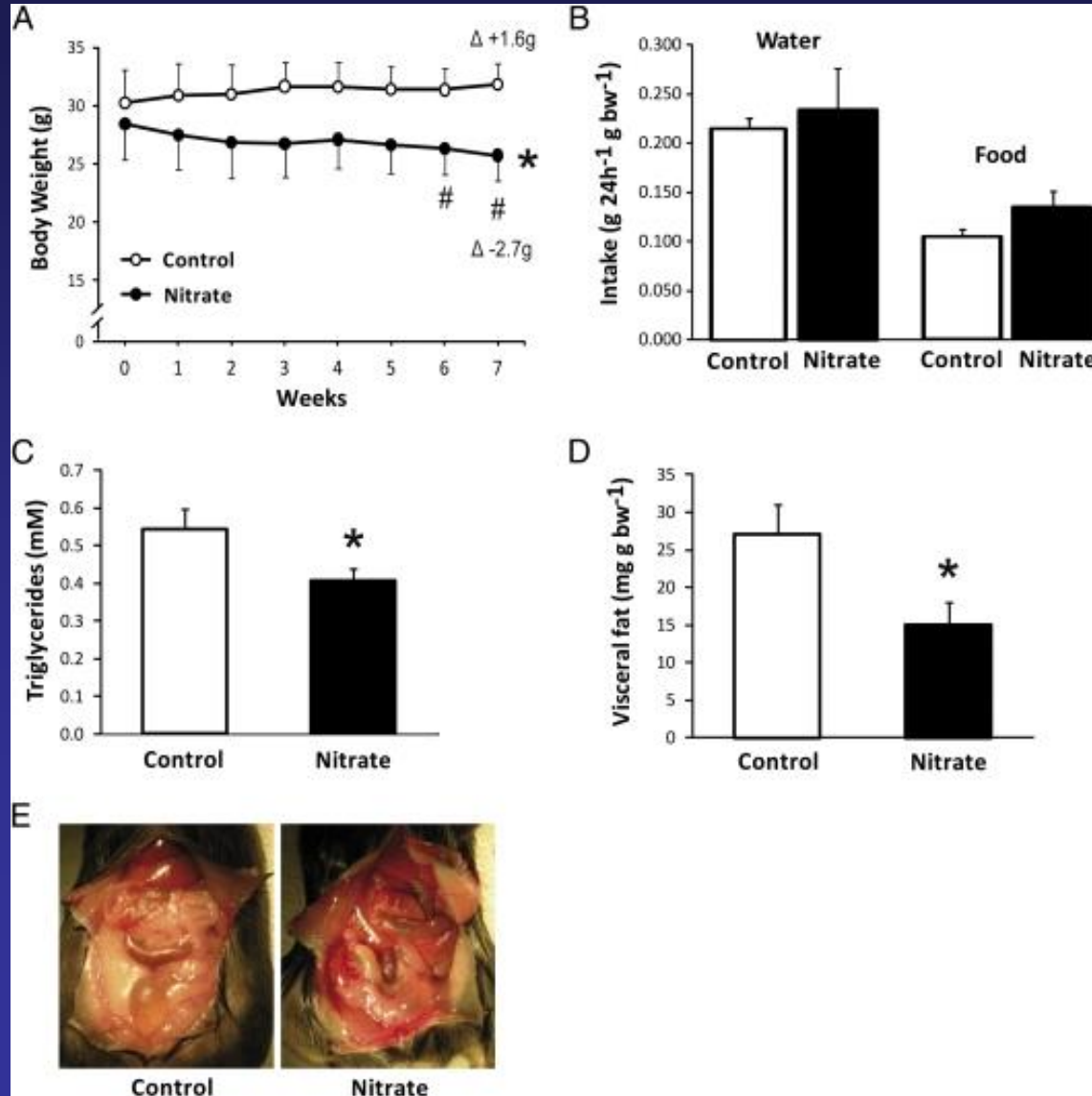
Diabetes Leads to Insufficient NO Production



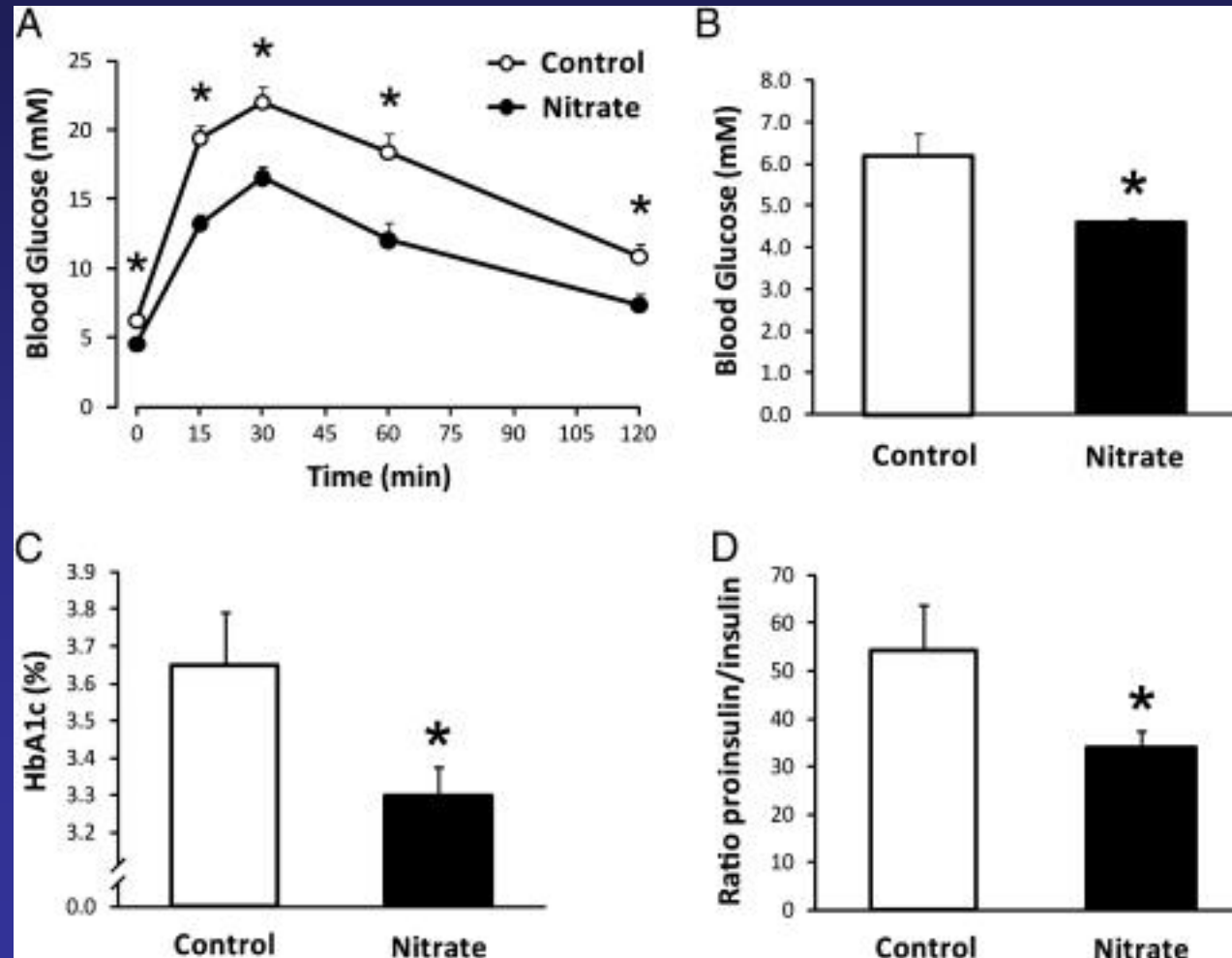
Perpetual Cycle of NO and Diabetes



Dietary nitrate reduces body weight and decreases the amounts of visceral fat and circulating triglycerides in eNOS-deficient mice.

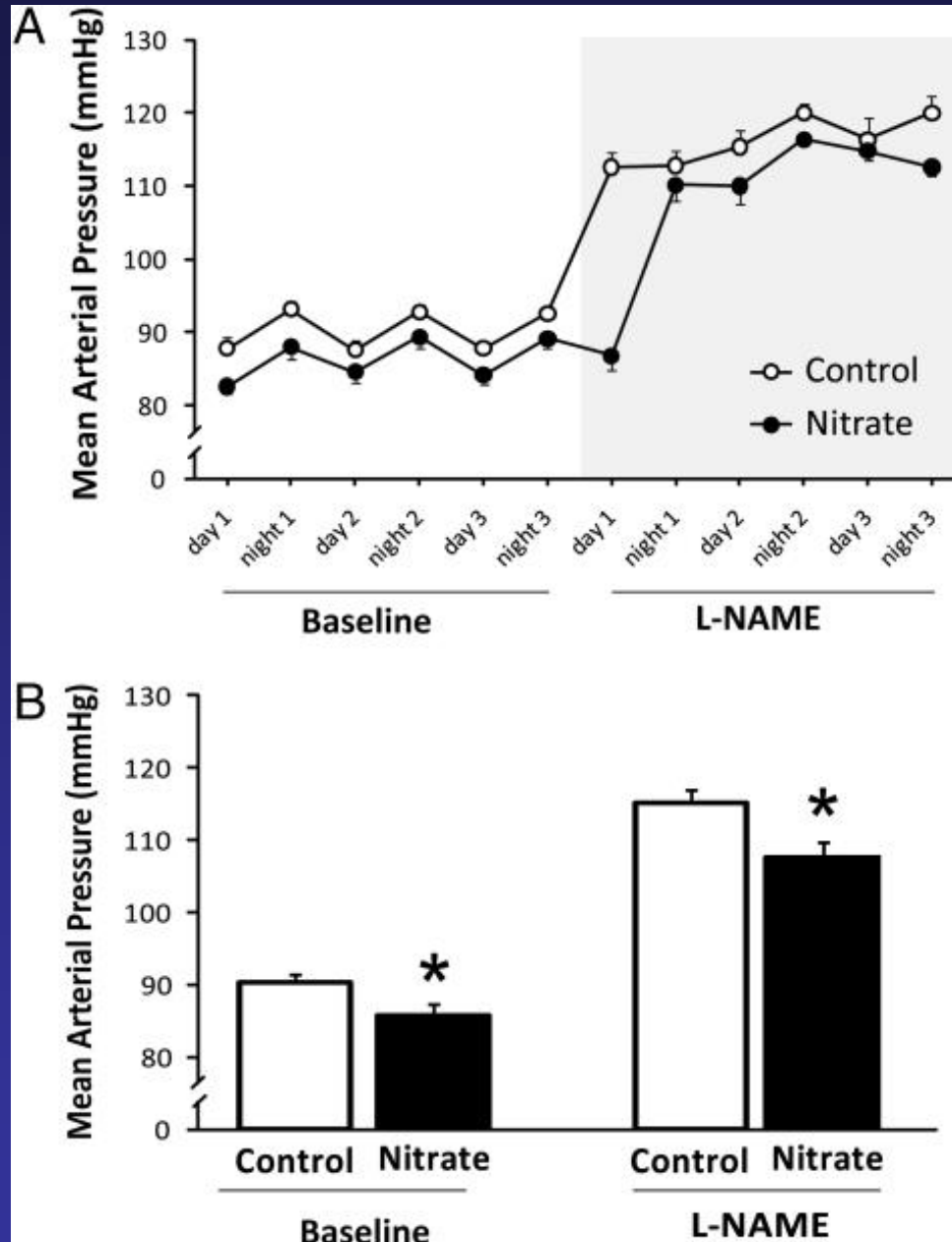


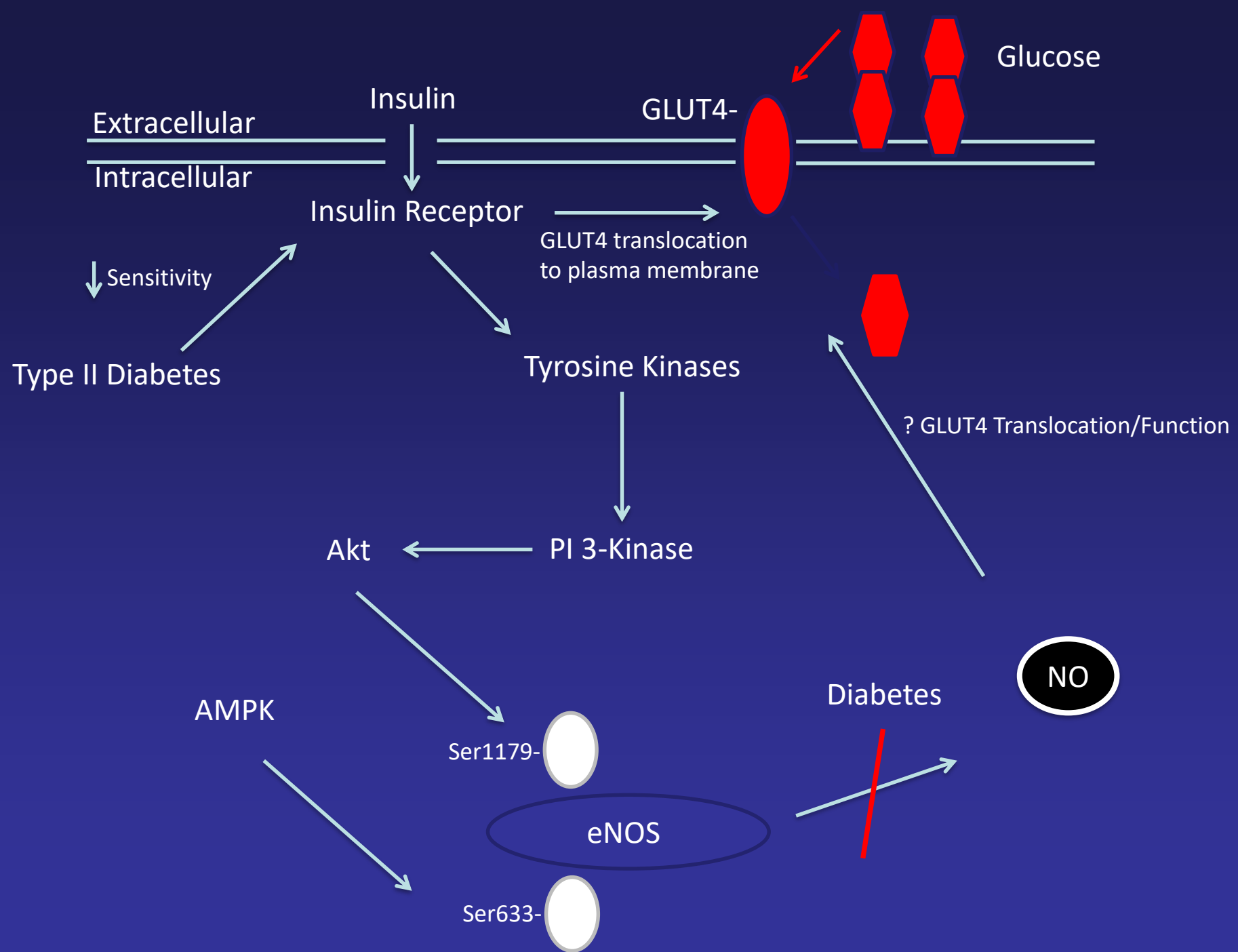
Dietary nitrate improves glucose tolerance and reduces fasting blood glucose in eNOS-deficient mice.



Effects of dietary nitrate on blood pressure.

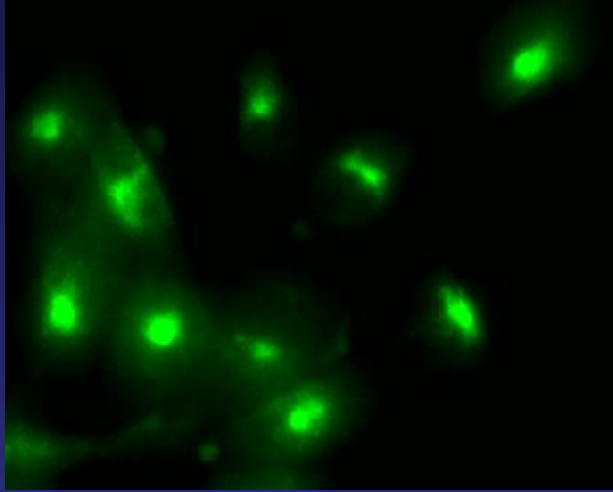
water (control) or water supplemented with sodium nitrate ($0.1 \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) for 8 wk.



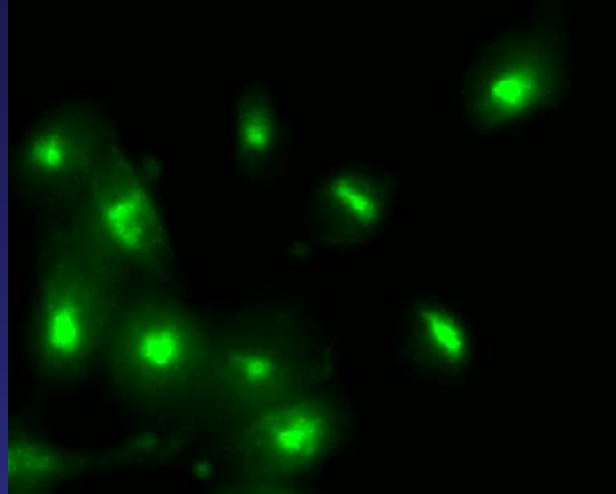


Control

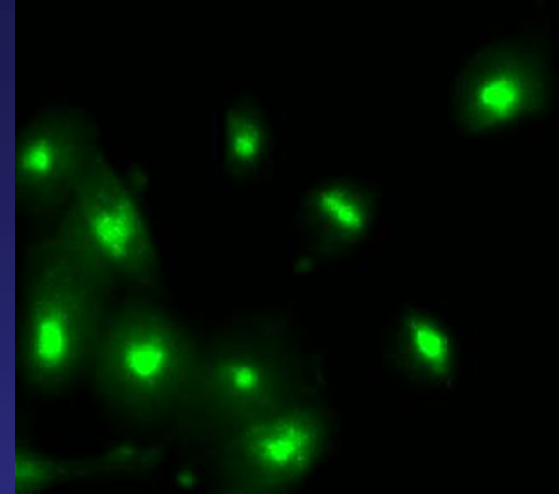
0 min



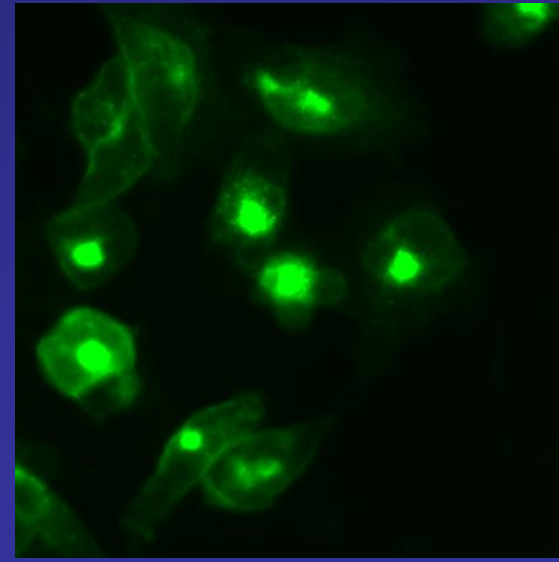
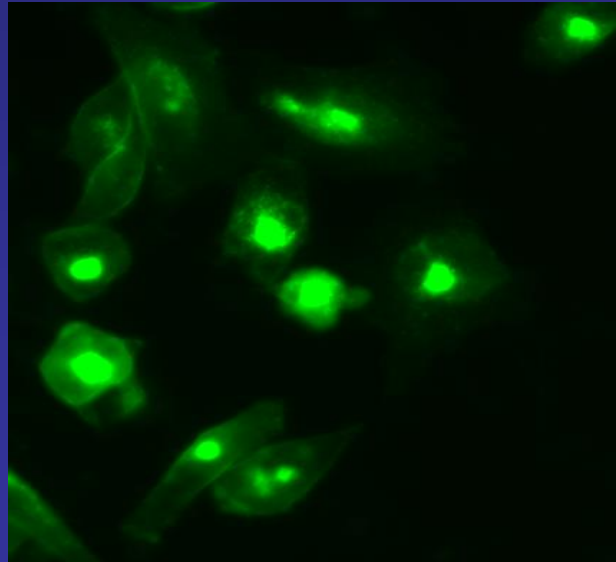
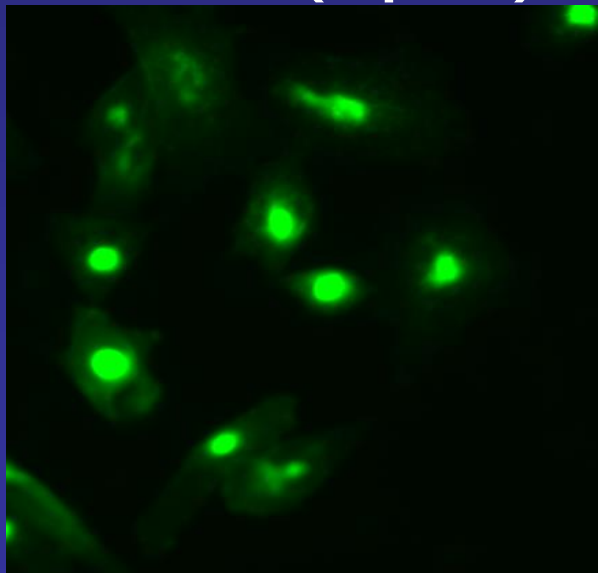
10 min

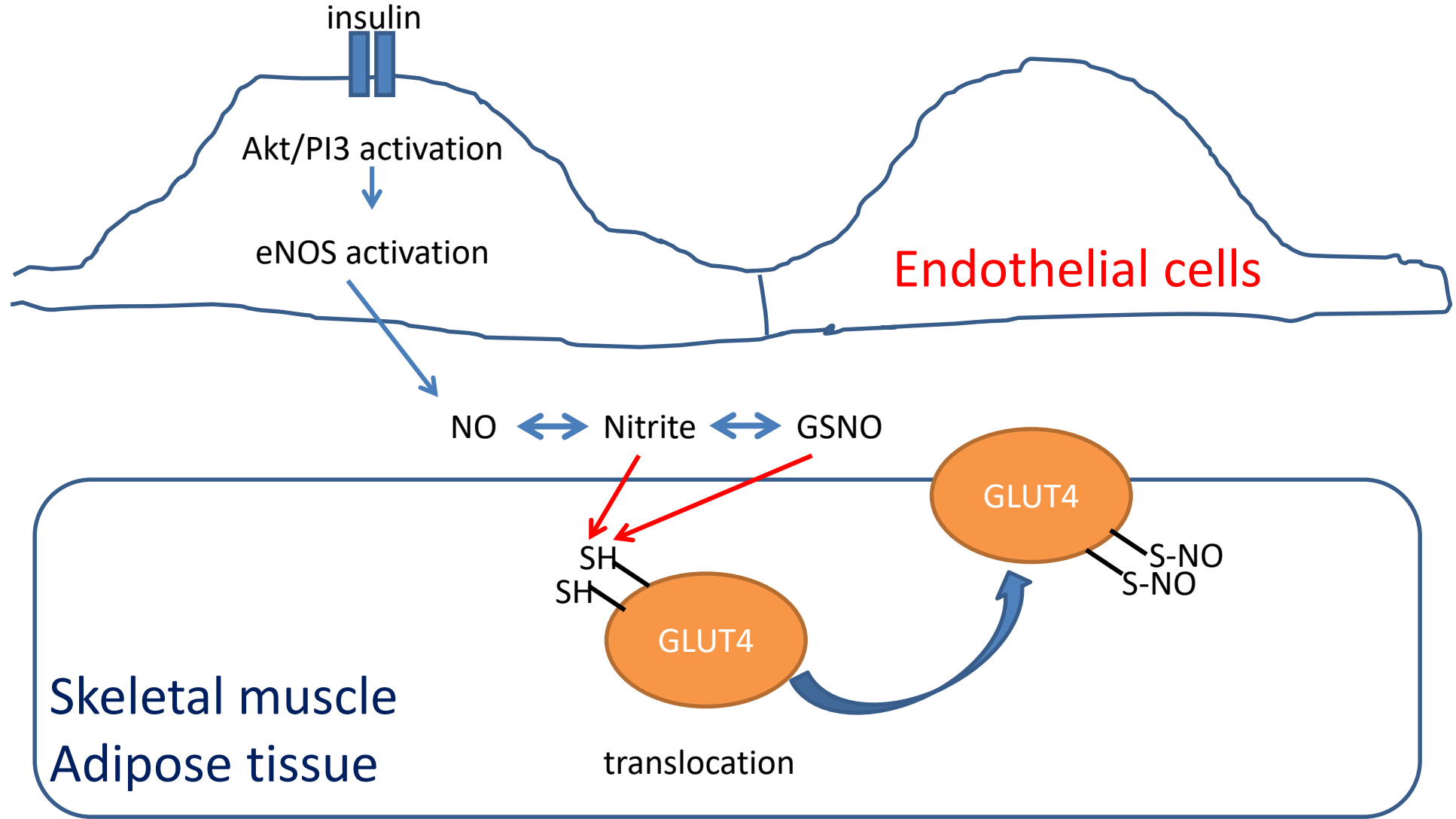


30 min



GSNO (1 μ M)



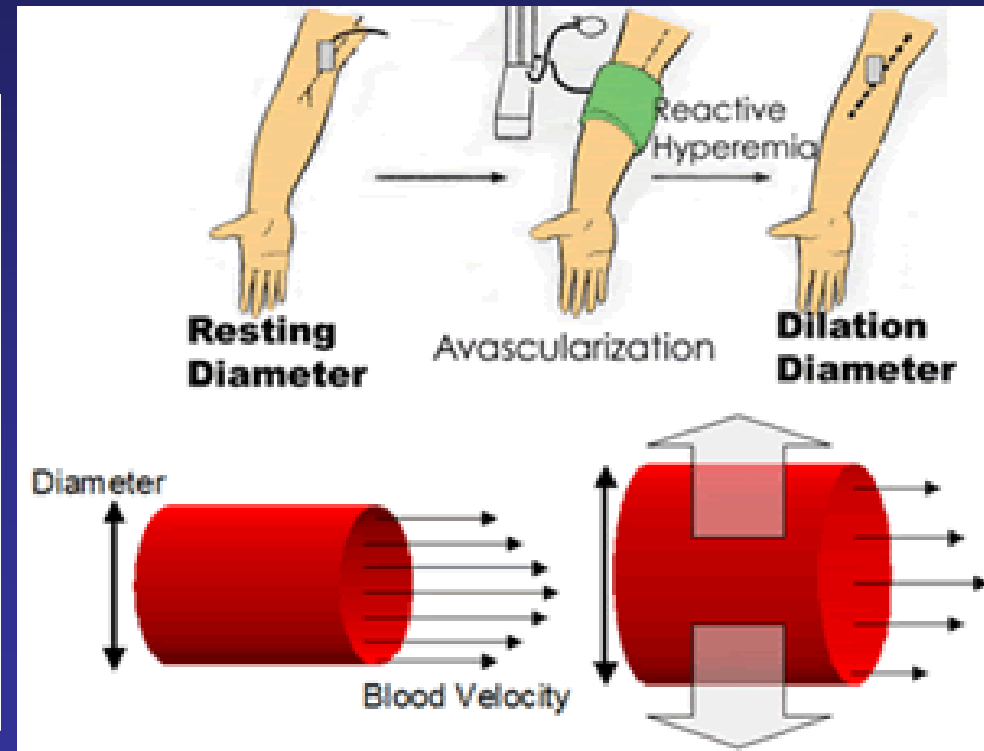
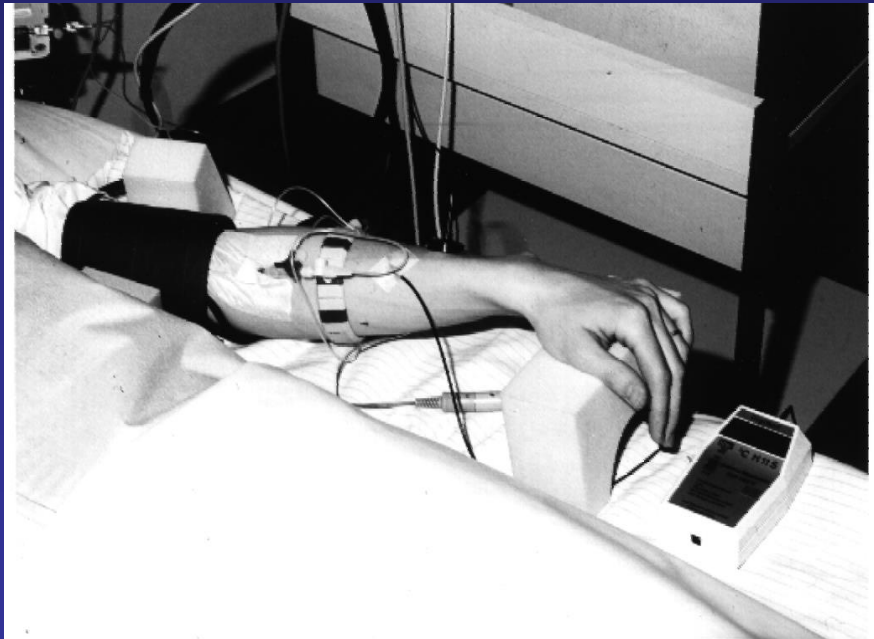


Disruption of Nitrate-Nitrite-NO Pathway That May Contribute to ED

1. Insufficient dietary intake of nitrate/nitrite rich foods
(green leafy vegetables, beets, etc)
2. Problems with nitrate uptake in duodenum
(sialin (SLC17A5) transporter mutations – Salla Disease)
3. Insufficient saliva production
(Sjogrens syndrome, parotidectomy)
4. Lack of oral commensal bacteria to reduce nitrate to nitrite
(use of antibiotics/antiseptic mouthwash, poor oral hygiene)
5. Insufficient stomach acid production – Achlorhydria
(use of PPI's, H. Pylori infection, iron overload)
6. Increased oxidative stress that scavenges NO

NO Diagnostics

Flow Mediated Dilatation for Endothelial Function

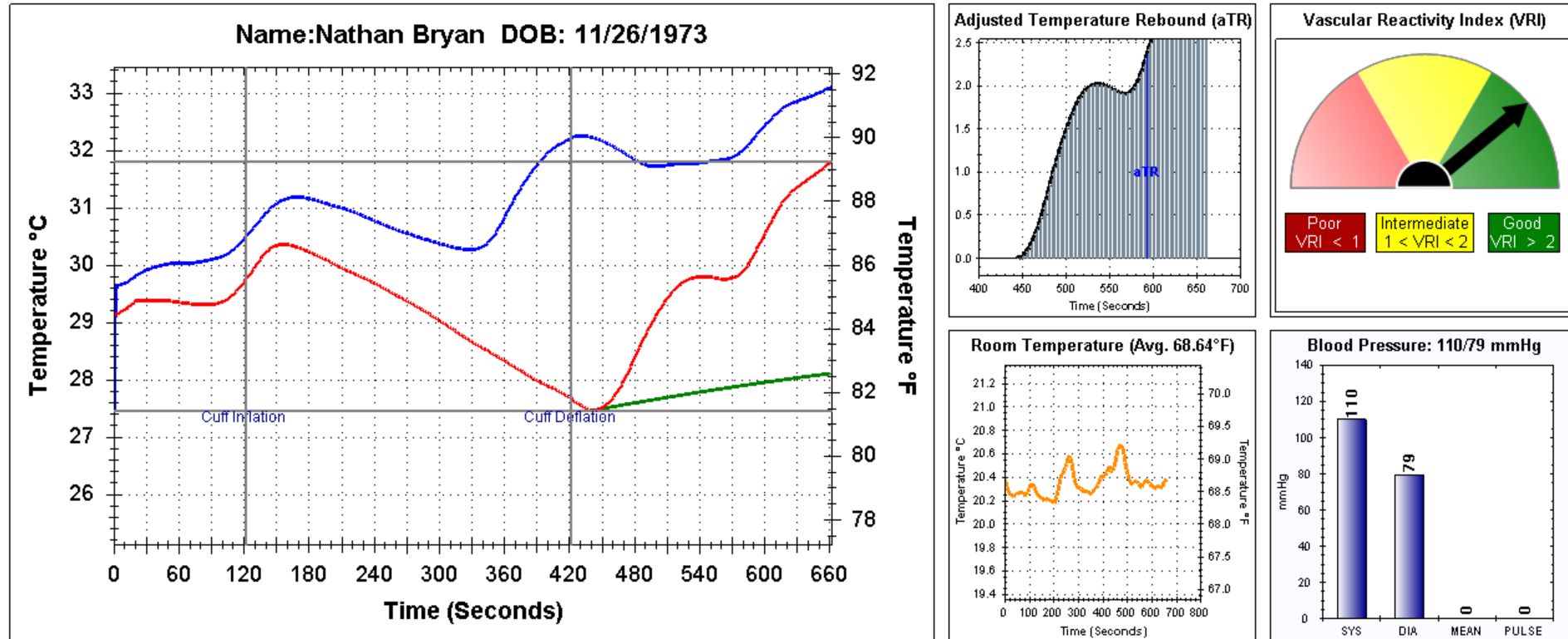


VENDYS®

Vascular Function Test

Digital Thermal Monitoring of Endothelial Function and Vascular Reactivity

— Right Finger Temperature — Left Finger Temperature — Zero Reactivity Curve



Quality Check:

Cold Finger	✓
Sympathetic Response	✓
Stabilization	✓
Finger Room Delta	✓
Cold Room	✗
Fluctuating Room Temp	✓
Right vs Left	✓

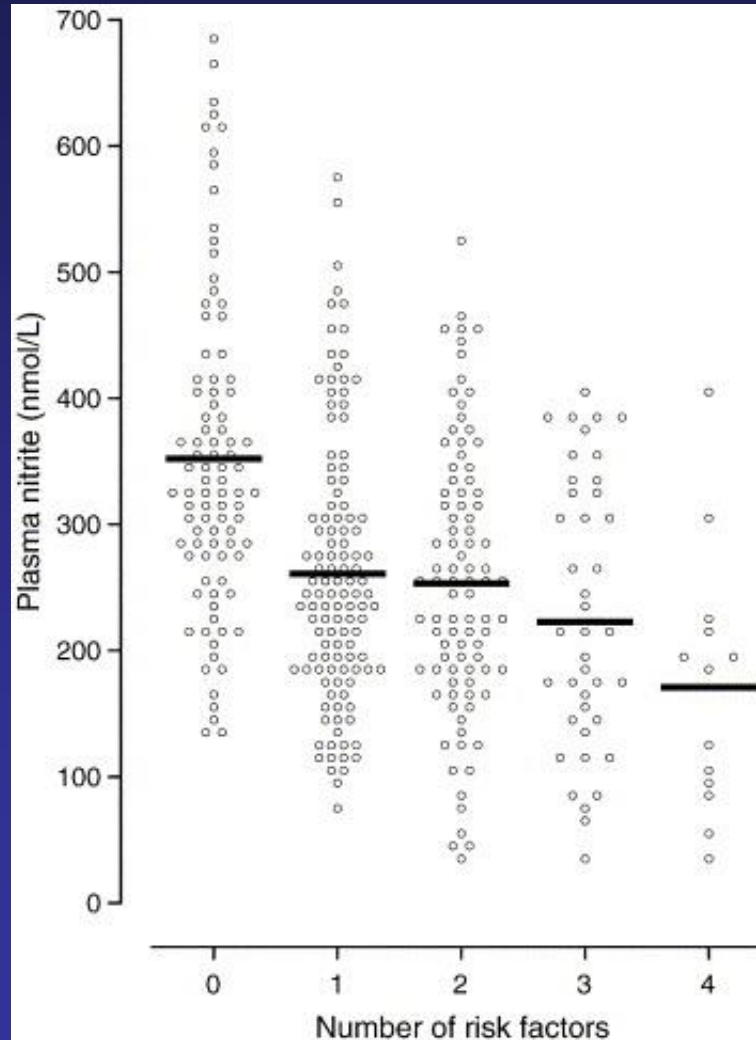
*Note: Cold Finger Flag check was disabled.

Vascular Reactivity Index
VRI = 2.34

ENDTHELIX

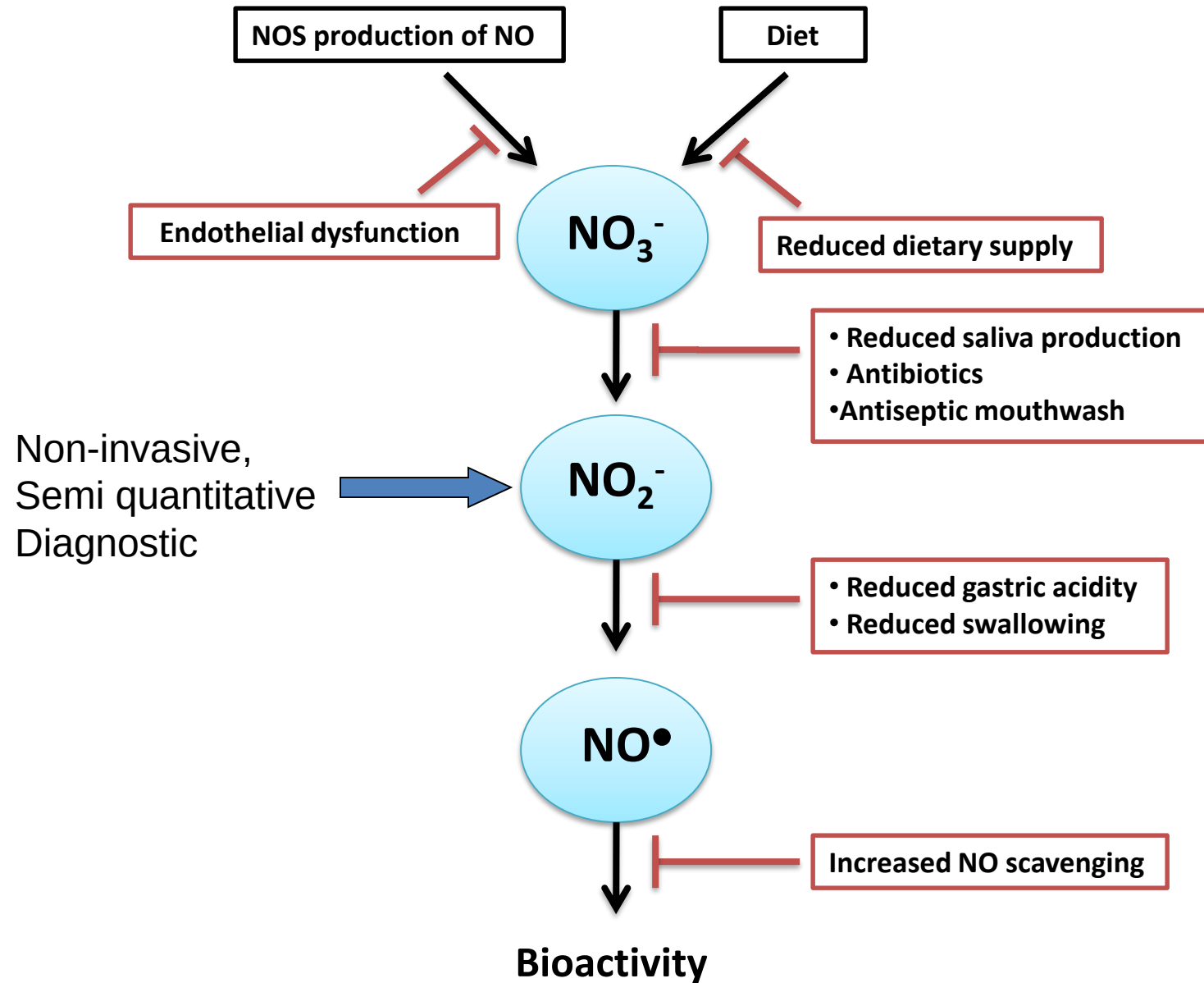
Test Date:
4/26/2014 1:04:56 PM

Plasma nitrite concentrations reflect the degree of endothelial dysfunction in humans.



RISK FACTORS
Hyperlipidemia
Arterial hypertension
Smoking
Age (45 males: 55 females)

Sampling Salivary Nitrite as a Biomarker for Total Body NO Availability



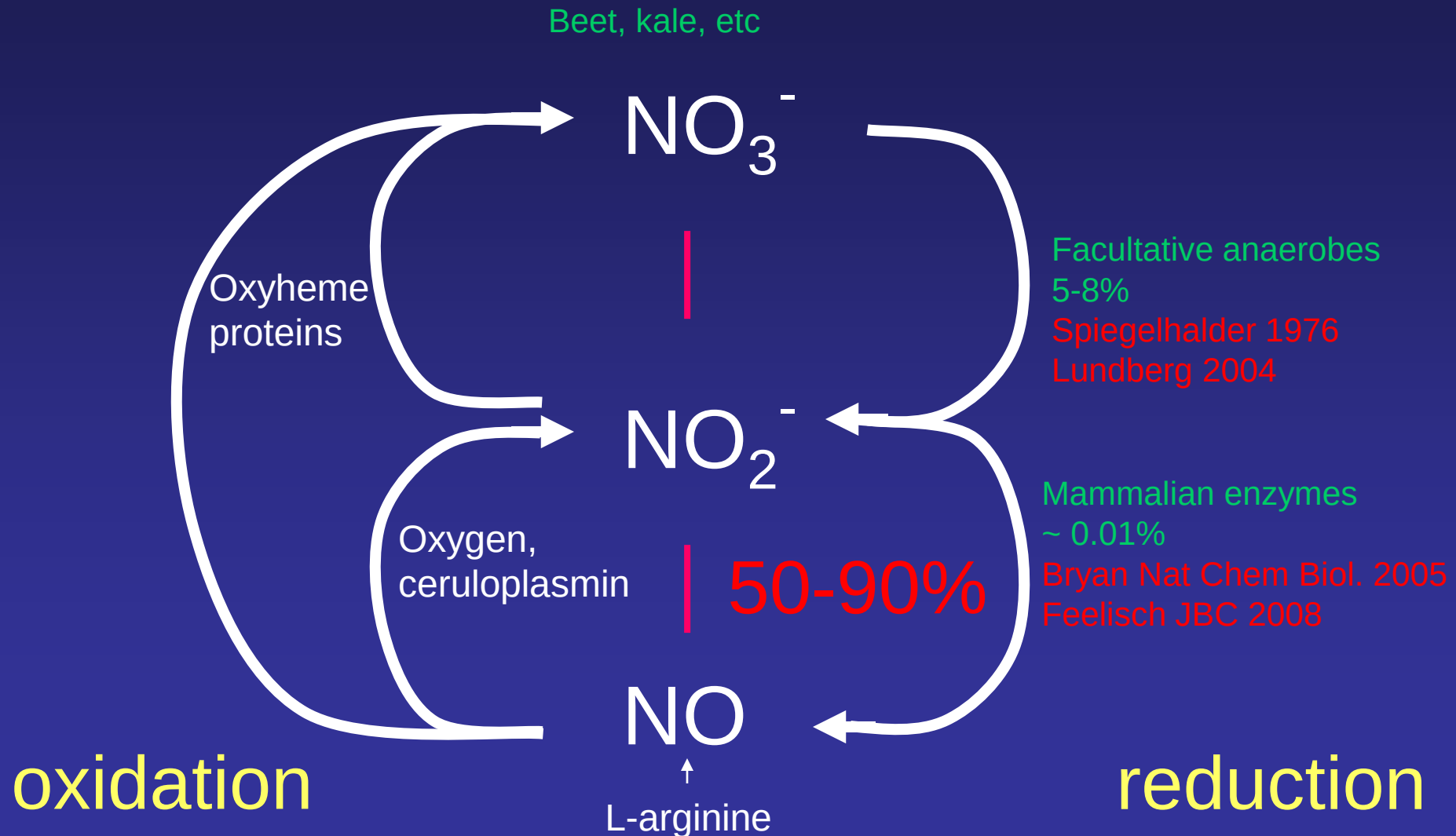
The First and Only Non-invasive NO Diagnostic

Simple to use
Instant, easy-to-read results



So then how do we develop a safe,
efficacious and consistent NO-based
therapy?

Manipulating the NO System Through Diet and Nutrition



Lowering blood pressure by 5 mmHg
reduces risk of stroke by 34% and
Ischemic heart disease by 21%

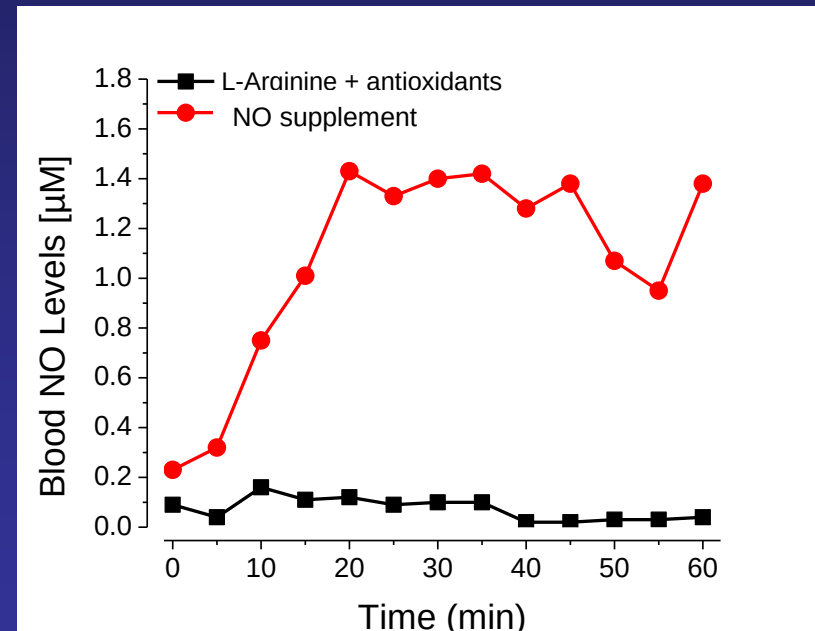
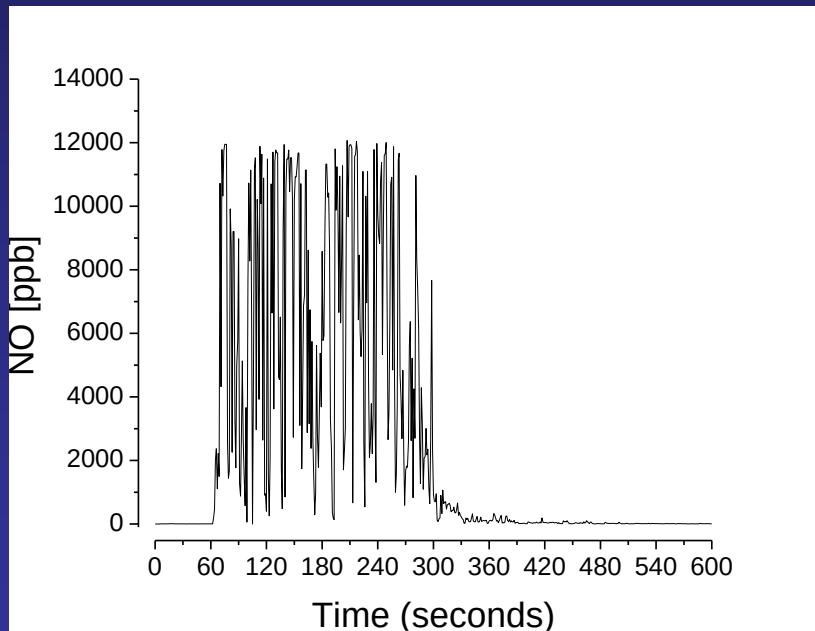
Health Technol Assess. 2003;7(31):1-94.

Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.

Law M, Wald N, Morris J.

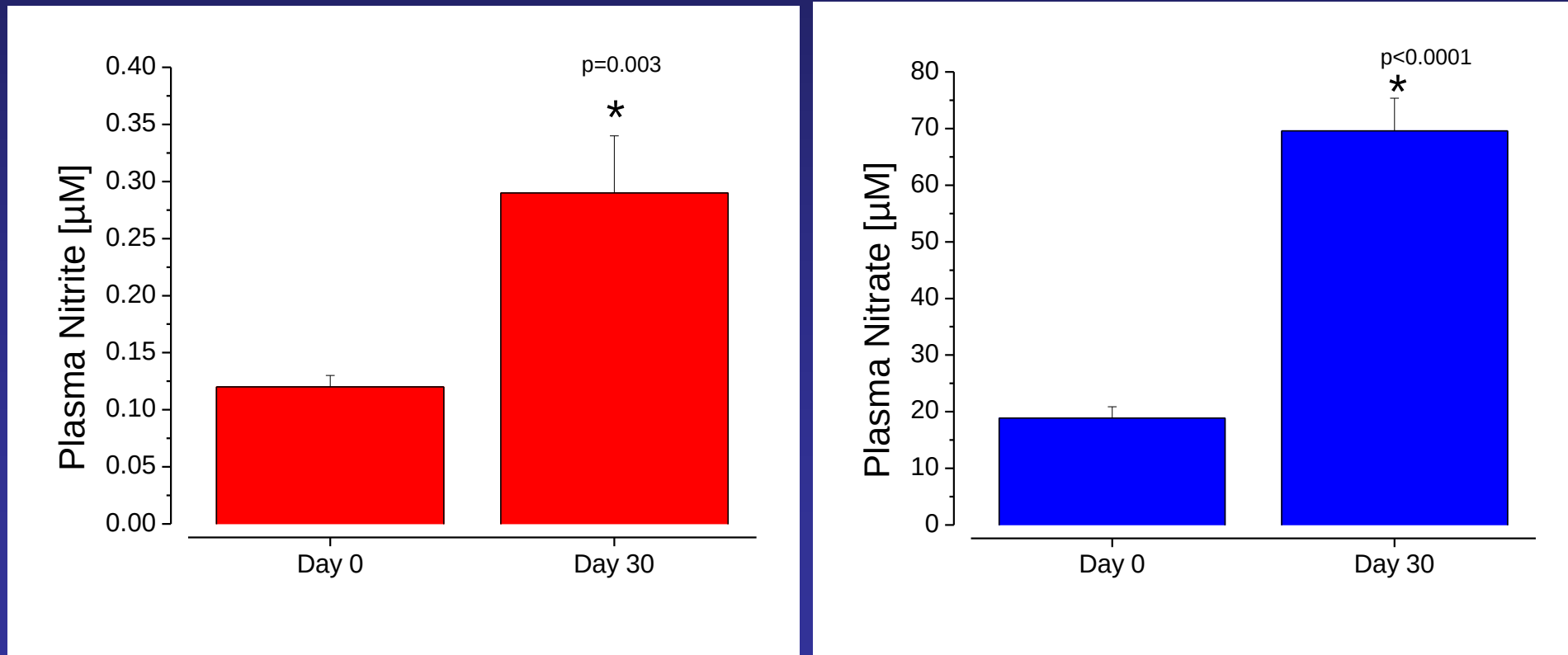
NO Supplement Clinical Trial Results

Strong & sustained Nitric Oxide activity



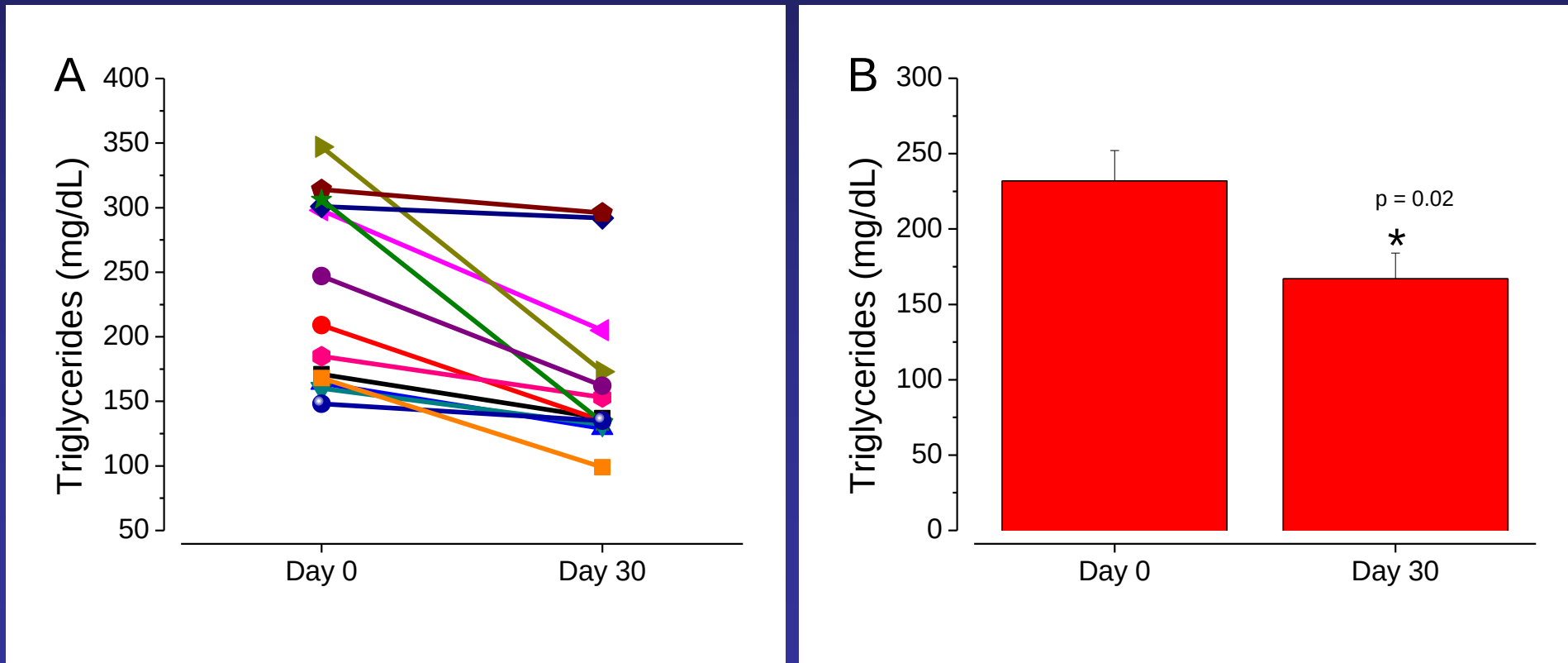
NO Supplement Clinical Trial Results

30-day regimen increased
plasma nitrite and nitrate in patients



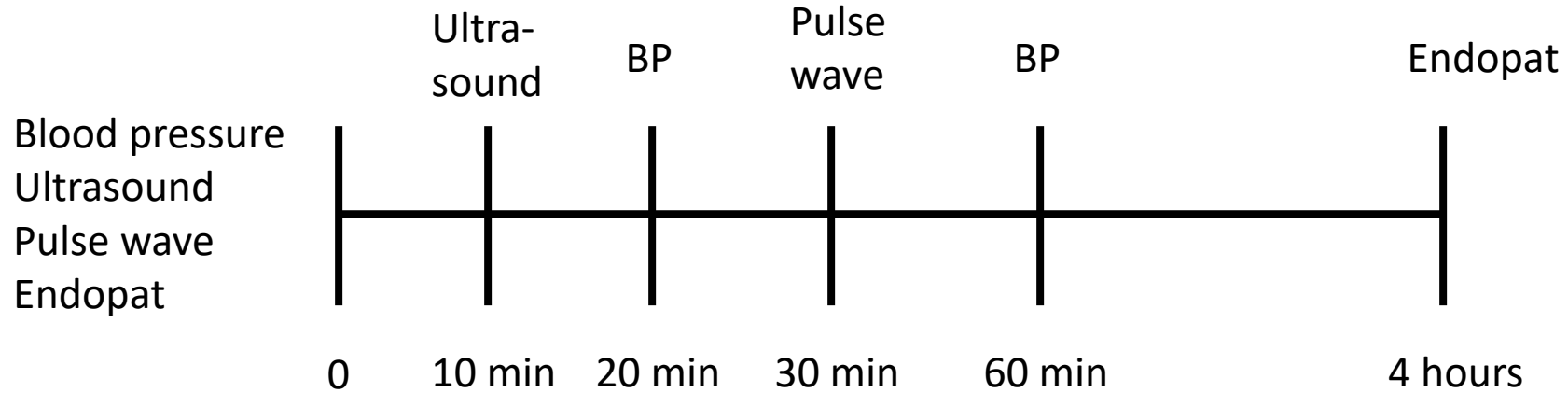
NO Supplement Clinical Trial Results

Significant reduction in patients
with elevated triglycerides



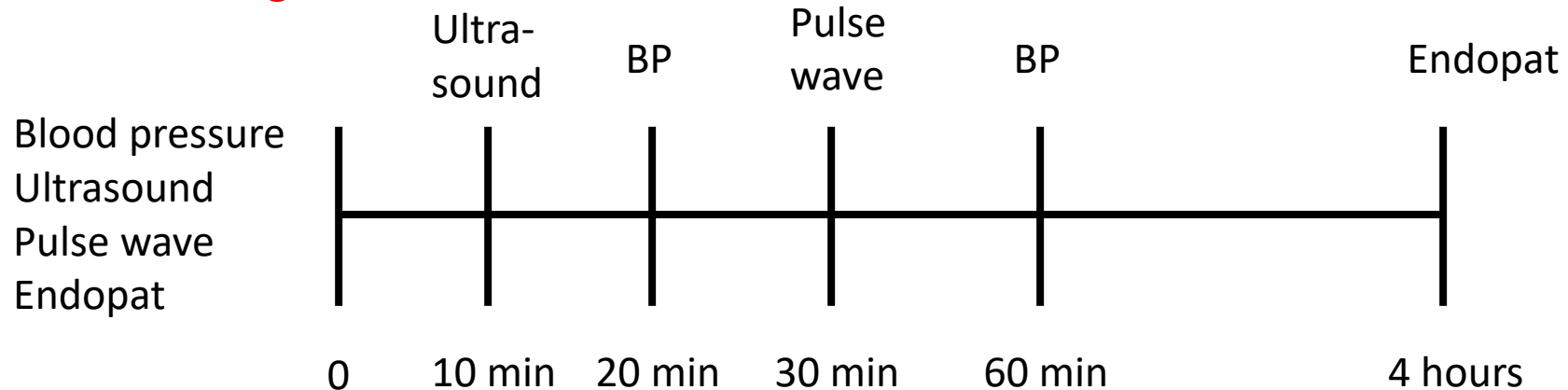
Hypertension Study Protocol

Active lozenge

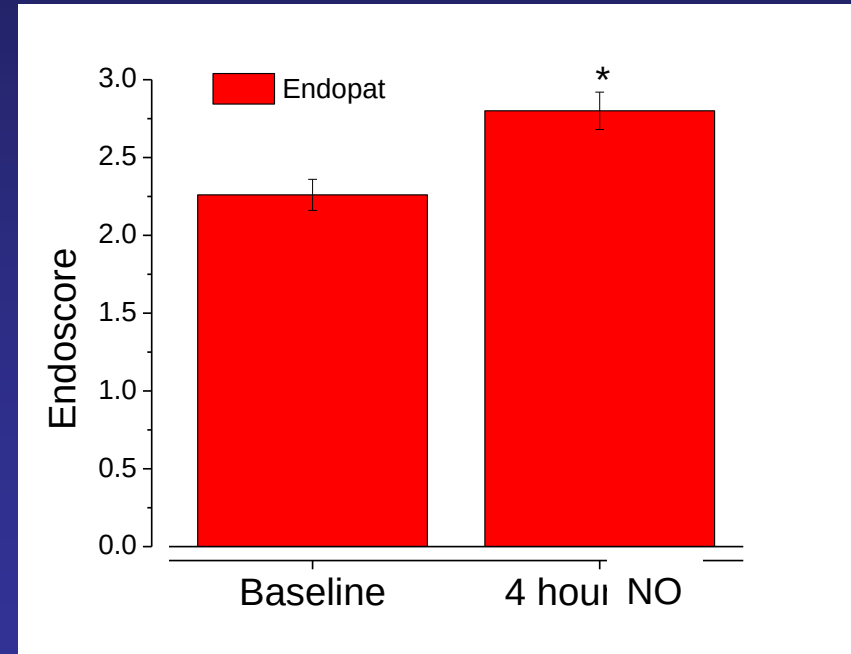
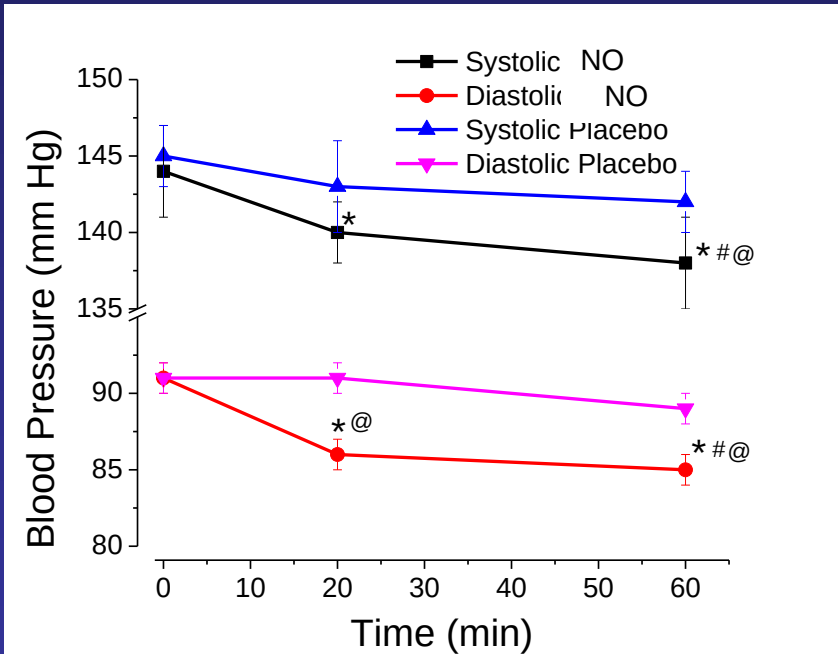


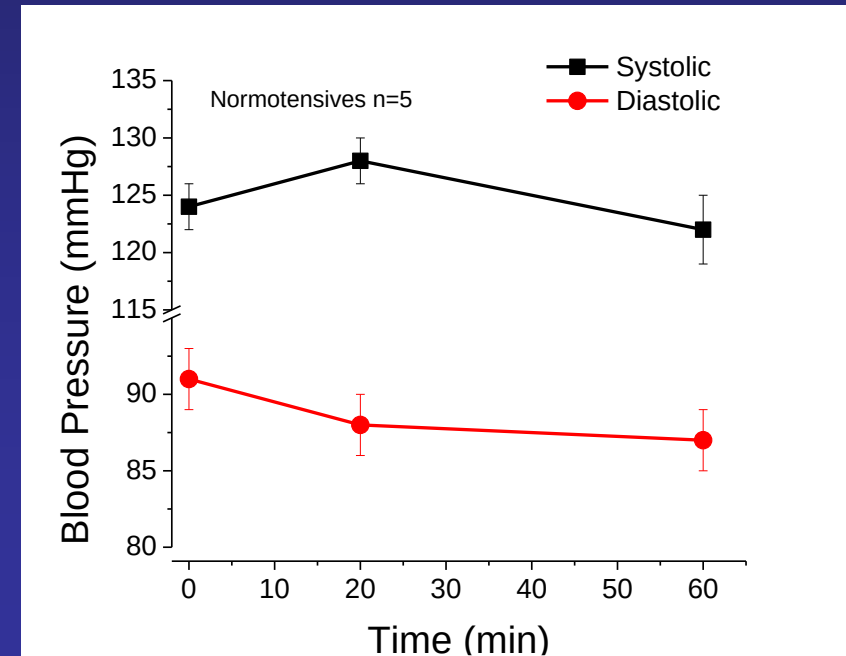
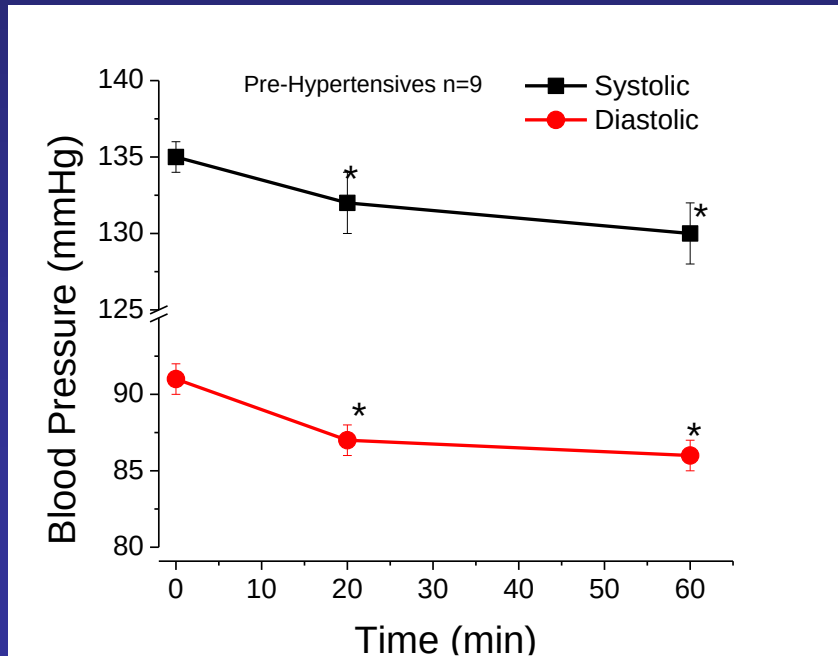
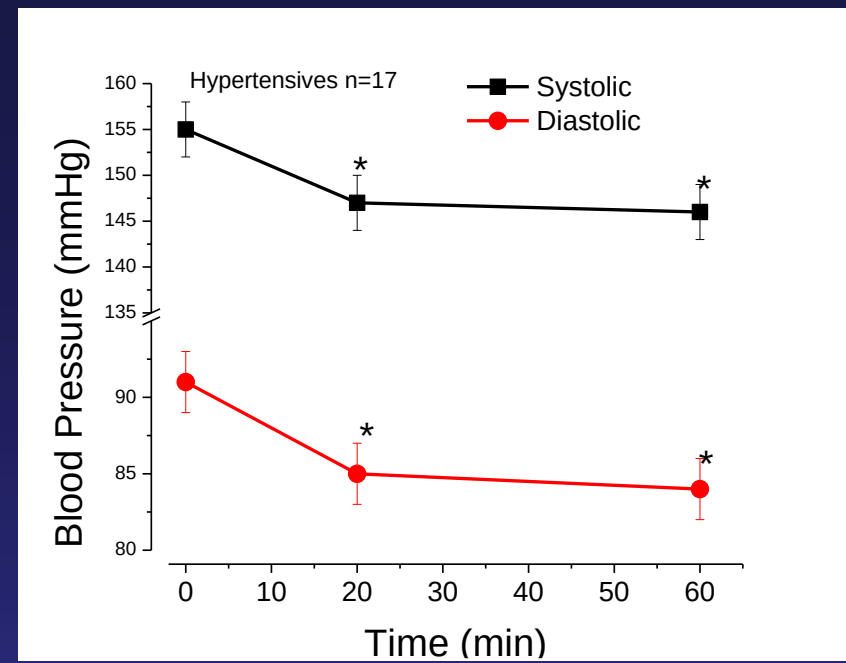
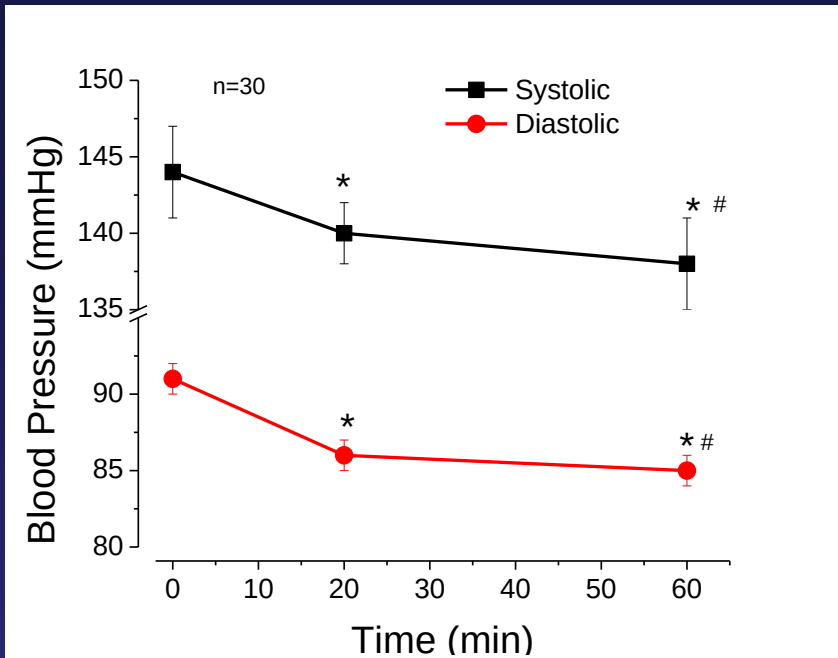
3 week washout

Placebo lozenge

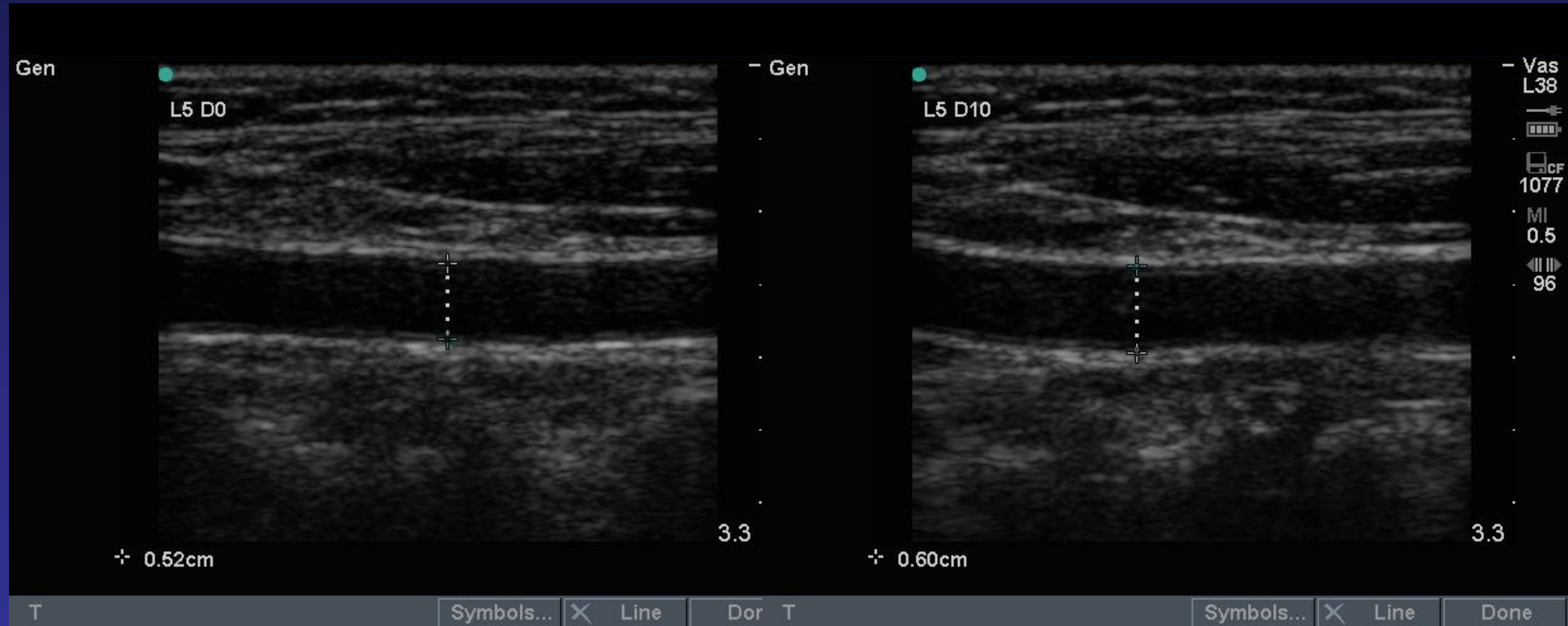


Hypertension Trial – Vanderbilt Univ



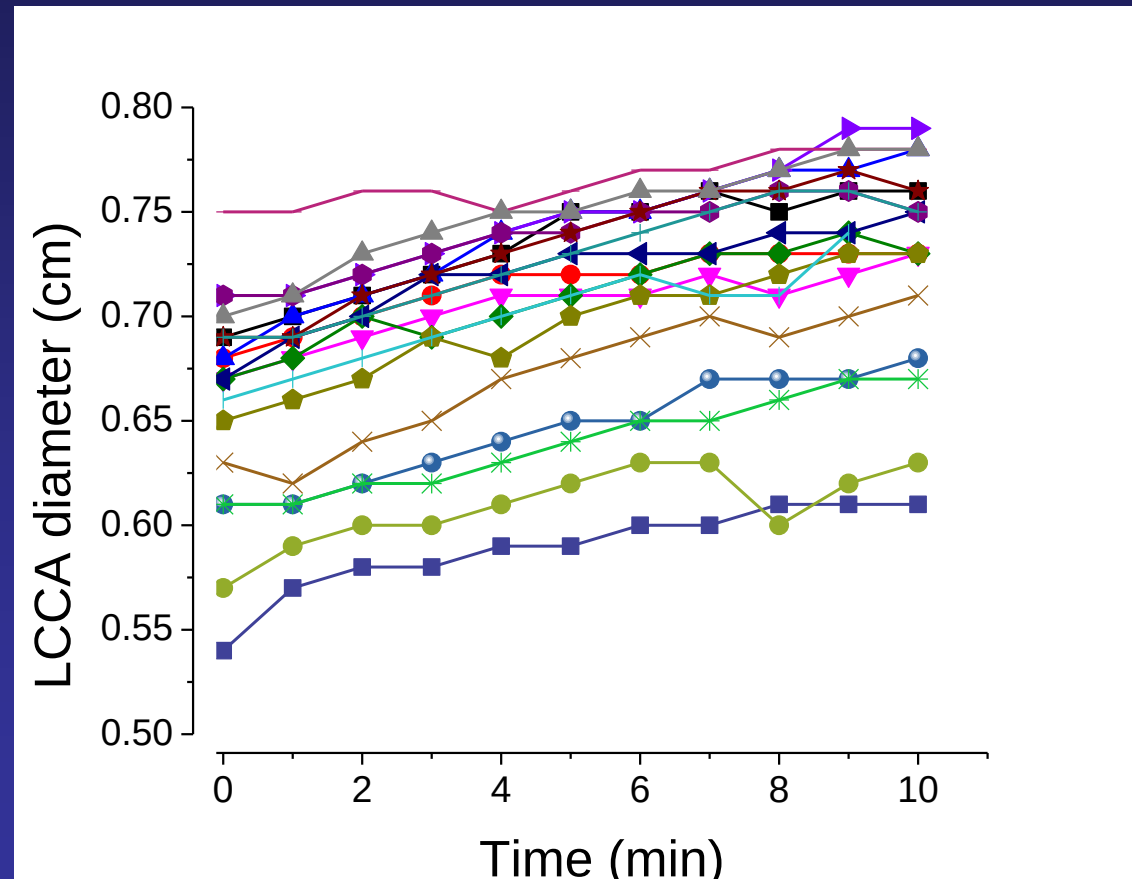


Representative Ultrasound Before and 10 minutes after NO Supplement



13% increase in vessel diameter causes
a 34% increase in blood flow

NO Supplement Dilates Carotid Artery within 90 Seconds



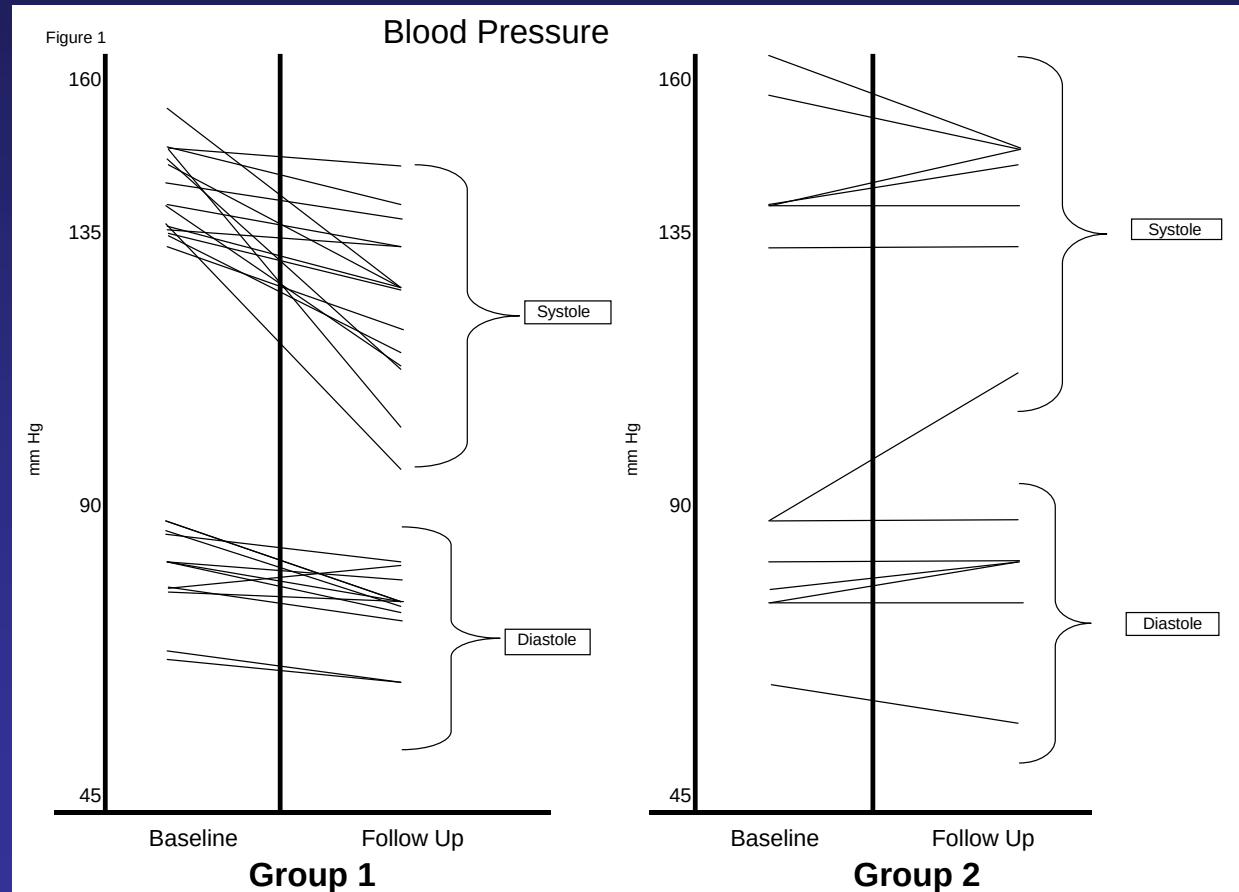
Average Changes after 30 minutes

Table 1: Vascular Compliance before and after treatment

	Baseline	After NO lozenge	p value
Mean Arterial Pressure (mm Hg)	114 ± 3	108 ± 3	0.003
Heart rate (beats per min)	77.4 ± 2.4	76.2 ± 2.0	0.26
Pulse Pressure (mm Hg)	44 ± 3	38 ± 2	0.007
Central Systolic Pressure (mm Hg)	127 ± 3	122 ± 3	0.01
Central Diastolic Pressure (mm Hg)	95 ± 2	94 ± 3	0.25
Central Pulse Pressure (mm Hg)	31.4 ± 1.9	28.7 ± 1.6	0.07
Cardiac Output (L/min)	5.4 ± 0.2	5.1 ± 0.2	0.07
Total Vascular Resistance	1.3 ± 0.03	1.3 ± 0.03	0.65
Augmentation Pressure (mm Hg)	6.2 ± 0.8	4.3 ± 0.6	0.02
Augmentation Index@75	21.2 ± 2.5	15.4 ± 1.7	0.01
Pulse Wave Velocity (m/s)	8.6 ± 0.4	8.3 ± 0.4	0.005

Pre-hypertension trial
Cedars Sinai Medical Center
PI: Ernst Schwarz MD, PhD

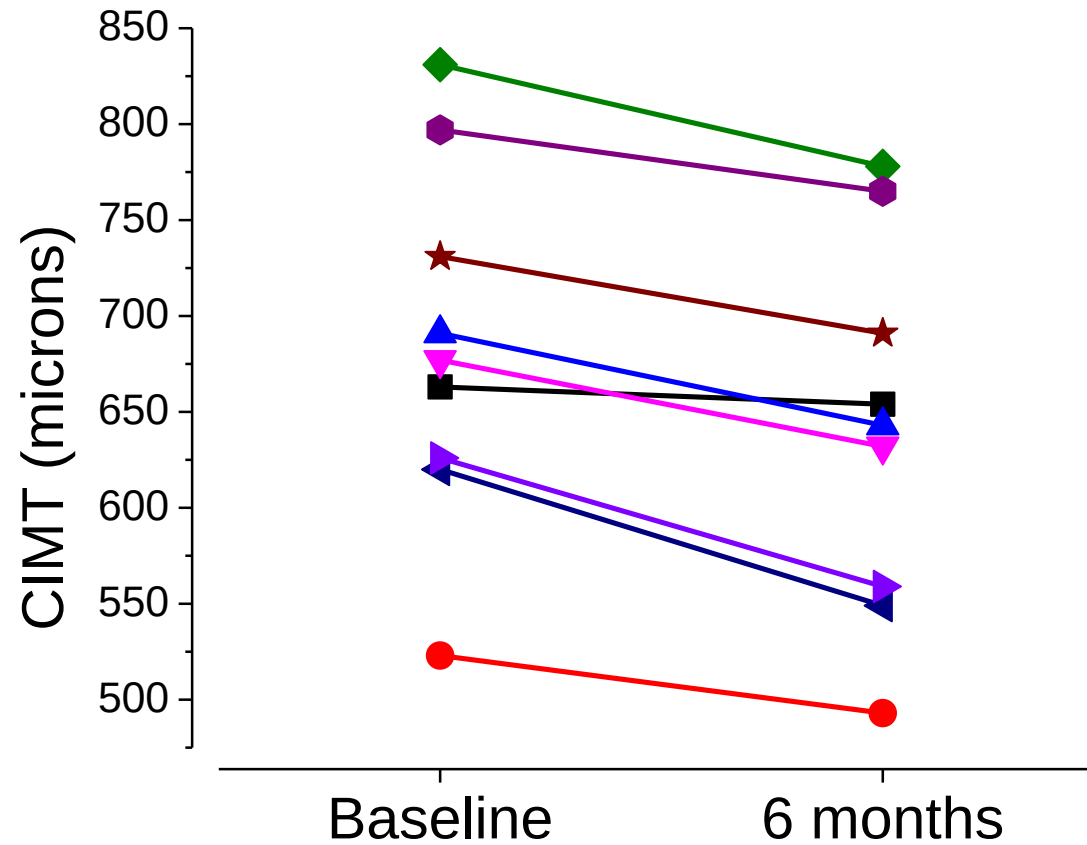
Pre-Hypertension Trial – Cedars Sinai School of Medicine



30 Day Placebo controlled Trial

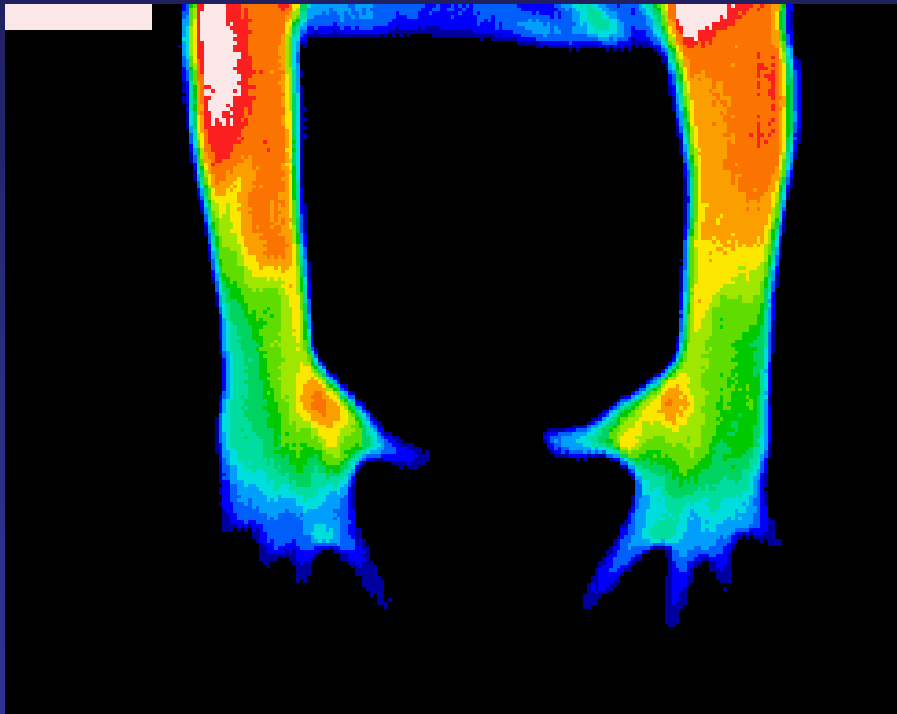
	Group 1 (mean ± SD)			Group 2 (mean ± SD)			Baseline: NO vs placebo (p-value)	Follow- Up: NO vs placebo (p-value)
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
BP (mmHg, systole; diastole)	138±12; 84±5	126±12; 78±4	12; 6 reduction (p<0.001)	138±21; 80±8	135±17; 82±8	N.S.	0.19; 0.012	0.26; 0.25
Heart Rate (bpm)	75±9	76±8	N.S.	80±10	79±8	N.S.	0.14	0.33
6-Minute Walk Test (meters)	596±214	650±197	55 improvement (p<0.005)	590±8	606±225	N.S.	0.25	0.35
SF-36v2 (PCS; MCS)	48±10; 40±9	50±8; 45±7	p<0.05	43±10; 37±9	37±11; 37±7	significant worsening (p<0.05)	0.08; 0.06	0.08; 0.03

NO Supplement Leads to Plaque Regression

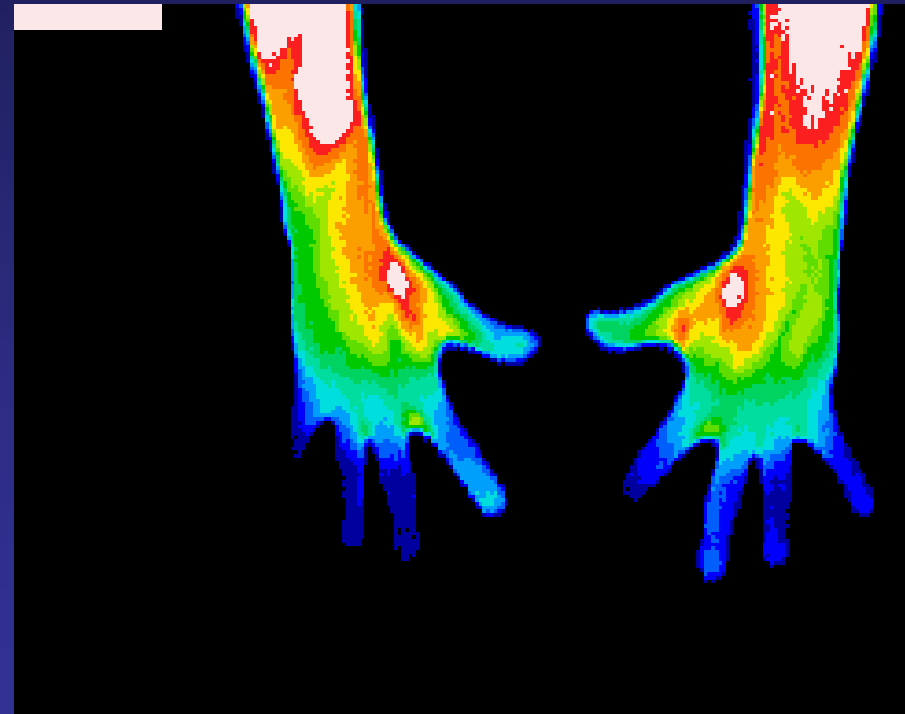


Thermographic Images

Before NO

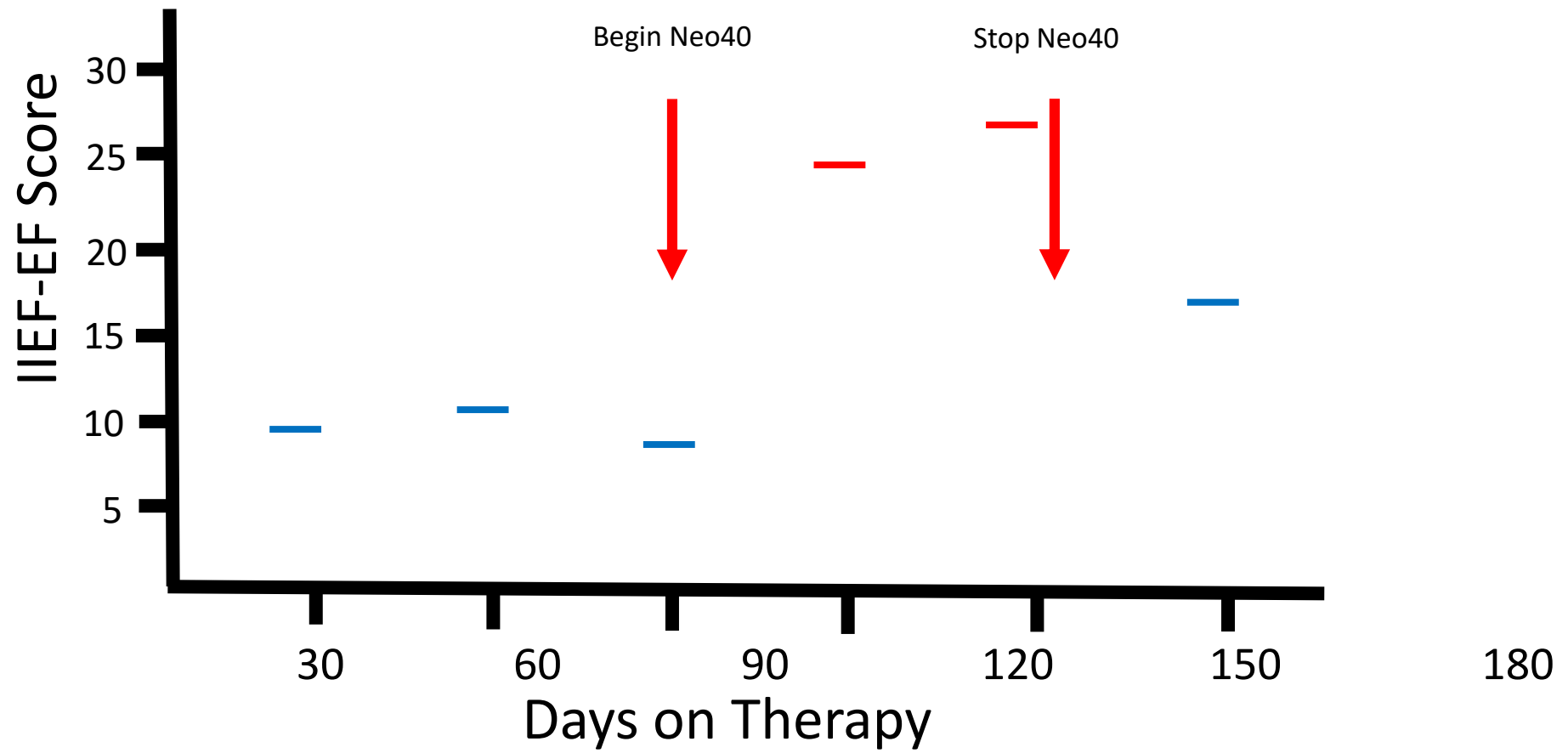


10 min After NO



49 yof smoker with Reynaud's Syndrome

Combination with PD5 Inhibitors



Important Considerations for Nitrate-Based Technologies

1. All beets/vegetables are not created equal
 - growth conditions
 - time of harvest
 - processing, heat, packaging, etc.
2. Liquid products can de-stabilize NO
 - pH < 3 (acid labile components)
3. More is not better
 - safety first
4. Patients/consumers must have oral nitrate-reducing bacteria
5. Patients/consumers using PPI and antiseptic mouthwash will not respond

Important Considerations for L-Arginine/L-Citrulline-Based Technologies

1. Must have a functional NOS
 - most NO-deficient patients have dysfunctional NOS
 - must also have supporting co-factors to recouple NOS
2. L-arginine can activate Herpes virus
3. High dose L-arginine can do more harm than good
 - VINTAGE trial (Schulman JAMA 2006)
 - PAD trial (Wilson Circulation 2007)
4. There is not a single human disease caused by L-arginine deficiency

What are Patients Saying?

The first night after my very first dose, I had improved circulation in my hands. My spouse is now taking it and reports improved stamina and increased circulation as well. As a woman going through menopause, I find the increased circulation is a definite benefit in the bedroom.

- Cat S, Port Carling Ontario

I think that your product has been instrumental in bringing my BP in line. As a side effect, this product seems to improve sexual functioning dramatically.

-Larry Y., Saskatoon, SK

CONCLUSIONS

- There are profound effects of NO on health and disease
- Loss of NO production causes ED and subsequent onset and progression Of cardiovascular disease.
- L-arginine therapy is ineffective at restoring NO production in the older patients or patients with endothelial dysfunction
- Enhancing NO production in the oral cavity combats pathogenic bacteria, suppresses inflammation and supports cardiovascular integrity
- This may allow for dietary and nutritional strategies for restoring NO and amelioration of chronic disease

Nutrition and Health

Series Editor: Adrienne Bendich Ph.D., FACN

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Nitrite and Nitrate in Human Health and Disease

Nitrite and Nitrate in Human Health and Disease delivers a comprehensive review of nitrite and nitrate biology, from basic biochemistry to the complex physiology and metabolism of these two naturally occurring molecules in the human body. Well-organized and well referenced chapters cover the rich history of nitrite and nitrate, sources of exposure, and the physiological effects when consumed through foods containing nitrite and nitrate. The chapters are written by leading experts, all of whom share their research and perspectives in order to help define the context for benefits vs. any potential risks associated with nitrite and nitrate use, either through dietary ingestion or therapeutic dosing. This diverse collection of authors includes vascular biologists, physiologists, physicians, epidemiologists, cancer biologists, registered dietitians, chemists, and public health experts from five countries in both academia and government. *Nitrite and Nitrate in Human Health and Disease* provides a balanced view of nitric oxide biochemistry, and nitrite and nitrate biochemistry in physiology and in the food sciences.

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Nitrite and Nitrate in Human Health and Disease

 Humana Press

Questions?