

DR. HYMAN+



Why Endothelial Health Is Critical
To Healthspan And Longevity

LONGEVITY “EXPERT” IN TWYMAN FAMILY

MISSION 106+

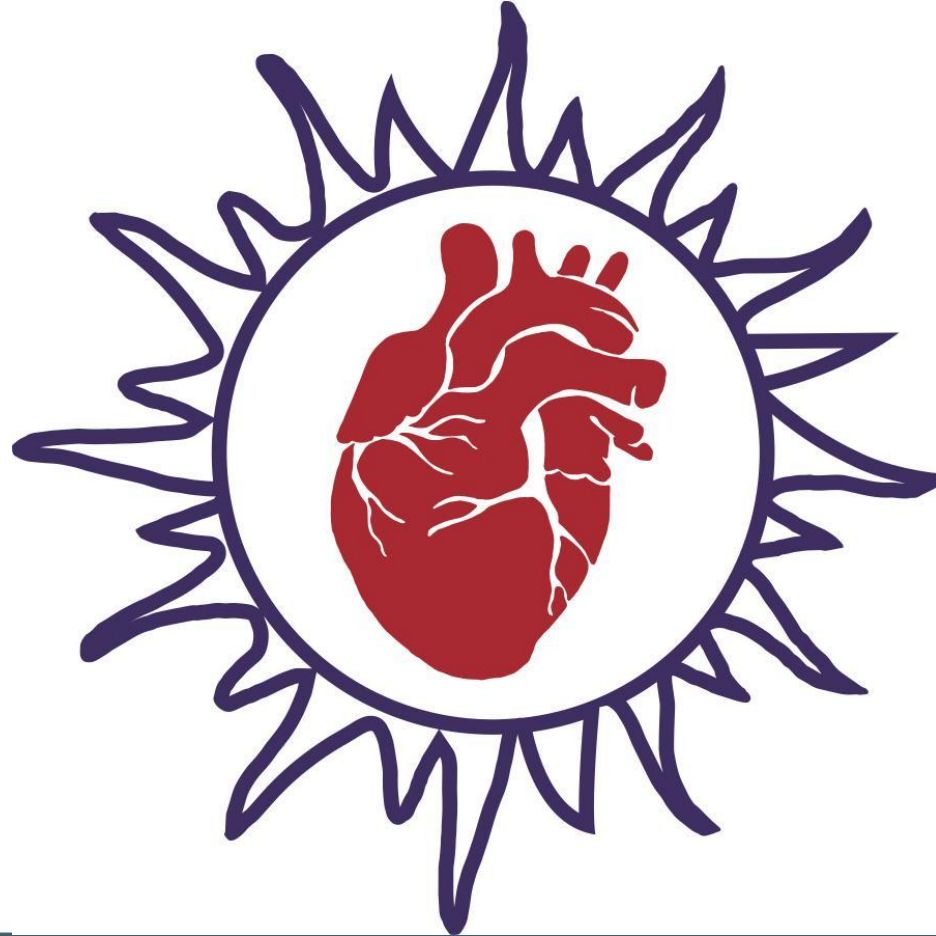
- ▶ Great-Grandma Ola (1893 - 2000)
- ▶ Lived alone till age 100
- ▶ Avoided doctors
- ▶ Sedentary / Never exercised
- ▶ Ate junk
- ▶ Sleep?
- ▶ Healthy mitochondria
 - ▶ Apo E 2
 - ▶ Loss of function PCSK9



Where You Don't Want To Meet Your Cardiologist







Agenda

What is the endothelial glycocalyx and why is it important for cardiovascular health

What are the crucial tests for the early detection of subclinical atherosclerosis and what can be done to prevent having a cardiovascular event

The truth behind cholesterol, statins, and their impact on overall performance

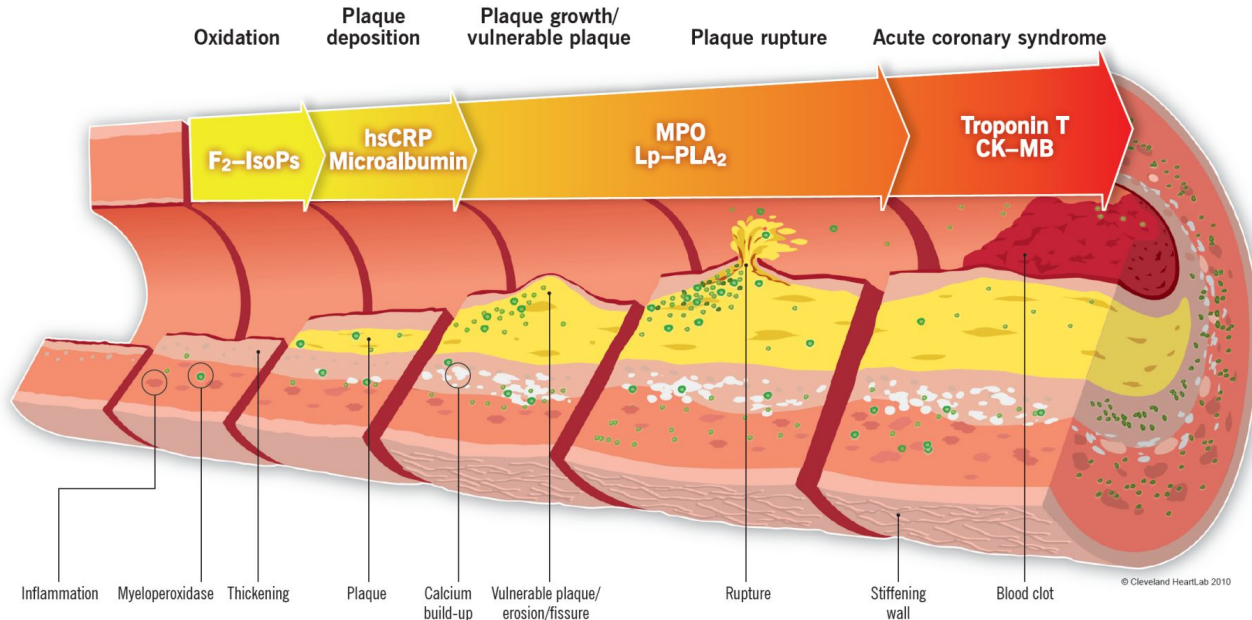
ED = ED

Mitochondrial Health

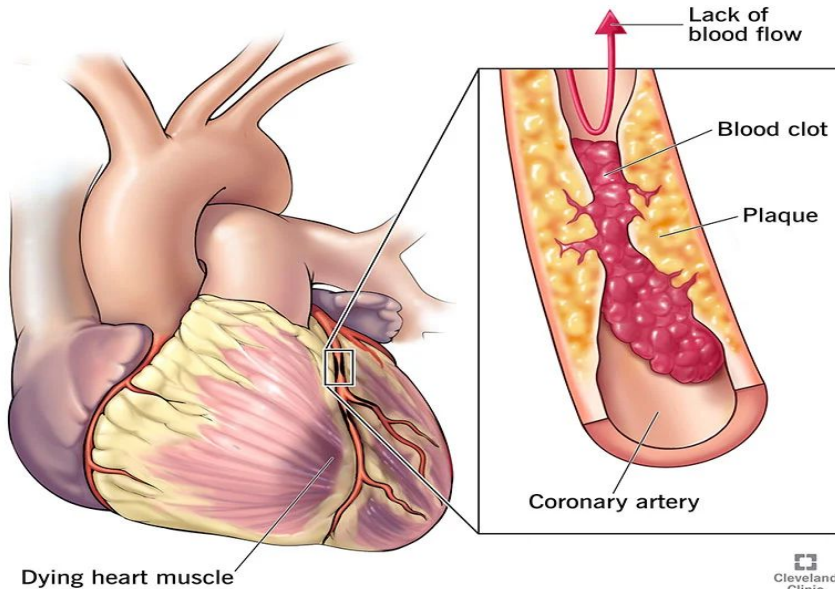
Photobiomodulation (PBM) - “Red Light Therapy”



How NOT To Have A Heart Attack



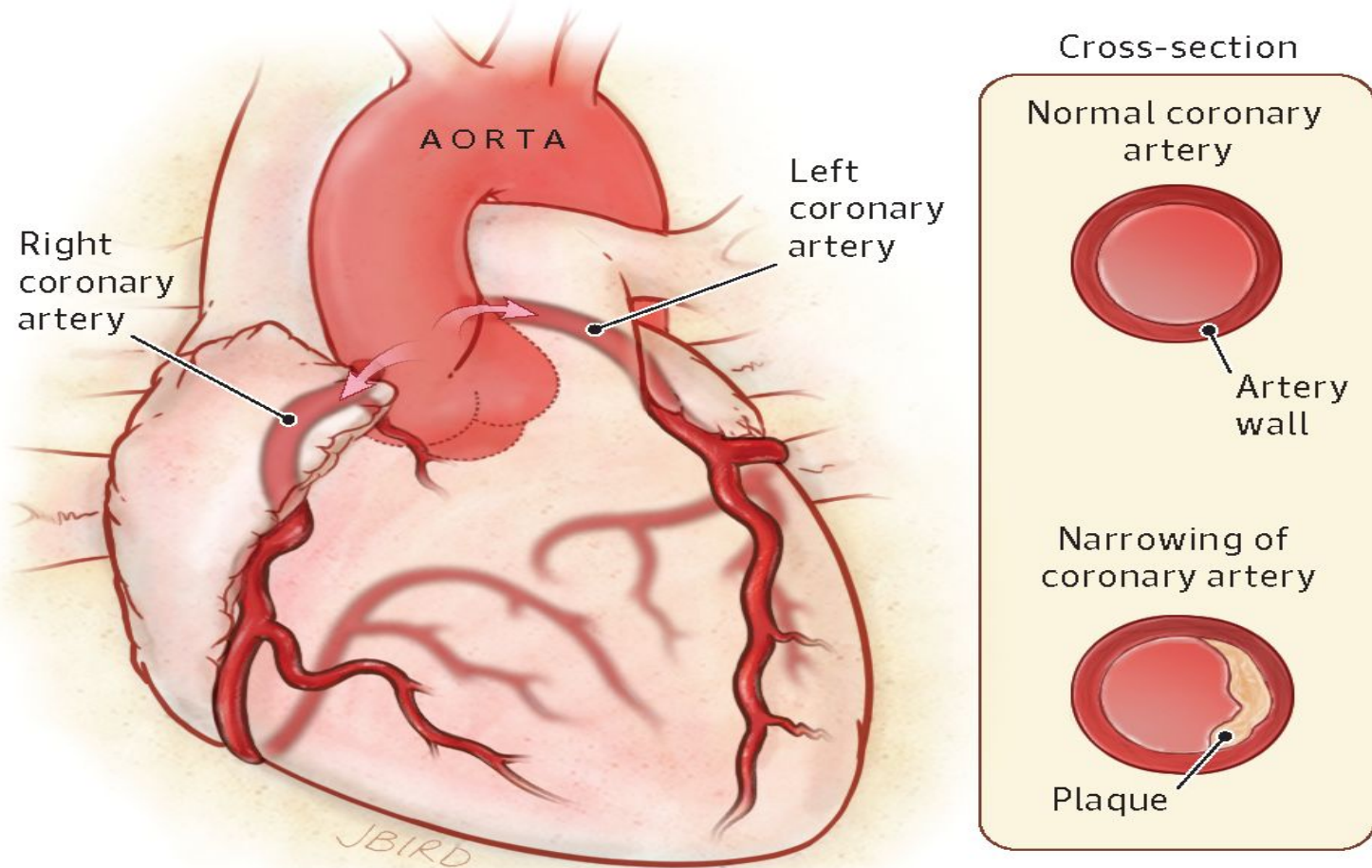
Heart Attack



Cleveland
Clinic
©2021

- Every 40 seconds a person in the US suffers a MI
- Over 800K MI/Year
- 1st MI - 605K
- Recurrent MI - 200K
- 1:5 MI are “silent”
- 360,900 Died in 2019

The coronary arteries run on the surface of the heart and send smaller branches into the heart muscle. They supply the heart muscle with blood carrying oxygen and nutrients.





Labs

There is no such thing as “good” or “bad” cholesterol

Residual Risk Factors

Inflammation Markers

Lipoproteins / Apo B / Lp(a)

Insulin / Glucose / A1c

Full Thyroid Panel with antibodies

Vitamin D

Omega 3

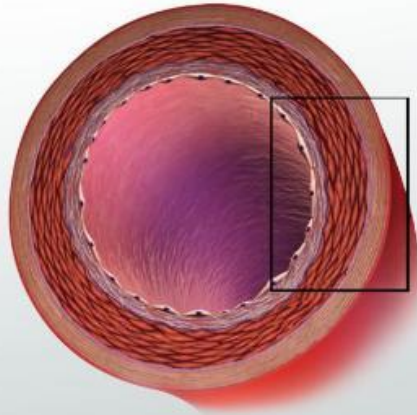
Homocysteine, Uric Acid, ADMA/SDMA

Genetics - 9p21, KIF6, Apo E



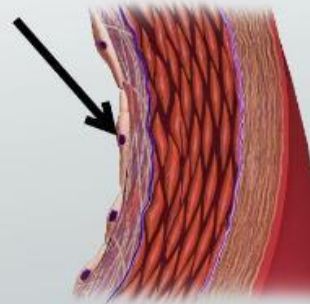
Heart Disease Starts With Endothelial Dysfunction

WHAT ARE ENDOTHELIAL CELLS?



endothelium

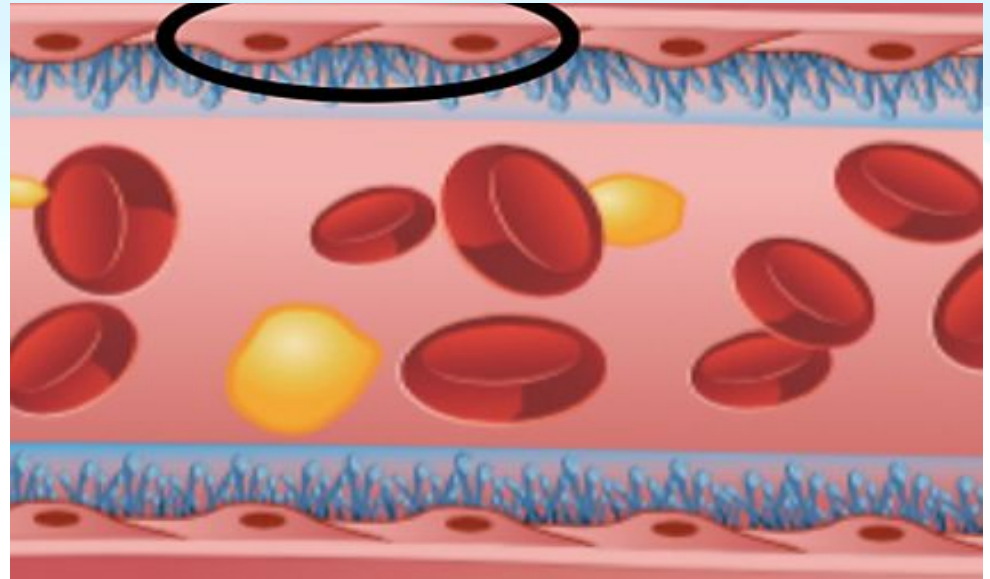
they form a one-cell-thick

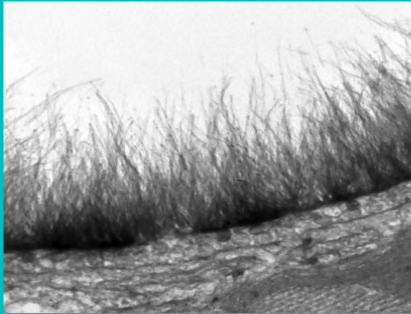
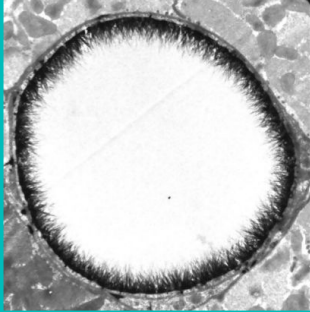


©Study.com

The Endothelium

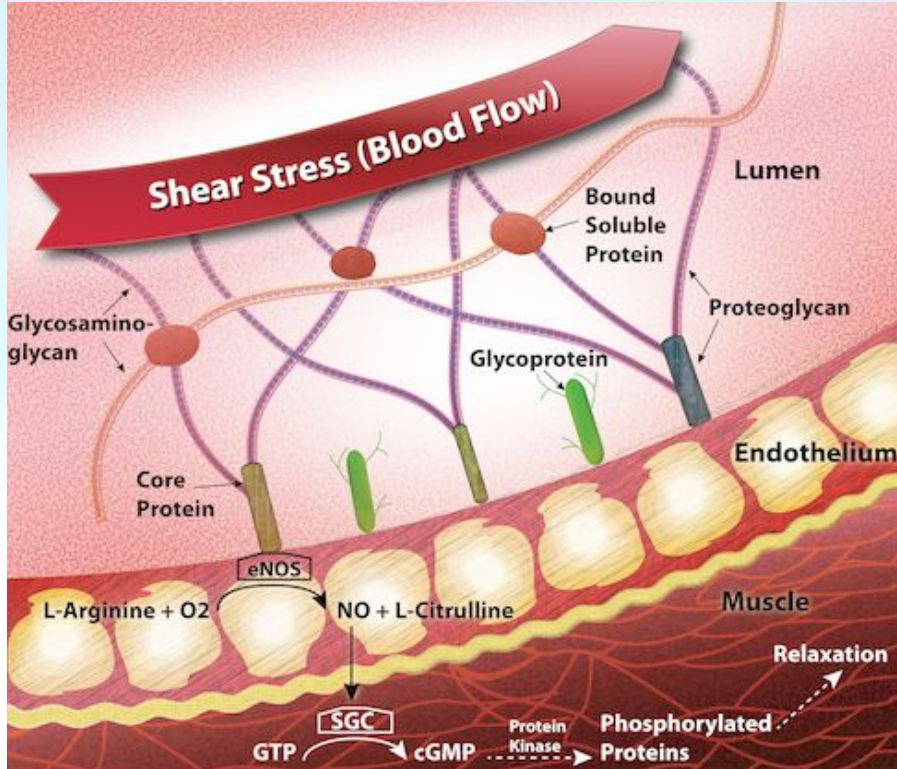
- Maintains normal vascular tone and healthy blood pressure
- Serves as a transport barrier to help control vascular permeability
- Possesses antithrombotic and fibrinolytic properties
- Modulates interactions between the blood vessel wall and circulating leukocytes and platelets
- Secretes vasoactive substances that regulate various functions





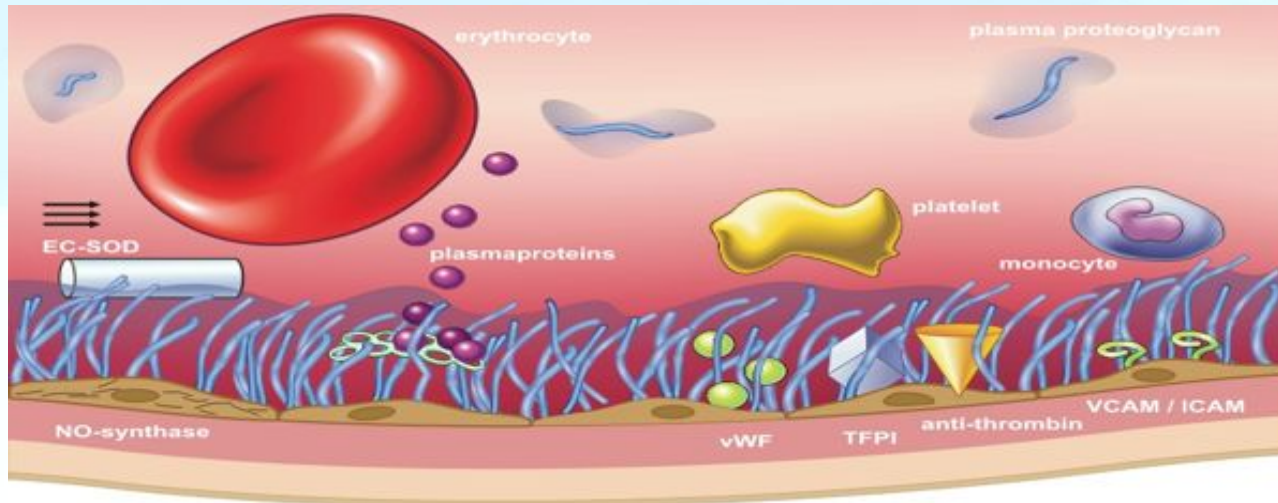
The Endothelial Glycocalyx (EGX)

- The endothelial glycocalyx (“sugar coating”) is a microscopically thin gel-like layer that coats the entire luminal side of the vascular endothelium and provides a non-adherent shield
- Composition
 - Proteoglycans (PG)
 - Glycoproteins
 - Glycosaminoglycans (GAGs)
 - Plasma Proteins



DeSilva, et al, A4M Medical Journal (2016) Winter: 92-95

Functions Of The EGX



The EGX: A SMART Barrier

Selective:

Selectively permeable barrier that prevents cholesterol, platelets, leukocytes and other circulating blood components from sticking to vessel walls

Micro-thin:

Approximately 1,000 EGX layers would equal the thickness of one sheet of paper

Antioxidant:

Harbors antioxidative enzyme superoxide dismutase (SOD) that reduces oxidative stress and keeps nitric oxide (NO) available in the vascular system

Regulator:

Regulates vascular permeability, inflammation, coagulation, and fluid balance

Transducer:

Senses shear stress of blood flow and sends signals to the endothelium to produce nitric oxide

How The Glycocalyx Degrades

Fragile But Resilient

Glycocalyx: A Proxy for Endothelial Health

Causes of glycocalyx degradation:

- High levels of blood glucose and insulin
- Shear induced shedding
- Sodium
- Oxidative stress
- Toxins / Heavy Metals
- Infections
- Lifestyle factors (stress, sleep deprivation and sleep apnea, lack of exercise, etc.)
- Genetic factors
- Aging



Healthy vs. unhealthy
EGX

Glycocalyx Damage Precedes Endothelial Dysfunction

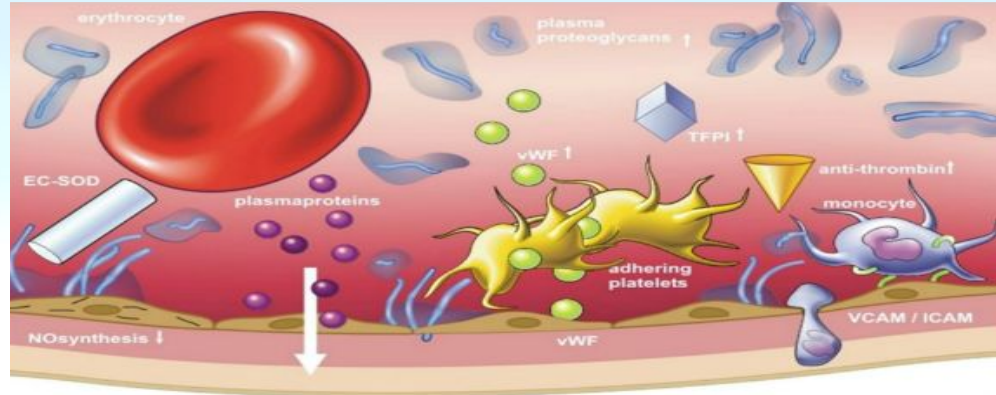
- **The EGX:**
 - Regulates **vascular inflammation** and protects the endothelium from inflammatory molecules
 - Harbors antioxidants that respond to **oxidative stress** (especially superoxide dismutase)
 - Partially made up of immunoglobins, which mediate **immune response** in the vascular system

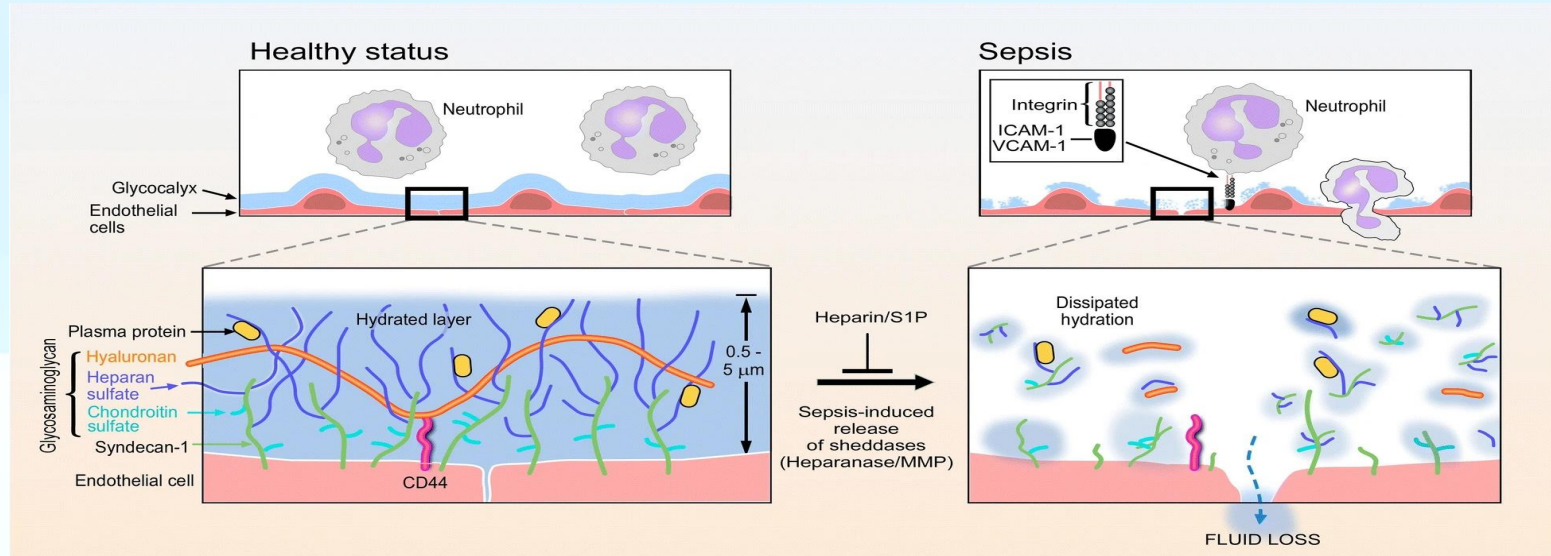


Healthy vs. unhealthy
EGX

Compromised Endothelial Glycocalyx Damage: Downstream Effects

- Reduced NO production
- Increased oxidative stress
- Increased macromolecule leakage
- DM complications
- Ischemia-reperfusion injury
- Increased platelet adherence
- Increased thrombin generation
- Increased leukocyte adhesion & diapedesis
- CHD and atherosclerosis

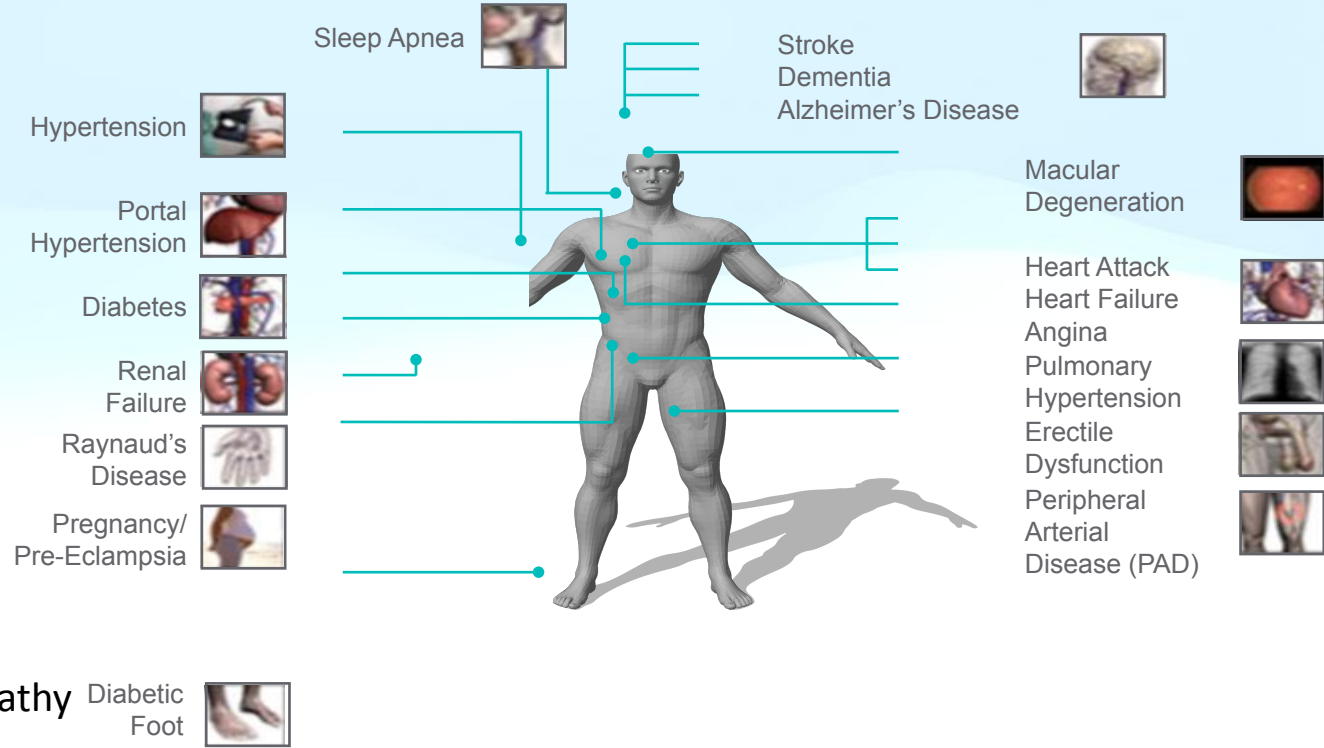




Endothelial glycocalyx structure during health and degradation during sepsis. *MMP* metalloproteinase, *S1P* sphingosine-1-phosphate, *ICAM-1* intercellular adhesion molecule 1, *VCAM-1* vascular cell adhesion molecule
 Uchimido, R., Schmidt, E.P. & Shapiro, N.I. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Crit Care* **23**, 16 (2019).
<https://doi.org/10.1186/s13054-018-2292-6>

Associated Pathologies

- Cardiovascular disease
- Stroke
- Atherosclerosis
- Peripheral artery disease
- Hypertension
- Diabetes and diabetic neuropathy
- Erectile dysfunction
- Other vascular issues



ED = ED

1-10% under Age 40

50% of 40-70 year olds

Medical Causes: prostate surgery, spine surgery

Medications: Beta Blockers

Alcohol

Anxiety, Depression, PTSD -> Counseling

Vasculogenic (Most Common)





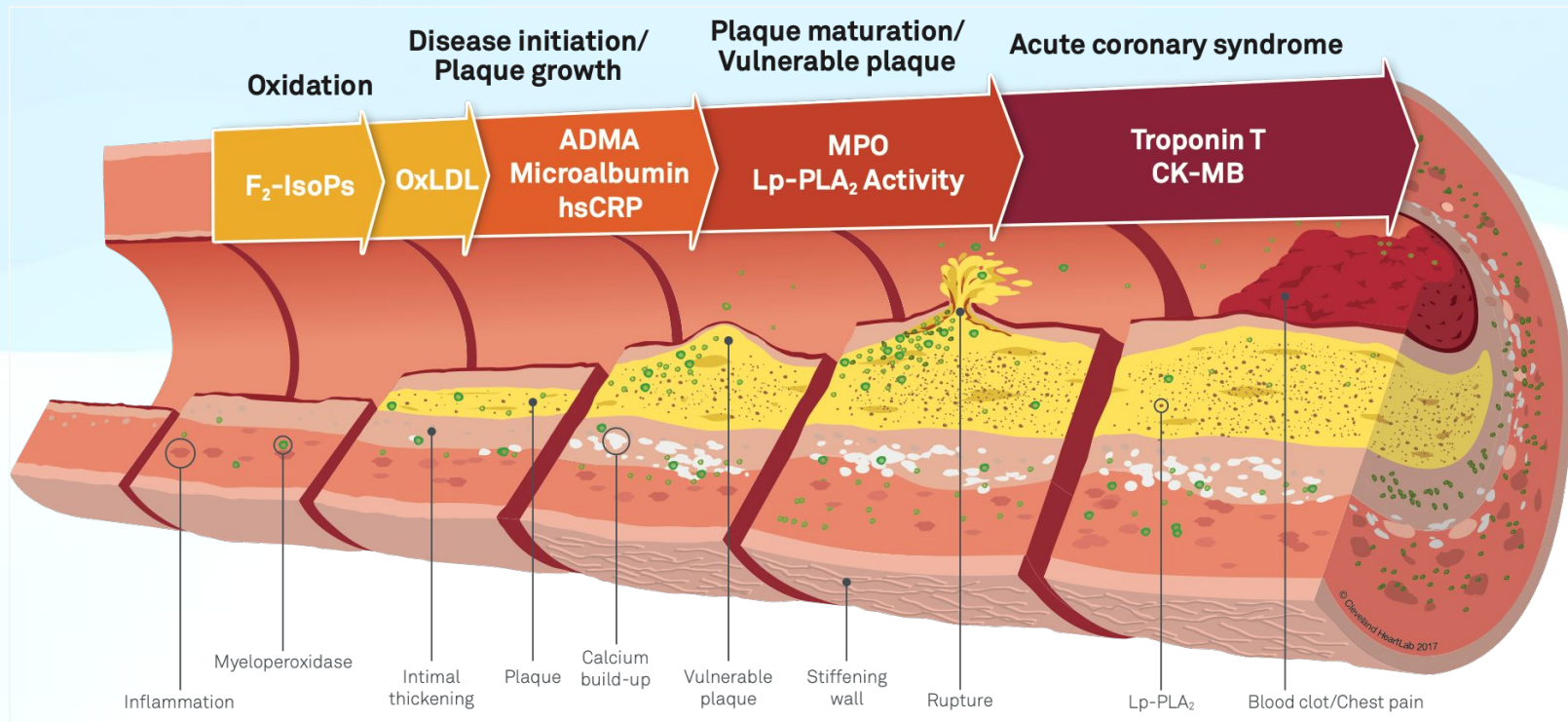
Functional Medicine Deep Dive



DR. HYMAN+

Cardiovascular Testing

Conventional vs Integrative



Conventional vs Integrative

- “Contents Of Blood” vs “Condition Of Artery Wall”
- Wait for symptoms -> EKG and stress test
- Assess arterial elasticity, central blood pressure, endothelial function, CIMT, CAC, Clearly CCTA

Measuring The Health of The EGX

- Direct imaging (Intravital Microscopy)
 - Orthogonal polarization spectroscopy (OPS)
 - Sidestream dark field (SDF)
- Shedding of GAGs and PGs
 - Liquid chromatography-mass spectroscopy (LC-MS)
 - Colorimetric assays (mainly ELISA)
- Volume via tracer dilution
 - Speculative
- Future? - MRI/MRA
- EGX dependent blood vessel functionality



Sublingual measurement, healthy volunteer

<https://braedius-medical.com/videos/>

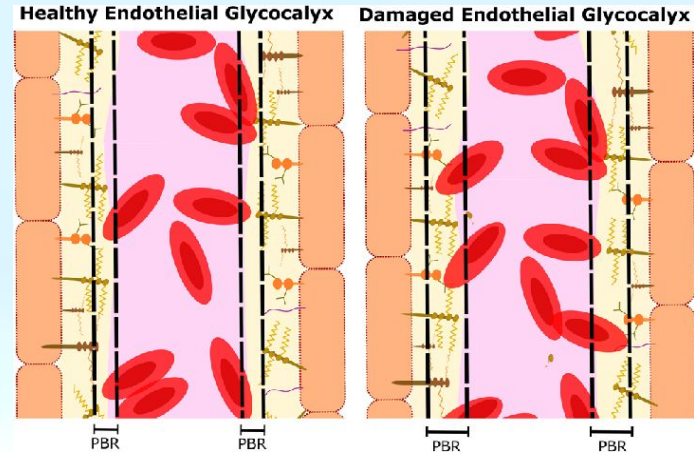


Sublingual measurement, critically ill patient

<https://braedius-medical.com/videos/>

PBR

- Perfused Boundary Region
- Reflects thickness of EGX
- Deeper penetration of RBC
- High PBR = Thinner EGX



The Microvascular Endothelial Glycocalyx: An Additional Piece of the Puzzle in Veterinary Medicine - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Schematic-representation-of-the-perfused-boundary-region-PBR-demonstrating-two_fig3_360971226 [accessed 23 Mar, 2023]

GAG-ome

JBC METHODS AND RESOURCES



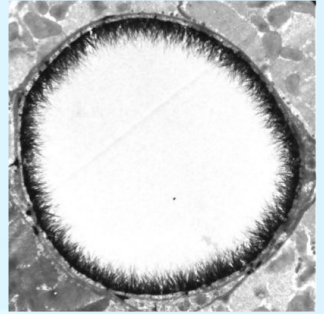
Analysis of normal levels of free glycosaminoglycans in urine and plasma in adults

Received for publication, October 11, 2021, and in revised form, January 5, 2022. Published, Papers in Press, January 8, 2022,
<https://doi.org/10.1016/j.jbc.2022.101575>

Sinisa Bratulic¹, **Angelo Limeta¹**, **Francesca Maccari²**, **Fabio Galeotti²**, **Nicola Volpi²**, **Max Levin^{3,4,5}**,
Jens Nielsen^{1,6}, and **Francesco Gatto^{1,*}**

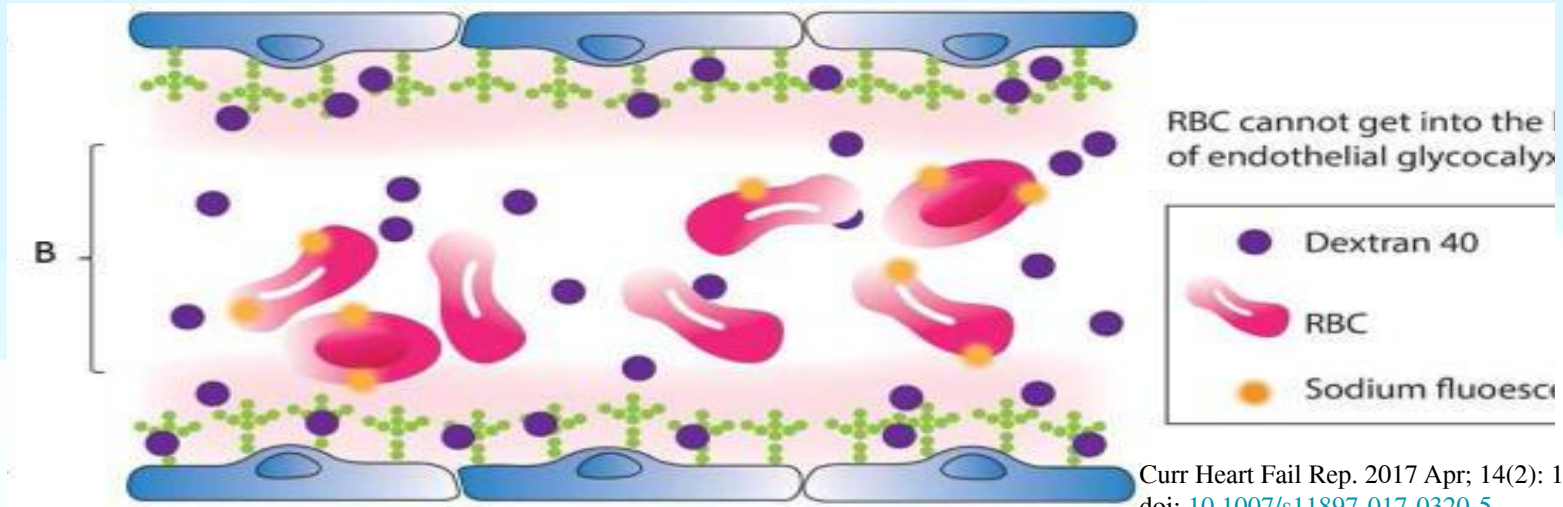
From the ¹Department of Biology and Biological Engineering, Chalmers University of Technology, Göteborg, Sweden; ²Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy; ³Department of Molecular and Clinical Medicine/Wallenberg Laboratory, Institute of Medicine, and ⁴Department of Oncology, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; ⁵Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; ⁶Biolnnovation Institute, Copenhagen N, Denmark

EGX Volume Measurements



- Tracer dilution method (Dextran 40)
- Not clinically useful at this time

- Baseline blood draw: approximates circulating plasma volume in blood
- Infuse EGX permeable tracer
- Second blood draw
- Difference between the two blood draw volume measurements can be used to approximate EGX volume



Double tracer dilution method. The endothelial glycocalyx volume can be obtained by subtracting the circulating volume measured by labeled erythrocytes from the total circulation volume measured using dextran (or other tracer permeable to the glycocalyx layer).

Volume of endothelial glycocalyx = Total circulation volume measured using dextran 40 (A) – Circulation volume measured by labeled RBCs (B)

*RBC, red blood cell

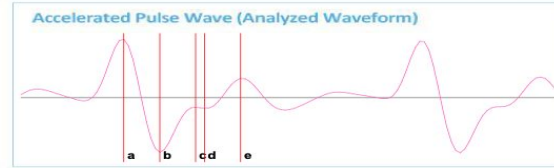
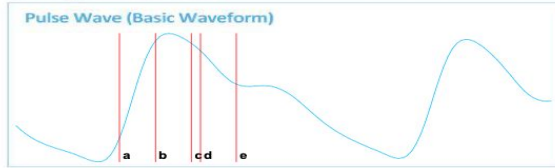
ACCELERATED PHOTOPLETHYSMOGRAPH REPORT

Name	Michael Twyman	Gender/Age	M / 47	Date	03-23-2023 13:16
------	----------------	------------	--------	------	------------------

Arterial Health Test

It is the test that shows the aging of blood vessel and peripheral blood circulation status by analyzing the minute signal detected at the finger tip.

Analysis of Pulse



Vascular Health Analysis



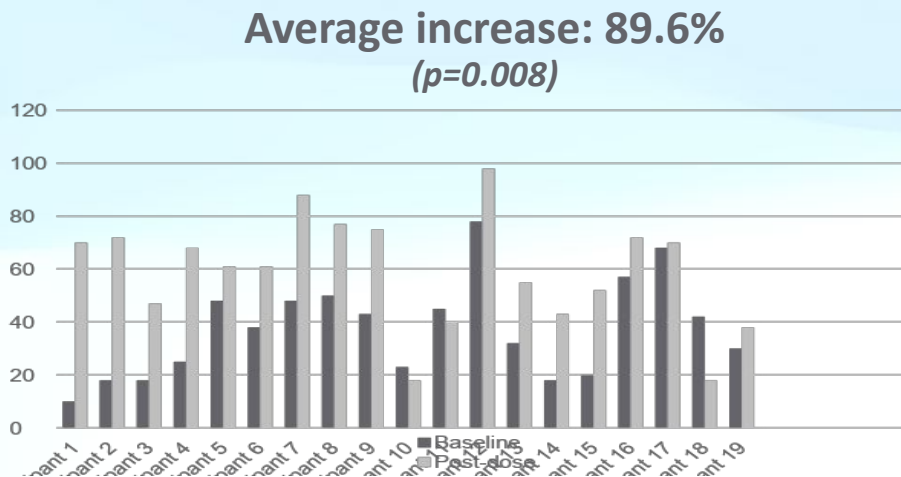
ITEM	MEASURED VALUE	SUB-OPTIMAL	NORMAL	OPTIMAL
AE	93	[Progress bar showing 93% in the Sub-Optimal range]		
PE	84	[Progress bar showing 84% in the Sub-Optimal range]		

※ AE : Arterial Vessel Elasticity
PE : Peripheral Vessel Elasticity

Level Analysis

Level	1	2	3	4	5	6	7
(%)	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Vessel States							
	Excellent	Good	Careful	Warning	Bad	Very Bad	

Arterial Elasticity Study (Human)



Finding:

Increased
arterial elasticity
(average increase
89.6%)

Arterial elasticity was
measured using MaxPulse,
an FDA-approved pulse
wave plethysmography
device

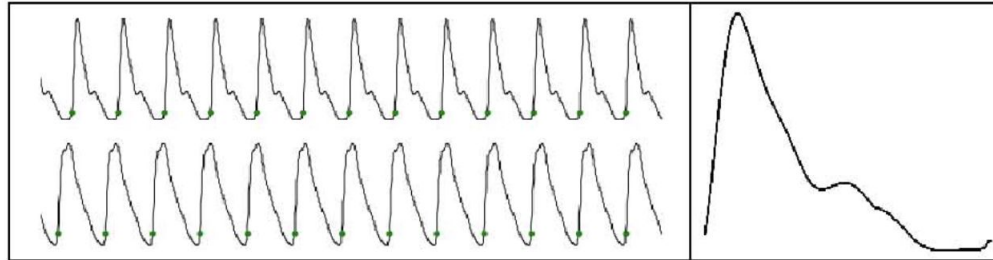
Patient Name: **John Smith**
 Patient ID: **P00** Group: **Clinical**
 Date Of Birth: **1/1/1981** Height: **165 cm**
 Age, Gender: **31, Male** Brachial BP: **120/80 mmHg**

Measurement Data:

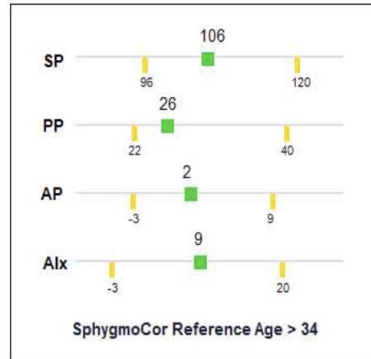
Note:

Date and Time: **2/8/2012 10:40 AM** Number Of Waveforms: **12**

Waveform Plot: Quality Control: **✓**

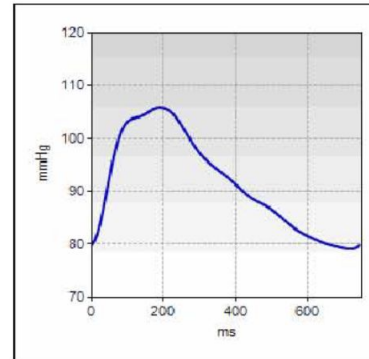


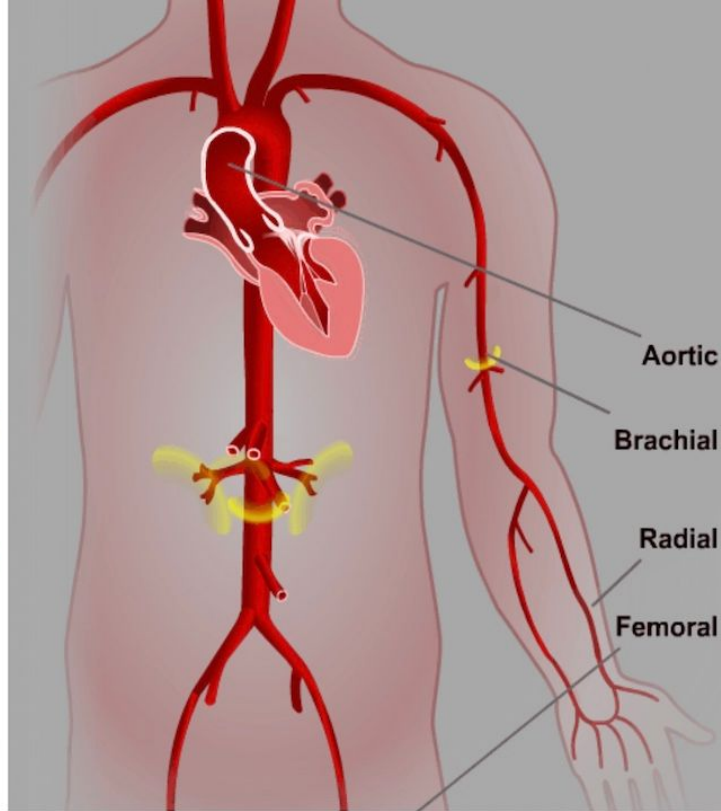
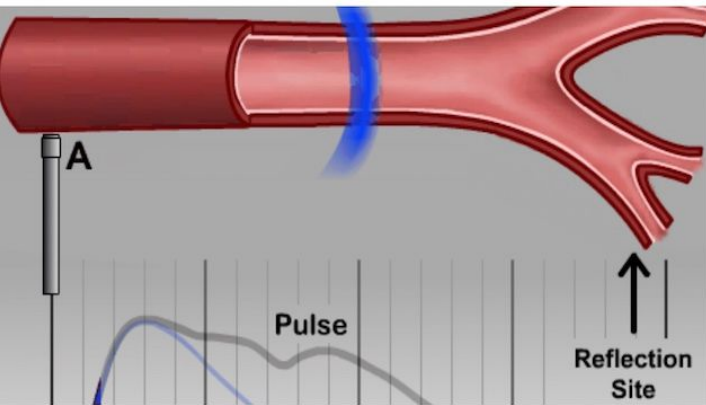
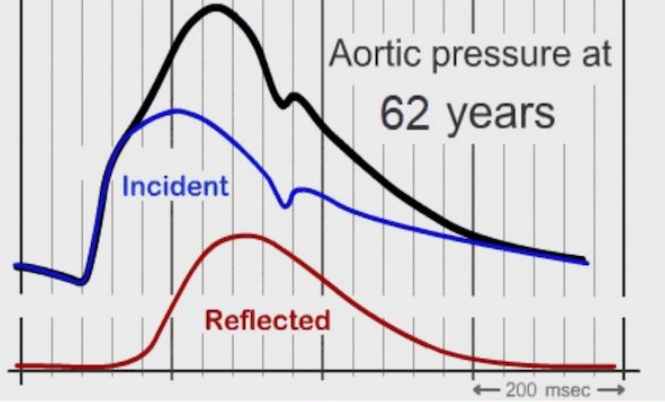
Clinical Parameters:



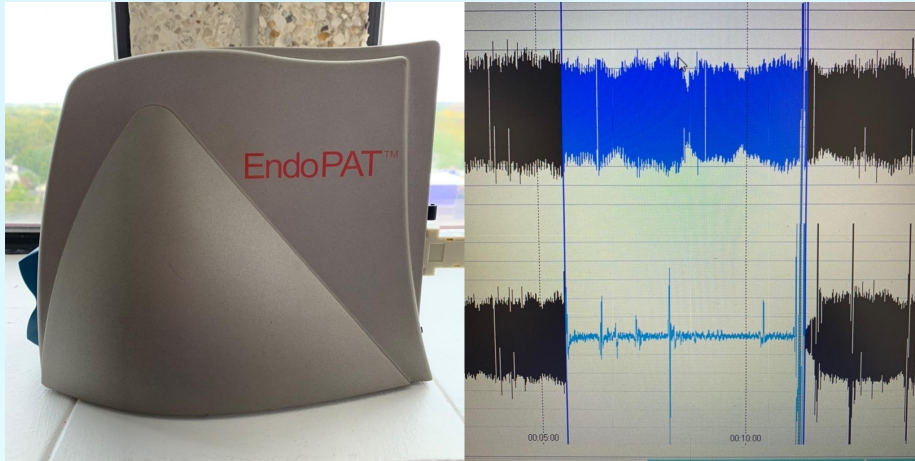
Central Pressure Waveform:

Aortic
 SP: 106
 DP: 80
 MAP: 91
 PP: 26
 HR: 81





<https://atcormedical.com/technology/ncbp/>

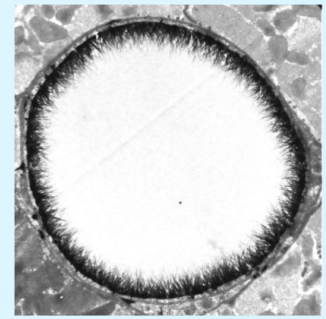


EndoPAT - Endothelial Function Testing

Endothelial Glycocalyx Regeneration

5 Strategies

5 Strategies



- Replacement of EGX components and/or stabilizers
- Lipid level reduction
- Glucose concentration reduction
- Immunosuppression
- Anticoagulation

EGX Regeneration - No Gold Standard

- Sulodexide (80% HS and 20% DS)
- 3 Nutraceuticals
- Fresh frozen plasma (FFP) and albumin

Colloids

- Albumin
 - Erythrocyte-derived sphingosine-1-phosphate (S1P) provided to the endothelium
 - S1P suppresses MMP activity
 - Inhibits syndecan-1 shedding

- FFP
 - Contains all of the plasma proteins that the EGX requires
 - Increases EGX thickness and lowered syndecan-1 levels
 - Contains fibrinogen which increases syndecan-1 protein expression

Rosuvastatin

- Impacted EGX volume
- Did not decrease EGX permeability
- Statins may have limitations as EGX regeneration agents

Metformin

- Few studies have explored effects on EGX
- Enhanced EGX density and length
- Reduced the hyperglycemia-induced EC surface expression of E-selectin and ICAM-1

Anti-Inflammatory Therapies

- Hydrocortisone
 - Alleviates EGX damage due to TNF- α
- Etanercept
 - Study of healthy volunteers reviewed E.coli LPS
 - Endotoxin induced elevation in HA and hyaluronidase abolished by Etanercept
 - Endotoxin induced reduction in EGX thickness was significantly limited by Etanercept
- Poloxamer-188

Anticoagulant

- Antithrombin

- Suppressed shedding of syndecan-1 and HS
- Prevents leukocyte adhesion
- EGX regenerative effects have not been consistent in studies

- Heparin

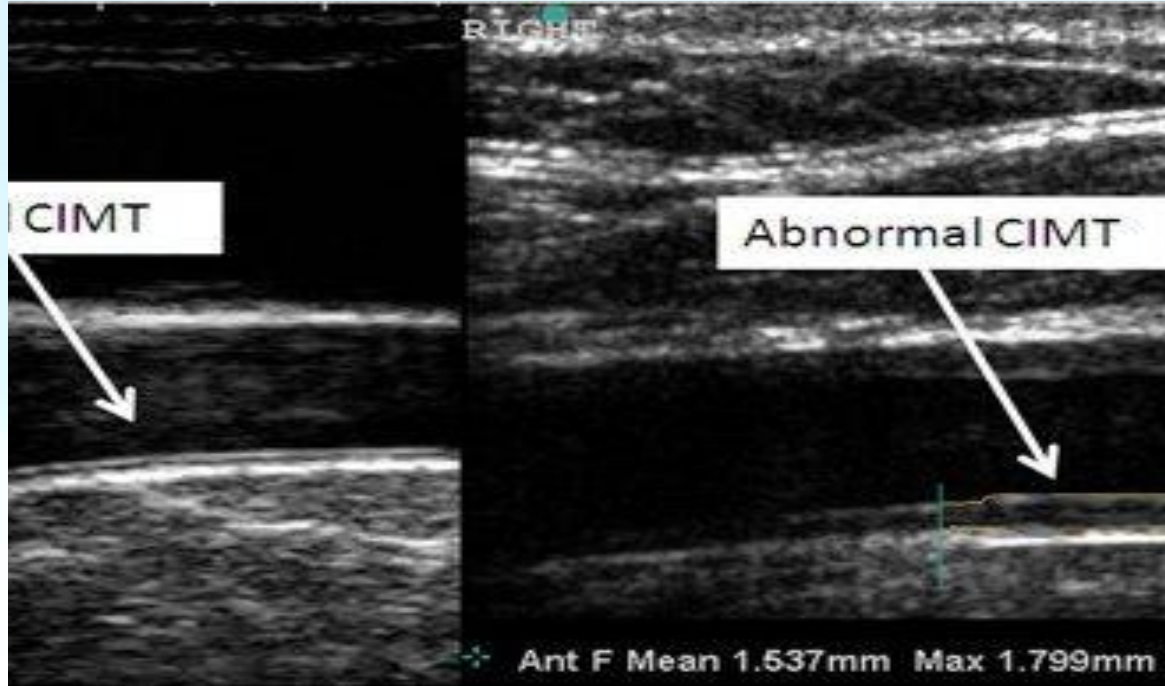
- Ambiguous effects on EGX
- Low molecular weight heparin can inhibit EGX shedding
- Competes with HS and thus release proteins bound to HS which degrades the EGX structure and impairs its function

A Brief Recap: The Endothelial Glycocalyx

- Damage to the endothelial glycocalyx precedes damage to the endothelium
 - EGX damage is the *first step* in endothelial dysfunction
- The EGX mediates all 3 finite responses - when healthy
- Governs the passage of lipids through the endothelial wall
- Regulates inflammatory processes in the vascular system
- Houses antioxidant components
- Plays an important role in regulating coagulation
- Triggers the production of nitric oxide in response to the shear stress of flowing blood
- The EGX is highly resilient

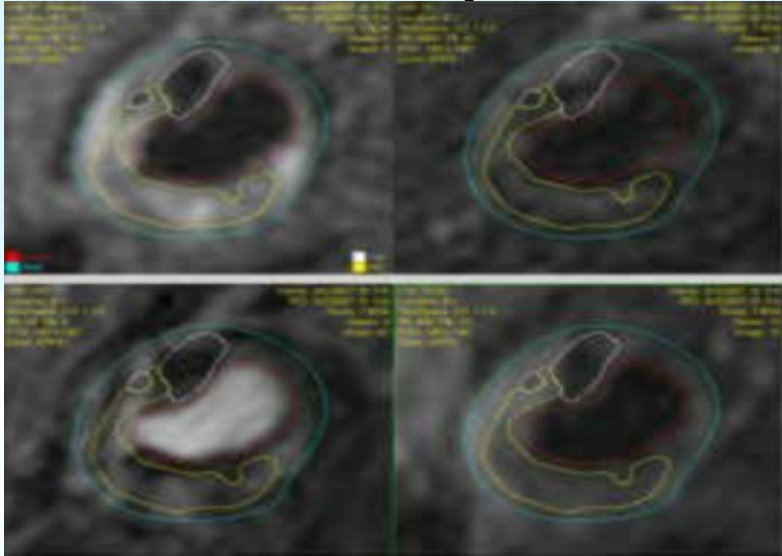
“A Man Is As Old As His
Arteries”

Thomas Sydenham

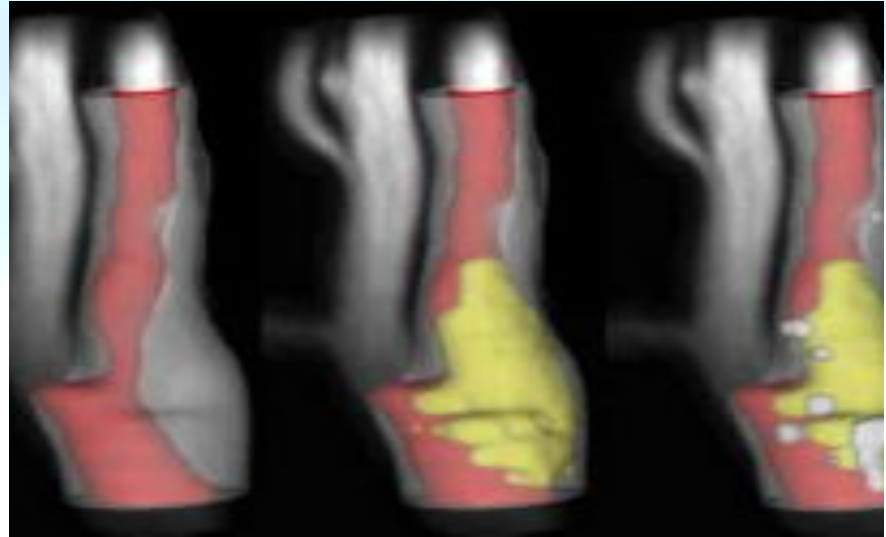


CIMT (Carotid Intima Media Thickness)

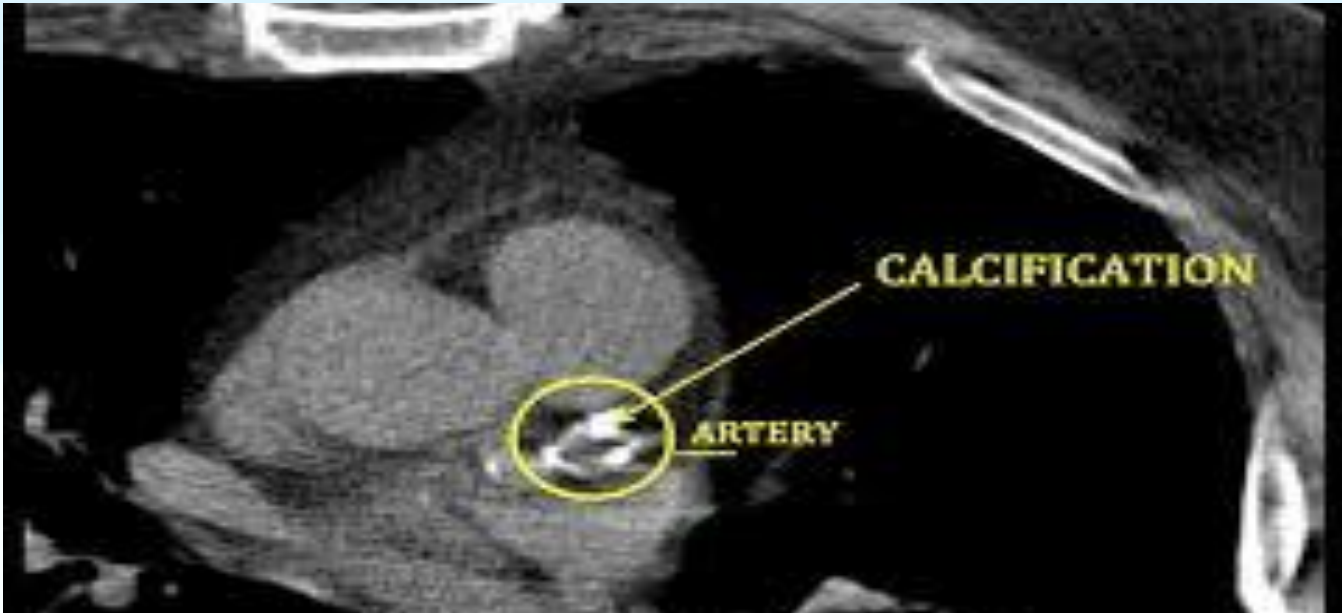
MRI Plaque View



<http://vpdiagnostics.com/plaque-analysis/>



Lipid-rich necrotic core (LRNC) of carotid atherosclerotic plaque



CT Coronary Calcium Scan



Recommendations for Calcium Score Screening

All asymptomatic males without known CAD between 45-75

All asymptomatic females without known CAD between 55-75

If under age limit, then >2 risk factors



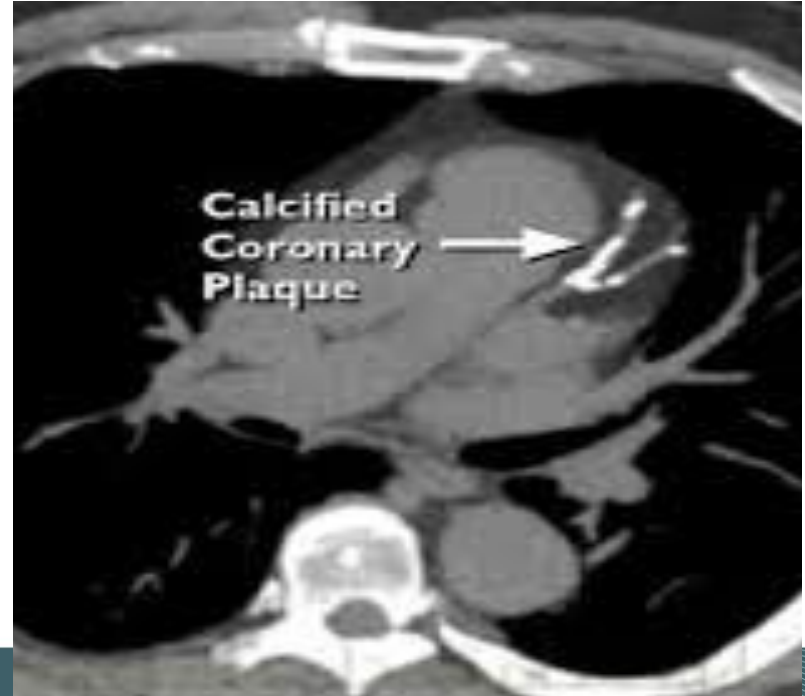
What Are The Odds?

60% of people will have a score over 0

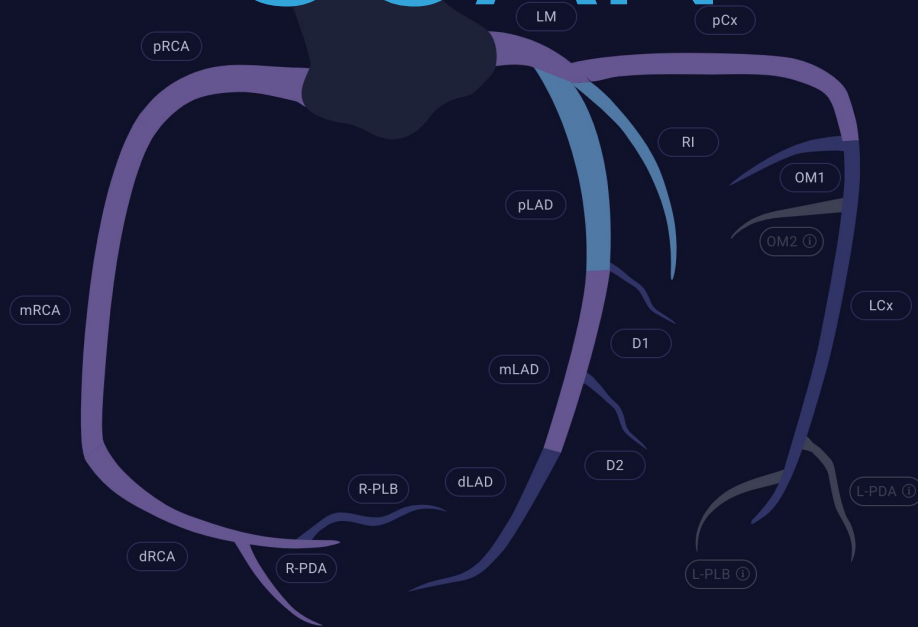
1:6 score over 400

1:29 score over 1000

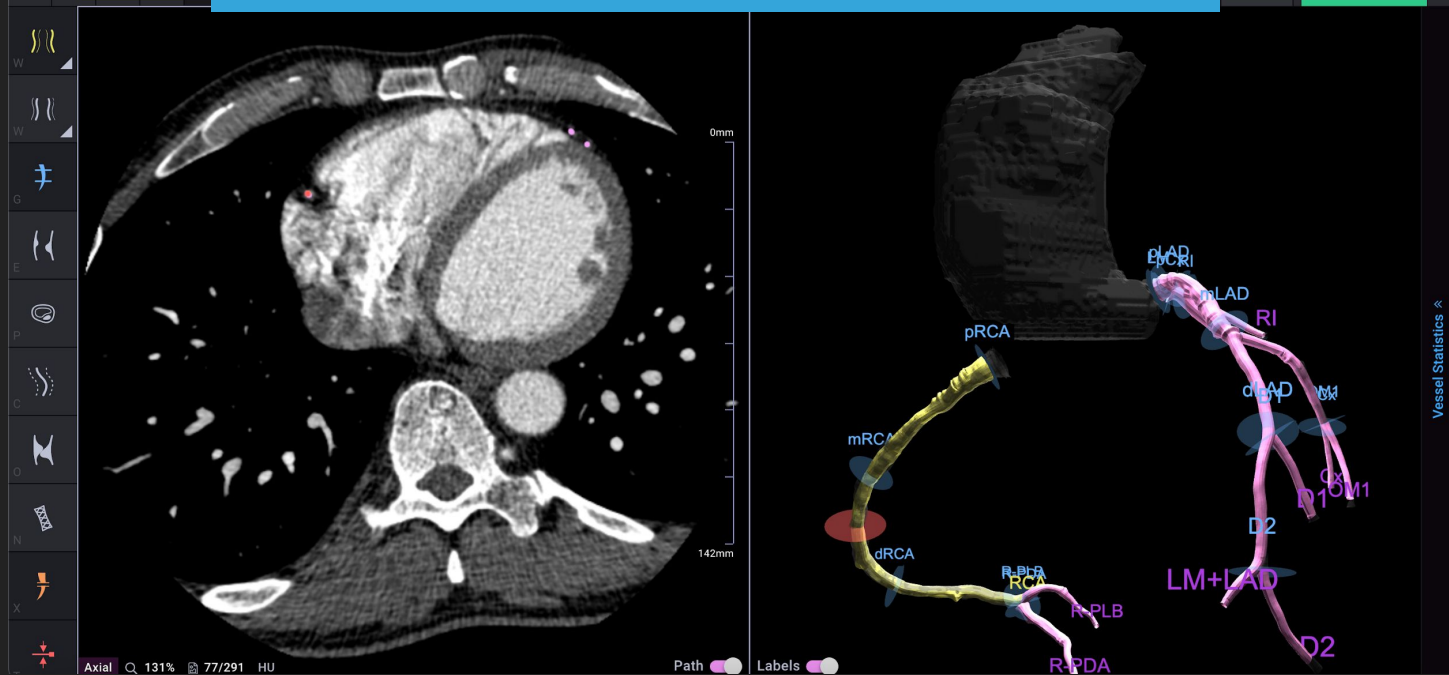
Highest Score I Have Ever Seen?

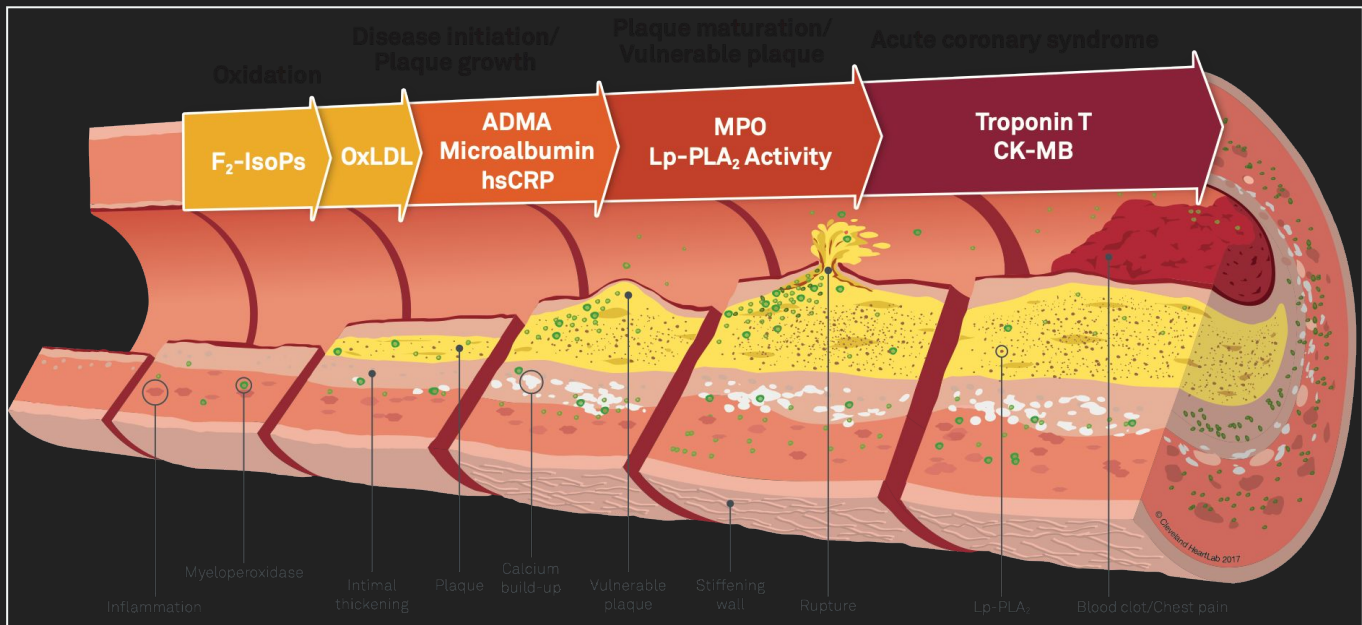


CLEERLY CCTA SCAN



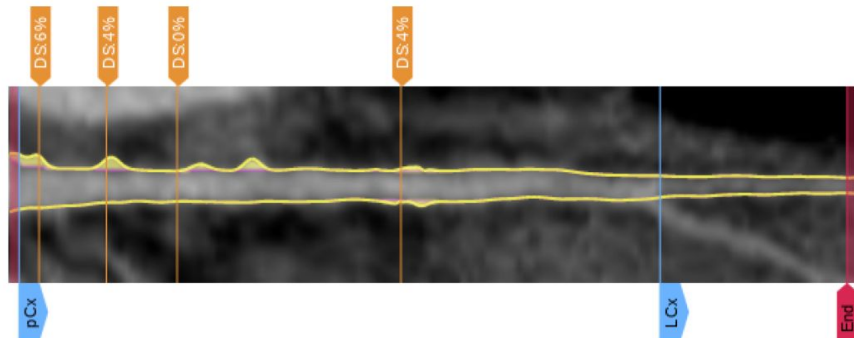
NEW "GOLD STANDARD"?





“ROADMAP”

Circumflex (Cx)



27.7 mm³ 8.6% PAV
Total Plaque Volume

0.8 mm³ 0.2% PAV
Total Low-Density-Non-Calcified Plaque Volume

27.7 mm³ 8.6% PAV
Total Non-Calcified Plaque Volume

0 mm³ 0% PAV
Total Calcified Plaque Volume

STENOSIS SEVERITY

6% Greatest Diameter Stenosis

VASCULAR REMODELING

1.3 Highest Remodeling Index

① A lesion spans the LM, pLAD, mLAD, pCx and RI with 15% in LM and 38% in pLAD and 10% in mLAD and 6% in pCx and 32% in RI.

SUMMARY

Summary

1. There is 200.3 mm^3 (9.6% PAV) of atherosclerotic plaque: [0 mm^3 (0% PAV) Calcified Plaque, 196.6 mm^3 (9.4% PAV) Non-Calcified Plaque, and 3.7 mm^3 (0.2% PAV) Low-Density-Non-Calcified Plaque].
There are 6 Two Feature Positive Plaques located in the *pRCA*, *mRCA*, *R-PDA*, *pLAD* and *pCx* segments.
2. There is no severe or moderate stenosis. There are 11 mild stenoses 1-49%: *pRCA*, *mRCA*, *dRCA*, *R-PDA*, *LM*, *pLAD*, *mLAD*, *pCx* and *RI*.
3. Dominance: *right-dominant*.

CLEERLY

ATHEROSCLEROSIS

Territory	Total Plaque Volume (mm ³)	Low-Density - Non-Calcified Plaque Volume (mm ³)	Non-Calcified Plaque Volume (mm ³)	Calcified Plaque Volume (mm ³)	Percent Atheroma Volume (%)
LM+LAD	111.8	1.5	111.8	0	15.9
RCA	60.8	1.4	60.8	0	5.9
Cx	27.7	0.8	27.7	0	7.8
Total	200.3	3.7	200.3	0	9.6

CLEERLY

STENOSIS

0

Severe
($\geq 70\%$)

0

Moderate Stenosis
(50%-69%)

11

Mild
($\leq 49\%$)

▲ *Understanding plaque burden to aid in the evaluation and treatment of CAD* □



An article in the *Journal of Cardiovascular Computed Tomography* defines a novel 4-tiered atherosclerosis plaque-burden *staging system* to assist providers in individualizing patient diagnosis and management of coronary artery disease.¹

WHY DOES IT MATTER?

Quantification of coronary artery disease (CAD) burden and plaque type has demonstrated to be strongest discriminant of future risk of Major Adverse Cardiac Events (MACE).² Atherosclerotic plaque burden also strongly correlates to stenosis severity as well as ischemia.

HOW SHOULD IT BE USED?

- ▲ Prior studies have independently shown that increasing Total Plaque Volume (TPV), Percent Atheroma Volume (PAV) as well as Non-Calcified Plaque (NCP) and Low-Density Non-Calcified Plaque (LD-NCP) are prognostic for future MACE.
- Useful for individualizing treatment regimens including pharmacological therapies for patients based on plaque volumes. □

Stage Description	TPV (mm ³)	PAV (%)	Medical Therapy	Possible Examples* (GDMT = Guidelines Directed Medical Therapy)
<i>Stage 0:</i> No Plaque	0	0	May not be necessary	Baseline GDMT. <i>Consider de-escalation.</i>
<i>Stage 1:</i> Mild Plaque	>0 to 250	>0 to 5%	Guideline-directed medical therapy	Statins. Ezetimibe.
<i>Stage 2:</i> Moderate Plaque	>250 to 750	>5-15%	Moderately Intensive	High Intensity Statins. Ezetimibe. Rivaroxaban. Aspirin. Inclisiran. Bempedoic Acid. Others
<i>Stage 3:</i> Severe Plaque	>750	>15%	Most Intensive	High Intensity Statins. Ezetimibe. Rivaroxaban. Aspirin. PCSK-9 inhibitor. Colchicine. Icosapent ethyl. Inclisiran. Bempedoic Acid. Others

*Medical therapy should be prescribed by a healthcare practitioner. These examples are for illustrative purposes alone.

Sources: 1. DOI: 10.1016/j.jcct.2022.03.001; 2. Chang HJ, Lin FY, Lee SE, et al. Coronary Atherosclerotic Precursors of Acute Coronary Syndromes. J Am Coll Cardiol 2018;71(22):2511-2522. DOI: 10.1016/j.jacc.2018.02.079

Cleerly, Inc. © 2022 | All rights reserved | <https://cleerlyhealth.com/indications-for-use> | Reproduction, adaptation, or translation of this document is prohibited without prior written permission of Cleerly, Inc.

Statins - Correct Tool?

Risks vs Benefits

Primary vs Secondary Prevention

“Particles Predict Risk”. There is no “good” or “bad” cholesterol

CT Coronary Calcium Score

Cleerly CCTA



Statin-Associated Myopathies

~10% of patients on statins report adverse muscle symptoms (SAMS)

Myalgias, Myopathy (Weakness), Cramping, “Flu” like symptoms, Tenderness, “Joint Pain”

Females, Elderly, and Renal Disease Patients are more likely to have symptoms

Genetic Variants in Apo E, CPT2, and SLCO1B1 can cause SAMS



Rhabdomyolysis

- Most Concerning Muscle Side Effect
- Increase Creatinine Kinase (CK) levels 10x Upper Limit Normal (ULN)
- Occurrence: 1.5 / 100,000 people

Myalgias on Statins

What To Do

Symptoms usually resolve within 2-4 weeks of stopping statin

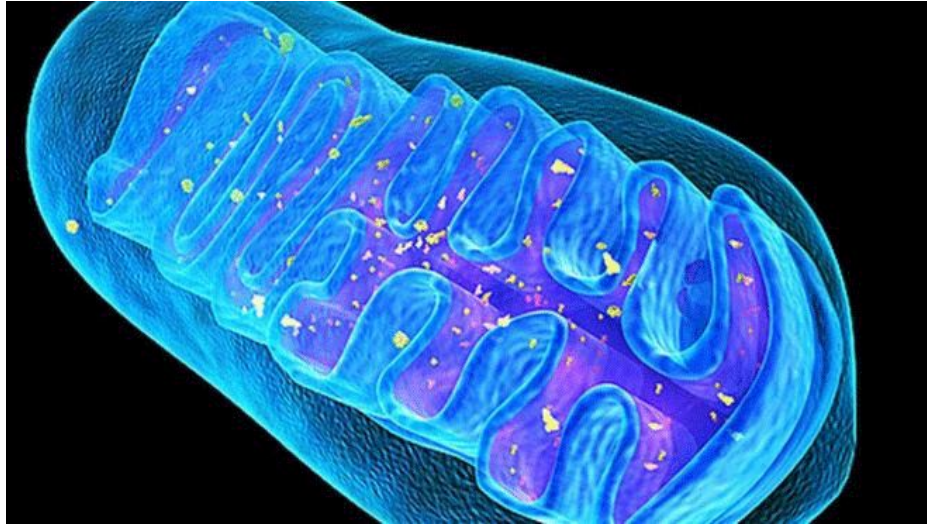
Decrease statin dose or change to different class of statin

Every other day dosing (QOD) or twice a week dosing

Non-prescription options (Bergamot, Berberine, Omega3, Niacin?) or other lipid lowering medications (Fibrates, Zetia, Nexletol, Repatha, Praluent)

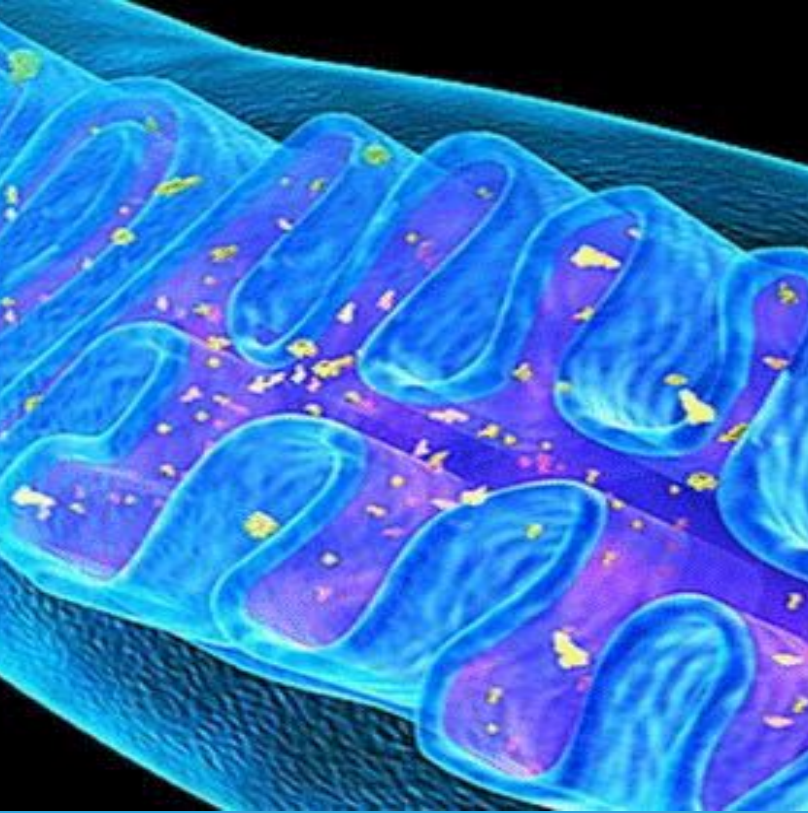
Optimize Vitamin D status and Thyroid Function

CoQ10 - Benefits possibly with 600-800mg daily



Mitochondria

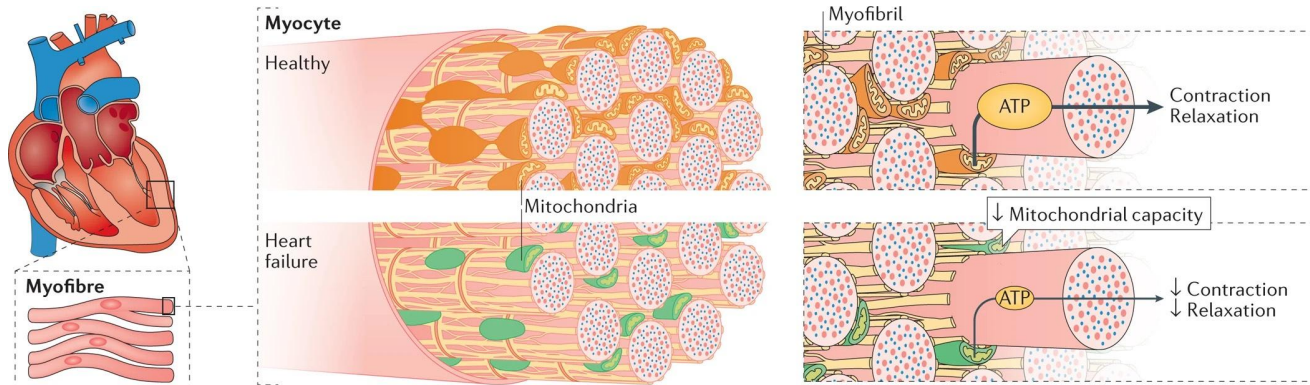
The location of 80-85% of chronic disease



WE ALL HAVE THE
SAME AMOUNT
OF TIME IN THE
DAY... WE DON'T
HAVE THE SAME
AMOUNT OF
ENERGY

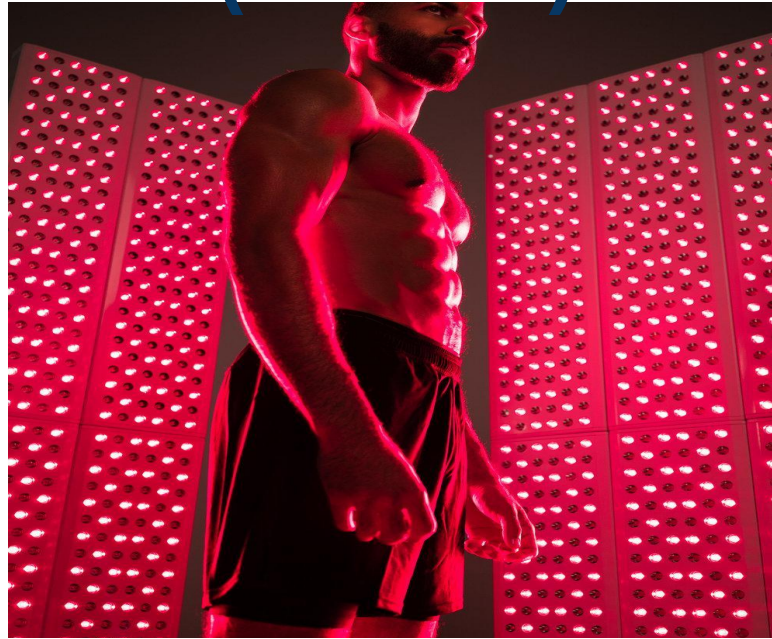
Michael Twyman, MD

Myocardial Muscle and Mitochondria



Nature Reviews | Cardiology

Photobiomodulation (PBM)





Olympians - Unfair Advantage?



Laser Therapy Course
Certificate of Attendance

This is to Certify that

Dr Michael Twyman

Has successfully completed a THOR Photobiomodulation Training Course on the application of Photobiomodulation Therapy, the physiological effects, clinical applications, dose, treatment techniques, safety and contraindications. Represents 8 hours education.

James Carroll
Course Leader

Thursday, 13th August 2020

THOR Photomedicine Ltd • United Kingdom • www.thorlaser.com

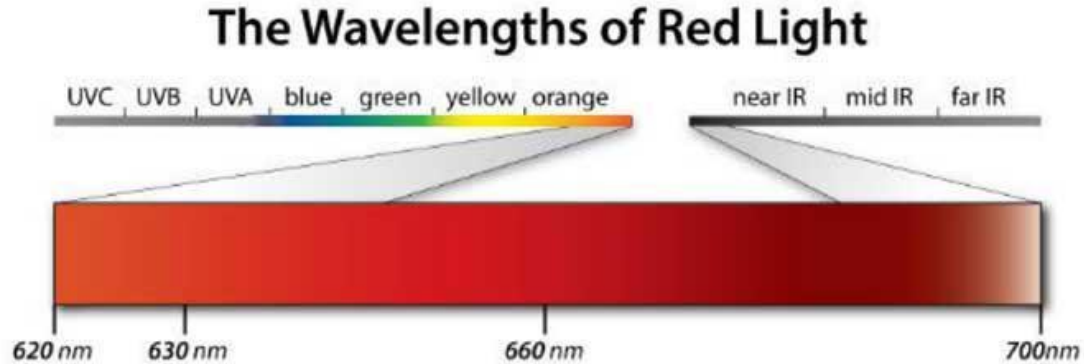
Light Guru In Training



DR. HYMAN+

Red / IR

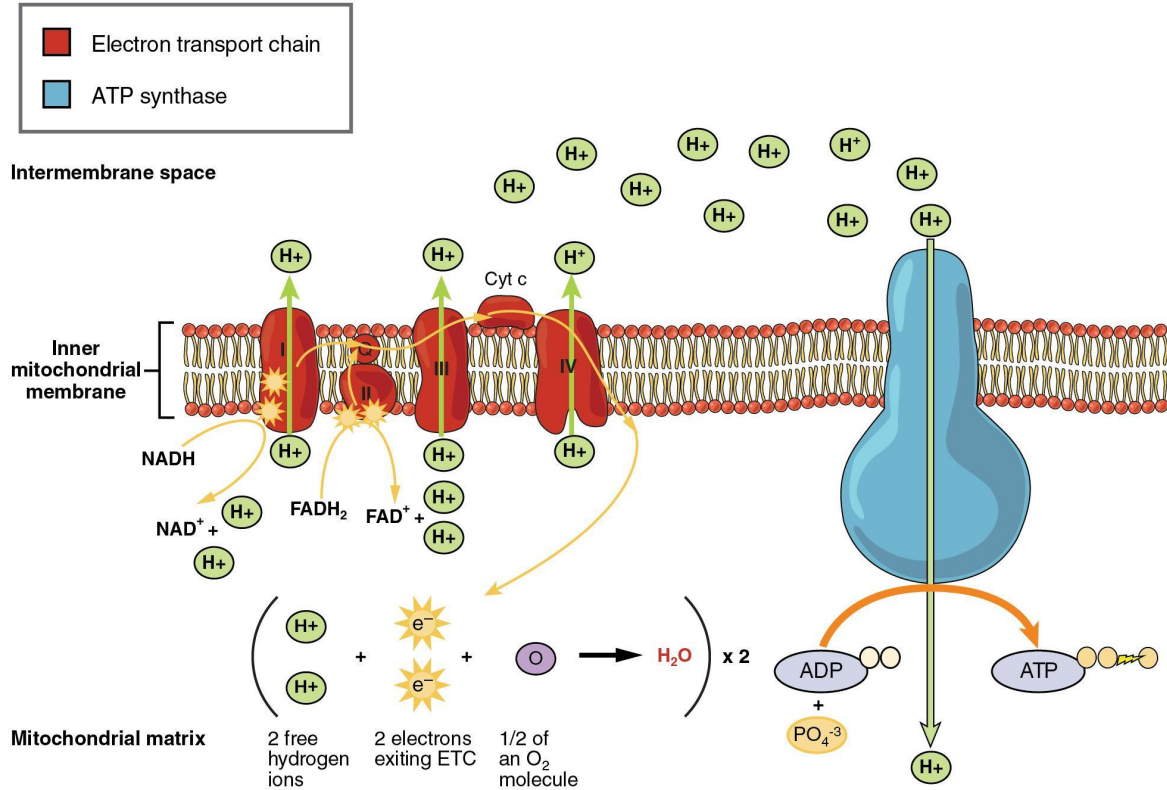
Main “Colors”



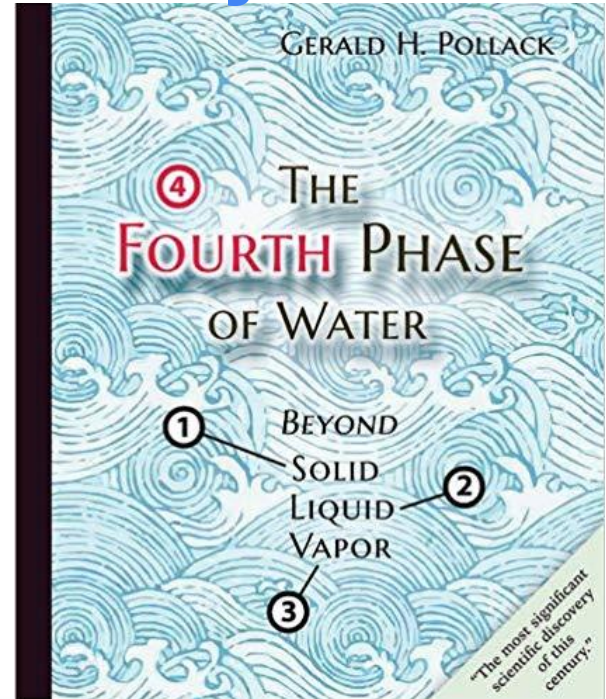
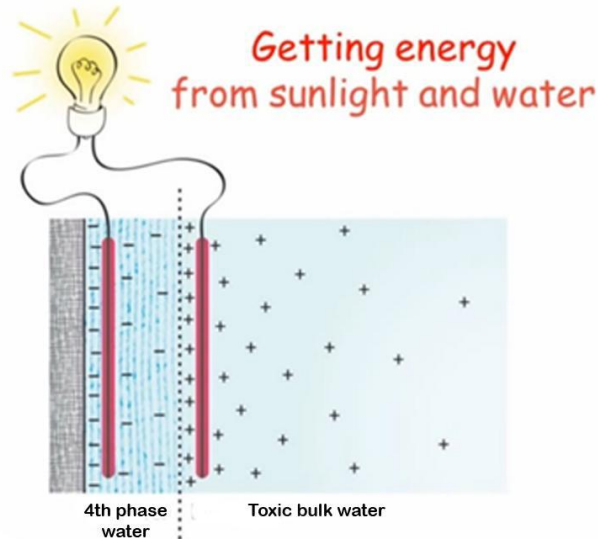
What Happens To Light ?

- Reflection (bounce off skin) - 63%
- Absorption (like Pacman)
- Transmission (xray)
- Scattering

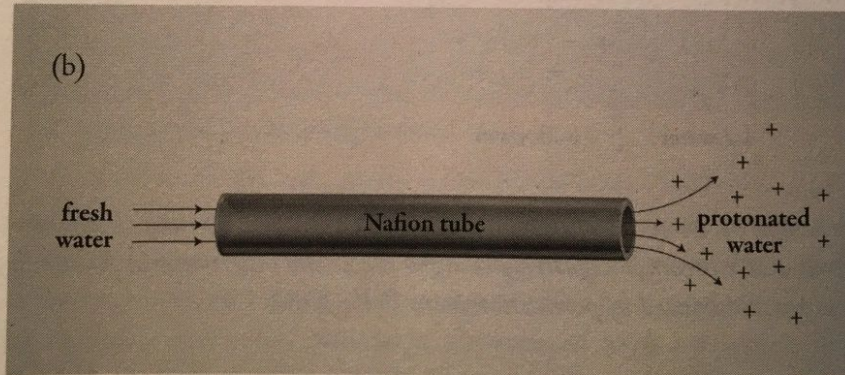
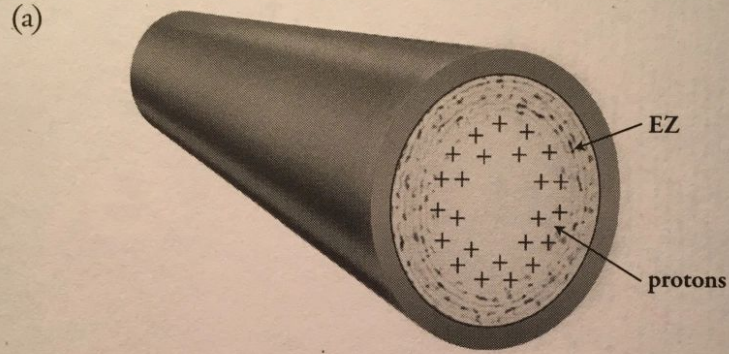
Primary	Secondary	Tertiary
Absorb by cytochrome c oxidase	Release Nitric Oxide (NO)	2nd Messengers
	Decrease ROS	Gene Transcription
	Increase ATP	Membrane Permability
		Growth Factors
		Enzymes
		SOD
		cAMP



Water as a Battery ?



Nafion tube filled with water



Taken from: <https://atlasbiologic.com/2017/10/30/h2o/>

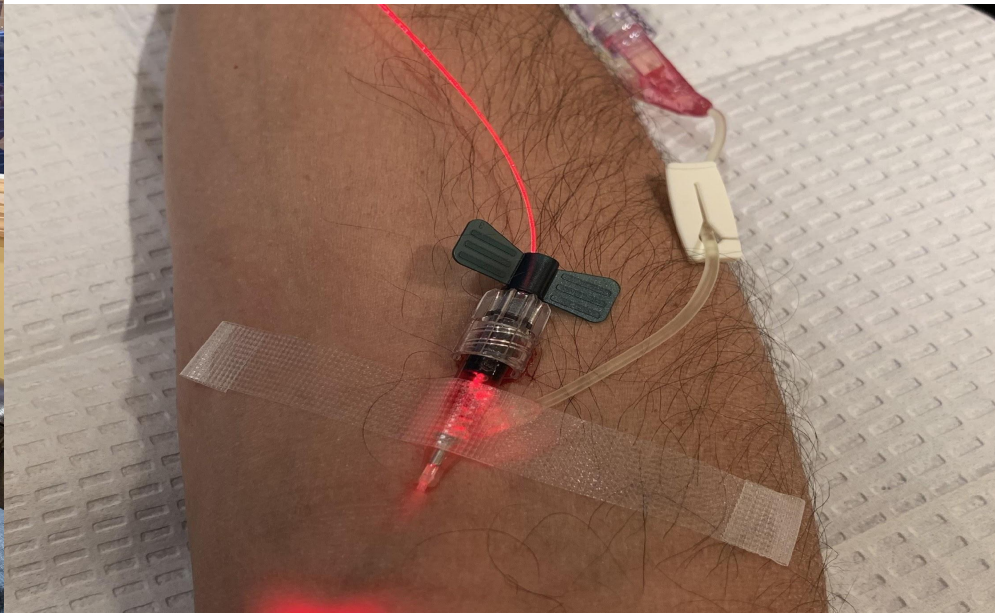
***Red Light Therapy
Treats The Heart
Mitochondria***



@electromagneticrevolution

Adjunctive laser-stimulated stem-cells therapy to primary reperfusion in acute myocardial infarction in humans: Safety and feasibility study

- 808 nm
- 900 mW laser
- Power density (10 mW/cm^2)
- Time (100 seconds)
- Fluence (1 J/cm^2)
- Admission, 24h, 3 days



IV Blood Irradiation (IVBI)

5 mW laser

10 sessions (3x/week)

20 min with 50% power (red to start - 635nm)

Each other laser is 10-15 min

9:31 Not Secure — timeoutmag.com

Timeout Magazine
Handball from all over the world

The Intravenous Laser Blood Irradiation therapy – Doping in Romanian handball?



photo: Madalina Donose

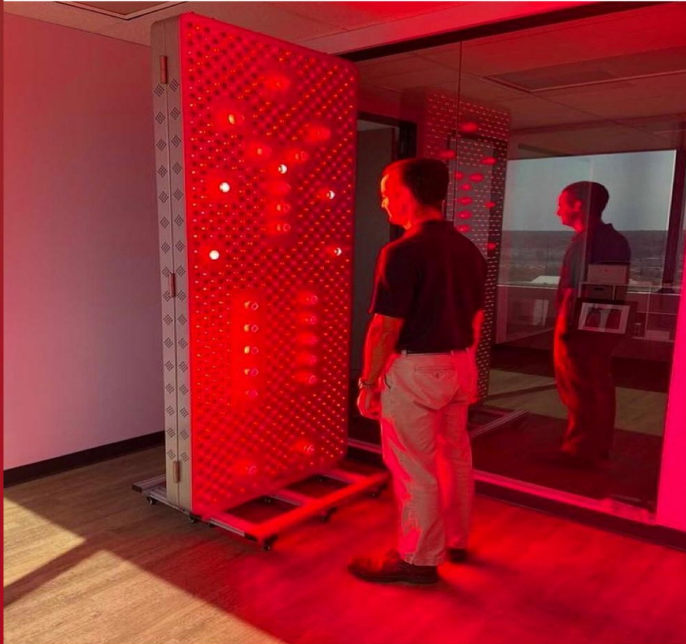
 **IBOLYA SZEKERES**
NOVEMBER 18, 2019

Until today not many of us have heard of the intravenous Laser Blood Irradiation therapy and even fewer people were aware of the fact that

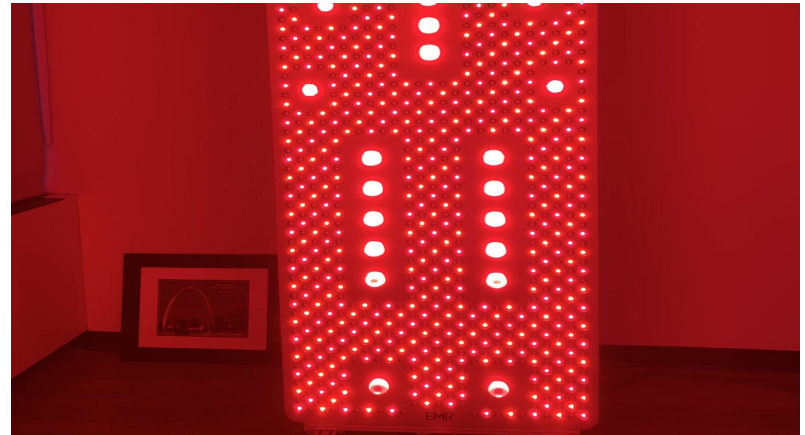
    



emrtekinc



emrtekinc @apollocardiology redlightdoc.com
@drtwyman @dk_2_





@drtwyman



@drtwyman

drtwyman.com