CHALLENGES TO MODELING THE LINKS BETWEEN MUSCLE PUMPS, MICROCIRCULATION AND FLUID FLOW TO SCAFFOLD IMPLANTS IN BONE

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Bone Chamber Lab

"ITS THE VASCULARITY, STUPID!"

PRINCIPLE FUNCTIONS OF VASCULATURE IN A TISSUE ENGINEERED SCAFFOLD

- NUTRIENT EXCHANGE
- CELL DELIVERY

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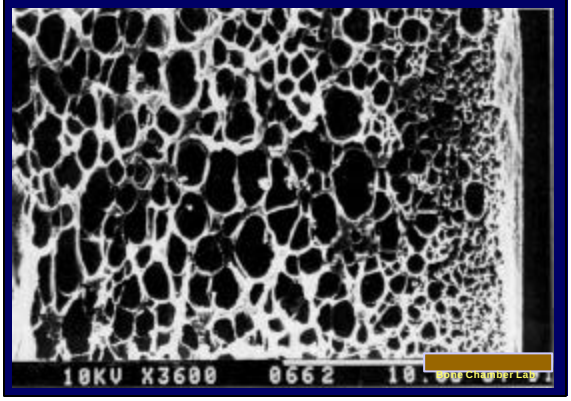
ENGINEERED PLLA SCAFFOLD



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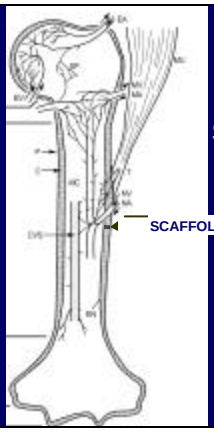

SCAFFOLD IMPLANTED IN TYPICAL LONG BONE

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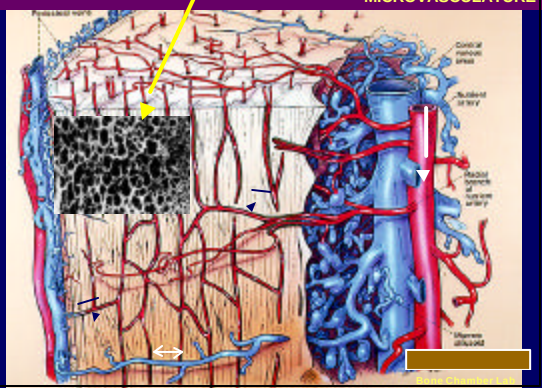
SCAFFOLD IN CORTICAL BONE SURROUNDED BY MICROVASCULATURE



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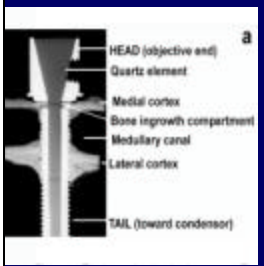
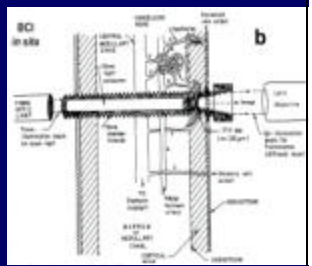
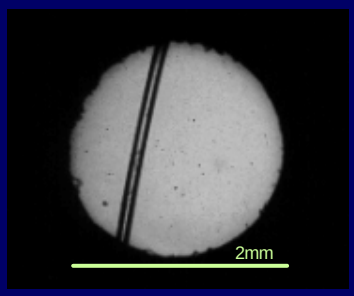
BONE WINDOW



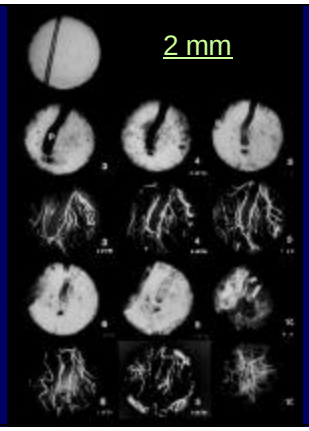


Bone Chamber Lab

100µm dia. PLG THREAD
IN A BONE CHAMBER COMPARTMENT



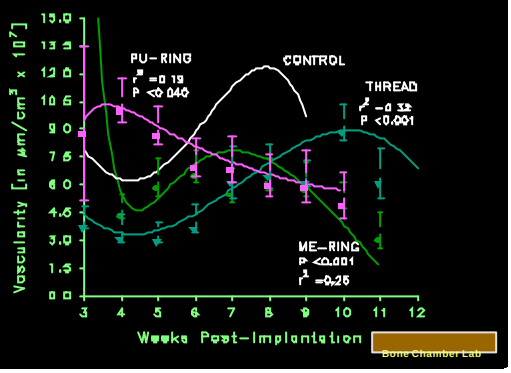
Bone Chamber Lab



IN VIVO
EROSION OF PLG THREAD DURING DEFECT HEALING

Bone Chamber Lab

ANGIOGENESIS AROUND ERODING PLGs



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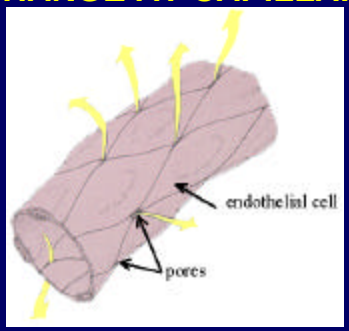
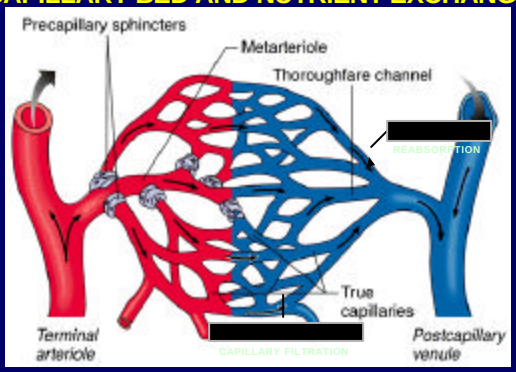
EXCHANGE AT CAPILLARIES



EFFLUX THROUGH PORES= CAPILLARY FILTRATION

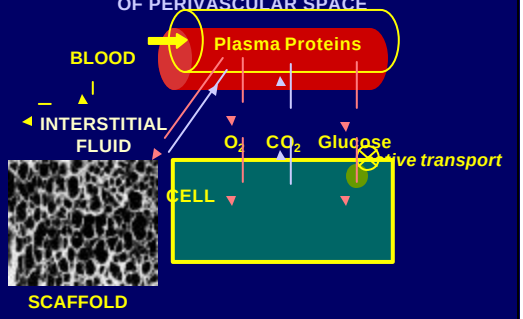
[TREZISE, 1998]

CAPILLARY BED AND NUTRIENT EXCHANGE



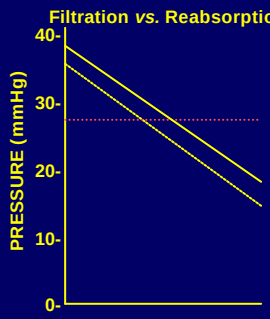
[TREZISE, 1998]

DIFFUSION BETWEEN BLOOD & INTERSTITIAL FLUID OF PERIVASCULAR SPACE



[Poland, 2001]

FLUID BALANCE DURING NUTRIENT EXHCANGE



Outward Forces:

1. Capillary blood pressure (P_c = 35 to 15 mmHg)
2. Interstitial fluid pressure (P_{IF} = 0 mmHg)
3. Interstitial fluid colloidal osmotic pressure ($?_{IF}$ = 3 mmHg)

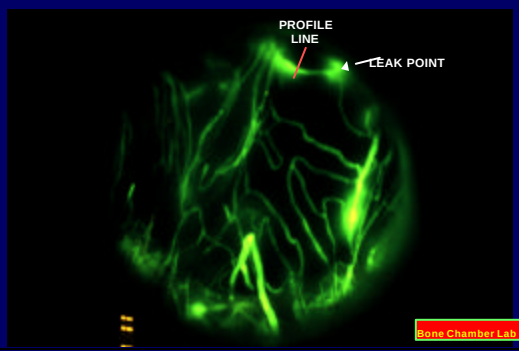
TOTAL = 38 to 18 mmHg

Inward Force:

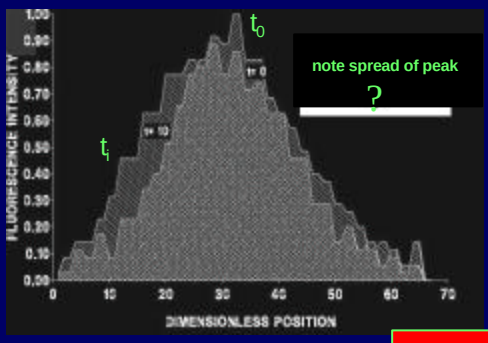
1. Plasma colloidal osmotic pressure ($?_c$ = 28 mmHg)

[Poland, 2001]

CAPILLARY FILTRATION IN BONE OF A LARGE MOLECULE (70 kDa)



SINGLE VESSEL LEAKAGE PROFILE



IS BONE CAPILLARY FILTRATION CONVECTIVE IN THE ABSENCE OF MUSCLE PUMPING?

Relative concentration at *x* after *t* seconds $\frac{C(x,t)}{C(0,t)}$?

$$?1 ? \frac{x^2}{2Dt}?\,?1 ? \frac{2}{?^{1/2}}\int_o^x e^{?t^2}dt?\frac{x}{?4Dt?^{1/2}} ? ?\frac{xe^{?\frac{x^2}{4Dt}}}{??dt?^{1/2}}?$$

where *D* is the unbounded fluid diffusion coefficient

(Nakamura & Wayland, 1975)

Bone Chamber Lab

RELATIVE PERMEABILITY TO FITC-DEXTRANS

ID	a nm	x µm	t sec	D $\frac{cm^2}{sec}$	D* $\frac{cm^2}{sec}$
#13	5.8	5.4	20	$3.27x10^{-7}$	$2.81x10^{-6}$
#13	5.8	5.4	20	$3.27x10^{-7}$	$7.96x10^{-7}$

D= free diffusion coefficient

D*= calculated relative diffusion coefficient

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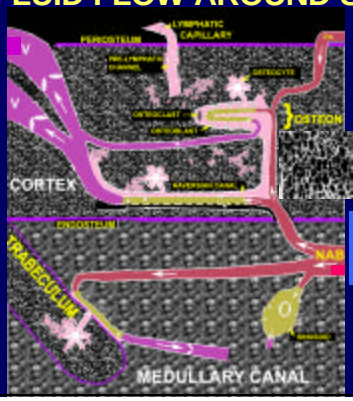
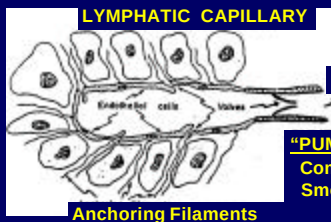
FLUID FLOW AROUND SCAFFOLD



WHITE/YELLOW ARROWS INDICATE FLOW

Bone Chamber Lab

LYMPHATIC CAPILLARY



2 - 4 L/day (? 125 ml/hr)

"PUMP"
Compression
Smooth muscle contraction

Anchoring Filaments

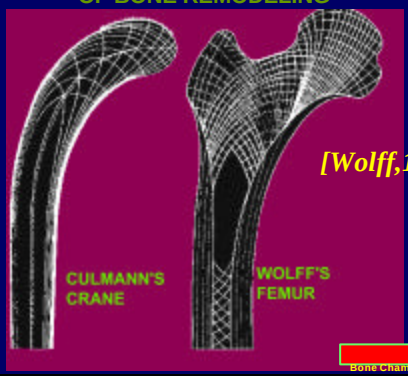
[Poland, 2001]

CONVECTIVE CAPILLARY FILTRATION IS NOT THE ONLY FLOW IN BONE

.....THE STORY OF BONE FLUID FLOW

Bone Chamber Lab

INSTANT HISTORY OF MECHANICAL MODULATION OF BONE REMODELING



[Wolff,1884]

Bone Chamber Lab

INSTANT HISTORY OF MECHANICAL MODULATION OF BONE REMODELING

NAME	CONCEPT	DATE
Julius Wolff SOLID CRANE	Living bones change in accordance with the stress and strain acting on them. BUT HOW?	1884
Iwao Yasuda ELECTRIC	Bone strain generates piezoelectric currents which modulate bone metabolism. DRY BONE	1953
Eiichi Fukada	Proteins are piezoelectric crystals	1957
Anderson & Ericksson FLUID	Modulation of bone metabolism requires wet bone and streaming potentials. Where is Wolff?	1970
Piekarski & Munro	Bone operates as a sponge with a dense, fluid filled matrix	1977

Bone Chamber Lab

WHERE FLUID FLOWS IN BONE

- IN BLOOD VESSELS (BLOODFLOW)
- FROM BLOOD VESSELS (CAPILLARY FILTRATION)
- OUTSIDE BLOOD VESSELS
  - CANALS (PERIVASCULAR)
  - CANALICULI (PERIOSTEOCYTE)
  - MINERALIZED COLLAGEN-PROTEOGLYCAN MATRIX (MICROPOROUS)

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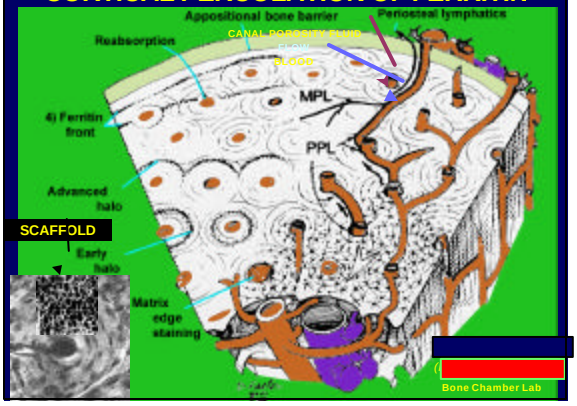
CORTICAL PERCOLATION OF FERRITIN



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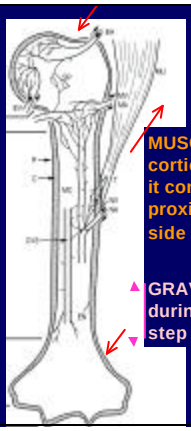
HEART-DRIVEN BLOOD PRESSURE IS NOT THE ONLY FORCE BEHIND CONVECTIVE CAPILLARY FILTRATION and is surely not the main FORCE driving FLUID FLOW IN BONE DURING SHORT PERIODS OF AMBULATION

Bone Chamber Lab

Two Sources Of Load On A Bone

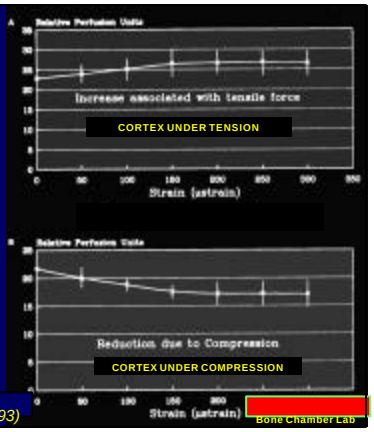


MUSCLE CONTRACTION: Inserts in cortical bone and pulls on cortex when it contracts, causing tension in proximal and compression in distal side of bone

GRAVITY: Weight of bone stretches it during lift and compresses it during step

Bone Chamber Lab

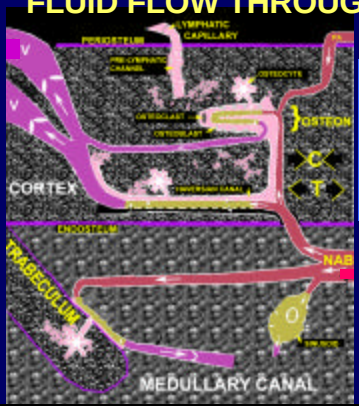
Effect of Bending on Bone Blood Flow



(McDonald & Pitt Ford, 1993)

Bone Chamber Lab

FLUID FLOW THROUGH BONE



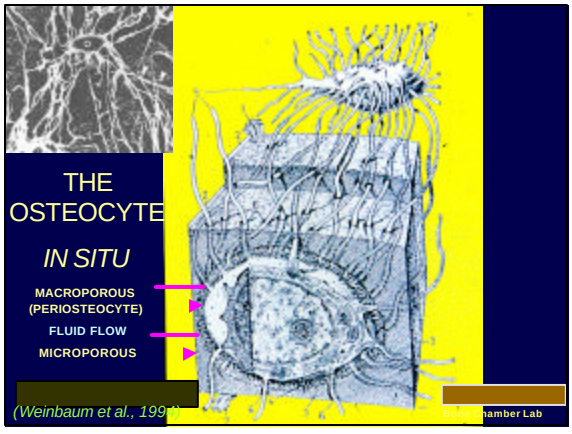
WHITE/YELLOW ARROWS INDICATE FLOW AND BLACK ARROWS INDICATE PRESSURE

Bone Chamber Lab

RECENT HISTORY OF MECHANICAL MODULATION OF BONE REMODELING

NAME	CONCEPT	DATE
Frangos et al.	Bone cells have mechanotransducers for fluid flow shear stress like those of endothelial cells	1989
Weinbaum et al.	Shear stress of bone fluid flowing over osteocytes causes surface strains which activate them	1994
Pollack et al.	POROELASTIC FLUID FLOW MODEL Streaming potentials are still a valid mechanism for modulating bone cell activity	1984, 2001

Bone Chamber Lab



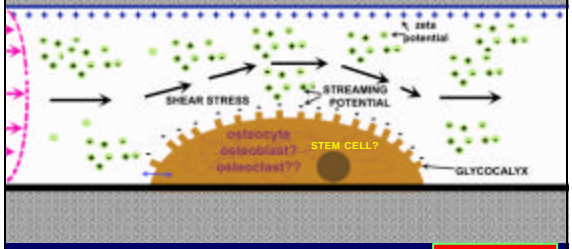
(Weinbaum et al., 1994)

Bone Chamber Lab

Flow Of Interstitial Fluid Over Bone Cells

WHICH STIMULUS MODULATES BONE REMODELING MORE, FLUID SHEAR STRESS OR STREAMING POTENTIAL?

AND IF THE CELL IS IMBEDDED IN A SCAFFOLD???????



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GIVEN THAT BLOOD IS THE ULTIMATE SOURCE OF FLUID ENTERING BONE.....

ARE BONE BENDING AND COMPRESSION THE ONLY GENERATORS OF PRESSURE FORCE DRIVING BONE FLUID FLOW???

CAN TRANSMURAL PRESSURE GRADIENTS IN BONE CAPILLARIES BE A SIGNIFICANT CONTRIBUTOR?

WHAT FORCE WOULD BE A REASONABLE SOURCE OF THIS CONTRIBUTION?

Bone Chamber Lab

THE MUSCLE PUMP

The circulation role it plays for the body

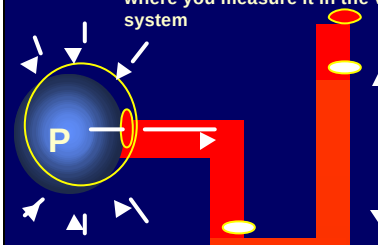
CHALLENGE: Try to stand on your own for 1/2 hour without twitching a skeletal muscle.

GRAVITY MAKES IT DIFFICULT TO MAINTAIN

- **POSTURE**
- **BLOOD SUPPLY TO HEART AND BRAIN**

Bone Chamber Lab

Hydrostatic pressure depends on where you measure it in the vascular system



$P = h \rho g$

P =Pressure
h =height
ρ=density
g =gravitational constant

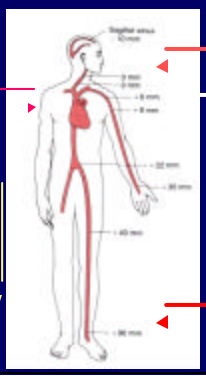
Hydrostatic Pressure

[Alexander, 2002]

Effect of Hydrostatic Pressure on Venous Pressures Throughout the Body

Heart level
CVP = 0 mmHg
(because heart pumps out any excess of blood that would accumulate at this level)

Every 13.6 mm distance away from the heart there is a 1 mmHg pressure change (also affects arterial pressure)

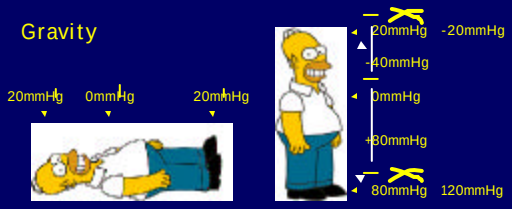


	Pressure	
veins	arteries	difference
-10	70	?P=80
0		
0		
0	100	?P=100
11		
22		
35		
40		
90	190	?P=100

[Alexander, 2002]

PRESSURE AND FLOW IN VEINS

Gravity

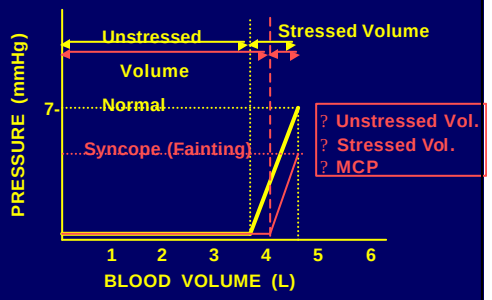


- Causes venous distension* in legs
  - ? VR, ? EDV, ? preload, ? SV, ? CO, ? MAP
  - causes orthostatic (postural) hypotension

***Venous volume 6-8 times arterial volume**

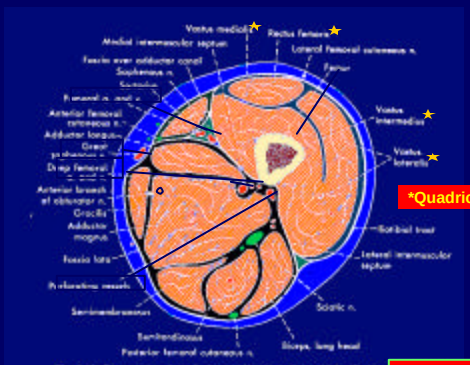
[DAVIES, 2000]

SYNCOPE (FAINTING)
Blood pooling in the extremities



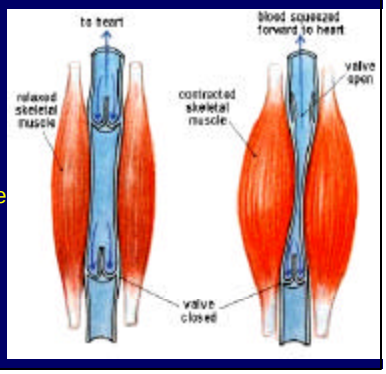
[Poland, 2001]

COMPARTMENTS OF A LIMB

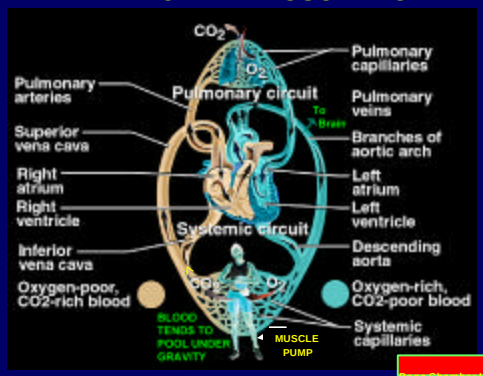


MUSCLE PUMP

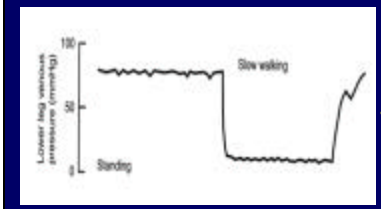
- Gravity helps pull the blood into the lower extremities
- Skeletal Muscle helps blood return to the heart (Venous Return)



THE NEED FOR THE MUSCLE-PUMP



Venous pressure and muscle pumping



[Alexander, 2002]

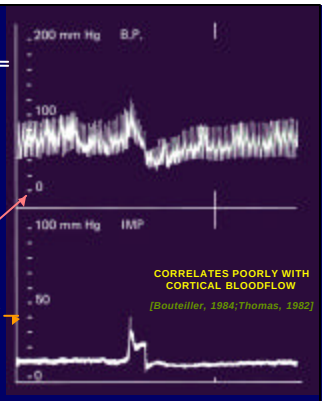
- **When the venous pressure is measured in a leg vein at rest (in a standing individual) the pressure is relatively high.**
- **However, immediately on starting rhythmic contraction of the leg, the valves force out fluid and pressure is decreased.**

HOW MIGHT THE MUSCLE PUMP ENHANCE BONE CAPILLARY FILTRATION'S CONTRIBUTION TO BONE/SCAFFOLD FLUID FLOW?

Bone Chamber Lab

Muscle Load

Effect of Quadriceps Muscle Contraction on BLOOD and IntraMedullary Pressure



(Ficat & Arlet, 1980)

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How Muscle Pump Generates FLUID Pressure In Bone

- FLUID-SATURATED BONE IS BENT BY MUSCLE
- VESSELS SUPPLYING FLUID TO BONE ARE COMPRESSED BY MUSCLE CONTRACTIONS --generating pressures as high as 570 mmHg (Sejersted et al., 1984)

(ALSO, DURING EXERCISE BLOOD PRESSURE CAN RISE ABOVE 180 mmHg)

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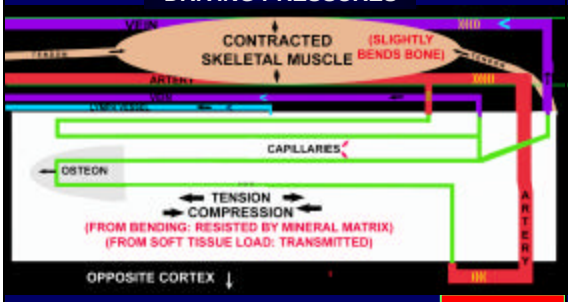
WHAT IS THE CONNECTION BETWEEN PRESSURE FROM MUSCLE PUMPING AND CAPILLARY FILTRATION?

Bone Chamber Lab

MUSCLE-PUMPED CAPILLARY FILTRATION

DRIVING PRESSURES



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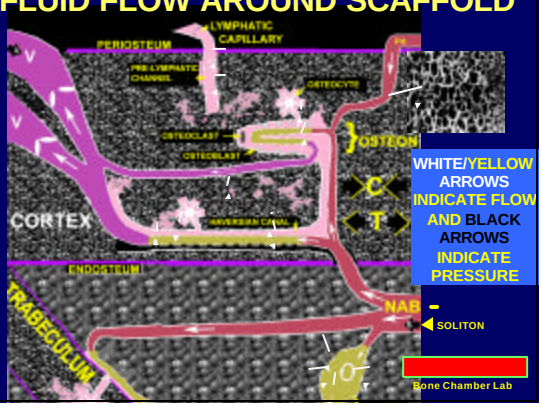
FLUID FLOW AROUND SCAFFOLD



WHITE/YELLOW ARROWS INDICATE FLOW AND BLACK ARROWS INDICATE PRESSURE

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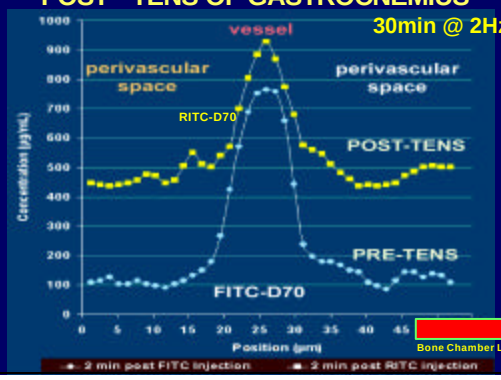
BONE CAPILLARY FILTRATION PRE- AND POST- TENS OF GASTROCNEMIUS



Bone Chamber Lab

Fluid Canicular Pore Pressure Induced by Mechanical Loading and Blood Pressure

$$p = A_1 \omega_0 \sin(\omega t + \varphi_1) + A_b p_b \sin(\omega t + \varphi_2) + p_0$$

Fluid Pressure Gradient Induced by Mechanical Loading and Blood Pressure

$$\frac{\partial p}{\partial r} = A_1 \omega_0 \sin(\omega t + \varphi_3) + A_b p_b \sin(\omega t + \varphi_4)$$

induced by mechanical loading

induced by blood pressure

Wang et al. (2001)

Relative Osteogenic Capacity of Different Driving Forces

Assume 100% osteogenic capacity for locomotion, in terms of induced peak shear stress.

Driving Forces →	Loco-motion	Posture	Pulse Blood Pressure	Muscle Increased IMP
	(200 ?? at 1 Hz):	(20 ?? at 20 Hz)	(10 mm Hg at 1 Hz)	(30 mm Hg at 20 Hz)
Capacity	100%	155%	0.5%	33%

Wang et al. (2001)

Blood flow during exercise

	at rest	moderate exercise
Digestive tract and liver	1350	600
Kidneys	1000	550
Skin	450	1700
Brain	650	650
Heart	150	550
Skeletal muscle	750	8000
Bone and other	**650**	450
Total cardiac output	5000	12500

blood flow in ml/min

HOW MUCH OF DECREASE IS DUE TO MUSCLE PUMP PRESSURE SOLITONS IN VEINS?

[TREZISE, 1998]

BUT, DOES THE

PRESSURE GRADIENT

DRIVING CAPILLARY FILTRATION PROVIDE SUFFICIENT FLOW TO *ACTIVATE* BONE CELLS

VIA **SHEAR STRESS** **[REQUIREMENT: 1.0 ?? (microstrain)]?**

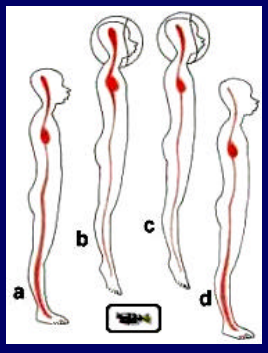
VIA **STREAMING POTENTIAL?**

Bone Chamber Lab

Microgravity

[Aerospace Medical Association, 1996]

Effect: Fluid Shift



HOW WOULD THESE SHIFTS EFFECT PERCOLATION THROUGH SCAFFOLDS AND BONE???

[Aerospace Medical Association, 1996]

Effects of Fluid Shift

- Facial Edema
  - Edema is an abnormal accumulation of watery fluid in the body tissues.
- Reduction in static leg volume - Fluid shift.
- Space Motion Sickness? - Fluid shift and sensory conflict.
- Headaches - Possibly due to higher blood pressure in the head.
- First an increase, and then a reduction in the size of heart muscle due to reduced workload.
- Orthostatic Intolerance - A decrease in blood volume leads to inadequate blood flow to the brain upon returning to Earth.

[Aerospace Medical Association, 1996]

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LAOH CORA KAISER FUND
UCLA DEPARTMENT OF BIOMEDICAL ENGINEERING

Bone Chamber Lab

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THANK YOU

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