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Texas

Friday, June 9, 2017 (Room 3)

14:00 - 14:55 WS #42: What is Nitric Oxide and Why Should You Care?

15:05 - 16:00 WS #54: What is Nitric Oxide and Why Should You Care? (Repeated)

What is Nitric Oxide and Why Should You Care?

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General Practice Conference and Medical Education
Rotorua, NZ – June 8-11, 2017

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

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

Objectives

- Provide an understanding of Nitric Oxide (NO) Biology
- The Role of NO in Inflammation and Hypertension
- Provide Evidenced Based Therapeutic Solutions to Safely and Effectively Restore NO Production

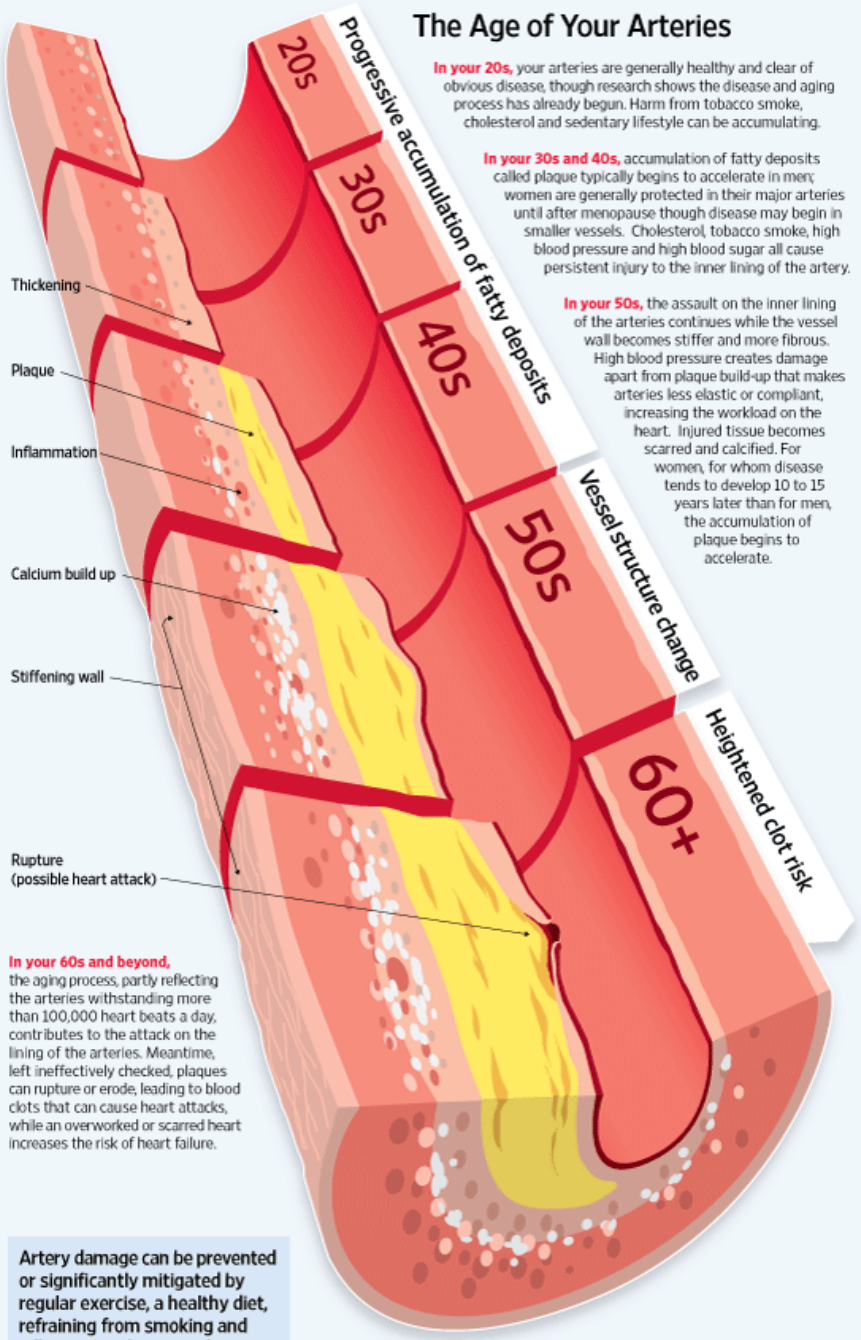
Who Needs Nitric Oxide Therapy?

Anyone who is aging
Anyone over the age of 40
People with circulation issues
Diabetics
People with low energy
People with sexual dysfunction or who desire improved performance in bedroom
Athletes wanting to improve performance
Anyone on antacids
Anyone interested in disease prevention

“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.

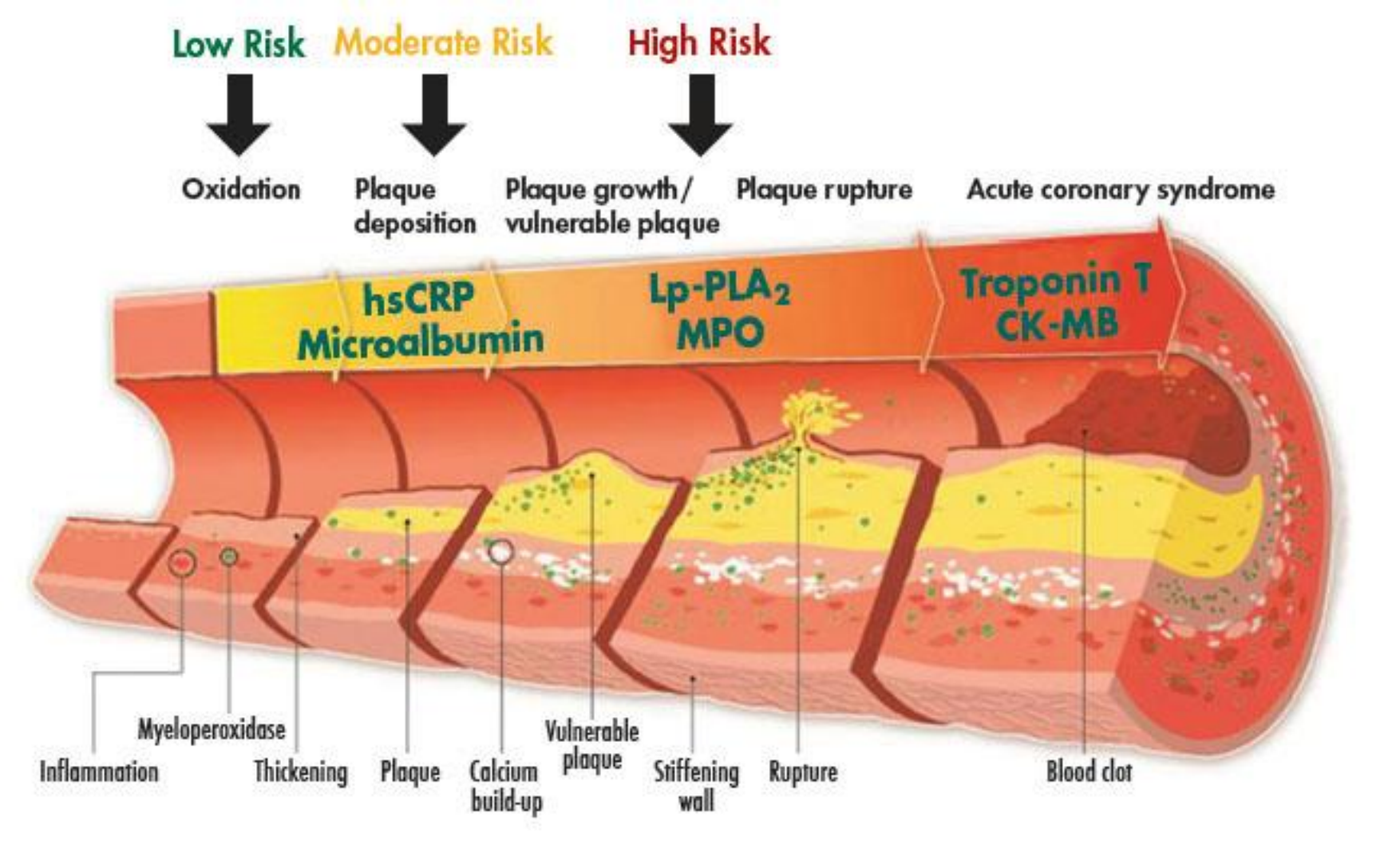
In your 50s, the assault on the inner lining of the arteries continues while the vessel wall becomes stiffer and more fibrous. High blood pressure creates damage apart from plaque build-up that makes arteries less elastic or compliant, increasing the workload on the heart. Injured tissue becomes scarred 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.

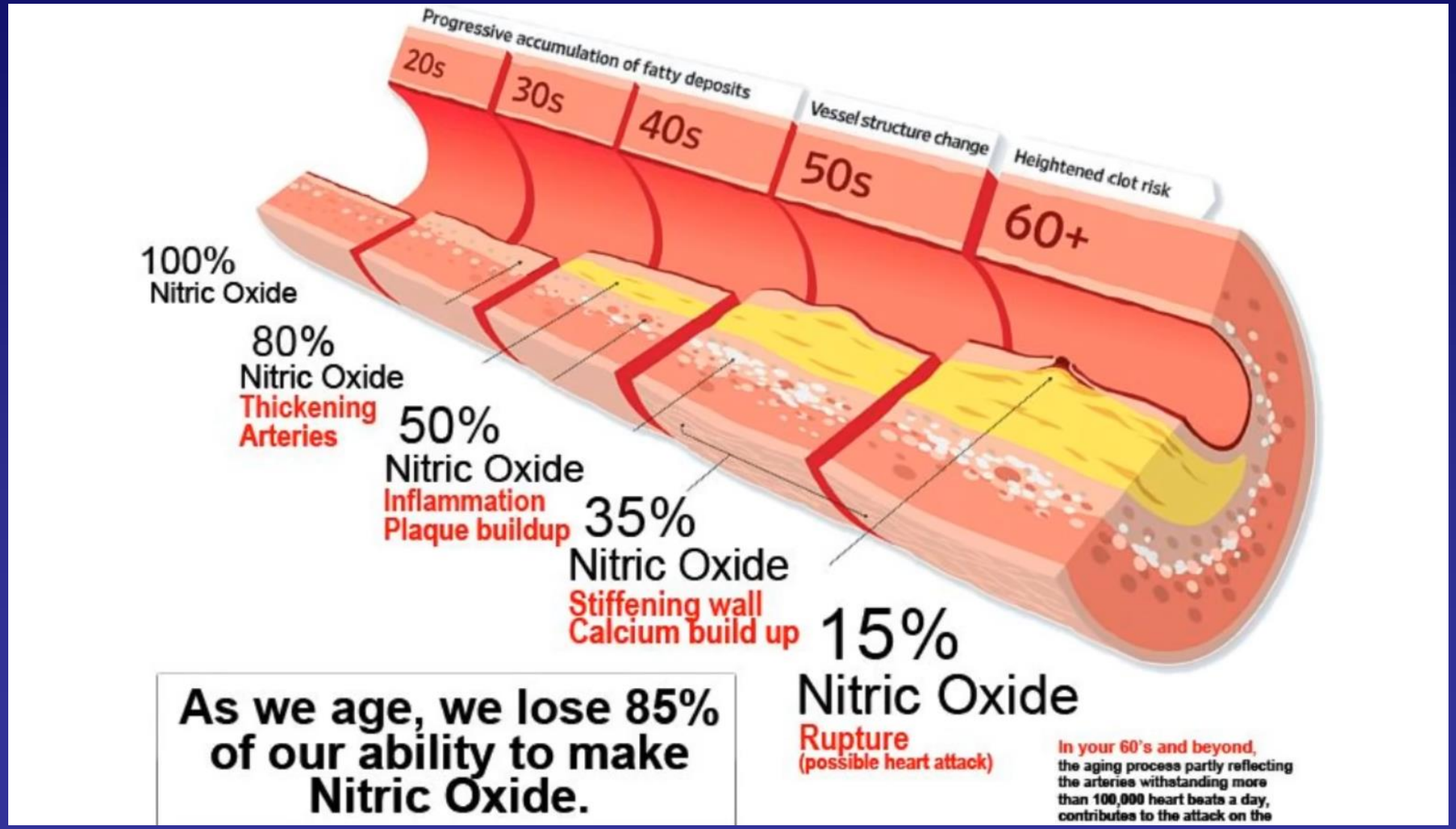
Artery damage can be prevented or significantly mitigated by regular exercise, a healthy diet, refraining from smoking and adherence to heart medicines.

Sources: Carl J. Pepine, University of Florida; WSJ reporting Illustration: Erik Brynildsen/The Wall Street Journal

Inflammatory Biomarkers Diagnostic For Different Stages of Vascular Disease



Loss of NO is Associated with Atherosclerosis



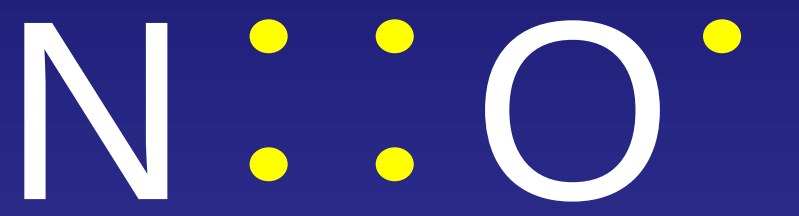
What Causes Arteries to Age?

1. Inflammation
2. Immune Dysfunction
3. Oxidative Stress

Safe and Effective NO Supplementation addresses these issues around arterial aging

How do we prevent, slow down
or reverse arterial aging?

Nitric Oxide



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

Immunology

Unspecific Immunity
Inhibition of Viral Replication
Transplant Rejection

Gastrointestinal/ Urogen

Peni
Pre-

Respiratory T

Bronchodila
Asthma, AF

Cell Pro

Apopt
Angiogenesis
Tumor Cell Growth

Central Nervous System

Learning and Memory
Pain Sensitization
Epilepsy
Neurodegeneration
Central BP Control

Regeneration

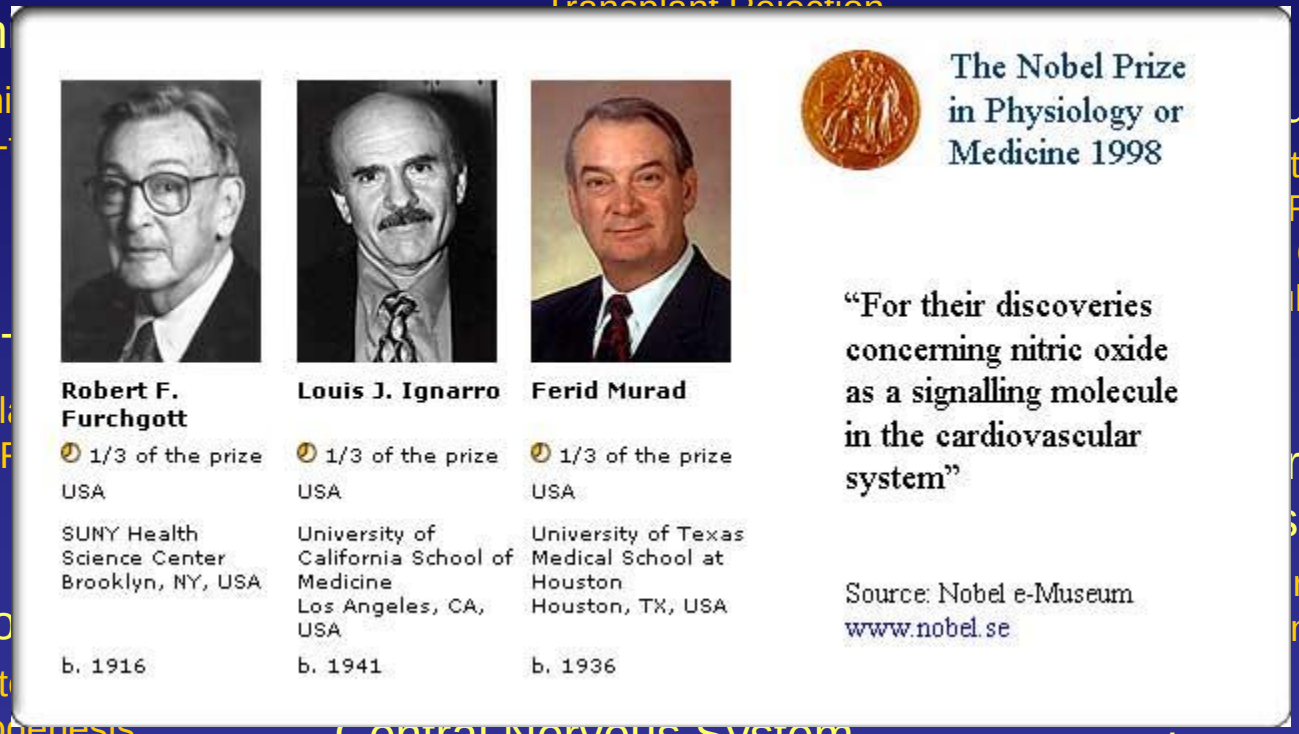
Mobilization of resident stem cells
Targeted differentiation

ular System

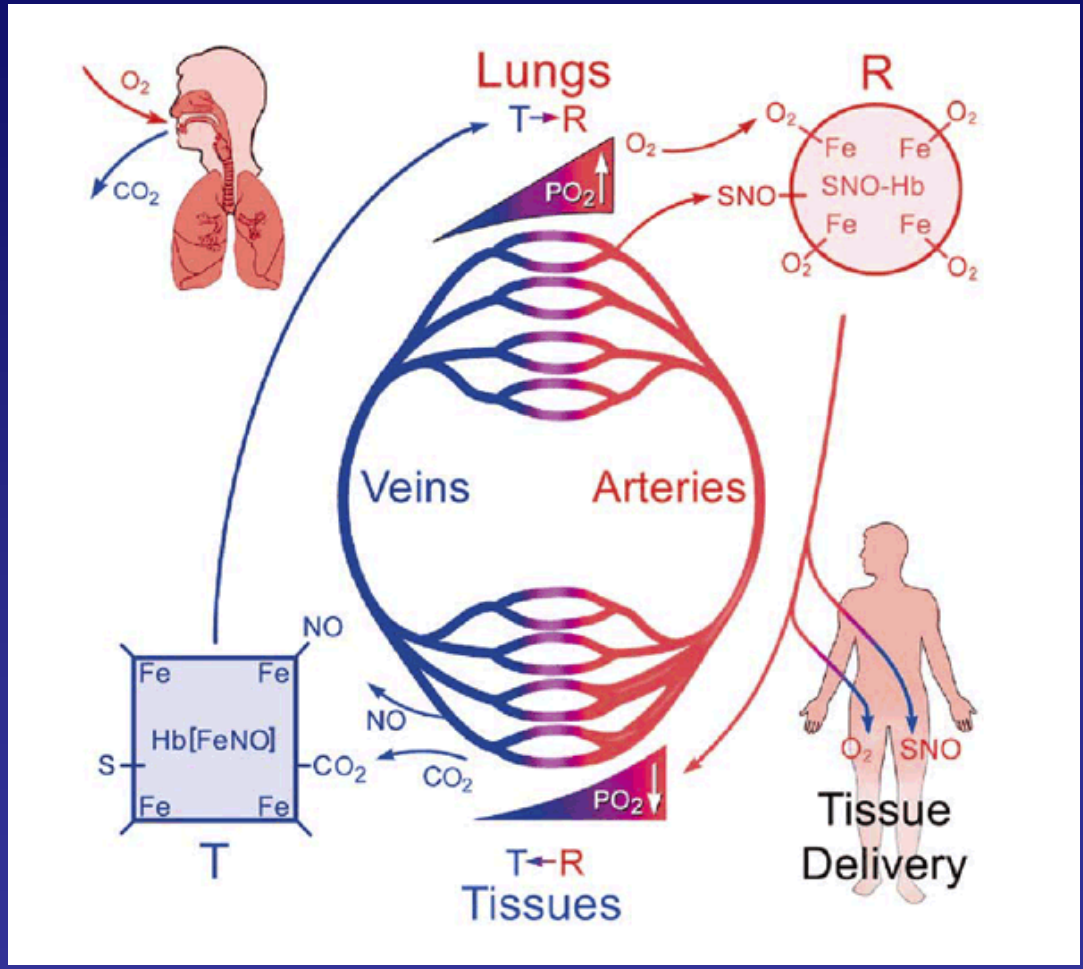
tion
Regulation
Contractility
lar Permeability

ral s System

rve-mediated
n



Nitric oxide is required for red blood cell delivery of oxygen from the lungs to tissue.

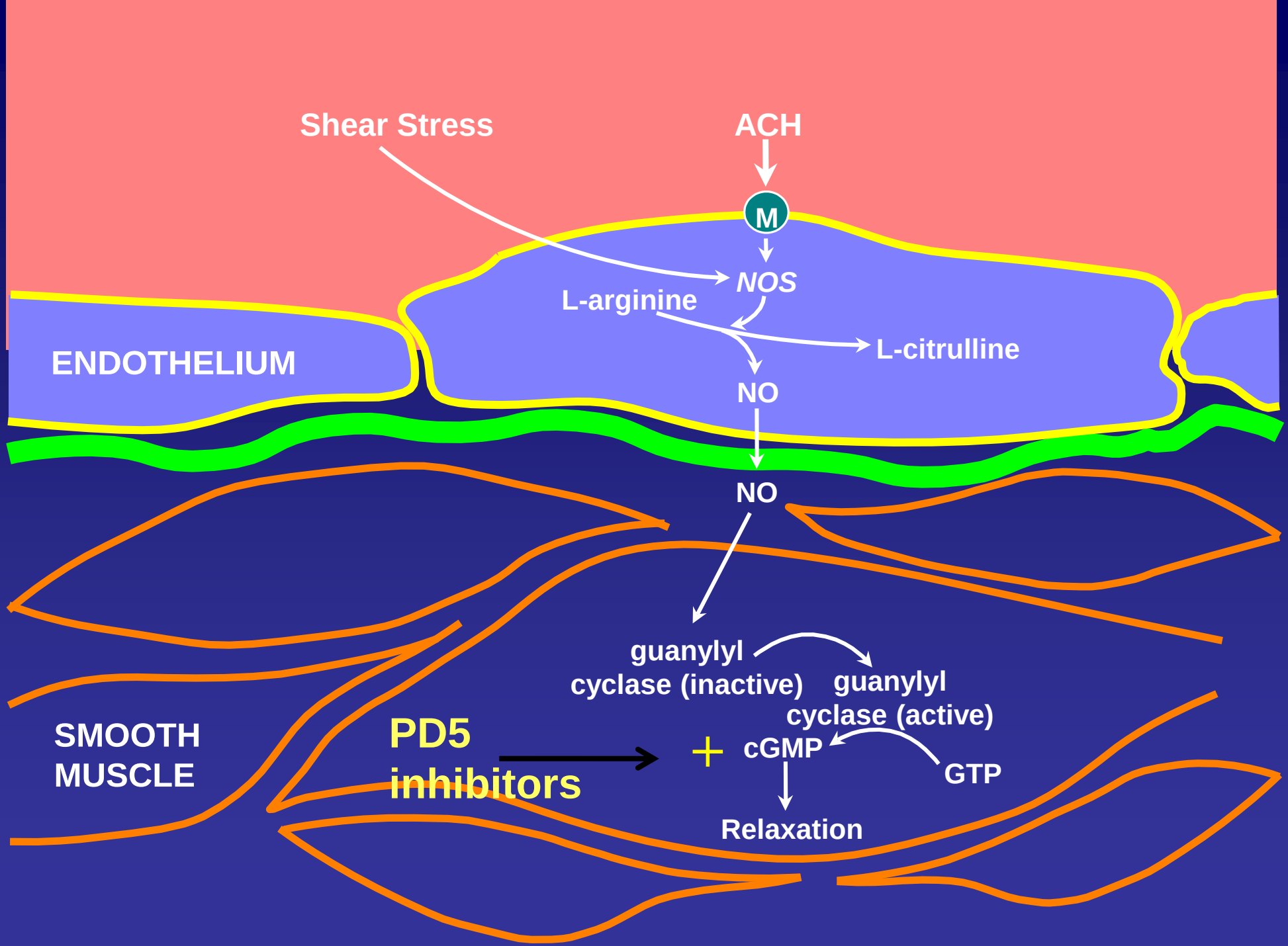


Zhang et al Proc Natl Acad Sci U S A. 2015 May 19;112(20):6425-30

Prof. Stamler says "blood flow to tissues is actually more important in most circumstances than how much oxygen is carried by hemoglobin. The respiratory cycle is actually a three-gas system."

When you cannot deliver oxygen to tissues and cells of the body, you are slowly dying

So how do we fix this fundamental Problem?


Shear Stress
ACH
M
NOS
L-arginine
L-citrulline
ENDOTHELIUM
NO
NO
guanylyl cyclase (inactive)
guanylyl cyclase (active)
SMOOTH MUSCLE
PD5 inhibitors
+
cGMP
GTP
Relaxation

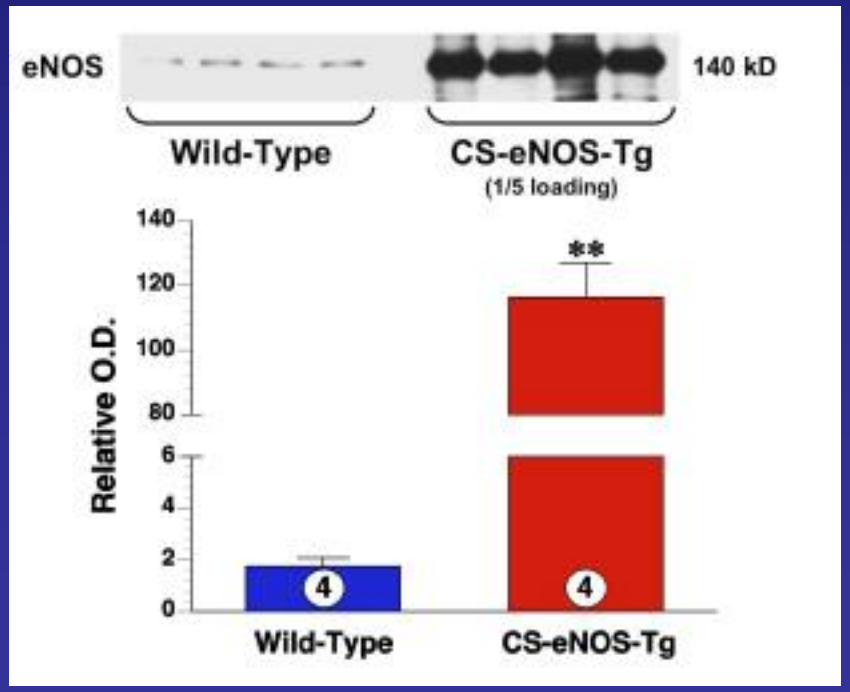
FACTS

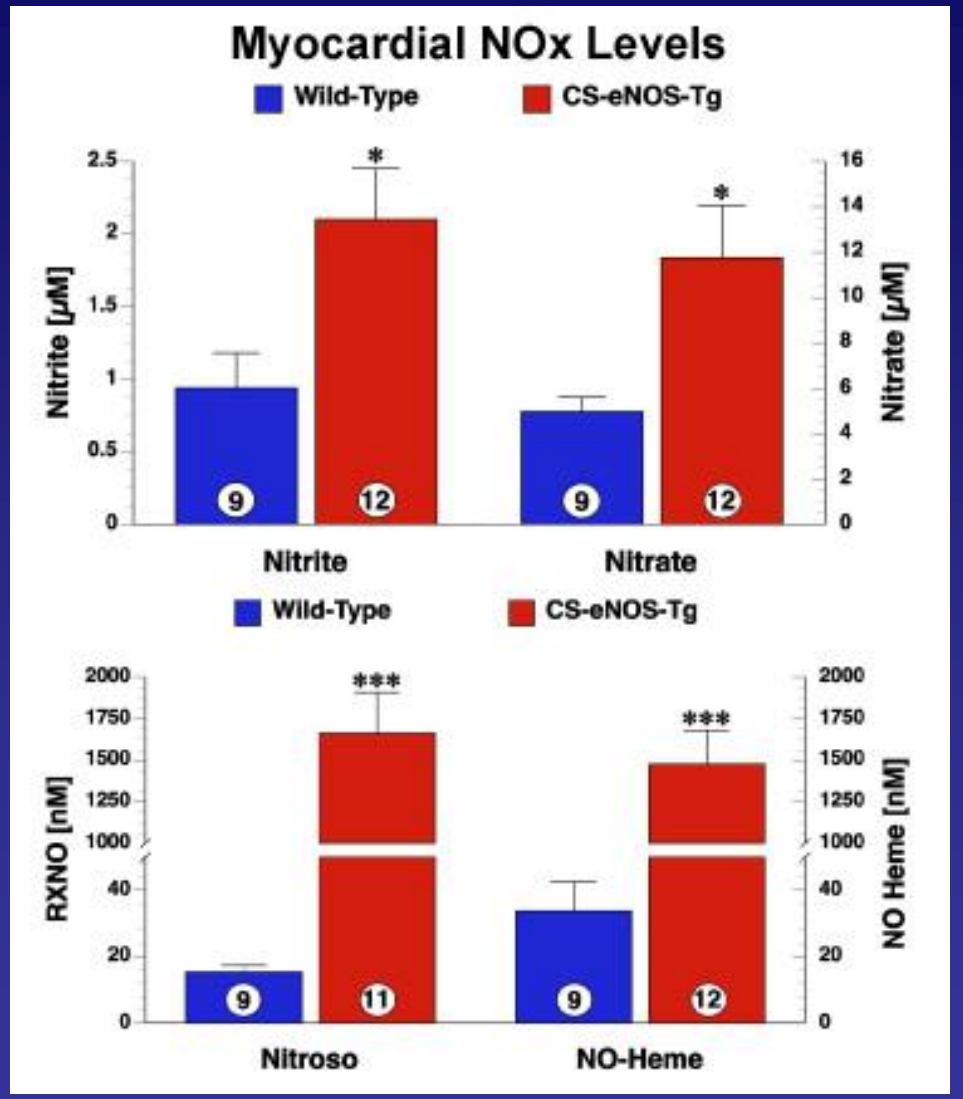
Cardiovascular disease (CVD) is the number one killer of both men and women in the U.S. Close to 1 million people die each year and more than 6 million are hospitalized due to CVD. The cost of CVD, in terms of health care and lost productivity, is over $270 billion and increasing as the baby boom population ages.

Ischemic heart disease, including myocardial infarction, remains the leading cause of morbidity and mortality in all industrialized nations

What is the physiological consequence of enhanced NO production in Ischemia-reperfusion injury?

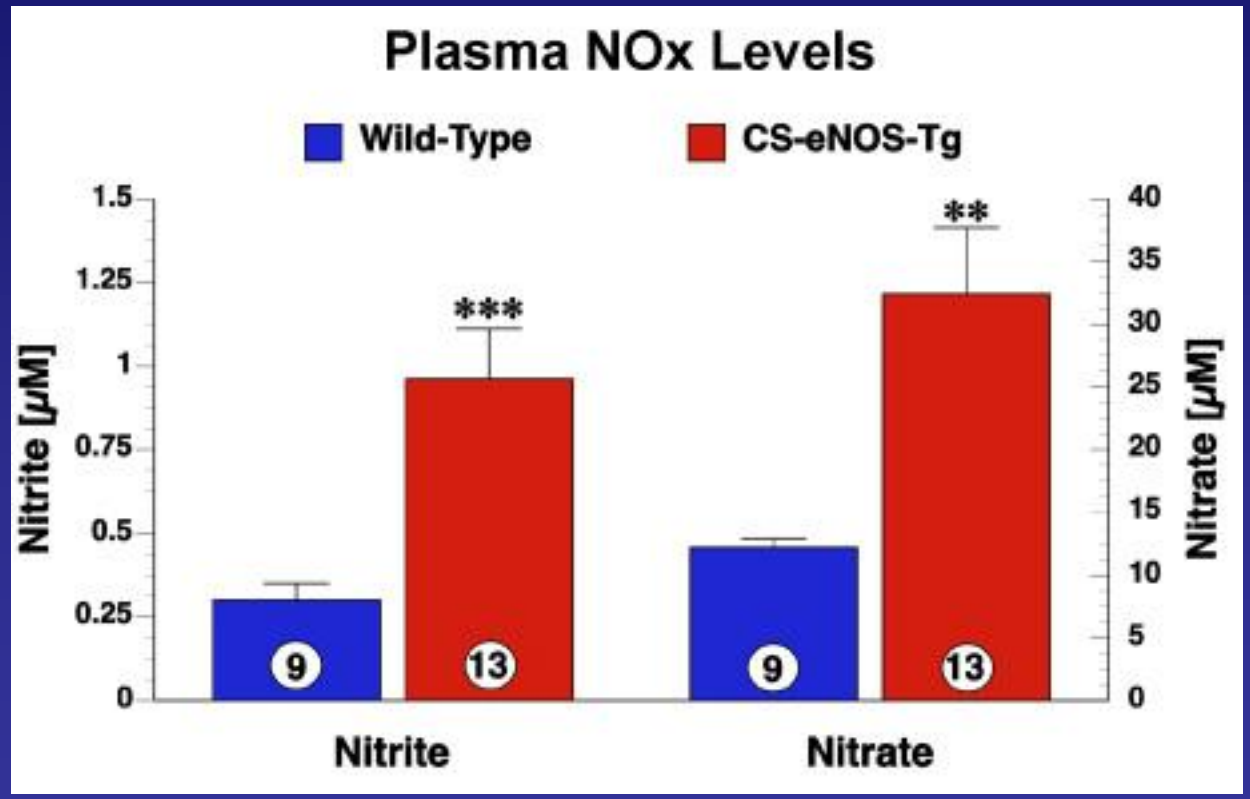
Cardiac Specific Overexpression of eNOS results in Increased Cardiac NO Production and Protects from I/R Injury





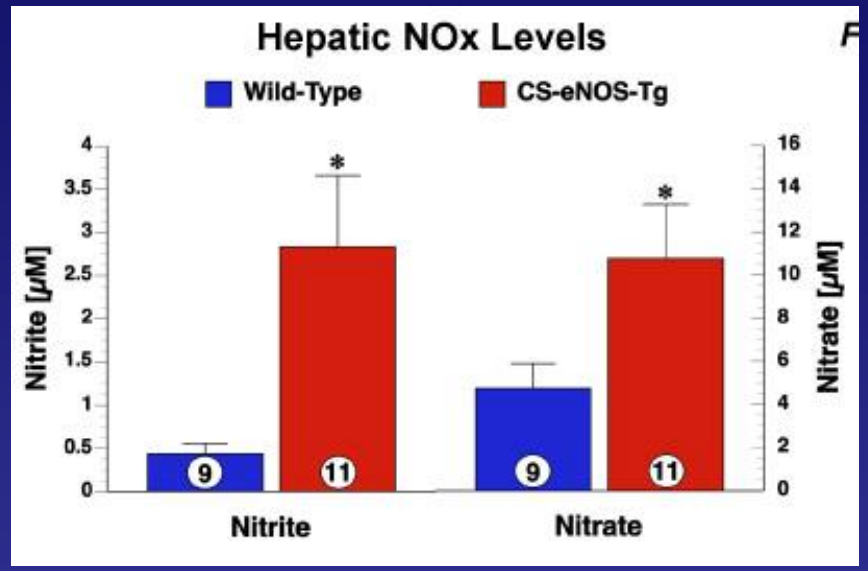
Elrod et al ATVB 2006

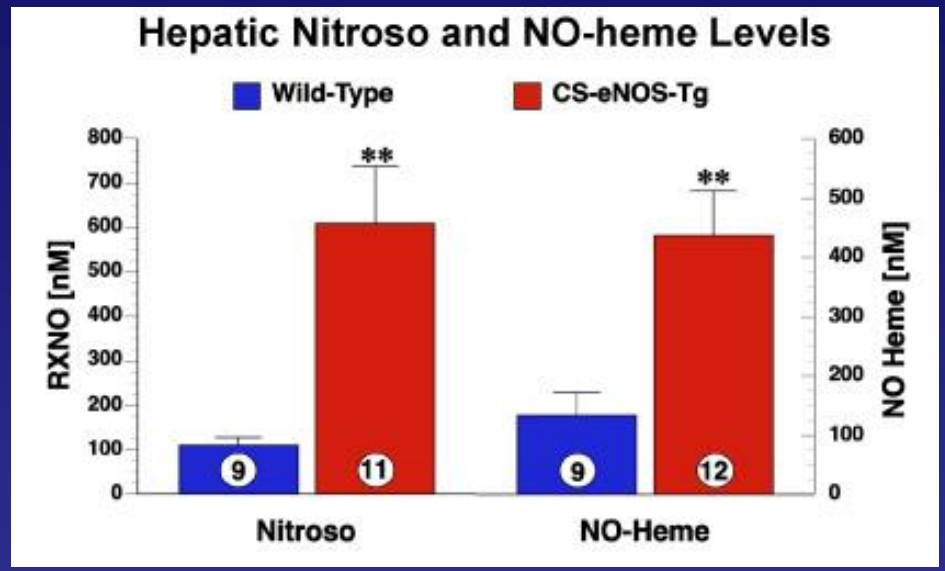
Increased Cardiac NO Production Results in Increased Circulating Nitrite and Nitrate

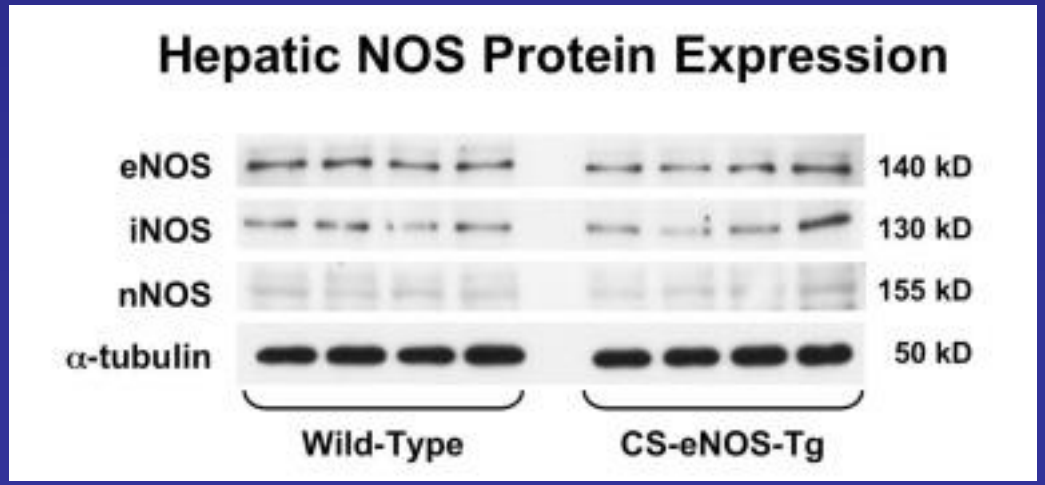


Elrod, PNAS 2008

Local NO Production in the Heart Results in Accumulation of NO Products in the Liver

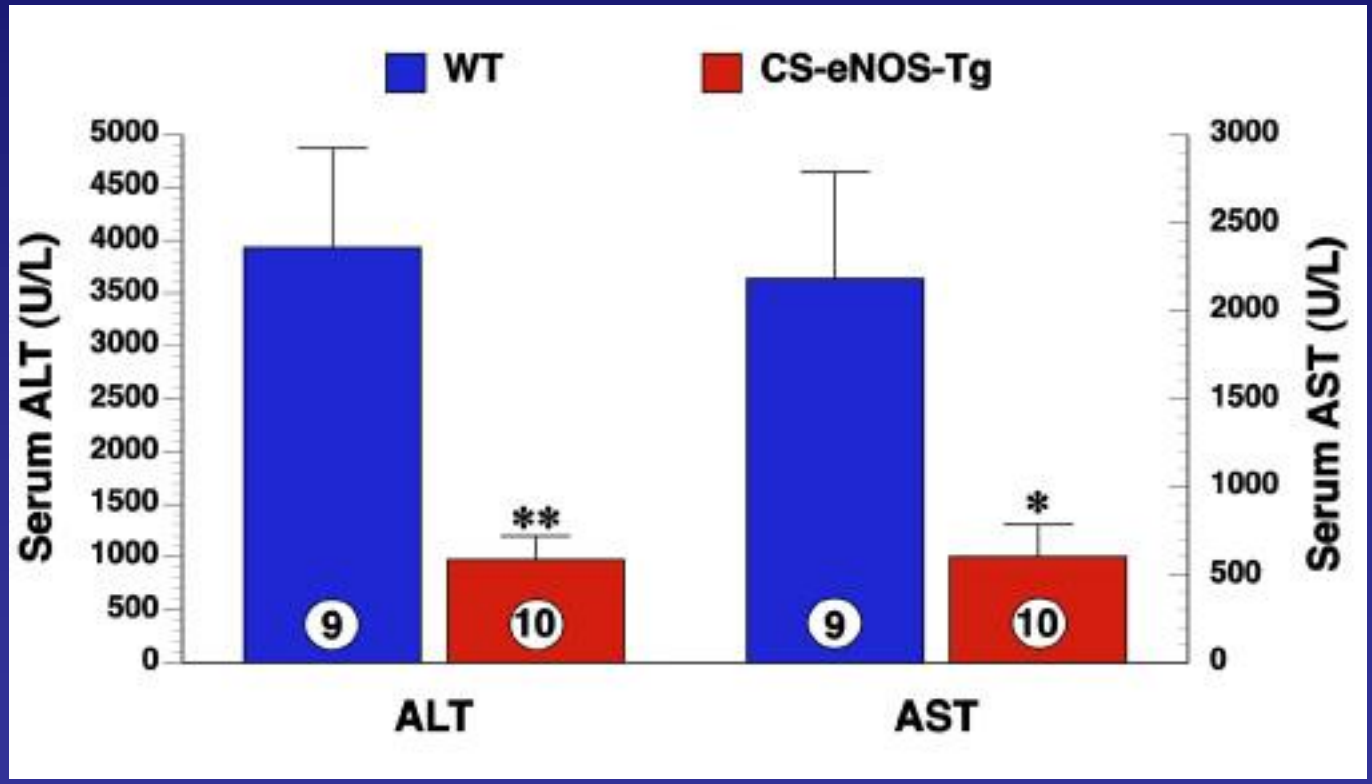






Elrod, PNAS 2008

Cardiac Derived NO Promotes Distant Organ Protection: Evidence for an Endocrine Role of Nitrite

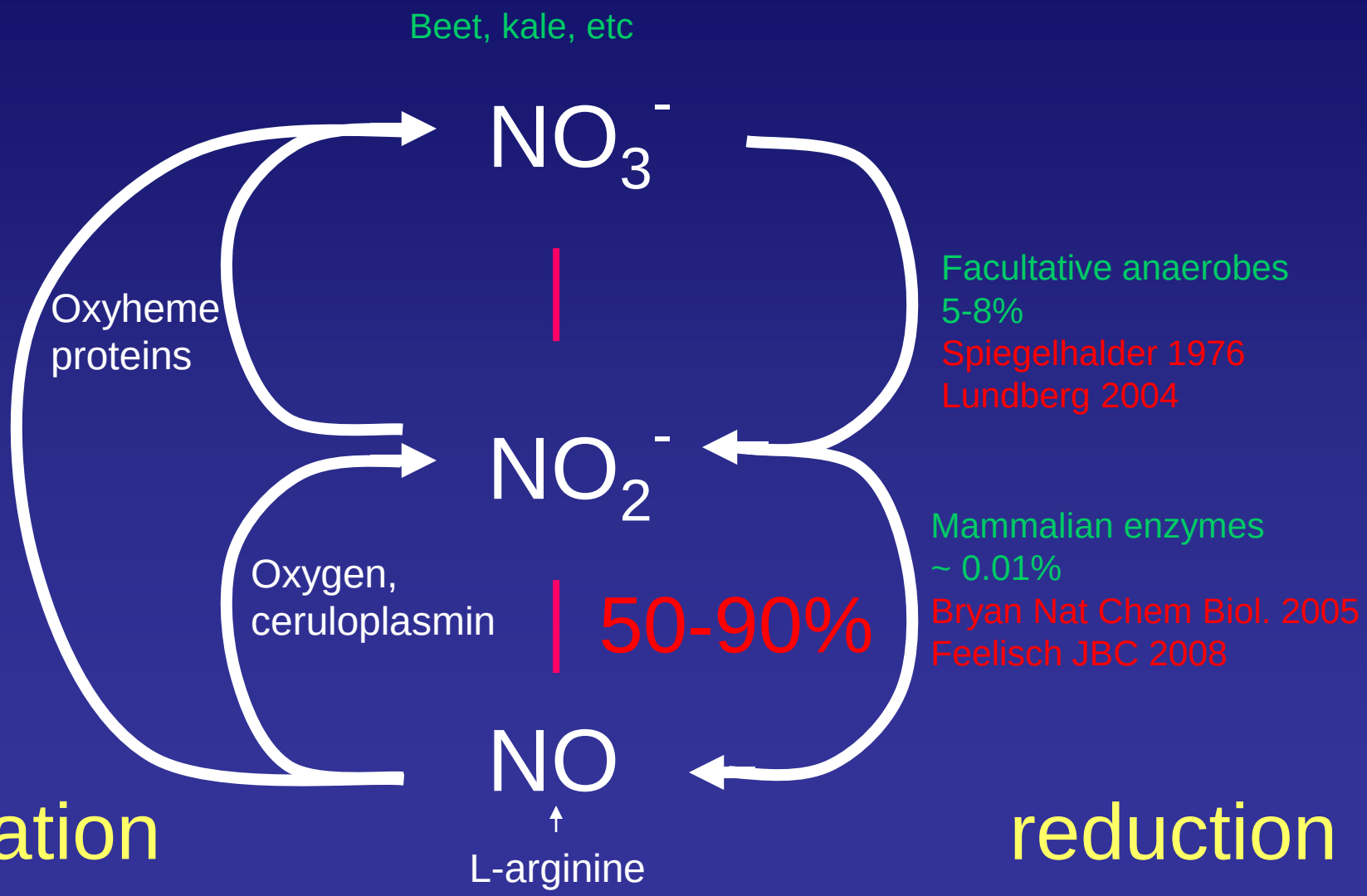


Elrod, PNAS 2008

The first demonstration of a hormone or endocrine effect of nitric oxide

New Concept: enhance nitric oxide in a single biological compartment and it will affect all organ systems

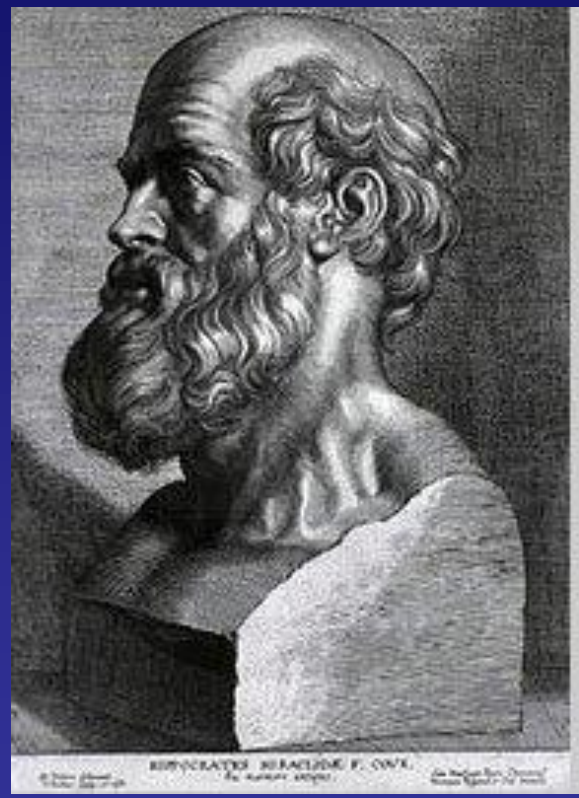
Nitrate-Nitrite-Nitric Oxide Pathway



New Concept

Is hypertension a symptom of oral dysbiosis?

Does this offer a new treatment modality for hypertension?



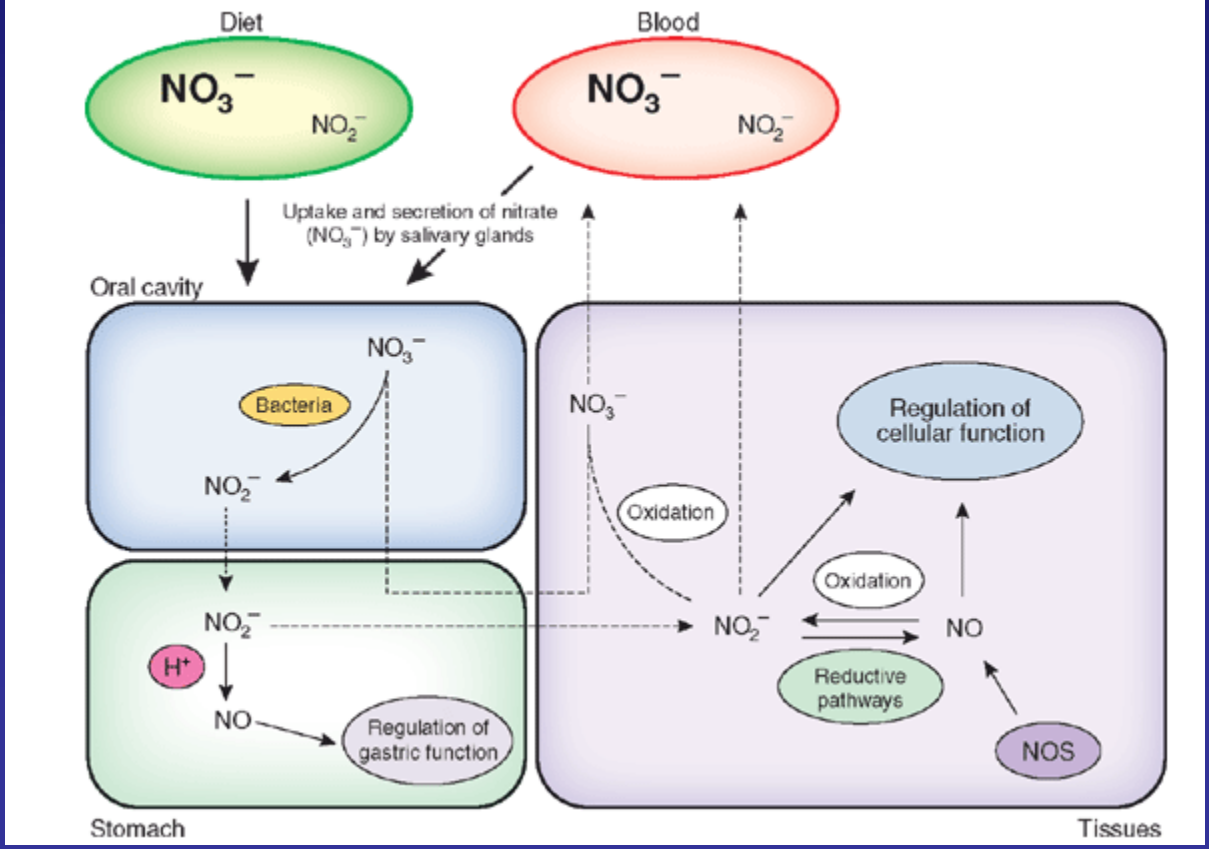
"Let food be thy medicine
and medicine be thy food"
– Hippocrates

PALEOSPIRIT COM

Can proper nutrition, food or Supplements provide NO support?

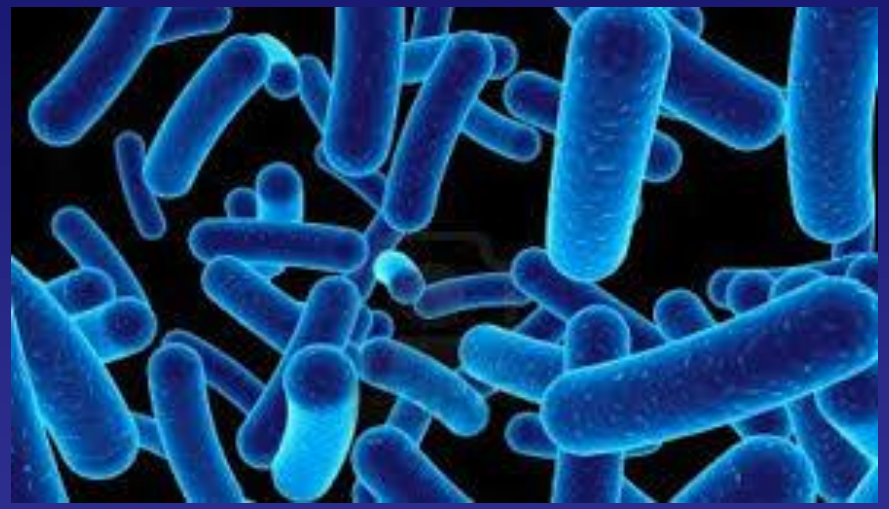
New Paradigm - Human Nitrogen Cycle

One-electron reduction is favorable to five-electron oxidation



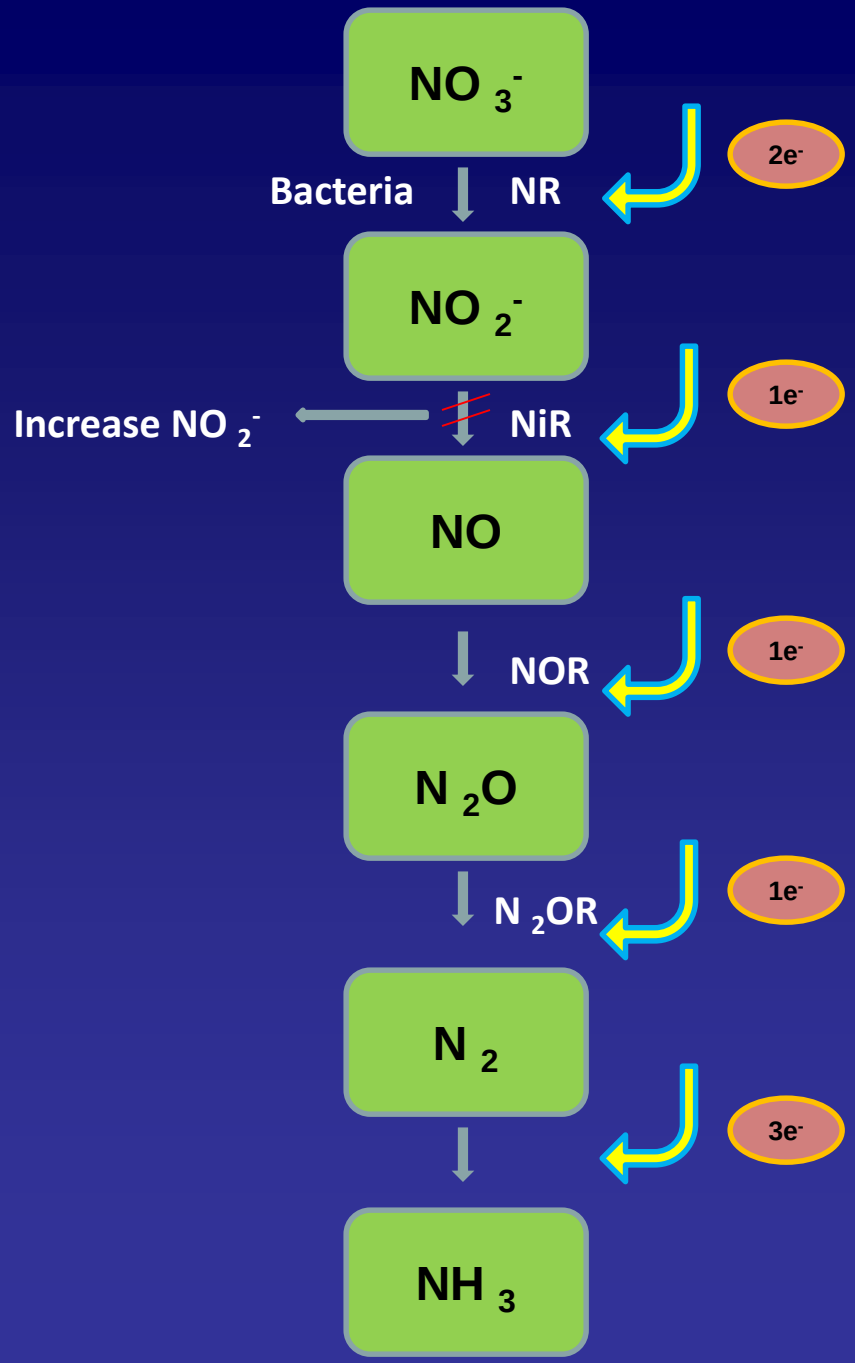
Dietary nitrate is rapidly absorbed into the bloodstream, where it mixes with endogenous nitrate from the NOS/NO pathway. A large portion of nitrate is taken up by the salivary glands, secreted with saliva and reduced to nitrite by symbiotic bacteria in the oral cavity. Salivary-derived nitrite is further 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.

Genetic Diversity



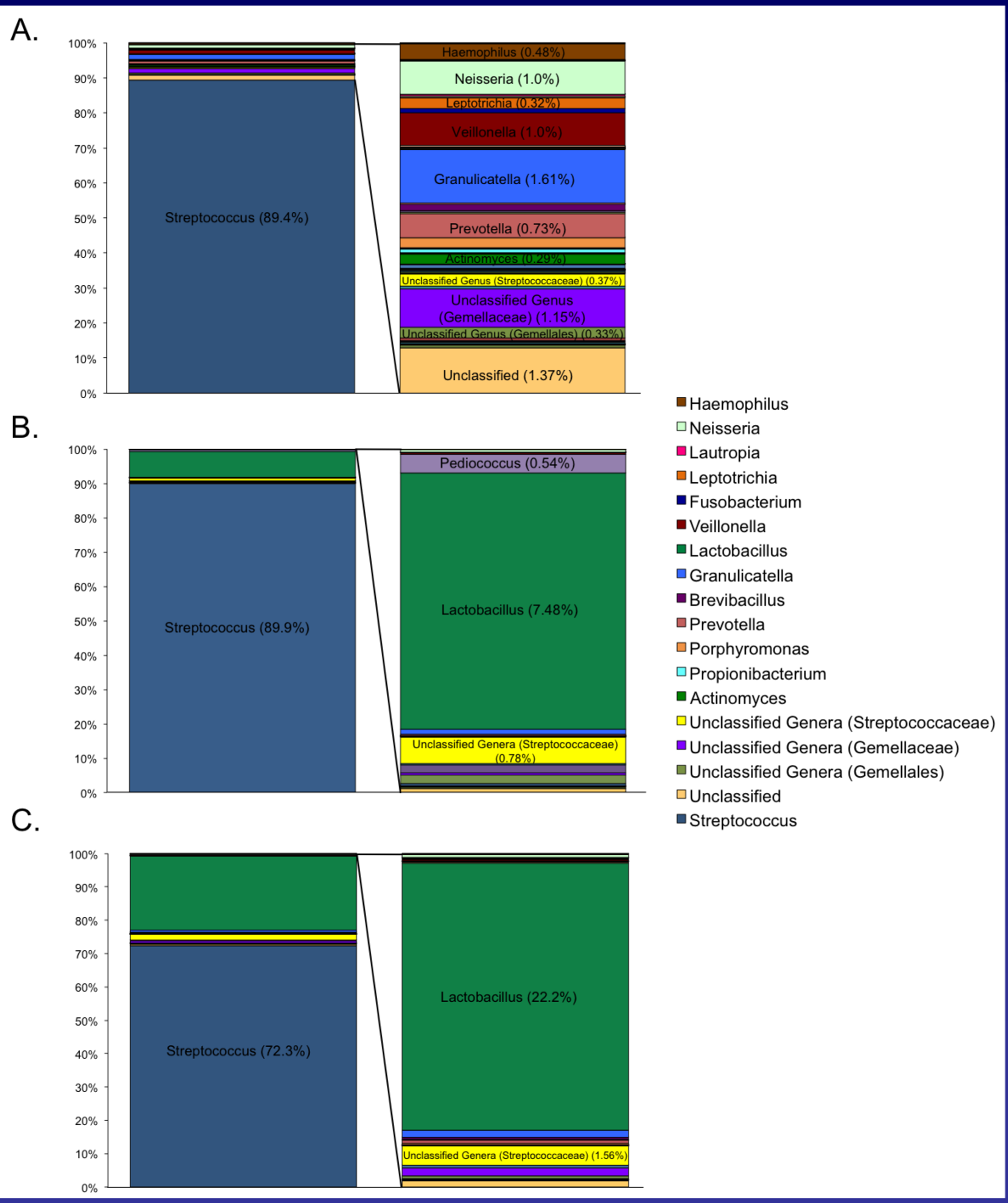
23,000 genes

3,000,000 genes



Ideal Community:

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



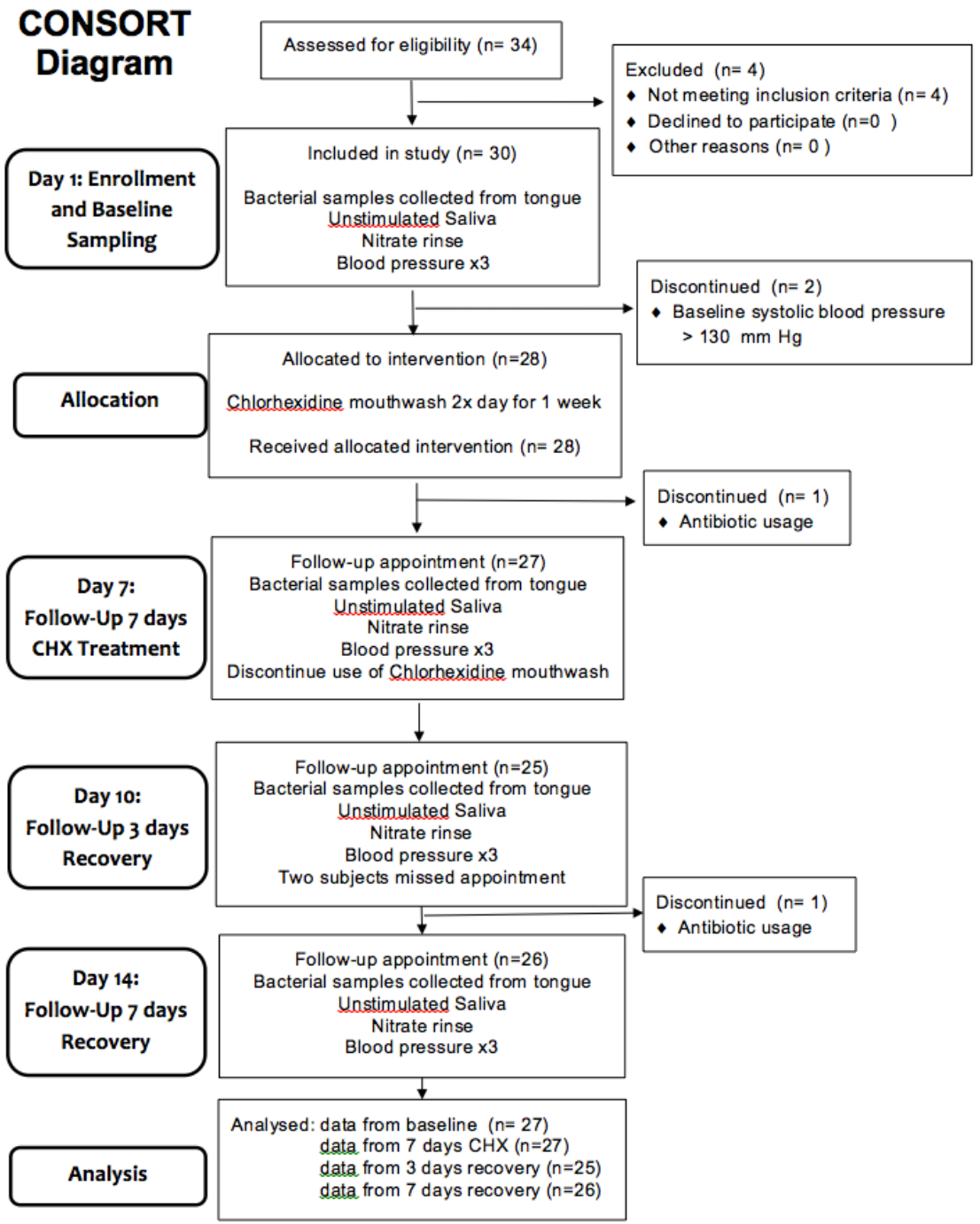
Best

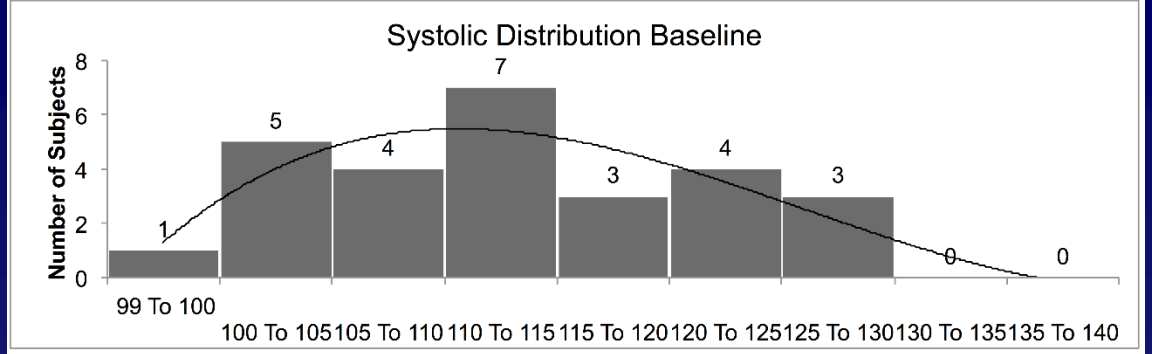
Intermediate

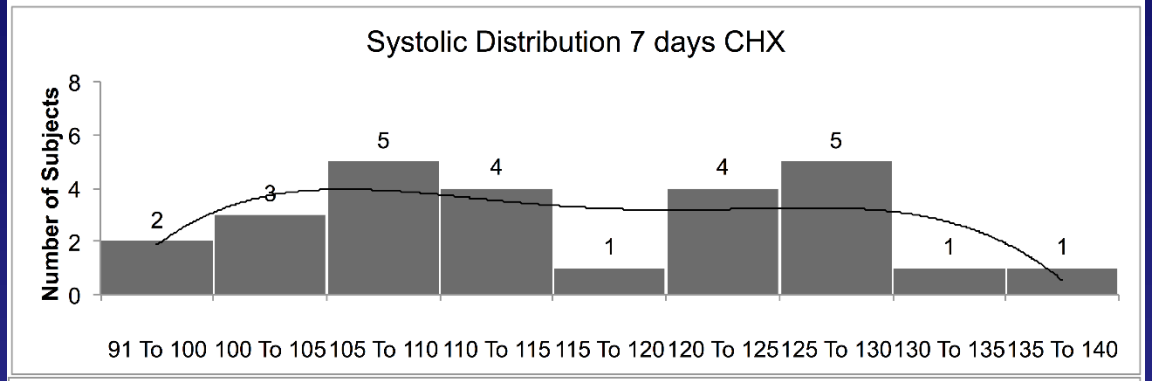
Worst

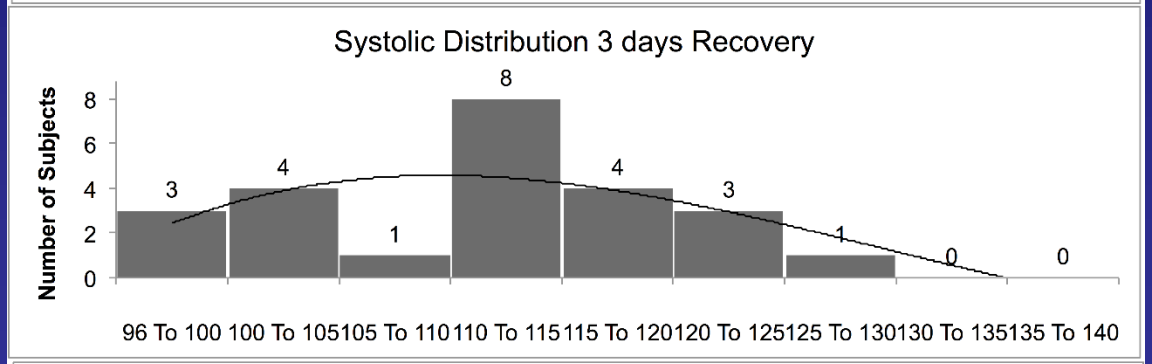
Hyde et al PLoS One (2014)

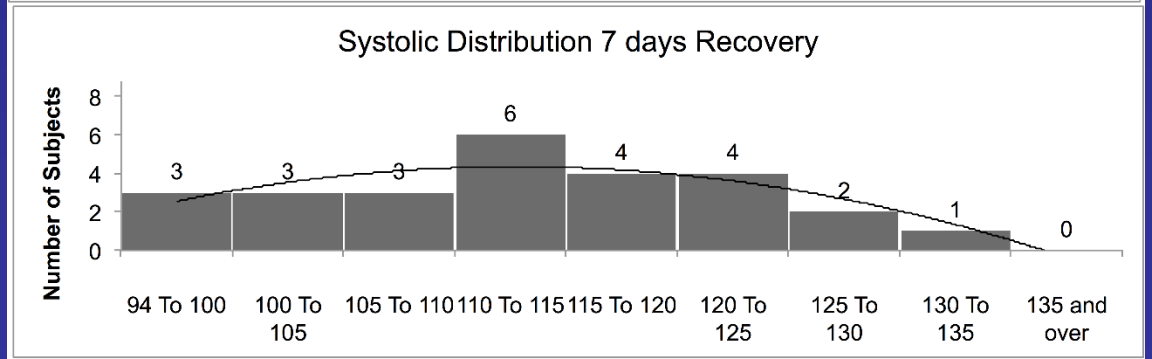
How Does Chlorhexidine Treatment Affect Diversity of Oral Microbiome And Nitrate Reduction in Healthy Subjects and what Effect Does this have on Systemic Blood Pressure?

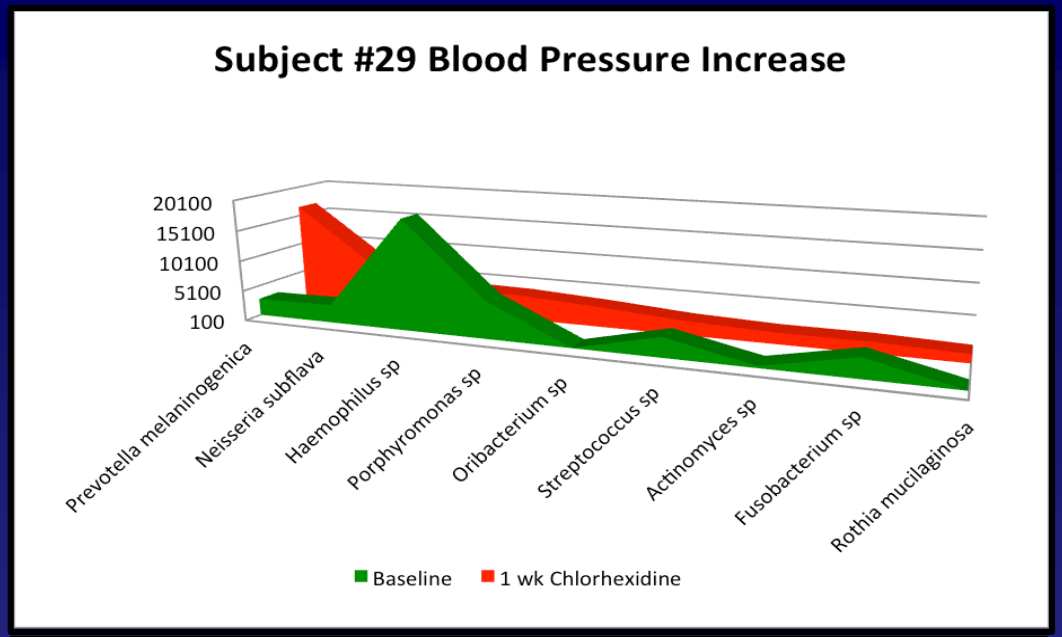

CONSORT Diagram
Assessed for eligibility (n= 34)
Excluded (n= 4)
♦ Not meeting inclusion criteria (n= 4)
♦ Declined to participate (n=0)
♦ Other reasons (n= 0)
Day 1: Enrollment and Baseline Sampling
Included in study (n= 30)
Bacterial samples collected from tongue
Unstimulated Saliva
Nitrate rinse
Blood pressure x3
Discontinued (n= 2)
♦ Baseline systolic blood pressure > 130 mm Hg
Allocation
Allocated to intervention (n=28)
Chlorhexidine mouthwash 2x day for 1 week
Received allocated intervention (n= 28)
Discontinued (n= 1)
♦ Antibiotic usage
Day 7: Follow-Up 7 days CHX Treatment
Follow-up appointment (n=27)
Bacterial samples collected from tongue
Unstimulated Saliva
Nitrate rinse
Blood pressure x3
Discontinue use of Chlorhexidine mouthwash
Day 10: Follow-Up 3 days Recovery
Follow-up appointment (n=25)
Bacterial samples collected from tongue
Unstimulated Saliva
Nitrate rinse
Blood pressure x3
Two subjects missed appointment
Discontinued (n= 1)
♦ Antibiotic usage
Day 14: Follow-Up 7 days Recovery
Follow-up appointment (n=26)
Bacterial samples collected from tongue
Unstimulated Saliva
Nitrate rinse
Blood pressure x3
Analysis
Analysed: data from baseline (n= 27)
data from 7 days CHX (n=27)
data from 3 days recovery (n=25)
data from 7 days recovery (n=26)

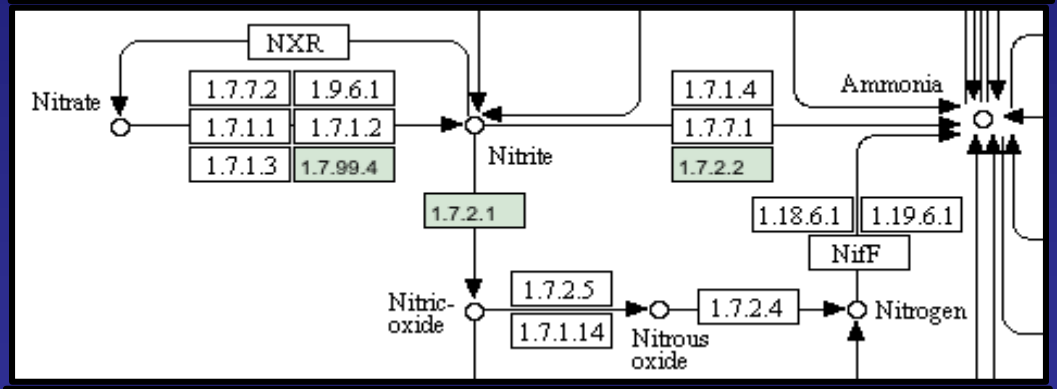

Systolic Distribution Baseline
Number of Subjects
0
2
4
6
8
1
5
4
7
3
4
3
0
0
99 To 100
100 To 105
105 To 110
110 To 115
115 To 120
120 To 125
125 To 130
130 To 135
135 To 140

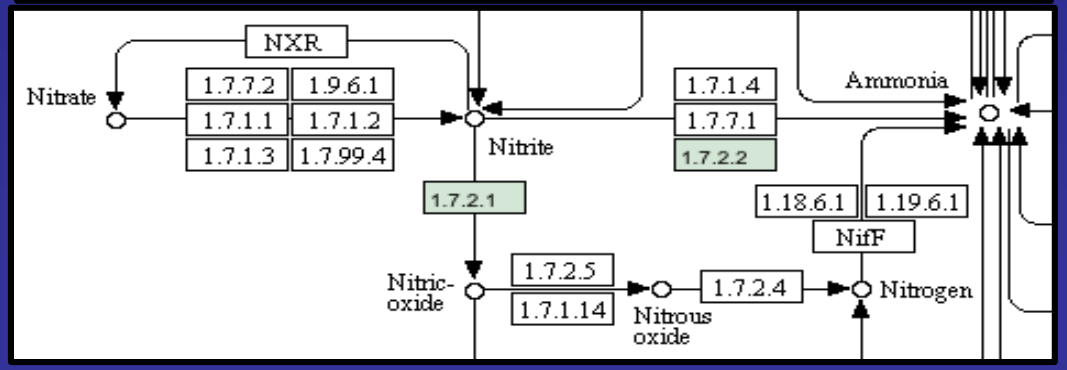

Systolic Distribution 7 days CHX
Number of Subjects
0
2
4
6
8
2
3
5
4
1
4
5
1
1
91 To 100
100 To 105
105 To 110
110 To 115
115 To 120
120 To 125
125 To 130
130 To 135
135 To 140


Systolic Distribution 3 days Recovery
Number of Subjects
0
2
4
6
8
3
4
1
8
4
3
1
0
0
96 To 100
100 To 105
105 To 110
110 To 115
115 To 120
120 To 125
125 To 130
130 To 135
135 To 140


Systolic Distribution 7 days Recovery
Number of Subjects
0
2
4
6
8
3
3
3
6
4
4
2
1
0
94 To 100
100 To 105
105 To 110
110 To 115
115 To 120
120 To 125
125 To 130
130 To 135
135 and over







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	Count	Percent
twice a day	22	81%
three times a day	5	19%

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

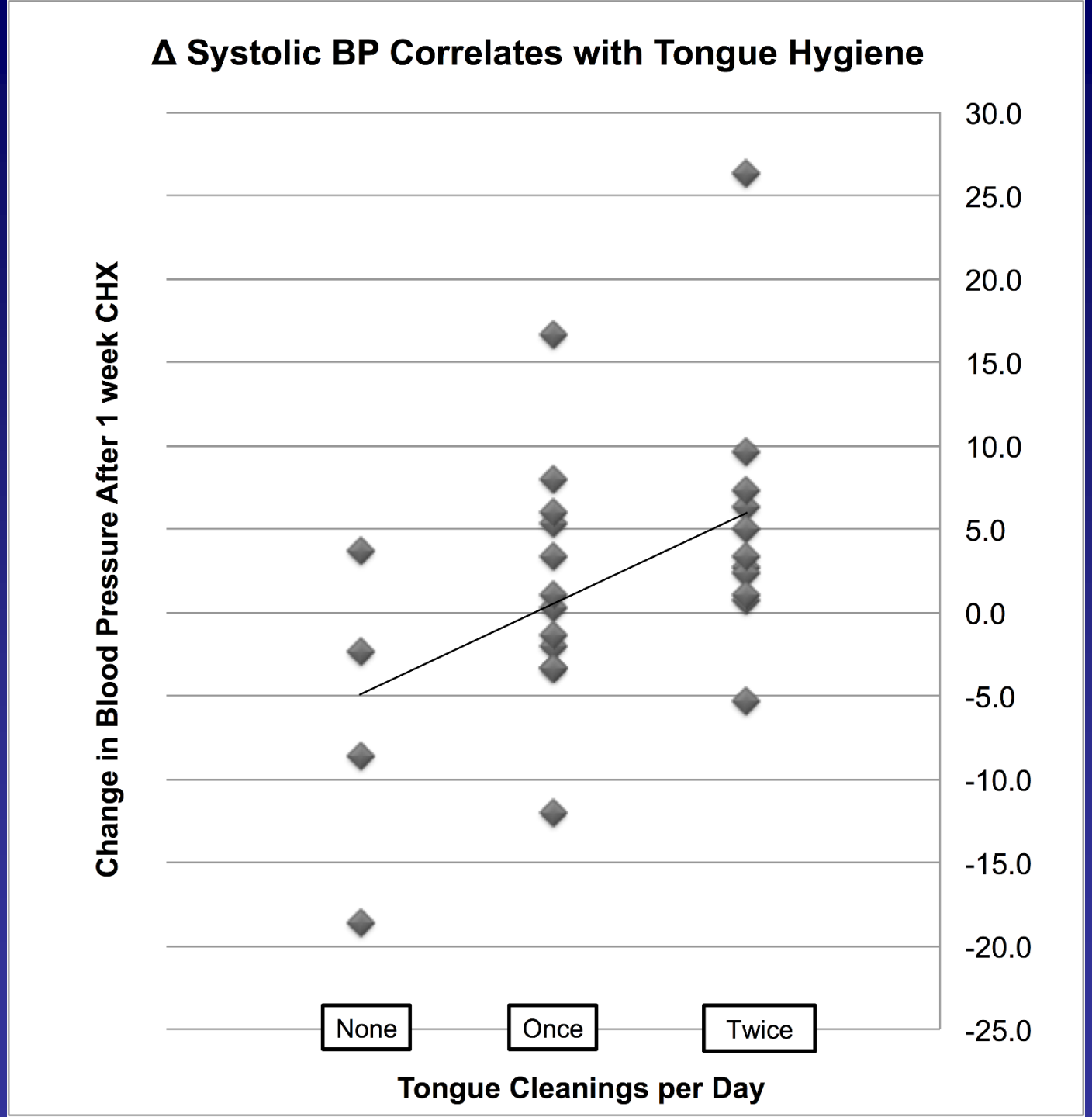
Clean tongue	Count	Percent
Less than once a week	4	15%
Once a day	13	48%
Twice a day or more	10	37%

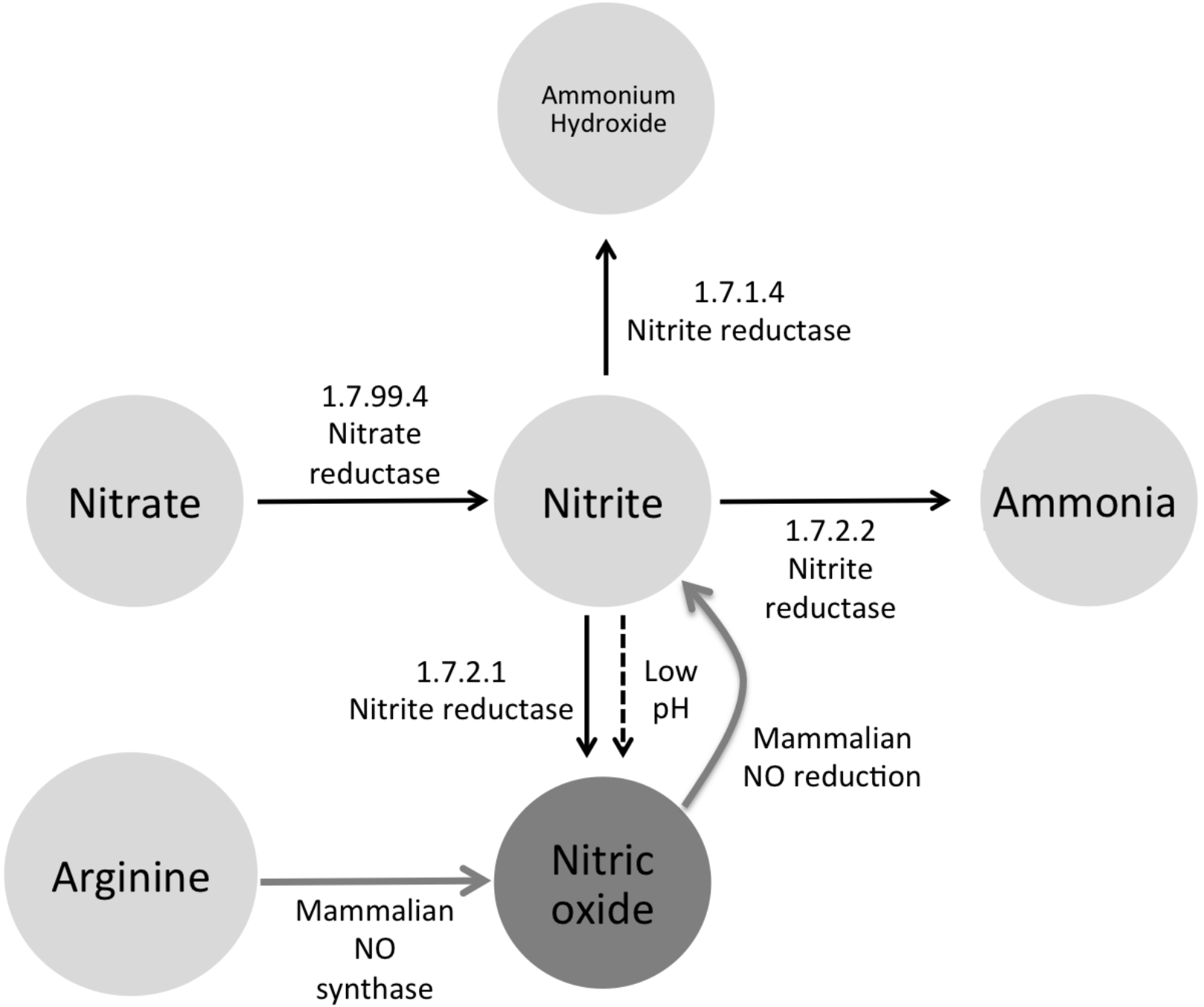
Mouthwash use	Count	Percent
As needed	5	19%
Once a day	16	59%
Twice a day	6	22%

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

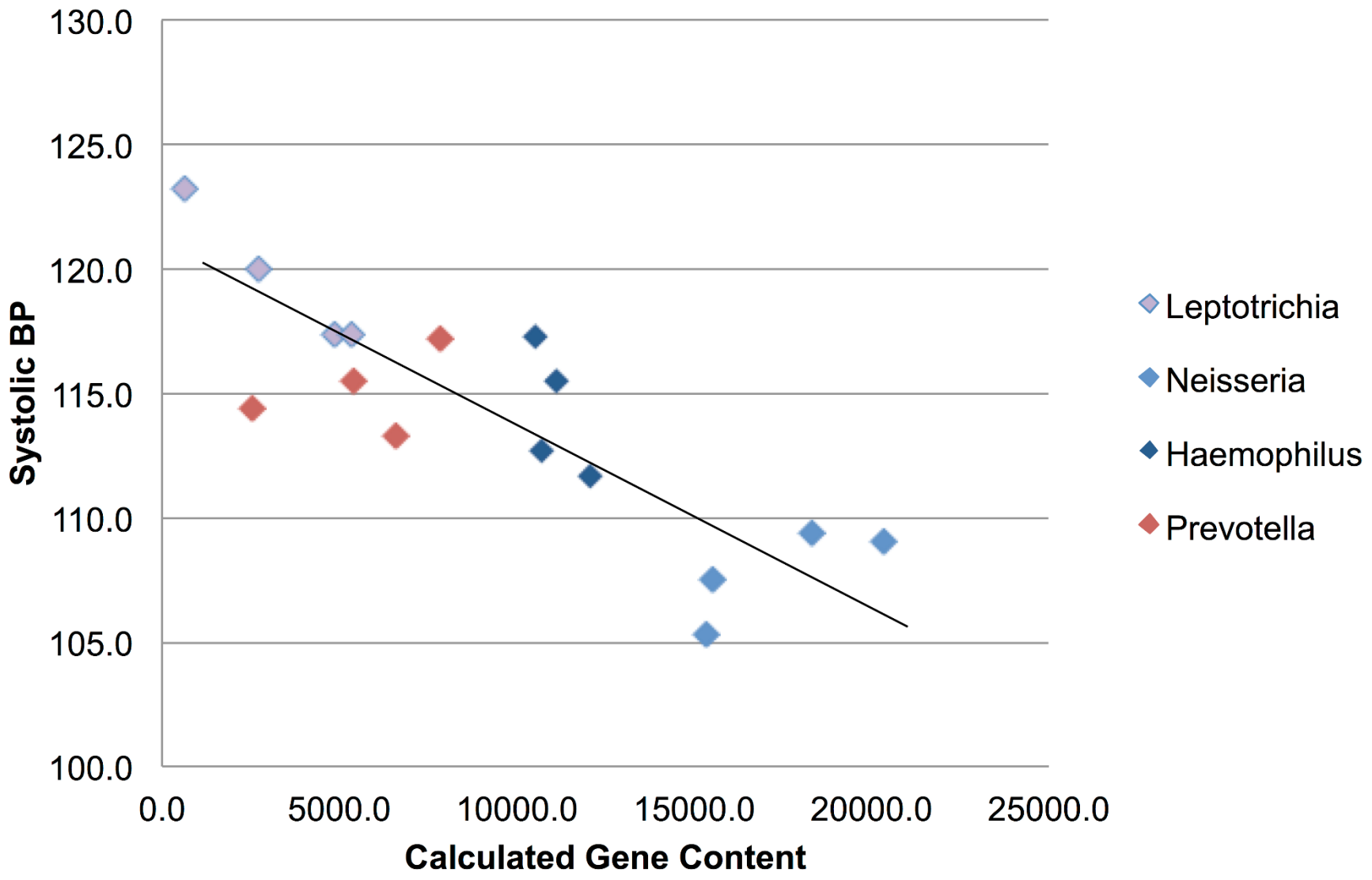
Type of Toothbrush	Count	Percent
Manual	10	37%
Electric	12	44%
Both manual and electric	5	19%

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


Δ Systolic BP Correlates with Tongue Hygiene
Change in Blood Pressure After 1 week CHX
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
None
Once
Twice
Tongue Cleanings per Day


Ammonium Hydroxide
1.7.1.4 Nitrite reductase
1.7.99.4 Nitrate reductase
Nitrate
Nitrite
Ammonia
1.7.2.2 Nitrite reductase
1.7.2.1 Nitrite reductase
Low pH
Mammalian NO reduction
Arginine
Nitric oxide
Mammalian NO synthase

Nitrite Reductase (NO-forming) Correlates with Systolic BP



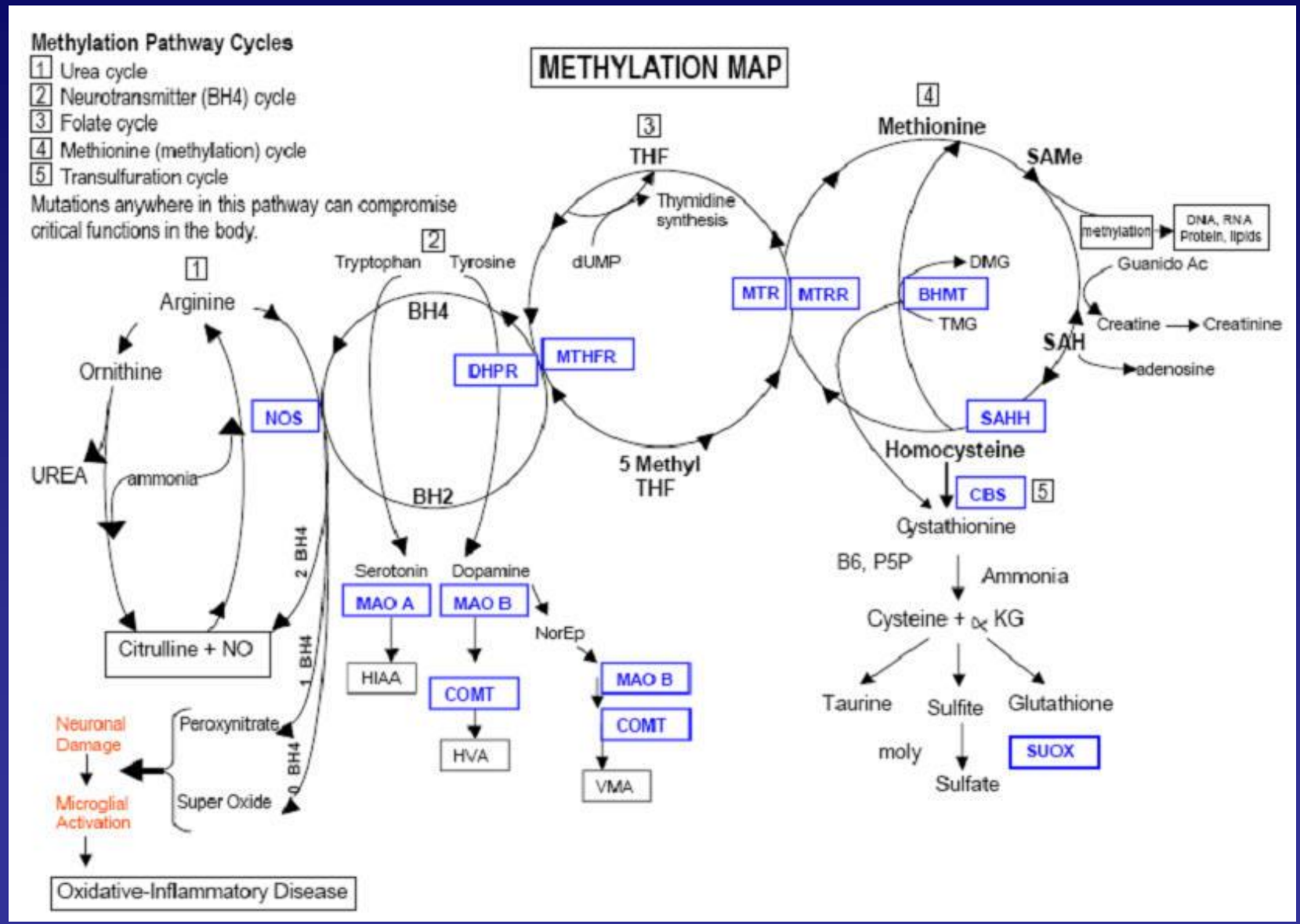
Disruption of Nitrate-Nitrite-NO Pathway

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)
4. Lack of oral commensal bacteria to reduce nitrate to nitrite
   (use of antibiotics/antiseptic mouthwash, poor oral hygeine)
5. Insufficient stomach acid production – Achlorhydria
   (use of PPI's, H. Pylori infection, iron overload)
6. Increased oxidative stress that scavenges NO

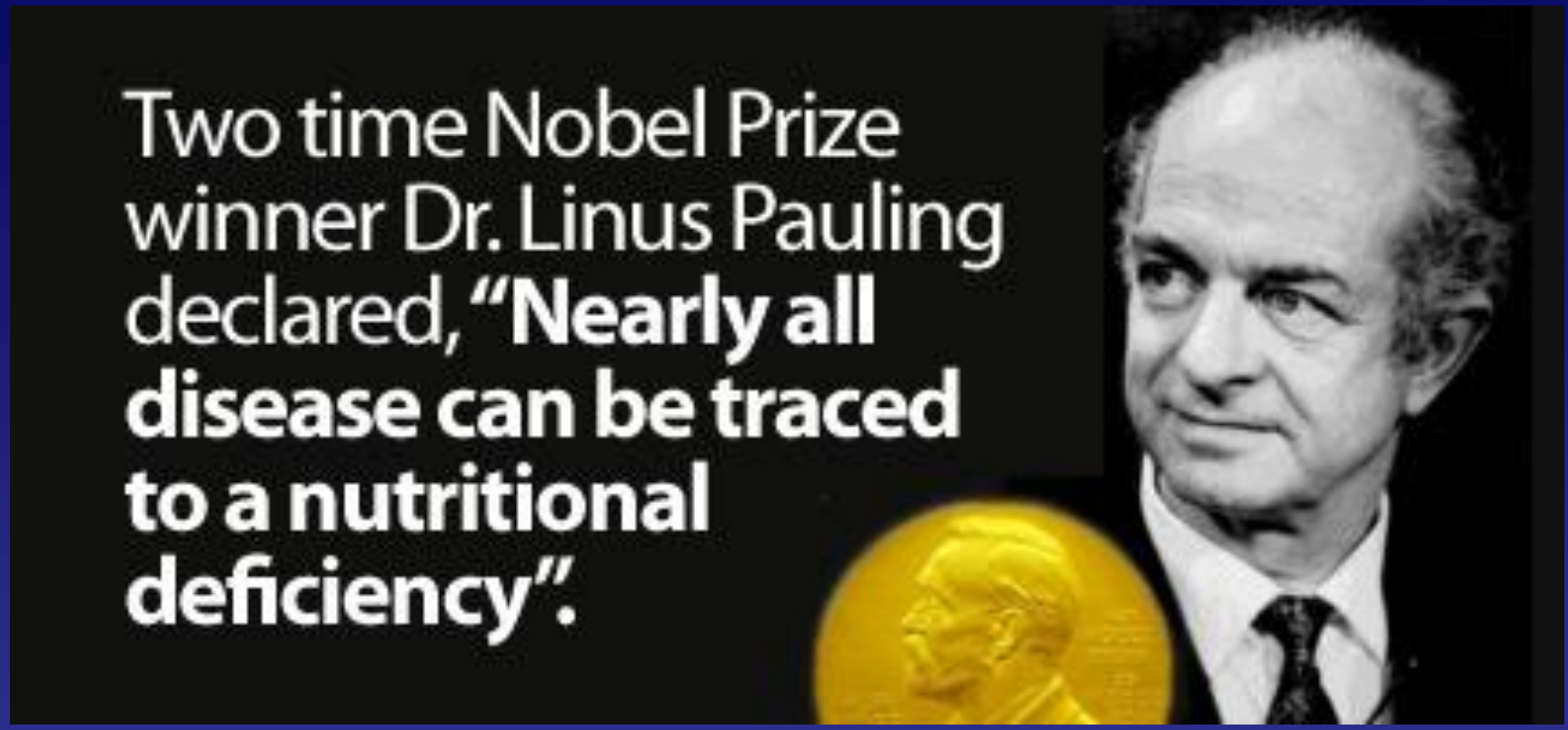
What might this mean?

- Absence of these select bacteria - a new risk factor for cardiovascular disease.
- Patients with periodontal disease , affecting the NO producing communities - possibly linking oral health to cardiovascular disease risk by disruption of NO production
- Use of antiseptic mouthwash or overuse antibiotics can disrupt nitrate reducing communities
- Patients taking proton pump inhibitors to suppress stomach acid production
- Develop this pathway as a primary therapeutic target to affect NO production

What about Genetic Testing?
Do Specific SNPs Affect NO Production


Methylation Pathway Cycles
1 Urea cycle
2 Neurotransmitter (BH4) cycle
3 Folate cycle
4 Methionine (methylation) cycle
5 Transulfuration cycle
Mutations anywhere in this pathway can compromise critical functions in the body.
METHYLATION MAP
1
Arginine
Ornithine
UREA
ammonia
NOS
Citrulline + NO
2 BH4
1 BH4
0 BH4
Neuronal Damage
Microglial Activation
Peroxynitrate
Super Oxide
Oxidative-Inflammatory Disease
2
Tryptophan
Tyrosine
BH4
BH2
DHPR
MTHFR
Serotonin
Dopamine
MAO A
MAO B
HIAA
COMT
HVA
NorEp
MAO B
COMT
VMA
3
THF
Thymidine synthesis
dUMP
5 Methyl THF
MTR
MTRR
4
Methionine
SAMe
methylation
DNA, RNA Protein, lipids
Guanido Ac
Creatine
Creatinine
DMG
BHMT
TMG
SAH
adenosine
SAHH
Homocysteine
CBS
5
Cystathionine
B6, P5P
Ammonia
Cysteine + α KG
Taurine
Sulfite
Glutathione
moly
SUOX
Sulfate

How do you overcome bacterial variability in populations?



Are we missing sufficient nitrite and/or nitrate that may be causing disease?

Hypertension is the #1 risk factor for development of cardiovascular Disease

2/3 Americans have Hypertension or Prehypertension

50% of those on anti-hypertensive meds are unmanaged

SPRINT Trial reveals lowering blood pressure reduces cardiovascular events and deaths from all causes

What is the Consequence of Sufficient and Adequate NO Production?

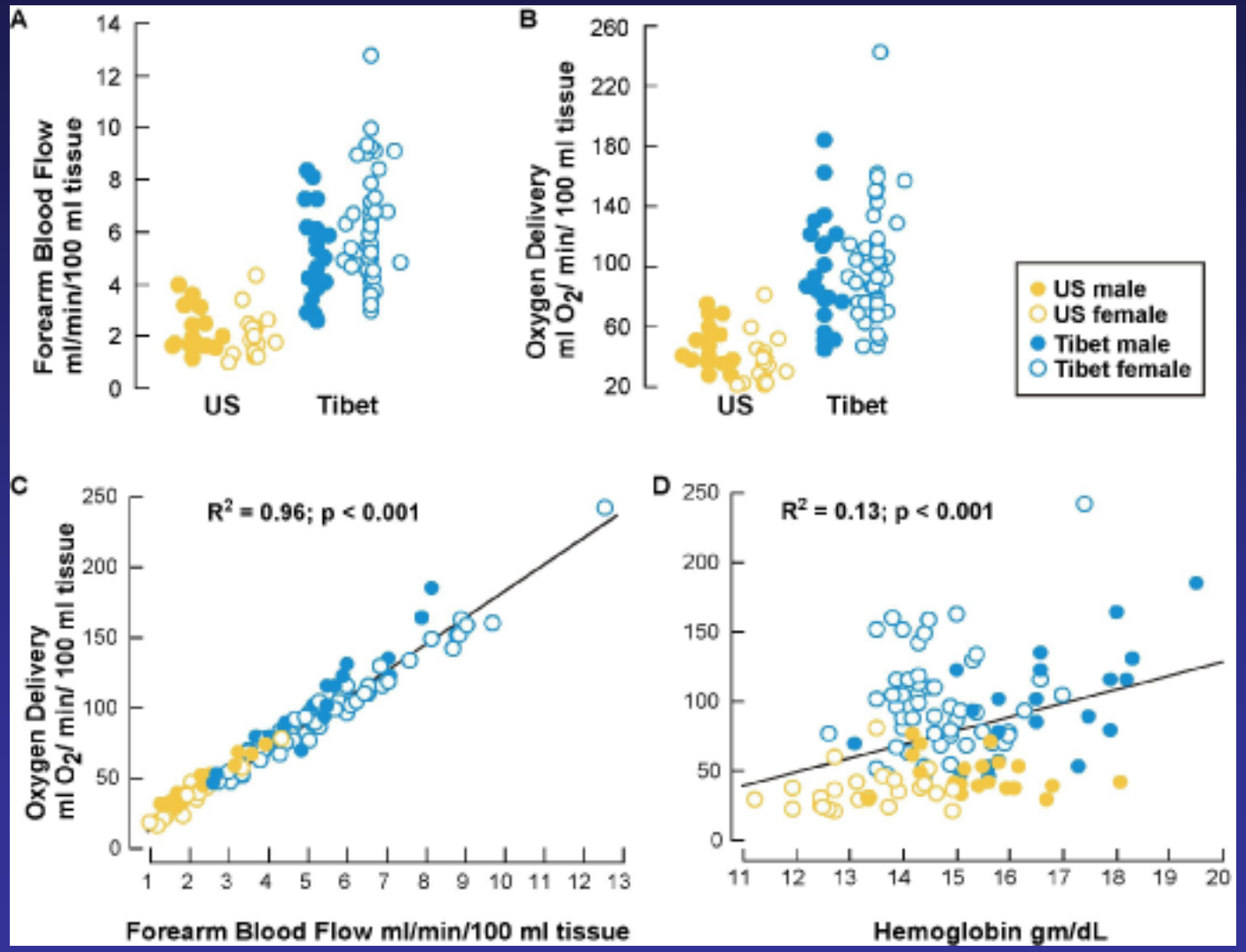
What is the Consequence of Insufficient NO Production/Availability?

Are there populations that represent these scenarios?

Study on Sub-Population of High Altitude Natives

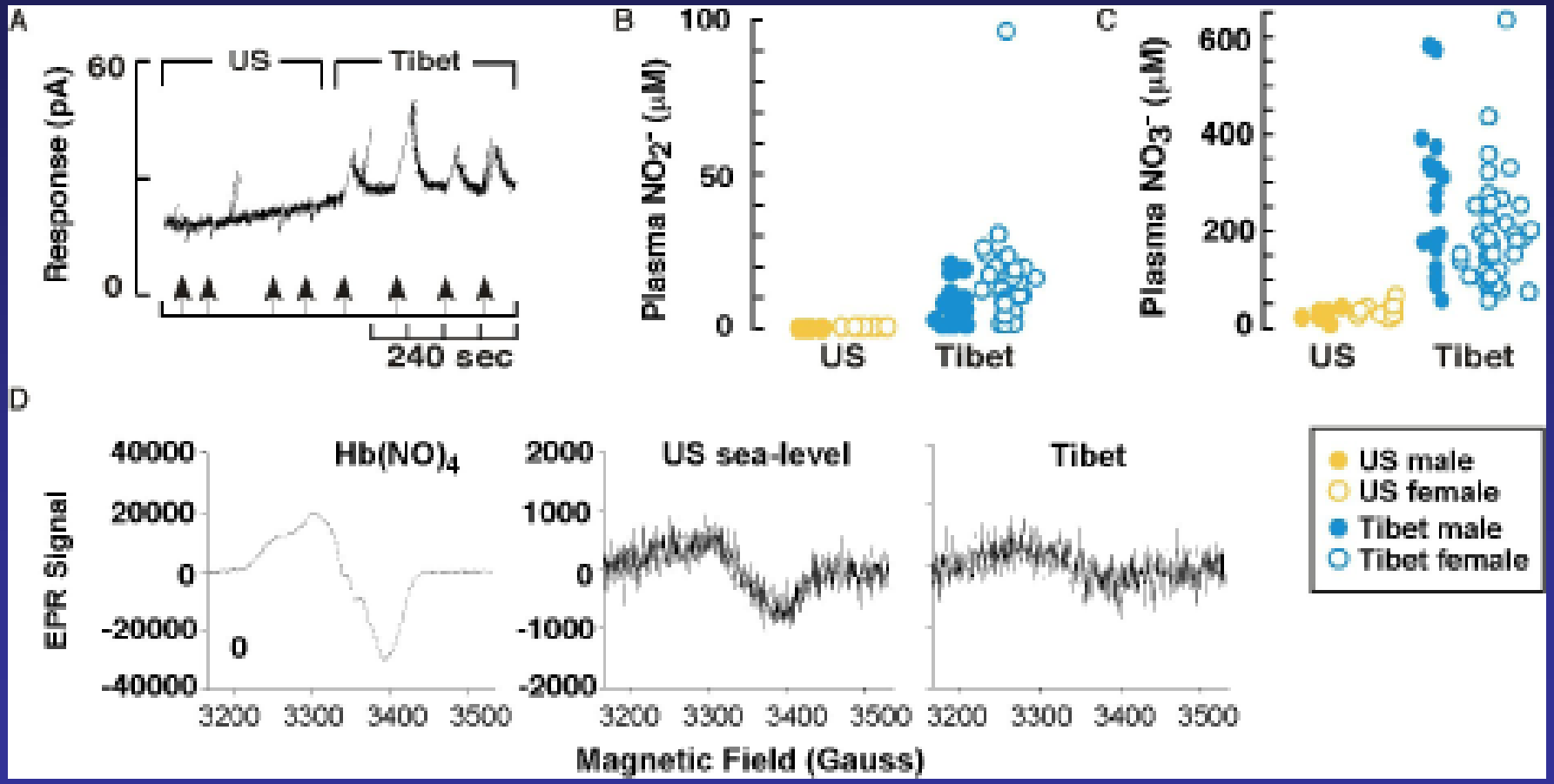
Is increasing nitrite and nitrate plausible in humans?
Is this a natural phenomenon?

Tibetan Highlanders Have Increased Blood Flow to Compensate for Decreased Ambient Oxygen



Erzurum et al. PNAS (2007)

Increased Blood flow is due to increased NO production and accumulation of nitrite and nitrate



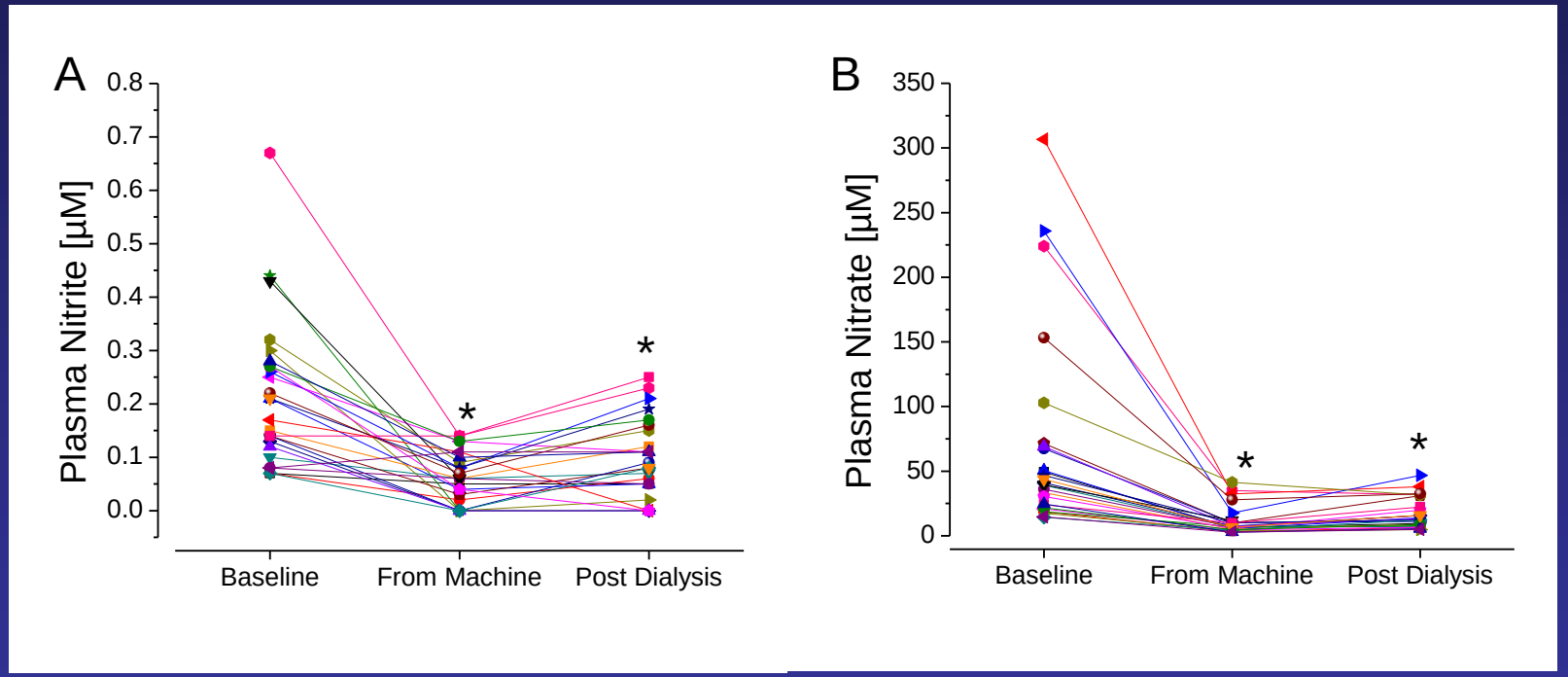
Erzurum et al. PNAS (2007)

Are there patients that become completely devoid of NO? If so, what is the physiological consequence?

Steady State NO in Dialysis Patients

- High cardiovascular death rates for patients on hemodialysis remain a serious problem.
- Cardiovascular mortality is considered the main cause of death in patients receiving dialysis and is 10 to 20 times higher in such patients than in the general population.
- Expected remaining lifetimes for dialysis patients are only one-third to one-sixth those of the general U.S. population. For a healthy 20-year-old, life expectancy is around another 58 years – compared to 14 years in dialysis patients. A 50-year-old dialysis patient can expect another six years.
- To date there is no molecular mechanism that has been shown to explain this increased mortality although nitric oxide has been implicated.

Results

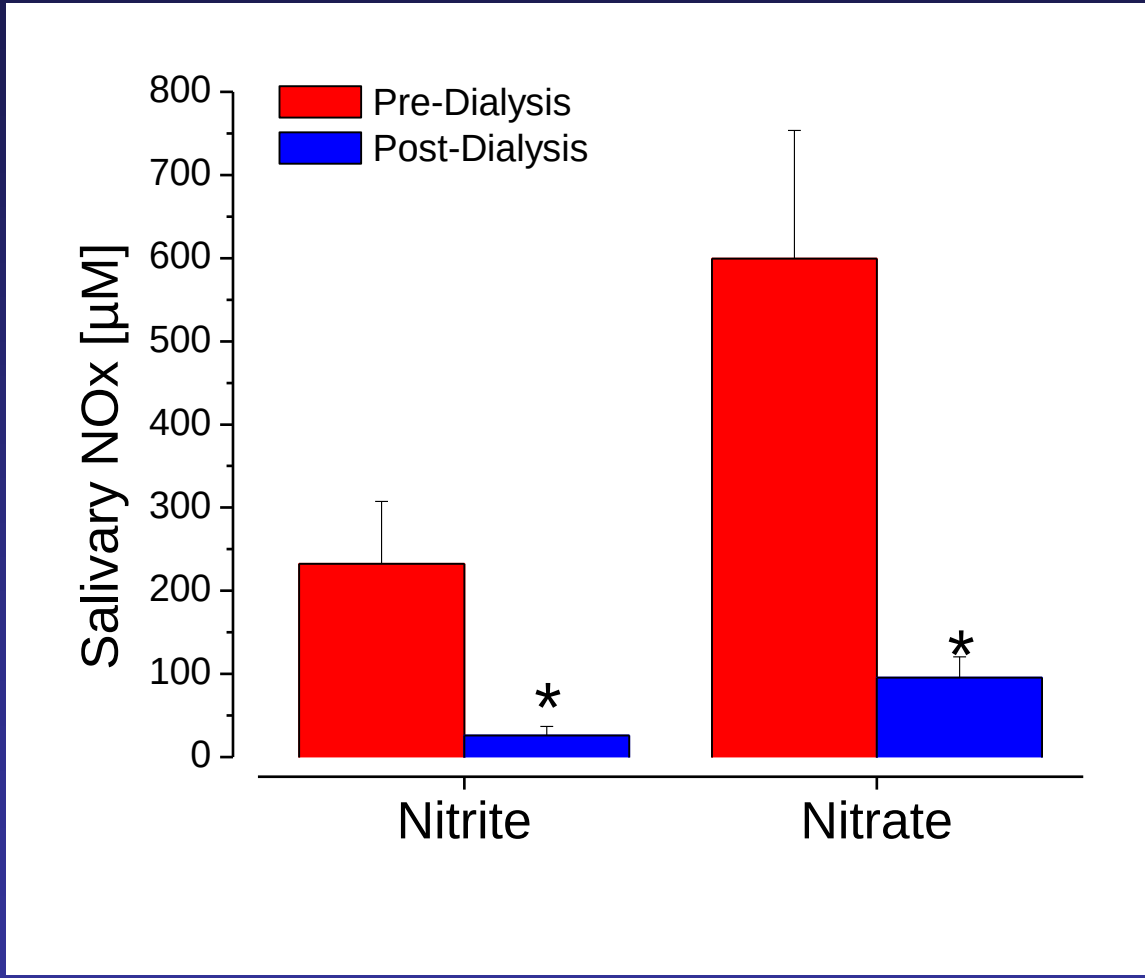


A single pass through the dialysis filter removes 67% of plasma nitrite and 84% plasma nitrate

Patients' total blood volume is filtered on average 40-50 times during the 4-5 hour session 3 times per week.

Bryan et al Free Rad Biol Med 2013

Results

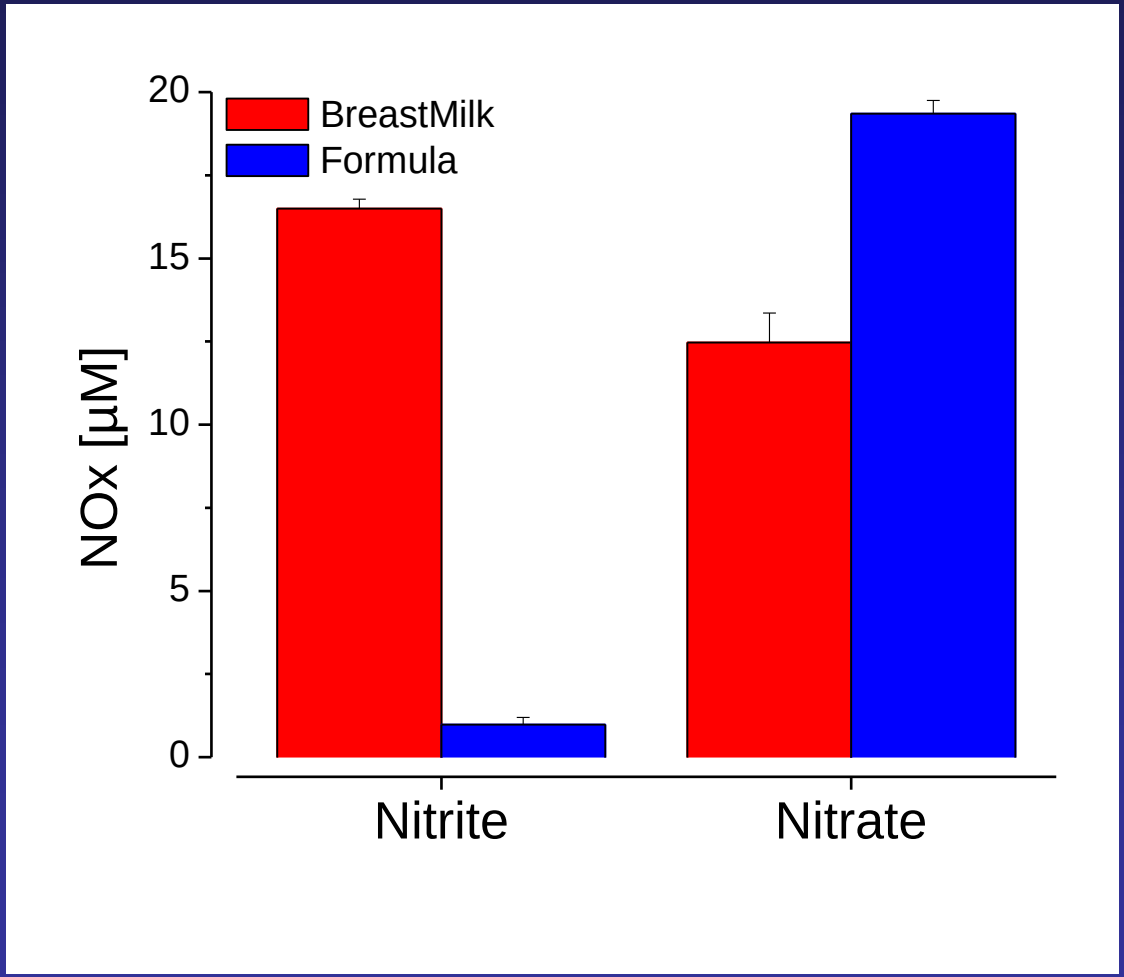


Dialysis removes as much as 90% of salivary nitrite and 85% of salivary nitrate disrupting the human nitrogen cycle to maintain NO homeostasis

Nitrite and Nitrate in Breast Milk

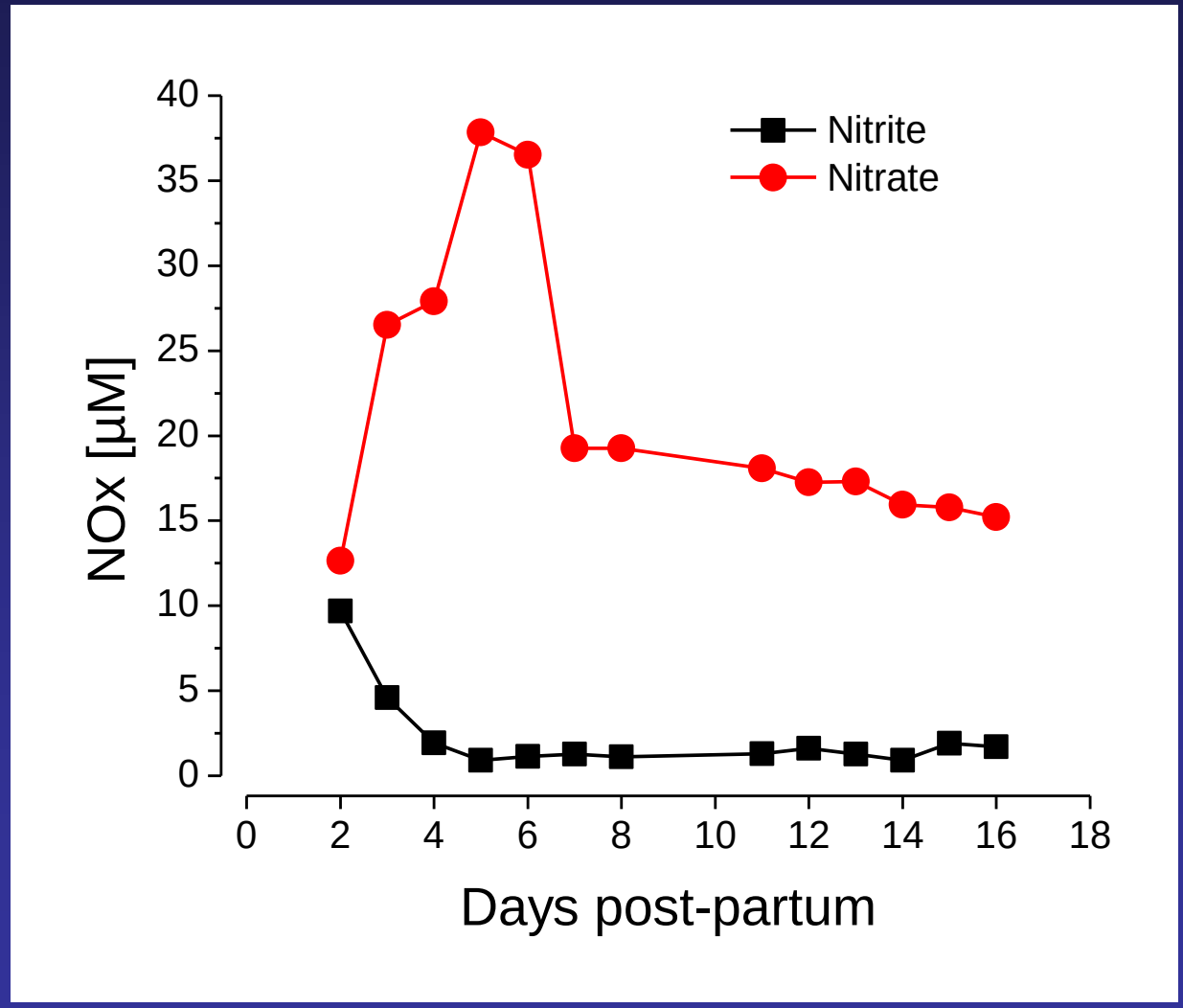
Nature’s Most Perfect Food

Nitrite in Breast Milk is Absent in Formula



0.25mg/kg

Nitrite is Enriched in Colostrum and Declines As Gut Bacteria Colonize



Hord et al
Breastfeeding Medicine
2011

Can Nitrite Overcome Variability Of Oral Microbiome and Inability to Reduce Nitrate and Affect Blood Pressure?

Safety Considerations

Acute toxicity:
1. methemoglobinemia
2. hypotension

The fatal dose of nitrite is 22-23 mg/kg body weight
(1.85g in 80kg human)
100 fold less than LD50 – FDA benchmark for safety

Long term toxicity: propensity to react with secondary amines to form carcinogenic low molecular weight N-nitrosamines

Prevent nitrosative chemistry by providing supra-stoichiometric Vitamin C or polyphenols relative to nitrite

Human body makes 20-40 mg nitrite per day
1. from NO oxidation (~10 mg)
2. from nitrate reduction (150mg X 0.05% = 7.5 mg)
3. saliva (15 mg per day)

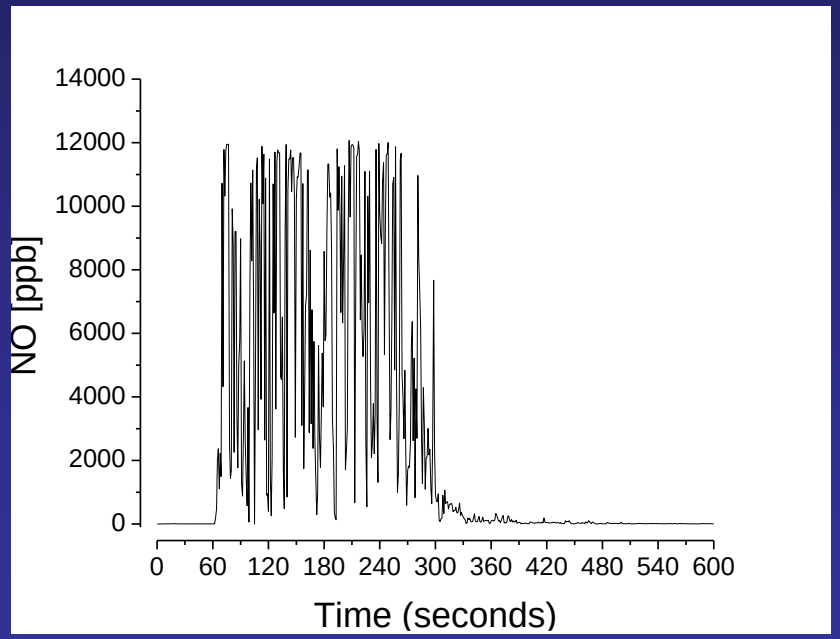
15 mg Nitrite
Oxygen independent nitrite reductase
Vitamin C (nitrosation inhibitor)

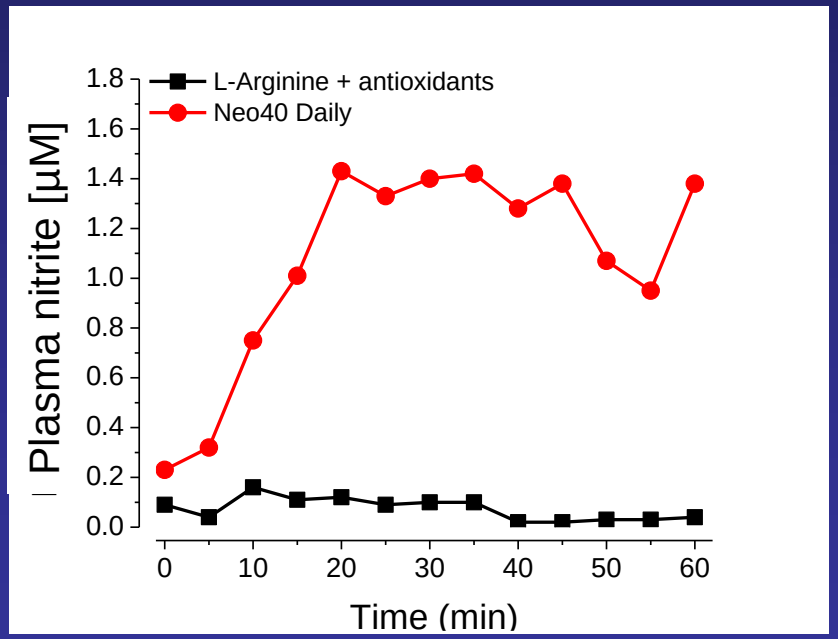
Orally disintegrating tablet in inert matrix that keeps active separated until dissolution

Generates 25-30 ppm NO gas upon dissolution for 5-6 minutes

NO lozenge Clinical Trial Results

Strong & sustained Nitric Oxide activity





Zand et al Nutrition Research 2011

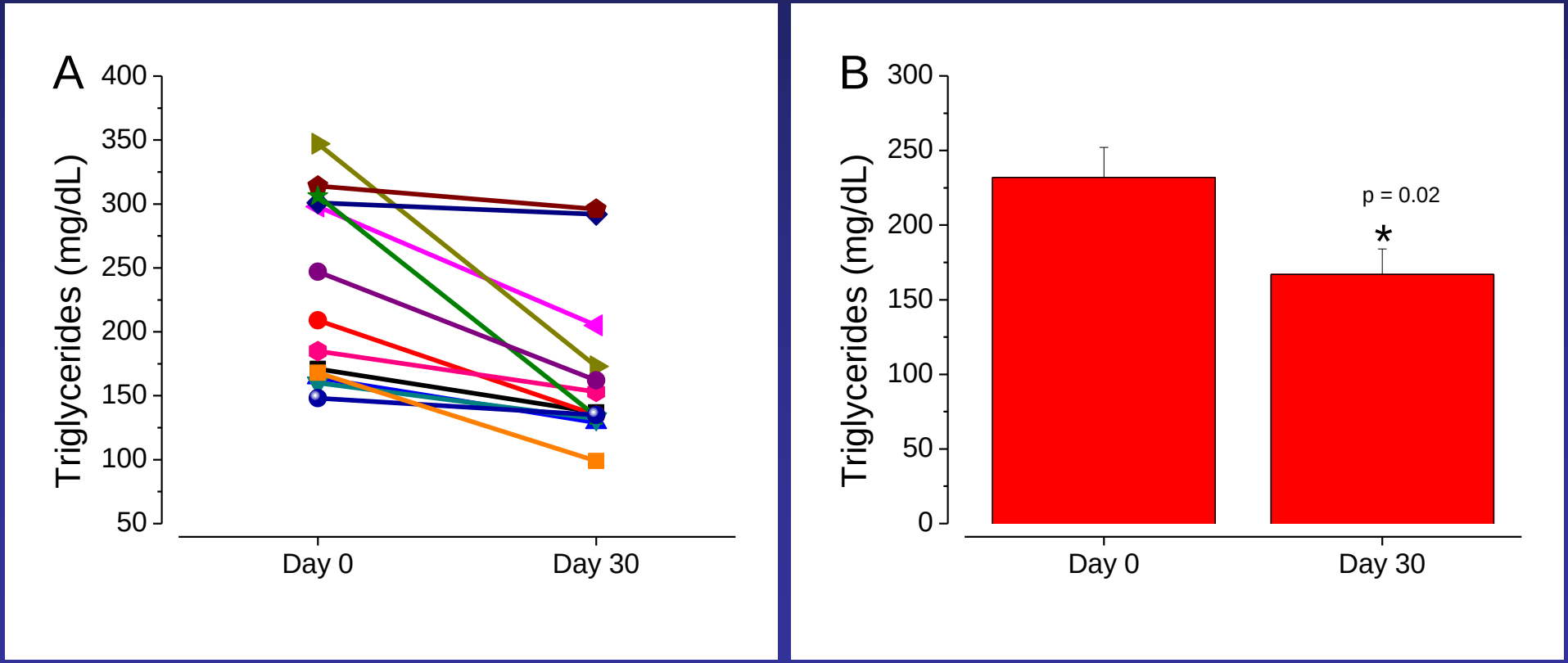
What Causes Arteries to Age?

1. Inflammation
2. Immune Dysfunction
3. Oxidative Stress

Increased oxidative stress is associated with elevated triglycerides

NO Clinical Trial Results

Significant reduction in patients
with elevated triglycerides

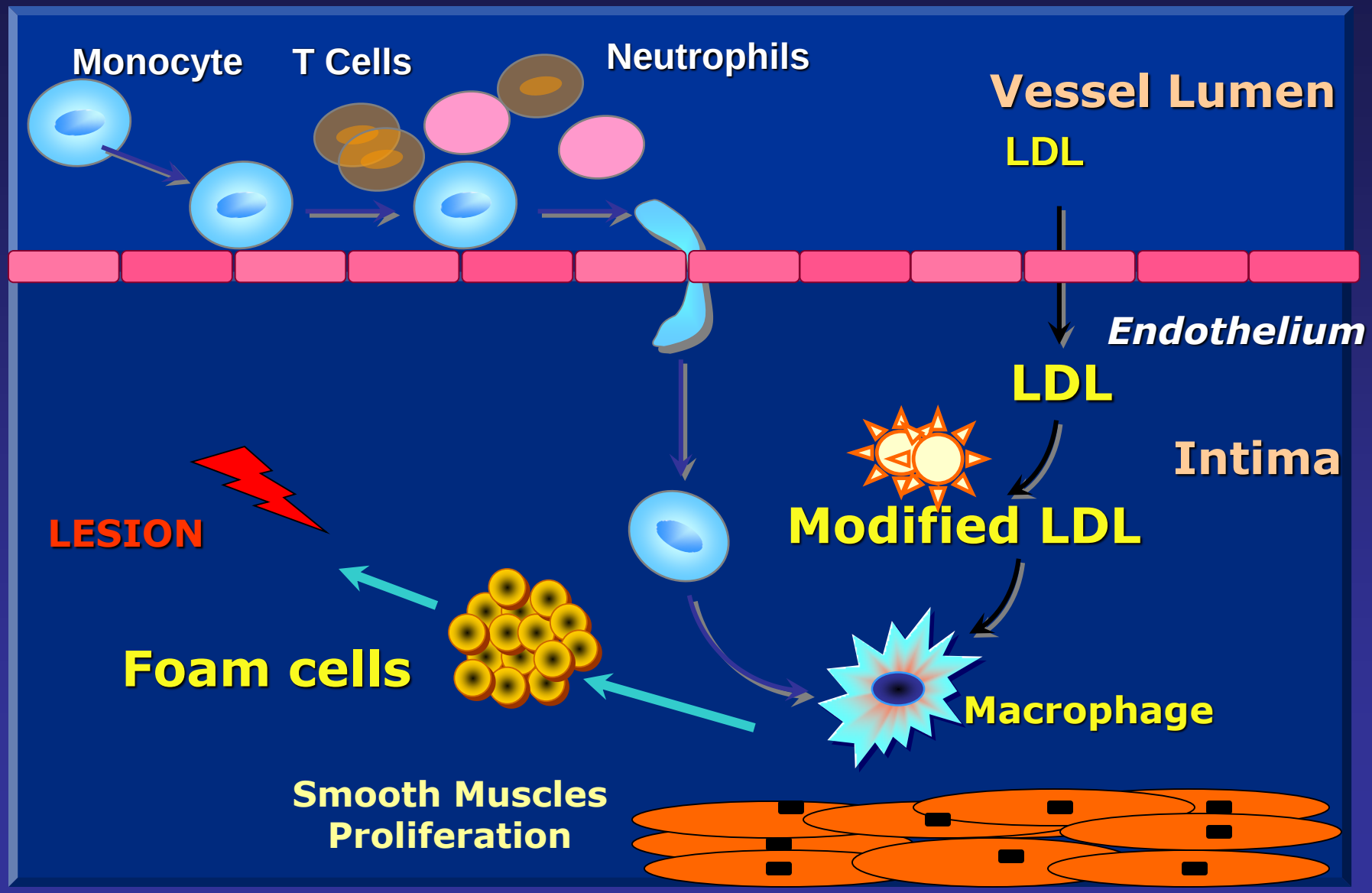


Zand et al Nutrition Research 2011

What Causes Arteries to Age?

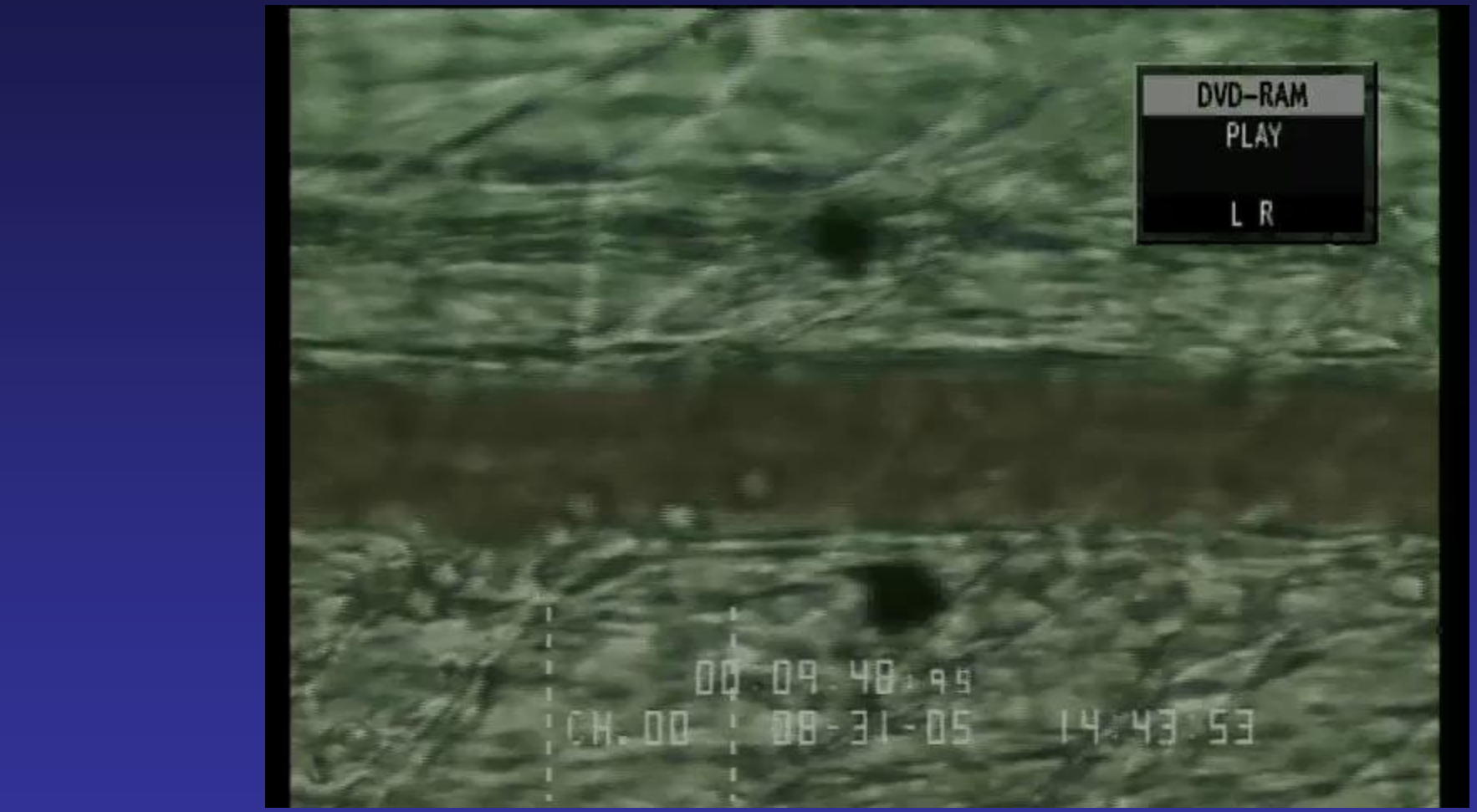
1. Inflammation
2. Immune Dysfunction
3. Oxidative Stress

Atherogenesis



Atherogenic Diet

Atherogenic Diet + NO



What Causes Arteries to Age?

1. Inflammation
2. Immune Dysfunction
3. Oxidative Stress

hsCRP is an acute marker of Inflammation

NO reduces hsCRP by 37% in 30 days

US Patent 9,119,823

What Causes Arteries to Age?

1. Inflammation
2. Immune Dysfunction
3. Oxidative Stress

Having high blood pressure puts you at risk for heart disease and stroke, which are leading causes of death in the United States

Achieving a target systolic pressure of 120 millimeters of mercury (mm Hg), reduced rates of cardiovascular events, such as heart attack and heart failure, as well as stroke, by almost a third and the risk of death by almost a quarter, as compared to the target systolic pressure of 140 mm Hg.

SPRINT trial

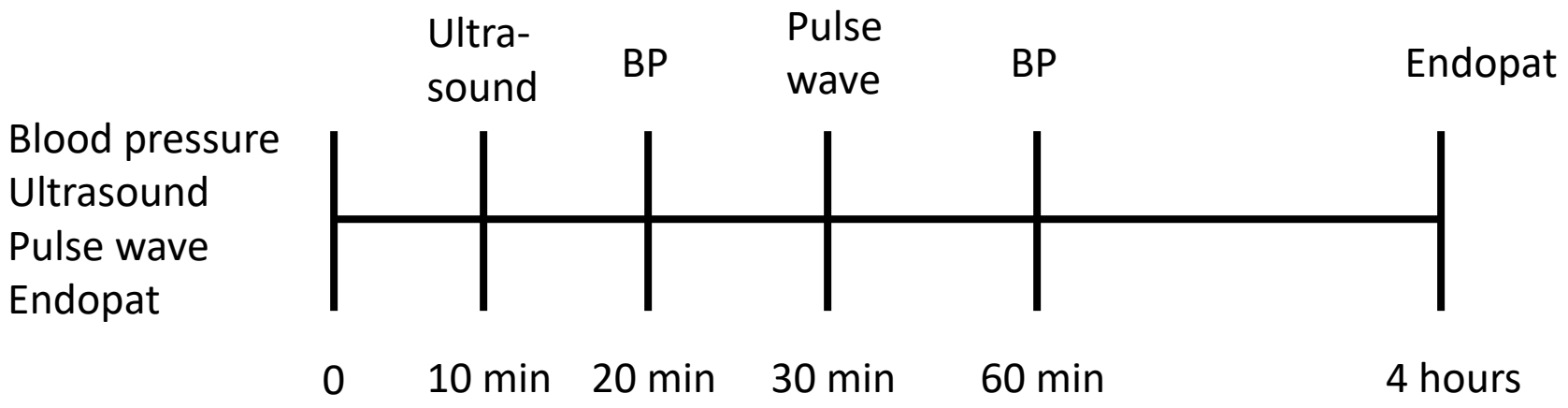
There are over 400 risk factors or markers for CVD

Most if not all can be corrected by restoring NO production

Hypertension is the #1 risk factor for development of cardiovascular disease

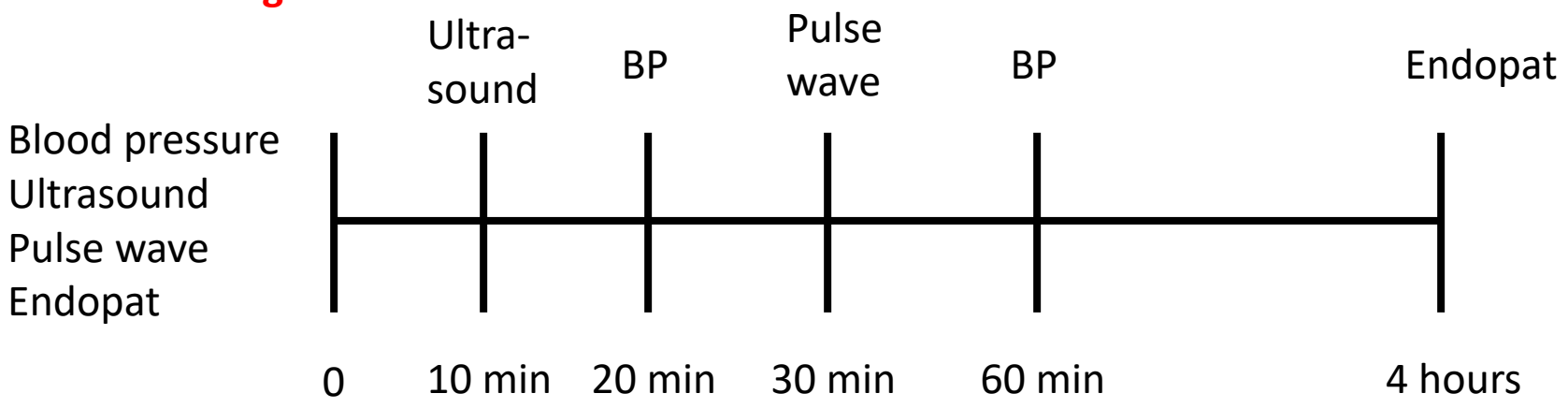
Hypertension Study Protocol

Active lozenge

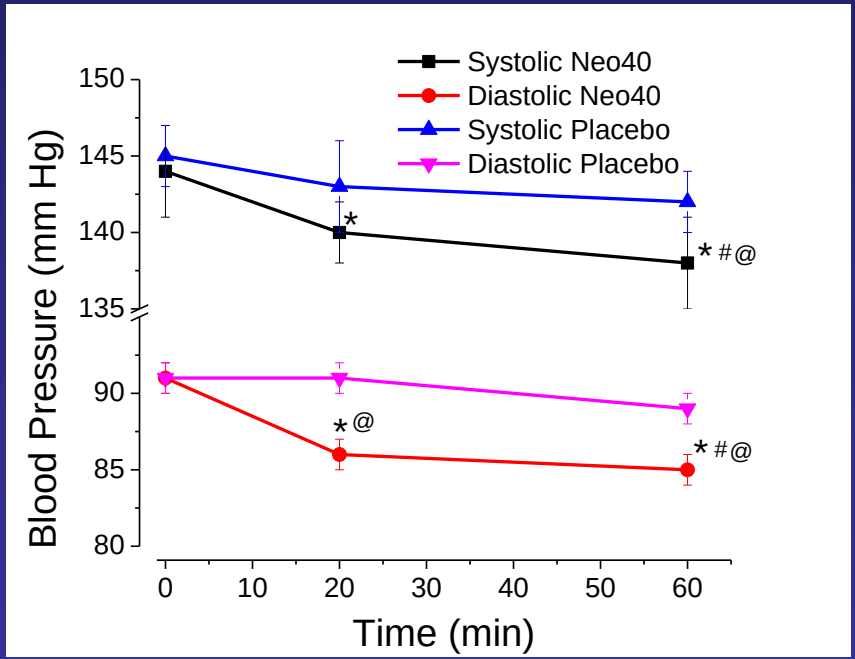


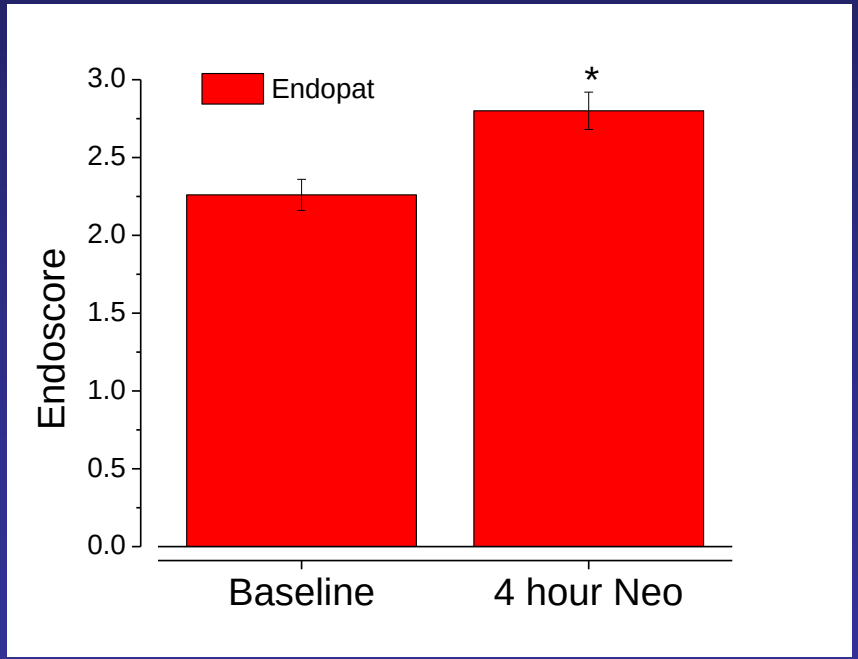
3 week washout

Placebo lozenge



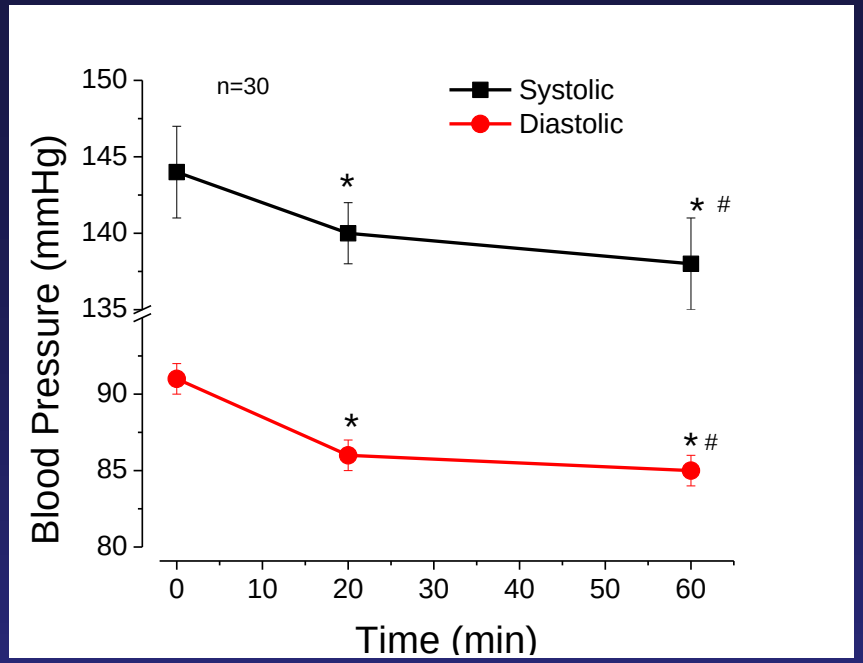
Hypertension Trial – Vanderbilt Univ

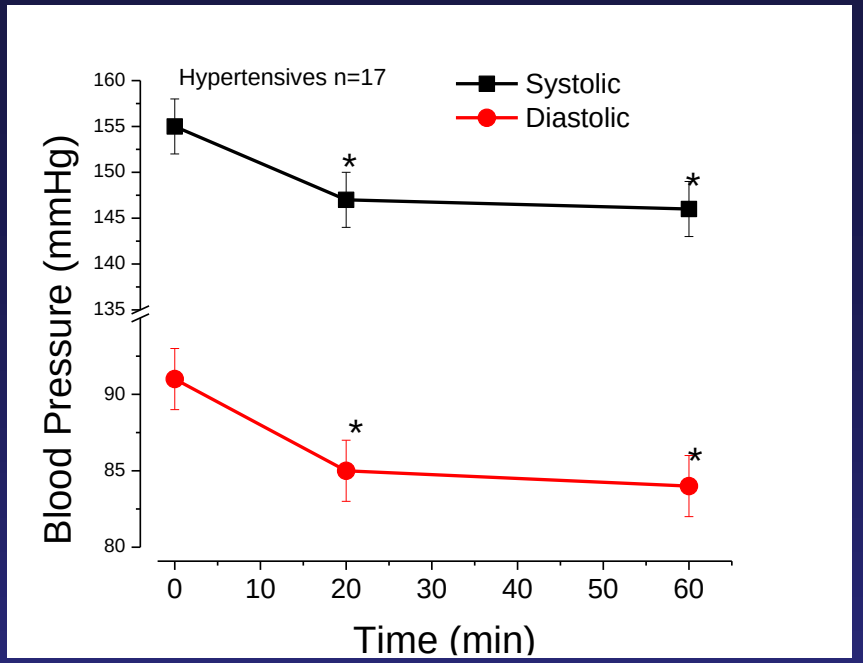


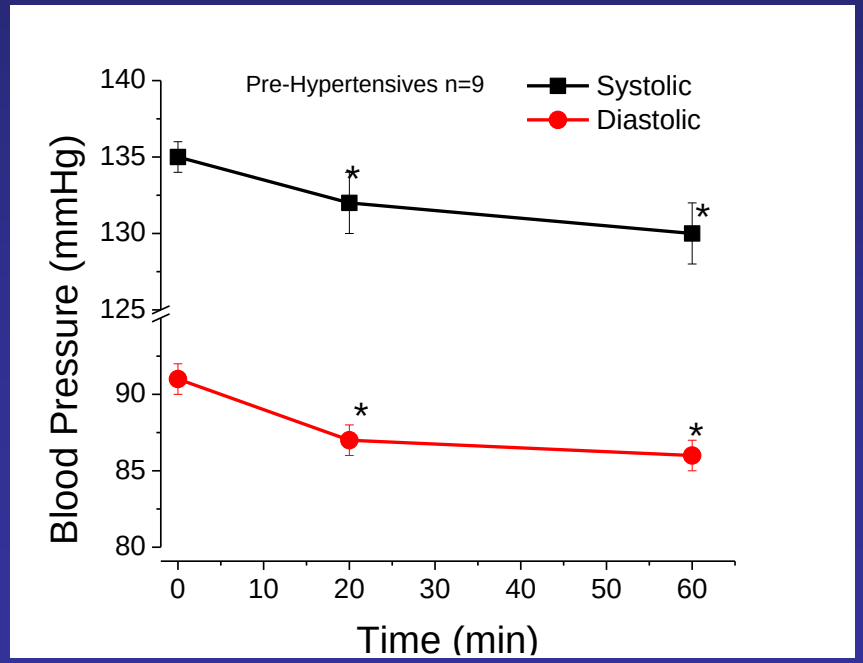


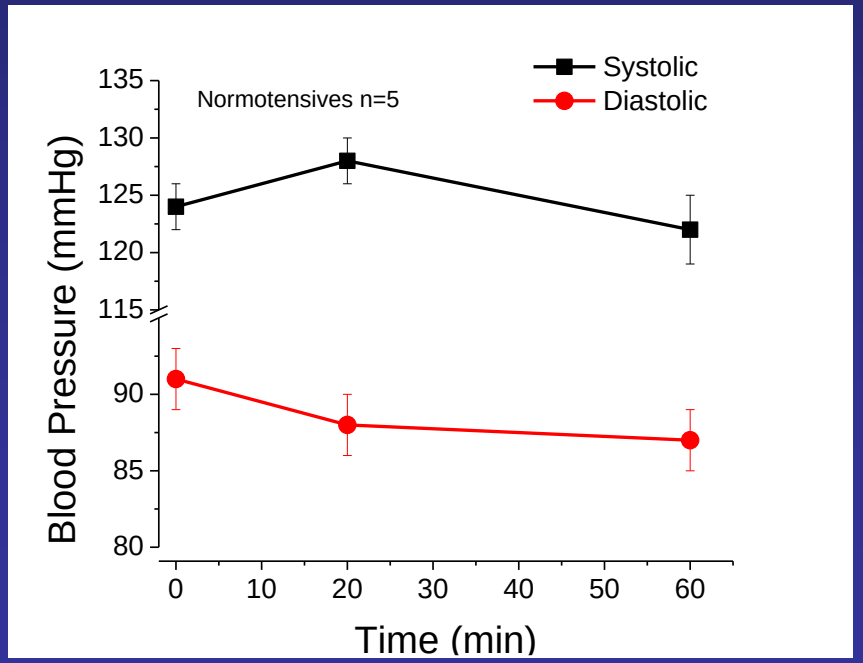
Flow mediated dilation

Houston, Hays JCH 2014

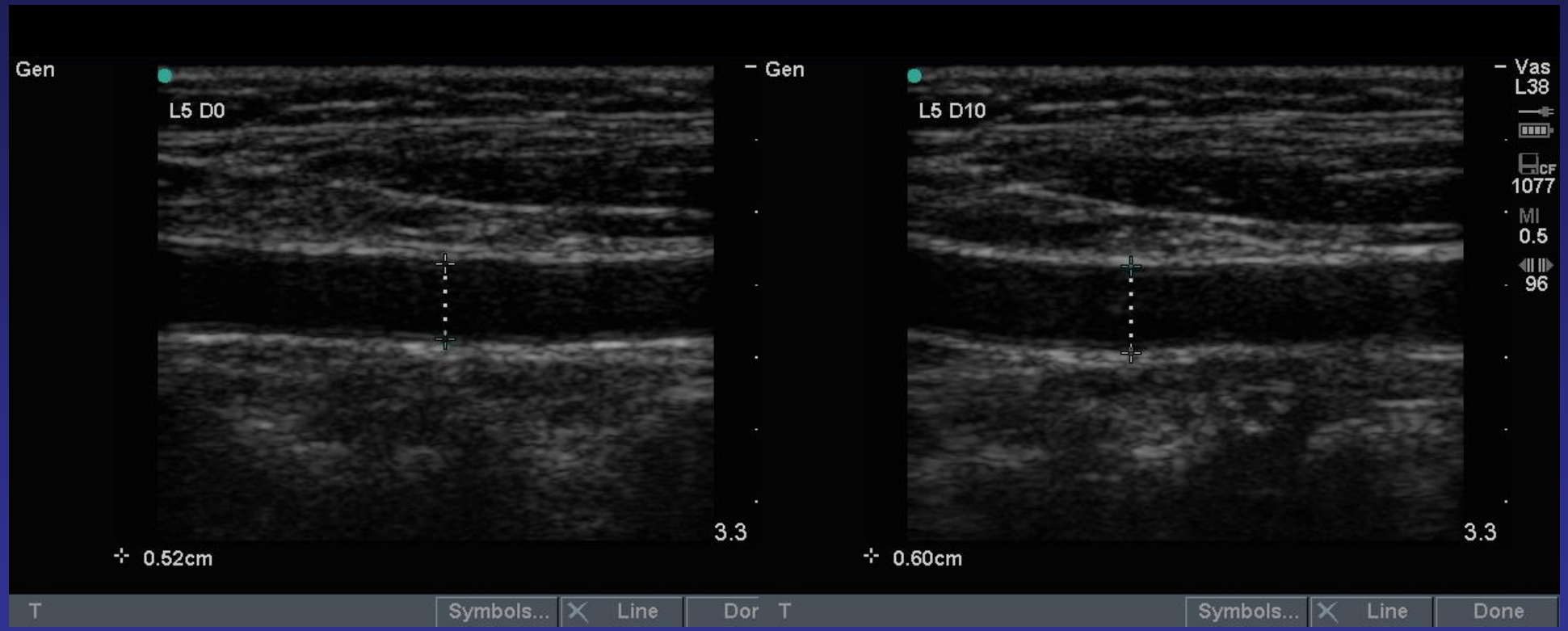

n=30
Systolic
Diastolic
Blood Pressure (mmHg)
Time (min)
150
145
140
135
90
85
80
0
10
20
30
40
50
60
*
*
* #
*
*
* #


Hypertensives n=17
Systolic
Diastolic
Blood Pressure (mmHg)
Time (min)
160
155
150
145
140
135
90
85
80
0
10
20
30
40
50
60
*
*
*
*


Pre-Hypertensives n=9
Systolic
Diastolic
Blood Pressure (mmHg)
Time (min)
140
135
130
125
90
85
80
0
10
20
30
40
50
60
*
*
*
*


Normotensives n=5
Systolic
Diastolic
Blood Pressure (mmHg)
Time (min)
135
130
125
120
115
90
85
80
0
10
20
30
40
50
60

Representative Ultrasound Before and 10 minutes after NO Lozenge



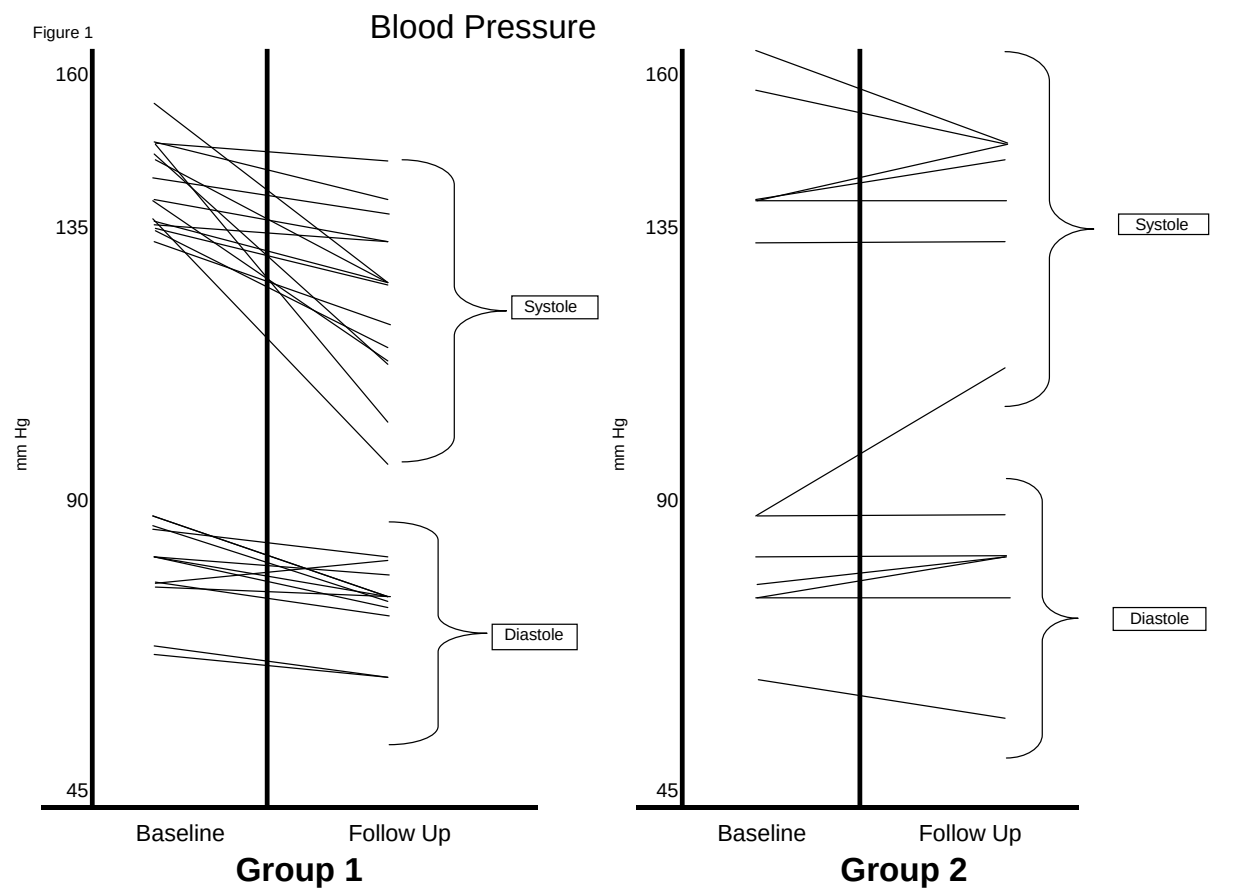
13% increase in vessel diameter causes a 34% increase in blood flow

Average Changes in 10 subjects
After 30 minutes

	AVG % Chg 7min
Systole	-8.29%
Diastole	-8.15%
MAP	-7.91%
Heart Rate	-1.09%
Central Systolic Pressure	-7.25%
Central Diastolic Pressure	-8.84%
Cardiac Output	5.31%
Total Vascular Resistance	-12.72%
Augmentation Pressure	-46.76%
Aug. Index@75 [90% C]	-60.37%
Pulse Wave Velocity [90% C]	-1.96%

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

Pre-Hypertension Trial – Cedars Sinai School of Medicine



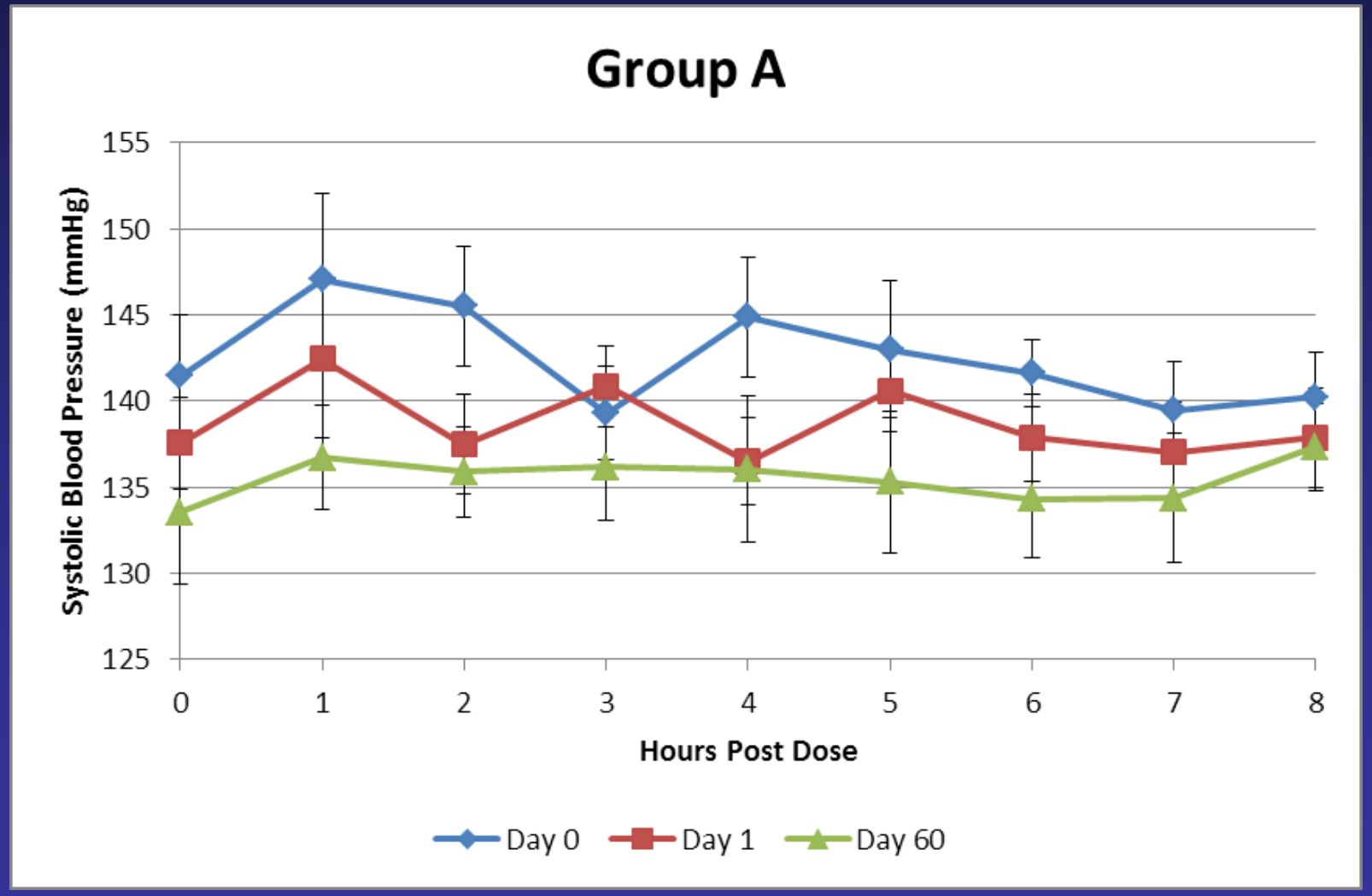
Biswas et al JCPT 2015

30 Day Placebo controlled Trial

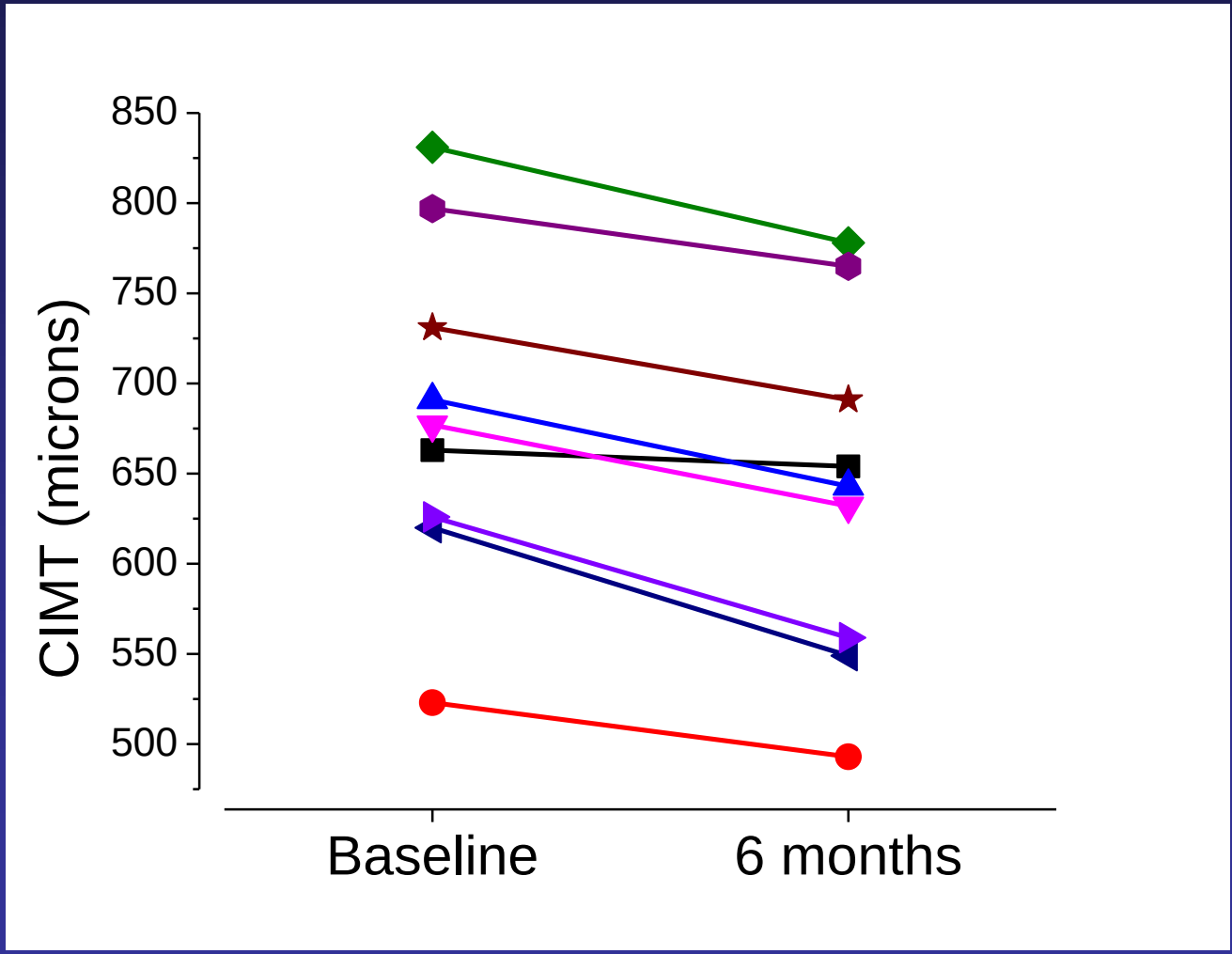
	Group 1 (mean ± SD)			Group 2 (mean ± SD)			Baseline: NO vs placebo (p-value)	Follow-Up: NO vs placebo (p-value)
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
BP (mmHg, systole; diastole)	138±12; 84±5	126±12; 78±4	12; 6 reduction (p<0.001)	138±21; 80±8	135±17; 82±8	N.S.	0.19; 0.012	0.26; 0.25
Heart Rate (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

Biswas et al JCPT 2015

Hypertension 60 day trial



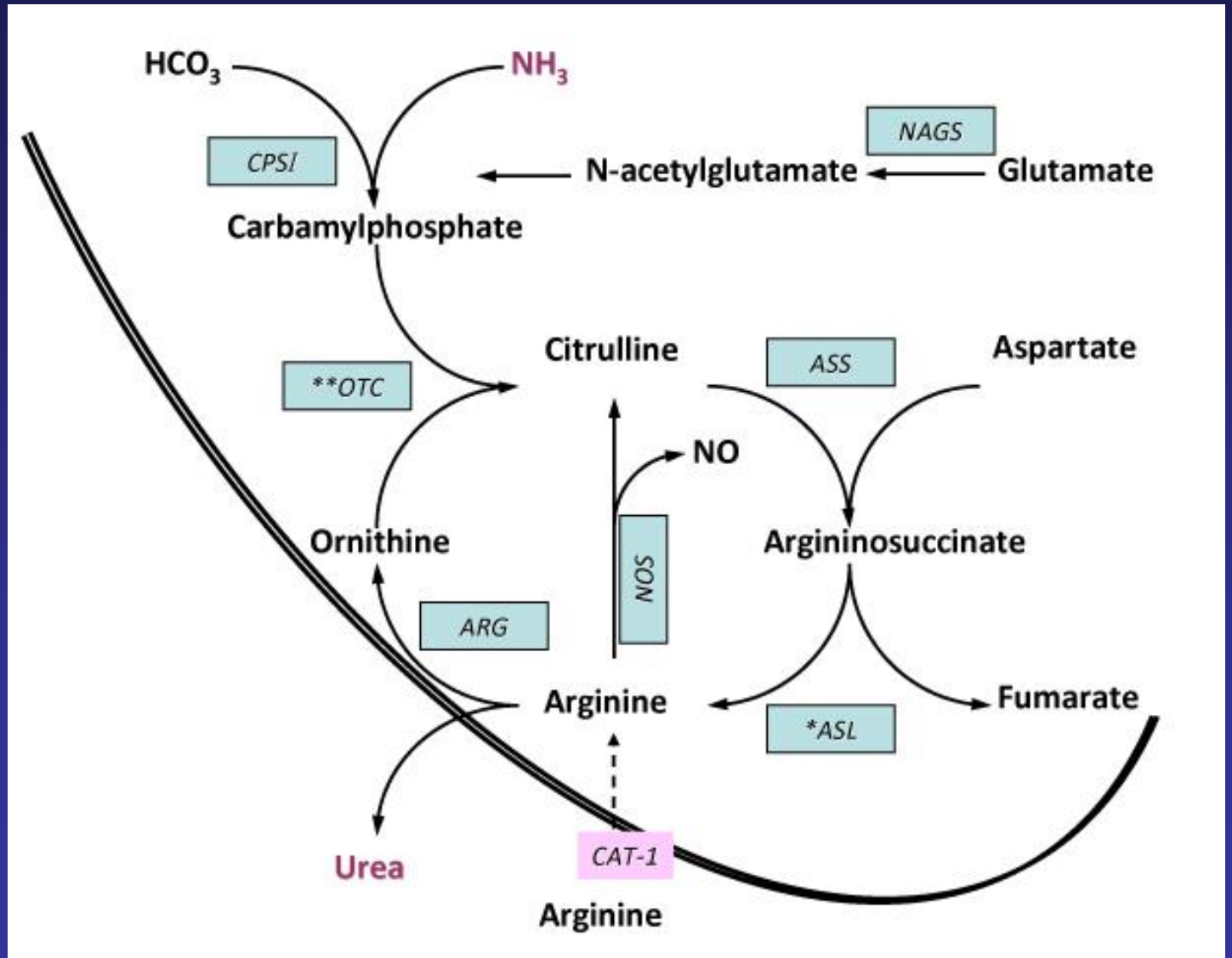
NO Supplement Leads to Plaque Regression



Edwin Lee MD – case report

NO Lozenge Rescues Inborn Error in Metabolism

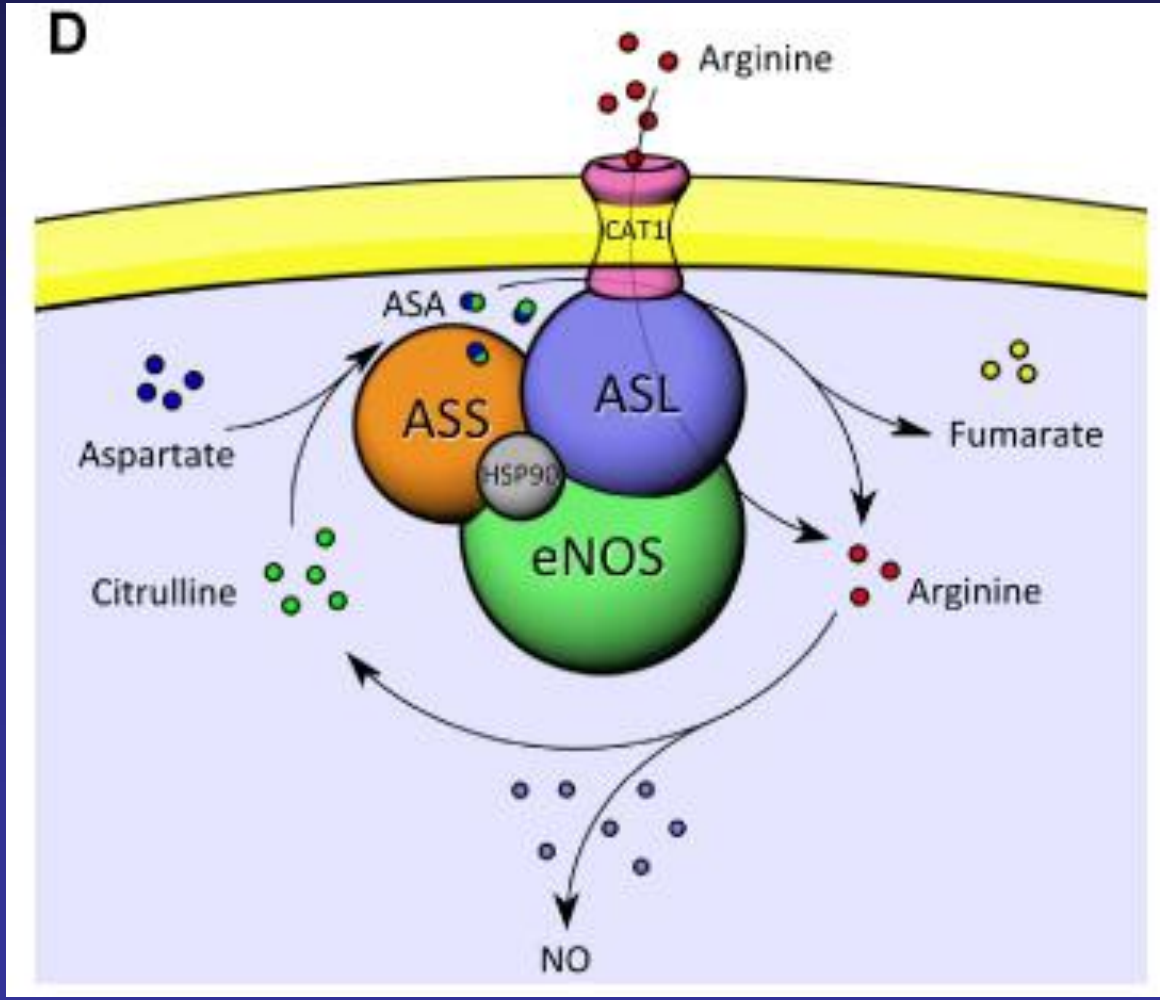
The Urea Cycle converts ammonia to urea for excretion



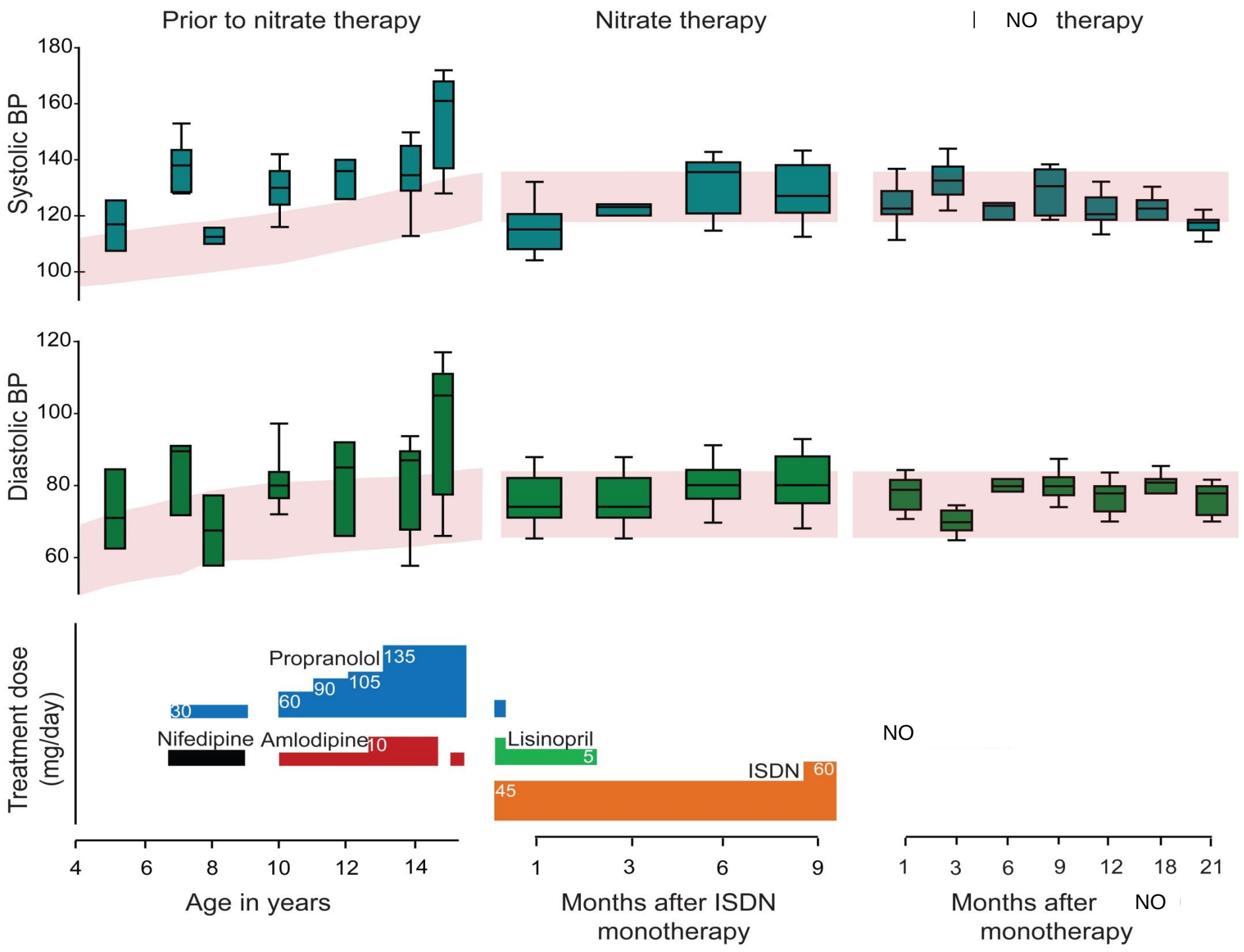
ASL deficiency is an Inborn error in metabolism

- Hyperammonemia
- In addition:
  - Progressive liver dysfunction and cirrhosis
  - Coagulopathy
  - Neurological dysfunction independent of recurrent hyperammonemia
  - Hypertension
  - Renal dysfunction
- More than hyperammonemia?

NOS Utilizes Intracellular L-Arginine from L-citrulline for NO Production



Erez et al Nat Med 2011


Prior to nitrate therapy
Nitrate therapy
NO therapy
Systolic BP
180
160
140
120
100
Diastolic BP
120
100
80
60
Treatment dose (mg/day)
Propranolol
135
105
90
60
30
Nifedipine
Amlodipine
10
Lisinopril
5
ISDN
60
45
NO
4
6
8
10
12
14
Age in years
1
3
6
9
Months after ISDN monotherapy
1
3
6
9
12
18
21
Months after NO monotherapy

Echocardiogram measurements before and after initiation of NO supplementation.

Left ventricle (LV) parameters	Before NO supplementation (z-score)	After NO supplementation (z-score)
LV diastolic septal thickness	2.26	1.33
LV diastolic dimension	-2.10	-0.36
LV diastolic wall thickness	3.59	2.24
LV systolic septal thickness	4.08	1.94
LV systolic dimension	-2.08	-0.67
LV systolic wall thickness	3.01	1.53

Echocardiogram measurements of LV dimensions taken before and 5 months after initiation of NO supplementation. All parameters demonstrate normalization.
Also increased the number of circulating endothelial progenitor cells

From: Bryan & Jamie
Sent: Wednesday, August 03
To:
Subject: Jon

Just wanted to share something with you guys. Jon wanted to play chess tonight with Bryan. They have done this forever. Bryan has tried to teach him how to play over the years. He knows the pieces by name and what move that they can make but has never been able to comprehend the strategy needed to be successful. For instance, he has never understood how he needs to "protect" his pieces. Tonight he actually "foiled" Bryan's plays without Bryan's guidance. He thought through his plays, planned ahead and won the game. Bryan helped him but he truly came up with the plays himself and won the game.

Bryan asked him if he had been taking "smart pills" and Jon told him yes, the purple ones. I think he is right!

Jamie

NEW PARADIGM FOR NO REGULATION

- There exists specific bacterial communities that provide the human body with continuous sources of nitrite and NO from dietary nitrate.

- Contributes to optimal cardiovascular health (regulates BP)

- Absence of these oral bacterial communities affects NO homeostasis.

- Individuals deficient in these commensal bacteria would be NO deficient and perhaps at increased risk for cardiovascular disease

- Low dose nitrite can overcome oral microbiome diversity and normalize blood pressure and reduce inflammation

CONCLUSIONS

- There are profound effects of NO on health and disease
- Recognizing NO insufficiency is critical for prevention of disease
- Implementing lifestyle modification and strategies to restore NO production is fundamentally important is health and well-being
- Implementing the basics of physiology and cell biology is critical for optimal health (Identify cause of disease, remove toxicant and restore physiology)
- Patients will not get better without restoration of NO

You cannot practice medicine effectively without correcting NO status in patients

Current Ongoing Clinical Trials

1. KGK Hyp-Prehyp trial
2. BCM Pre-eclampsia trial
3. Iowa Vascular Age trial
4. Schwarz Prehyp trial
5. BCM ASA trial
6. Cialis/NO Combo ED trial
7. THI Pulmonary Hypertension trial
8. Methodist PAD trial

All truth passes through three stages.
First, it is ridiculed.
Second, it is violently opposed.
Third, it is accepted as being self-evident.

—

Arthur Schopenhauer,
German philosopher (1788 – 1860)

Nutrition and Health
Series Editor: Adrianne Bendich Ph.D., FACN

Nathan S. Bryan, Ph.D. · Joseph Loscalzo, M.D. *Editors*

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 dieticians, 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.

Internal Medicine

ISBN 978-1-60761-615-3

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Bryan · Loscalzo *Eds.*

Nitrite and Nitrate in Human Health and Disease

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Series Editor: Adrianne Bendich

Nathan S. Bryan
Joseph Loscalzo *Editors*

Nitrite and Nitrate in Human Health and Disease

Humana Press