Endothelial Dysfunction and Aging

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Capt. Chesley “Sully” Sullenberger

- “At times we need to fly the plane not the instruments”

Endothelium…

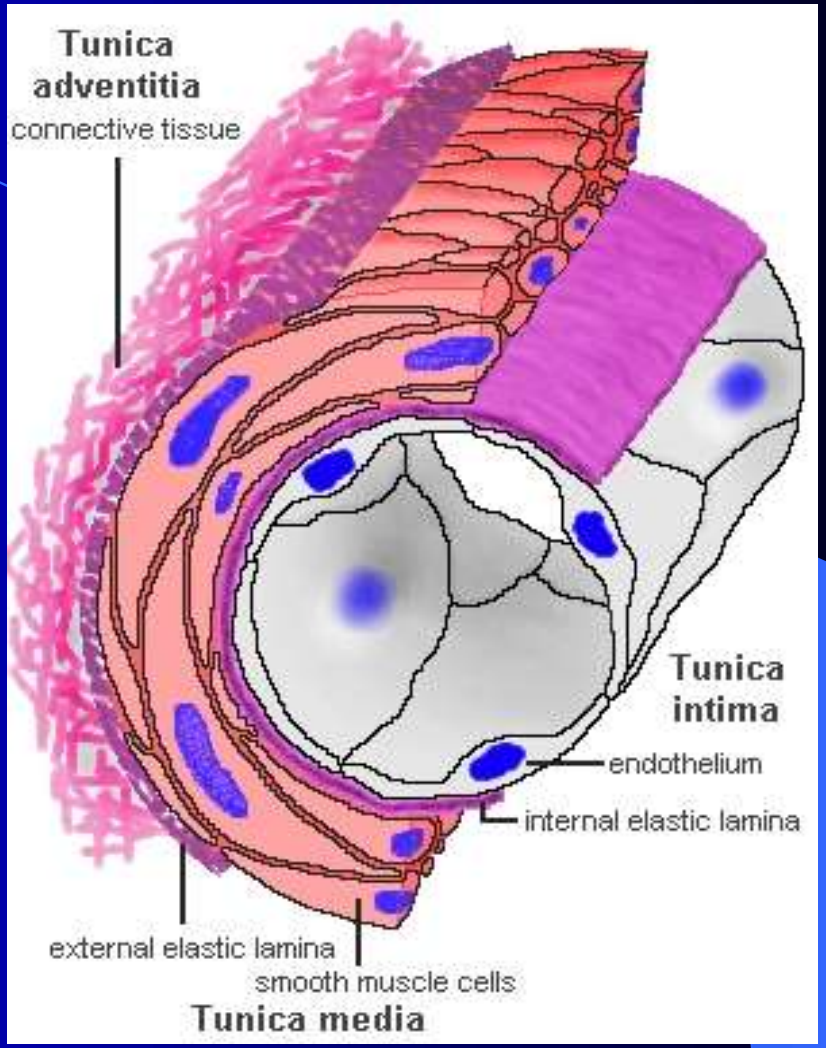
- 60,000 miles of blood vessels in an adult human body
- “endothelium,” form the inner lining of blood vessels and lymph vessels, forming a thin layer between the vessel walls and the flowing blood
- Interface between the blood and the rest or our body

Endothelium….

- Spread out, it would cover 3500 square feet
- Weighs only 6 ounces.

Endothelium….

- The endothelium is the body's natural defense against blood clots in arteries. When it is eroded away, the cells deeper in the artery start to clot the blood.
- Matrix GLA protein!!...



Basics…

- The vascular endothelium is a crucial regulator of vascular function and homeostasis
- Regulation of:
  - vascular tone and blood pressure
  - has antithrombotic properties (hepran sulfate),
  - modulates interactions between the blood vessel wall and circulating leukocytes and platelets
  - acts as a paracrine organ by secretion of vasoactive substances that mitigate these varied functions

- Cooke, J. P. (2000) The endothelium: a new target for therapy. Vasc. Med. 5:49-53.
- Anderson, T. J. (1999) Assessment and treatment of endothelial dysfunction in humans. J. Am. Coll. Cardiol. 34:631-638.

Basics…

- NO is generated in the endothelium by the conversion of the essential amino acid L-arginine to L-citrulline by the enzyme, endothelial NO synthase (eNOS)
- Both the L- and D-enantiomers of arginine are present within the human circulation
- Only L-arginine is recognized by eNOS as the substrate for production of NO

- Moncada, S. & Higgs, A. (1993) The L-arginine–nitric oxide pathway. N. Engl. J. Med. 329:2002-2012.
- Palmer, R. M., Ashton, D. S. & Moncada, S. (1988) Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 333:664-666.

Basics…

- The mechanism of benefit of L-arginine on endothelial function is unclear, because intracellular concentrations of L-arginine far exceed that required by eNOS….
- ***"Arginine paradox"*** is that L-arginine restores endothelial function in atherosclerotic patients, in whom there are elevated levels of asymmetric di-methyl-arginine, an endogenous inhibitor of eNOS.
  - 2004 The American Society for Nutritional Sciences
  - **Arginine and Endothelial and Vascular Health[1,]**

Basics…

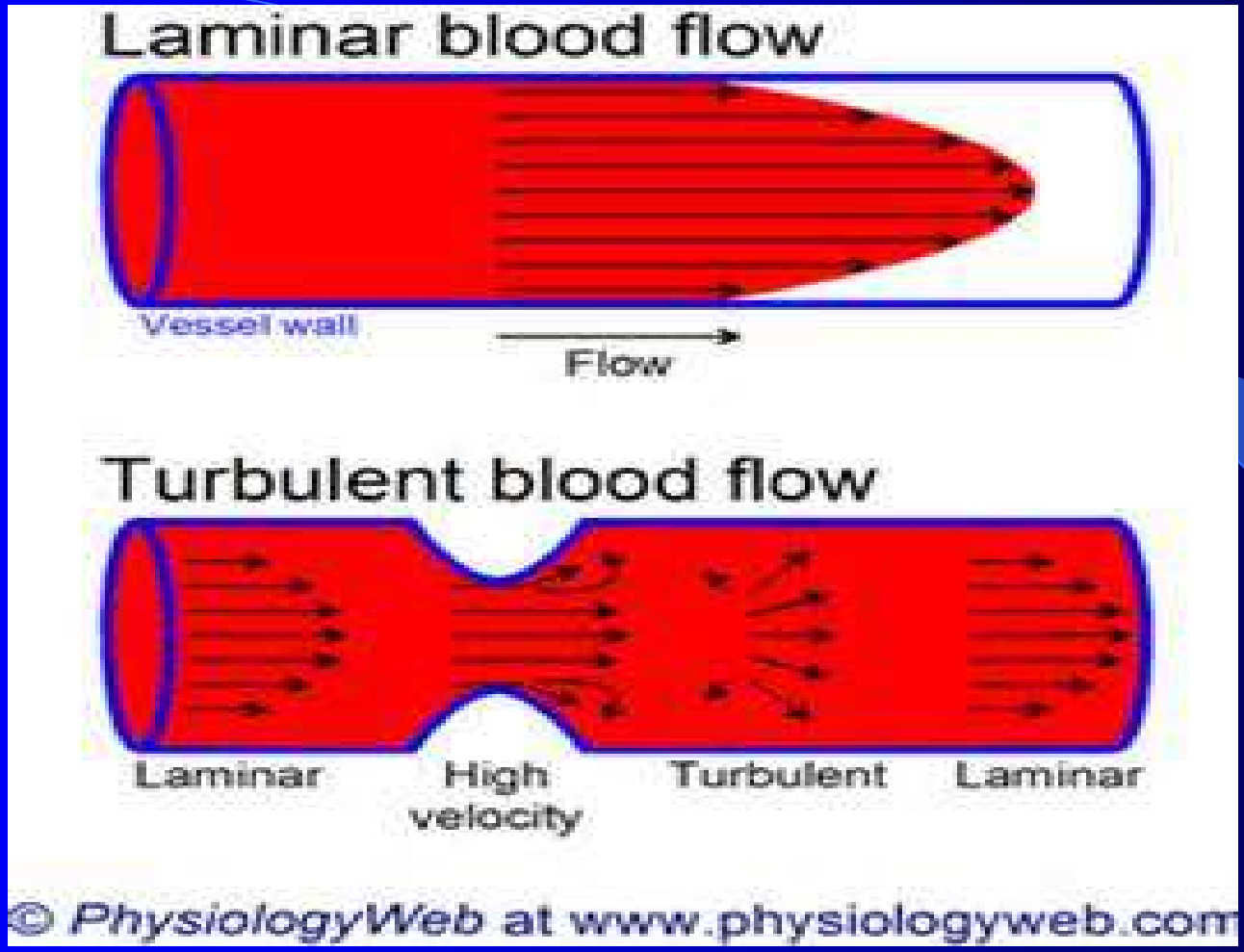
- Biochemical stimuli:
  - acetylcholine or bradykinin
  - shear stress,
    - …..activate receptors on the endothelial cell surface and cause influx of intracellular calcium, which activates eNOS
  - Moncada, S. & Higgs, A. (1993) The L-arginine–nitric oxide pathway. N. Engl. J. Med. 329:2002-2012.
  - Palmer, R. M., Ashton, D. S. & Moncada, S. (1988) Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 333:664-666.

Turbulent Flow

- Where does plaque typically form in an artery?
- What is turbulent flow?

Basics of Turbulent Flow

- A flow is laminar or turbulent depends of the relative importance of fluid friction (viscosity) and flow inertia
- The ratio of inertial to viscous forces is the Reynolds number


Laminar blood flow
Vessel wall
Flow
Turbulent blood flow
Laminar
High velocity
Turbulent
Laminar
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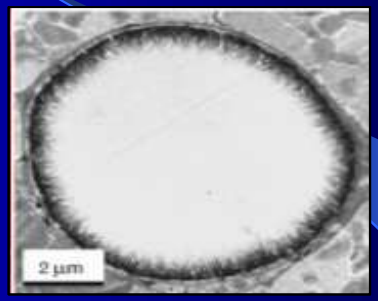
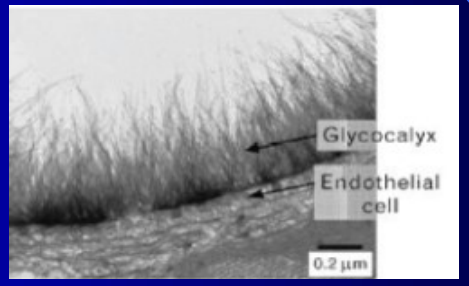
Basics…

- Furchgott et al.'s work established that Nitric Oxide (NO) is involved in:
  - Vascular tone
  - Inflammation
  - Coagulation
  - Oxidation

Endothelial Protective Membrane(Endothelial Glycocalyx)

- Thanks to improved imaging technology, scientists have recently identified a key component of the endothelium that is crucial to the arteries' **natural defense system: a hair-like gel layer..**
- It has been suspected that arteries probably have this sort of *natural barrier,* and that its health is linked to vascular conditions.

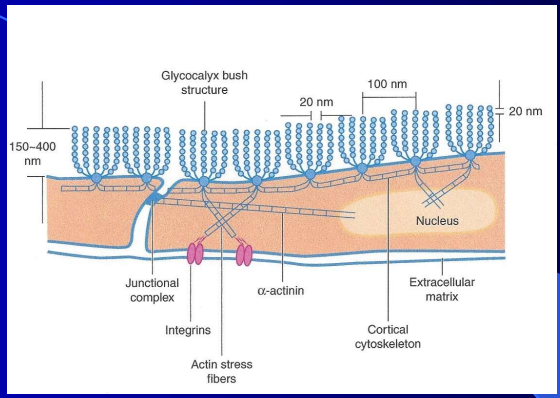


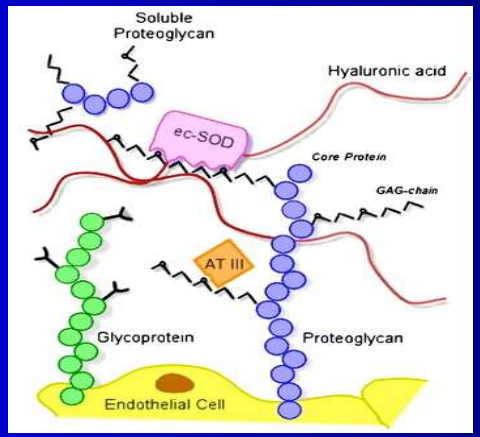


The arterial glycocalyx..photo micrograph

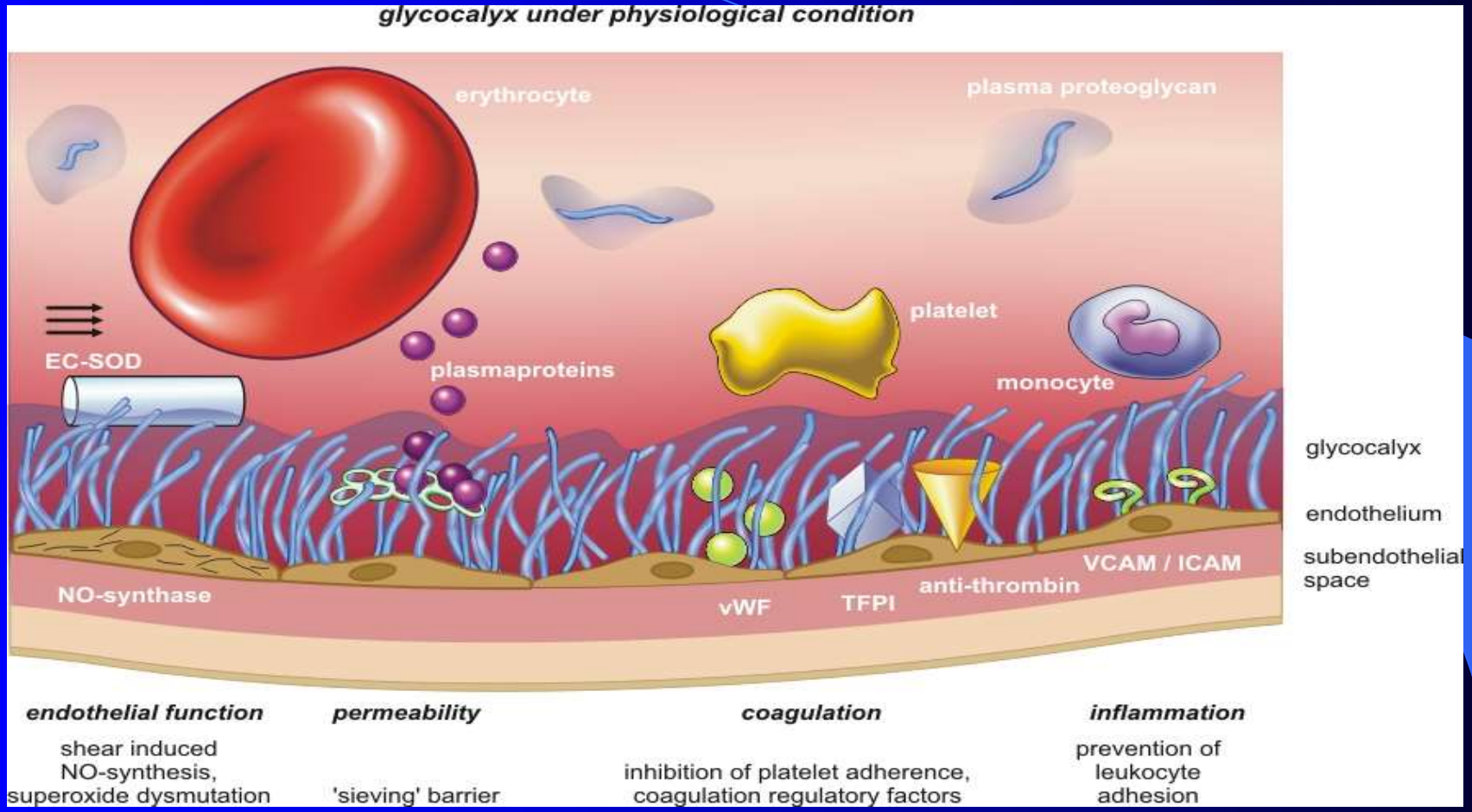
Arteries First line of defense…

- Made of a mesh of proteo-glycans, glycos-aminoglycans, glyco-lipids, glyco-proteins creating a slippery gel like layer

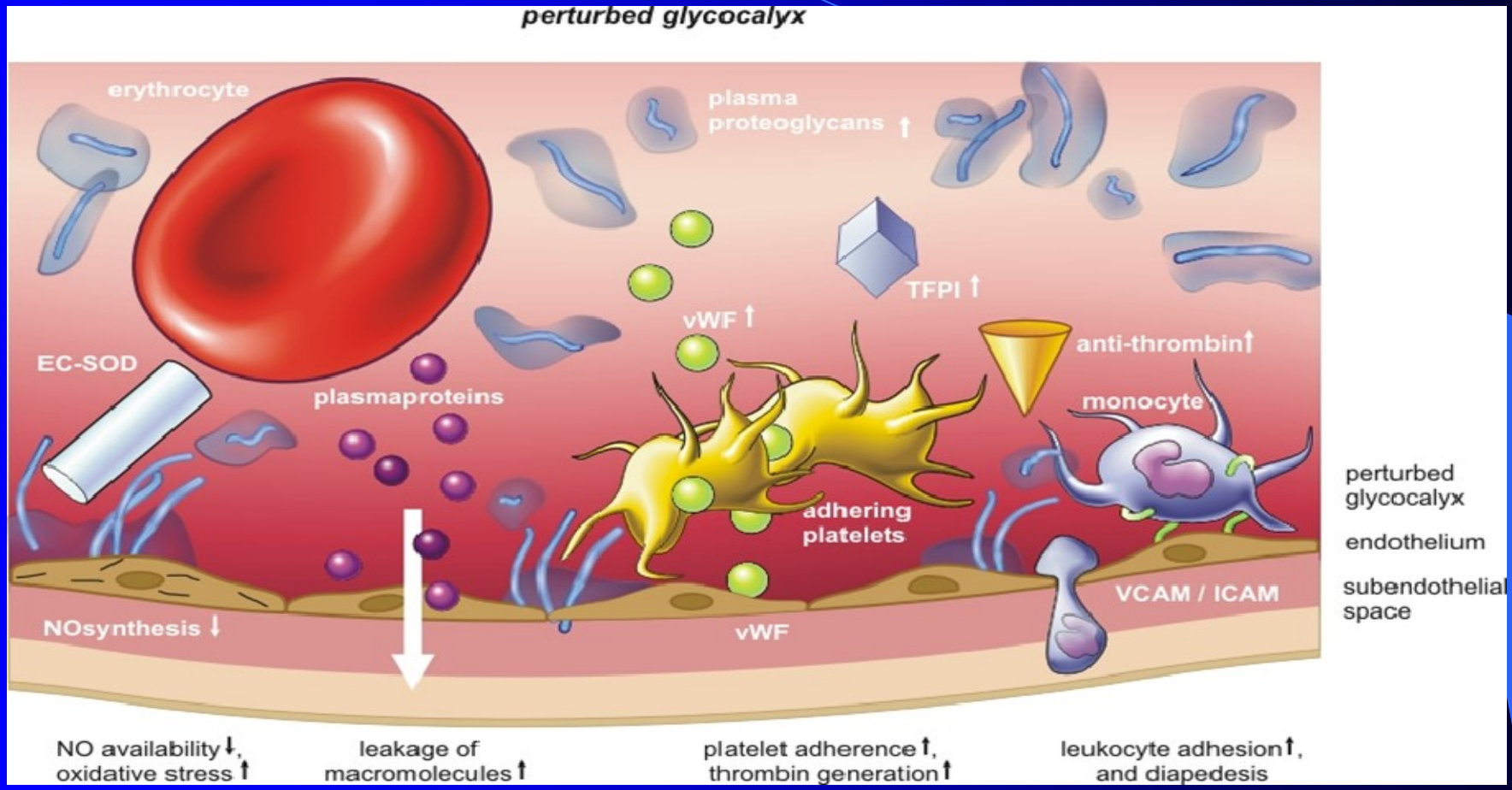




The Healthy Endo-Protective Membrane(Glycocalyx)

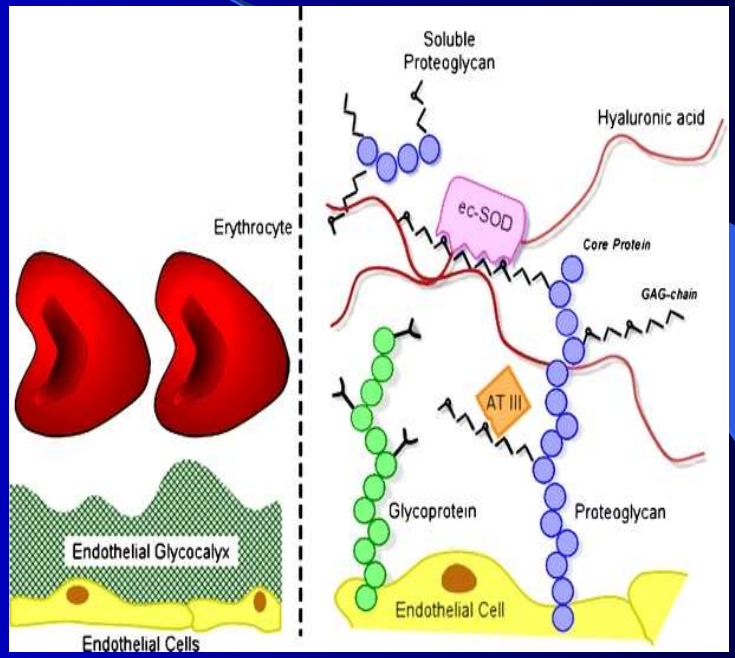


The Endo-Protective Membrane(Glycocalyx) in Disease



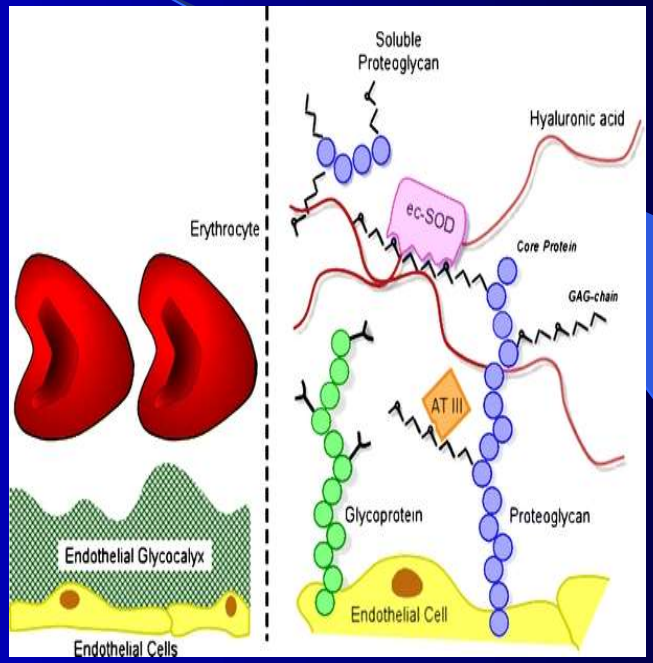
EPM(Glycocalyx) –Function--Limits Access(Barrier)…

- Limits access of circulating plasma components to endothelial cells membranes, such as…
- oxidized lipoproteins,
- activated platelets,
- sticky leukocytes.



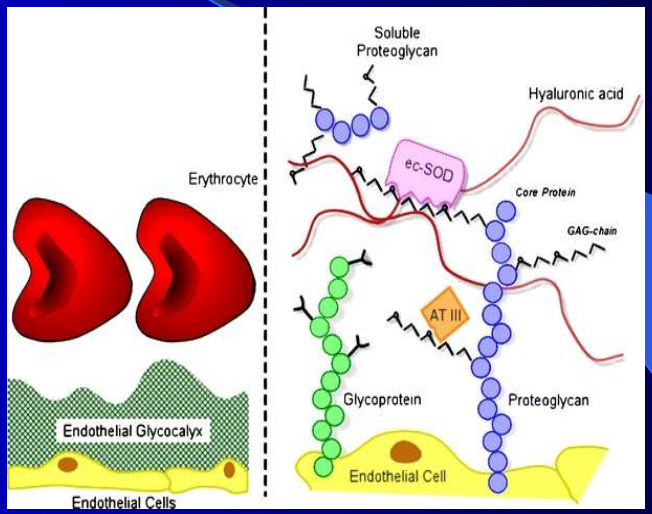
EPM(Glycocalyx) –Function-- Physiologically active structure …

- Provides an anti-inflammatory effect and thrombo-resistance to the artery by harboring proteins such as
- antithrombin III,
- tissue factor pathway inhibitors,
- lipoprotein lipase,
- vascular endothelial growth factor,
- extracellular superoxide dismutase etc.
  - all designed to keep the barrier intact.

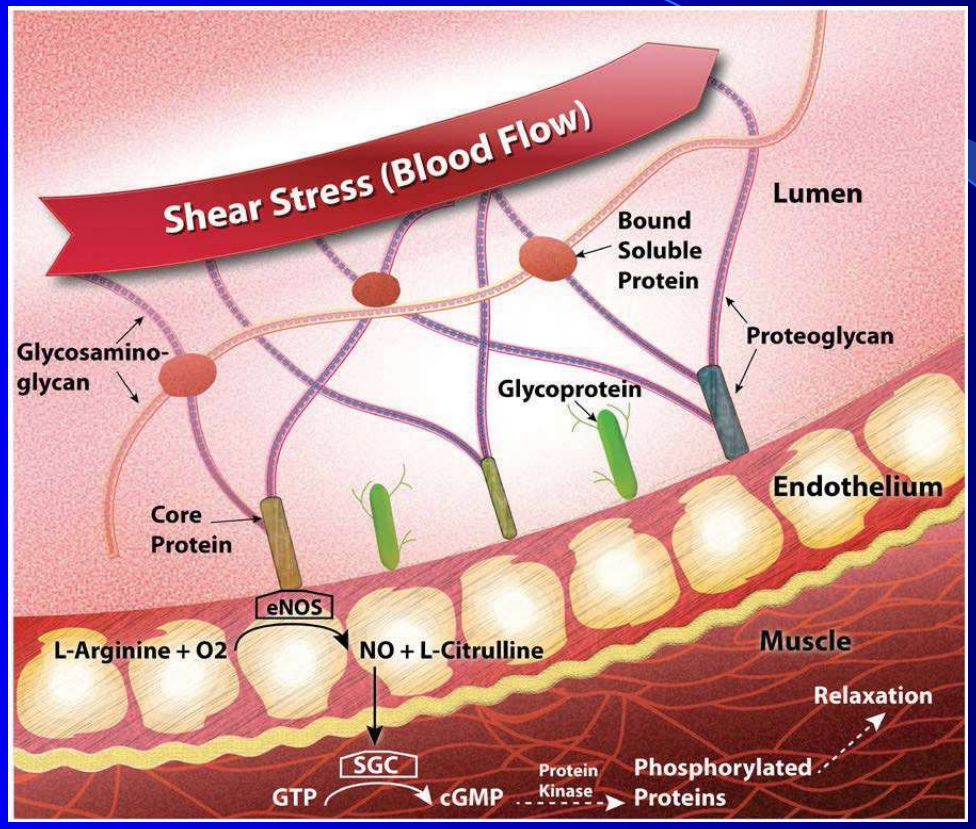


EPM(Glycocalyx)–Function-Physiologically active Structure …

- Responds to shear stress with alignment of the ‘hairs’ into the direction of the blood flow
  - → release of NO to maintain normal vascular tone
  - → synthesis of glycoaminoglycans (heparan-, DS-, CS-sulfates, and HA).

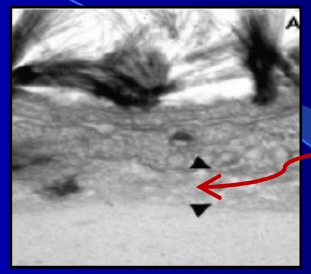


EPM (Glycocalyx)

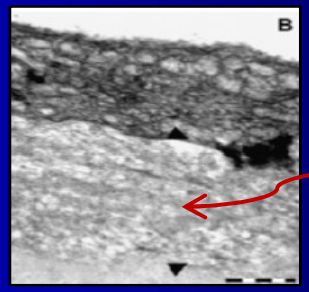


Known risk factors erode the EPM(Glycocalyx)

- All of the common risk factors we associate with heart disease damage and erode the EPM(Glycocalyx): age, high fat, and high sugar diets, smoking, high cholesterol, lack of exercise.
- But while these risk factors are indeed dangerous, it is ***NOT*** because they clog arteries like grease in a pipe. It is because they **attack and weaken** the performance of the EPM(Glycocalyx)
- Essentially, we have been targeting the right criminals, but for the wrong crimes.

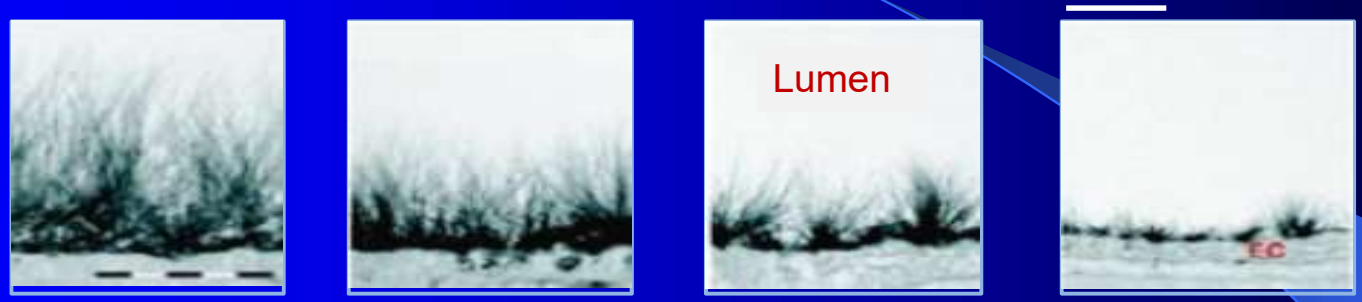


A robust, healthy endothelium



The endothelium has been eroded. The artery wall is swollen with fats and cholesterol

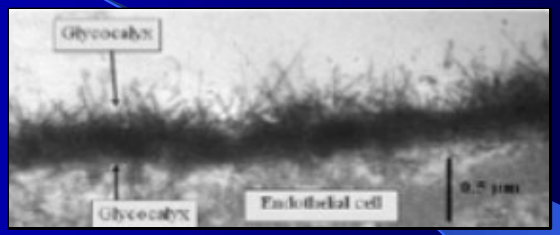
EPM(Glycocalyx) protects the artery...



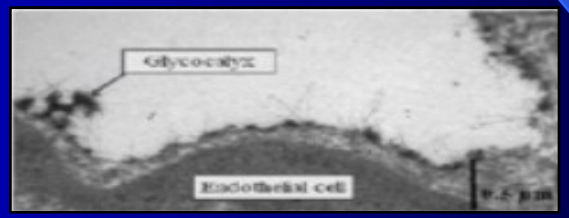
- On the left, you see an intact EPM(Glycocalyx) and progression of damage.
- When the EPM(Glycocalyx) breaks down, arteries lose their armor. They become susceptible to plaque penetration through their surfaces, which leads to rupturing and clotting.
- **We now know that a high fat or sugar meal damages the EPM and the body can take from 6-8 hours to restore it.**
- As we age the bodies natural synergy and ability to repair the EPM(Glycocalyx) is reduced and the loss is compounded by all the known risk factors.

Focus on the arteries…not the blood--Repair

- Need to replenish and rebuild the EPM(Glycocalyx), protecting and preserving the barrier function of our arteries.
- We need active ingredients that have **molecular structures similar to the EPM structure,** so nutrients are readily accepted by the body.
- **Therefore, unlike many heart disease treatments, we may need compounds that don't make the blood thinner. The blood stays the same; the arteries natural barriers are restored and remain healthy as they receive the nutrients they need.**



Healthy EPM(Glycocalyx) barrier



Depleted EPM(Glycocalyx)

Current Study

A Clinical Study of the Effects of Arterosil
on
Arterial Elasticity and Vascular Function

Pulse Wave Technology…

- Utilizes pulse wave analysis technology. The bloods pulse-wave is followed from the time it leaves the heart and travels through the blood vessels down to the finger
- The pulse-wave is a snapshot into the CV system and evaluates arterial elasticity (arterial stiffness)

Study Parameters

- 19 healthy human subjects randomly recruited (11 females age 22 to 64, 8 males age 30 to 60)
- Conducted at independent cardiology center on Baylor Medical Campus in Plano, Texas
- Vascular health evaluated using an FDA Class II plethysmography device

Study Protocol

- Baseline reading taken 2 hours (+/- 30 mins) post consumption of breakfast of choice
- Immediately after baseline reading one (1) capsule of brown seaweed was ingested

Study Protocol

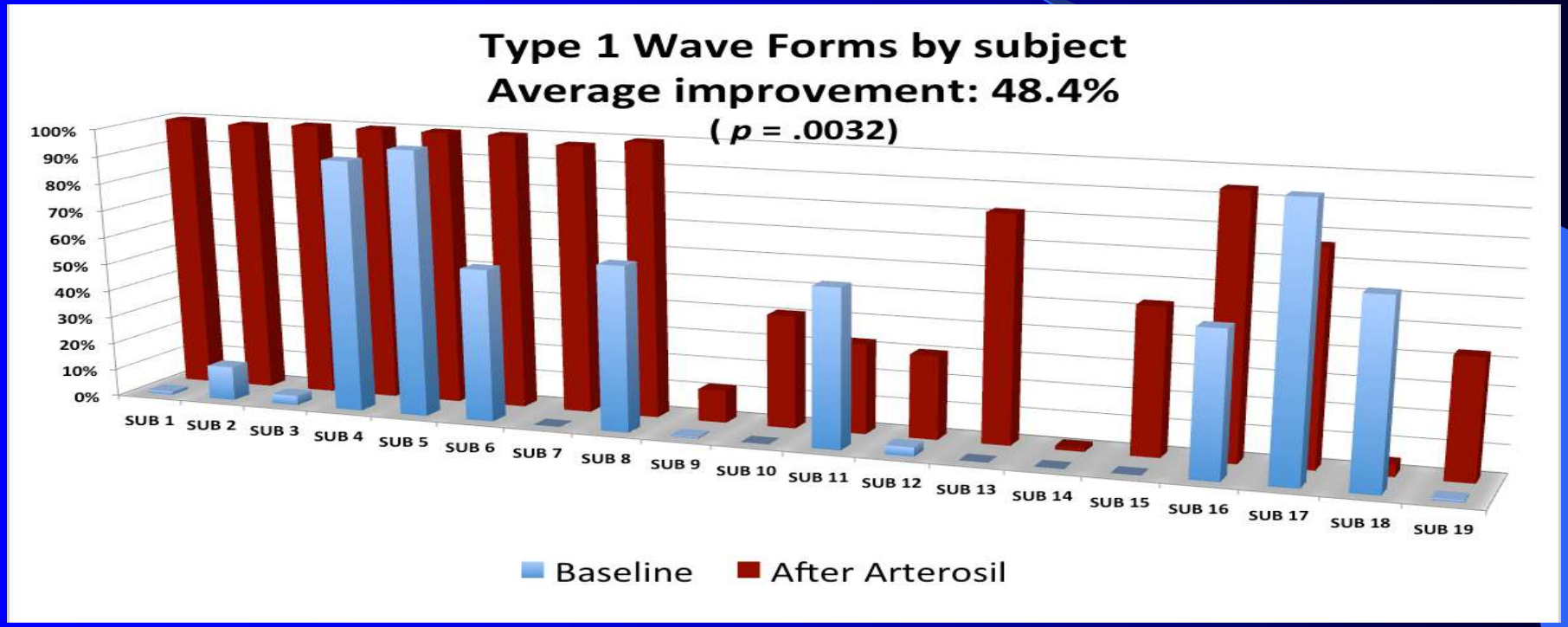
- Post-dose readings taken every 30 minutes for 3 hours
- Seven (7) readings total (Baseline, 30, 60, 90, 120, 150 & 180 minutes)
- No food or liquid consumed during testing period (other than water as needed)

Data Collected

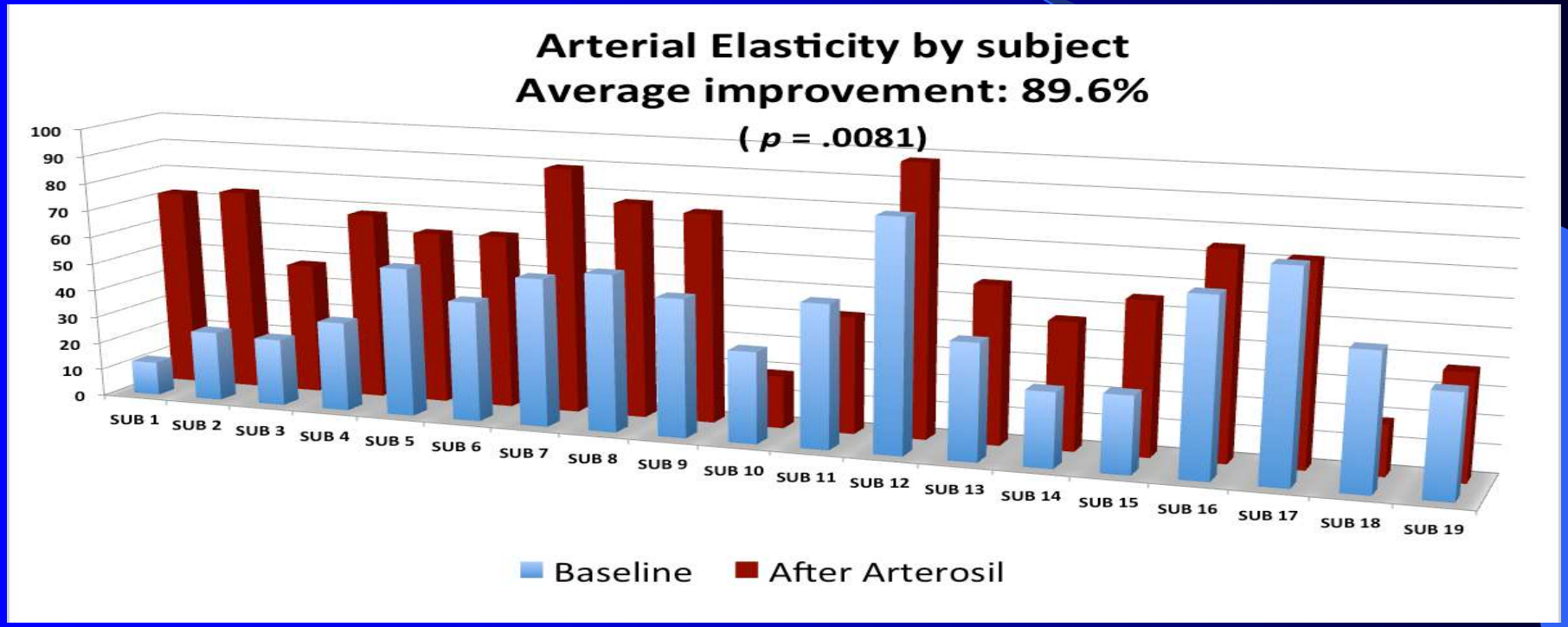
At each test the follow data were collected:

- - Percentage of Type 1 Wave Forms
- - Arterial Elasticity
- - Stress Resistance
- - Frequency Domain Power(dec. of TP measures ANS function)

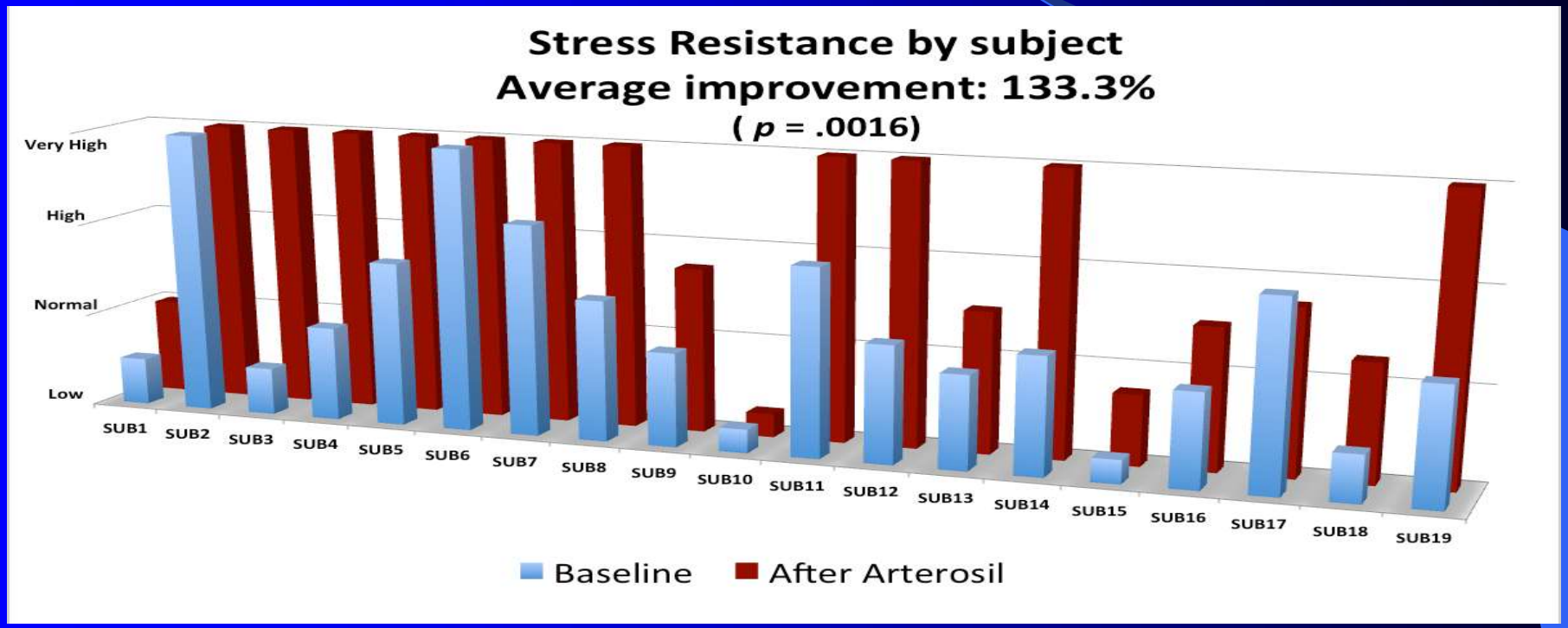
Type 1 Wave Forms: 48.4%



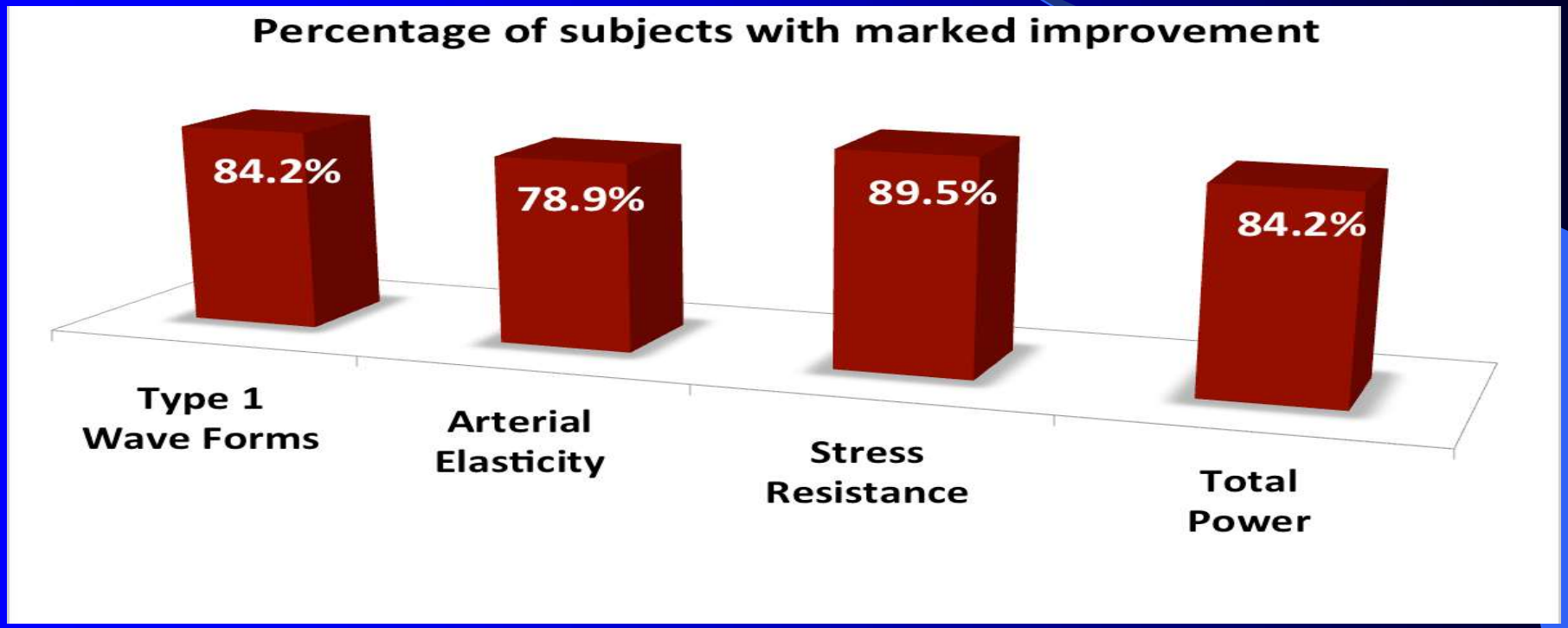
Arterial Elasticity: 89.6%



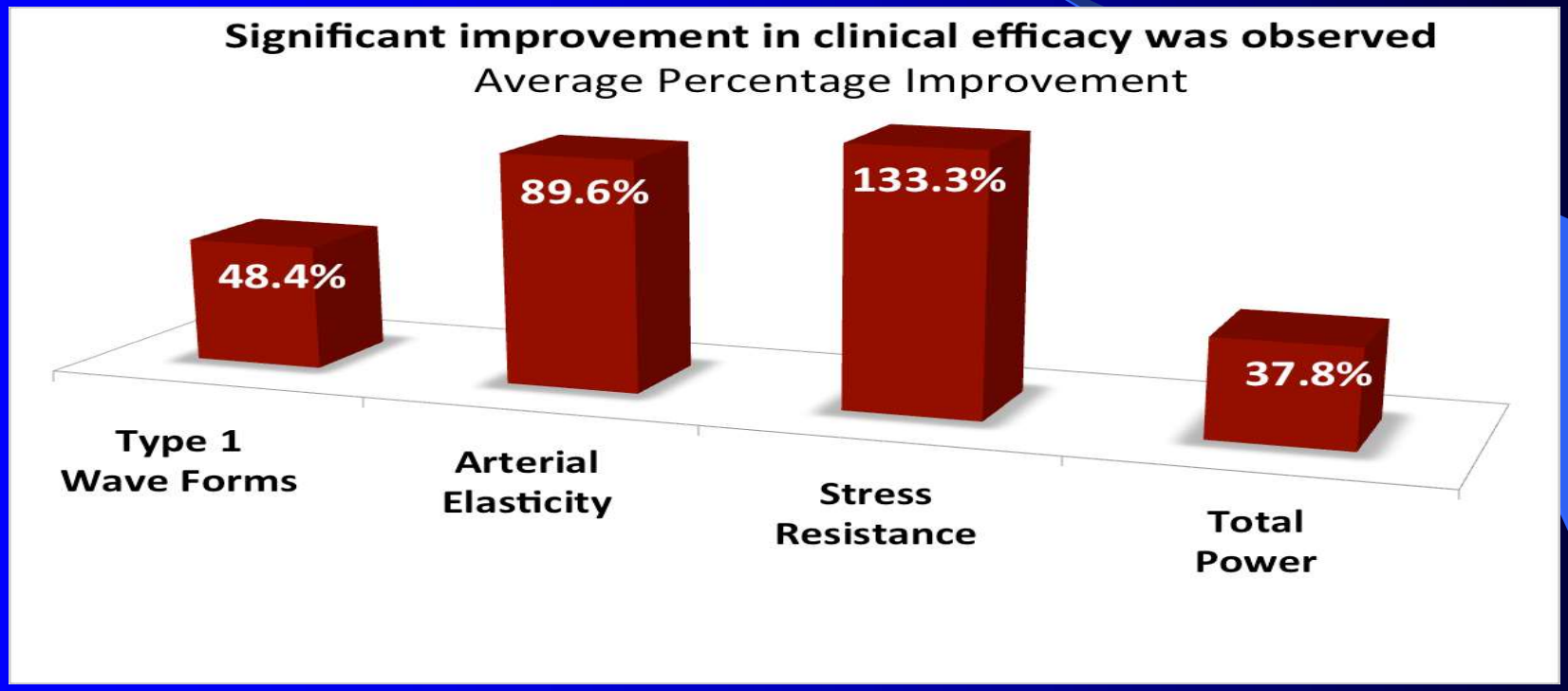
Stress Resistance: 133%



Percentage of Subjects with Marked Improvement



Summary of Improvement Observed



Endothelial Repair…

- Testosterone
  - does three things that can directly improve your endothelial function:
    - a) boosts nitric oxide levels by acting on NOS
    - b) lowers inflammation
    - c) protects your arteries from arteriosclerosis

Endothelial Repair…

- Excessive inflammation can also affect Leydig cell function and **reduce testosterone**.
- One study states that:
  - "There is evidence from many experimental studies that IL-6, TNF-alpha and IL-1beta ,inhibit Testosterone secretion by their influence on the central (hypothalamic-pituitary) and peripheral (testicular) components of the gonadal axis."

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Endothelial Repair…

- High “good fat” diet
- Exercise
- Pomegranate juice
- Mediterranean diet
- Nitrates. Foods that contain nitrates can boost your baseline nitric oxide.
  - Beetroot juice, spinach, lettuce and any green leafy vegetable

Some Thoughts…

- What role do anti-oxidants and anti-inflammatory supplements play in the Endo-Protective membrane layer?
- Should we all be more aggressively treating inflammation?

Continuing My Thoughts…

- If the brain is composed of 60% fat and the retina is composed of 65% fat, how much attention should we be paying to aggressively lowering cholesterol…!!!!
- What about stents and the Endo-protective(Gycocalyx) membrane layer…???

Keys to Success and Happiness

St. Francis of Assisi…

….Make me a channel of Your peace, where there is hatred let me sow Your love, where there is injury pardon, where there is doubt faith, where there is despair hope where there is darkness light, and where there is sadness joy…

God Bless You All…..

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