Applications of CFD in Mechanobiology and Medical Engineering

- **QIN Kairong(覃开蓉)[1,2,3]**

[1] Department of Mechanics & Engineering Science, [2] Institute of Biomechanics, Fudan University, Shanghai 200433, China

[3]Department of Biomedical Engineering, Graduate Sch. of Med., Univ. of Tokyo,113-0033, Japan

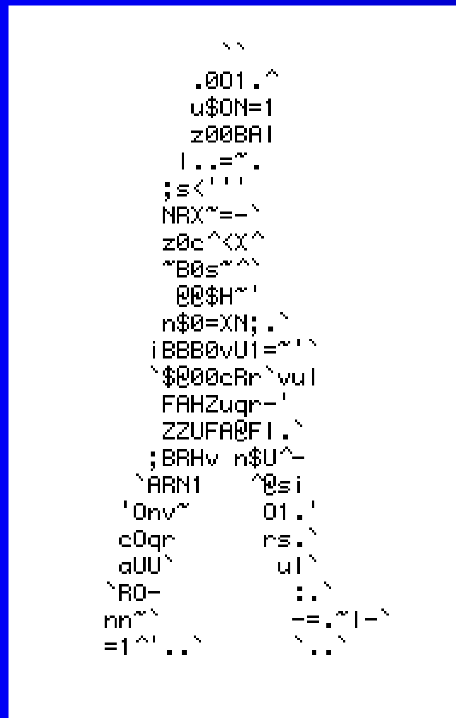
CFD -- The Third Method of Science
(Kelly, 1998)

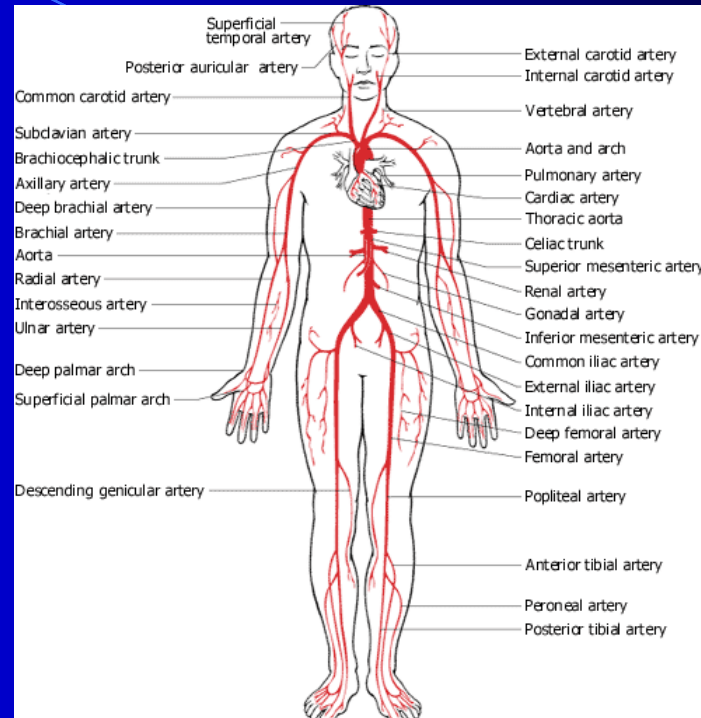
- Logic
- Experimentation
- Computer Simulation

Outline

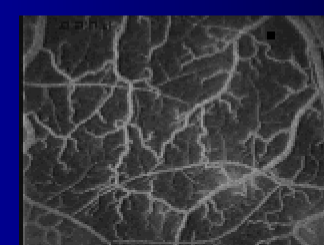
- Background
- Biomechanics *vs* Mechanobiology
- CFD in diagnosis and therapy of vascular diseases
- CFD in vascular tissue engineering
- CFD in cell mechanics
- CFD in TCM (Traditional Chinese Medicine)

Fluid Mechanics *vs* Life





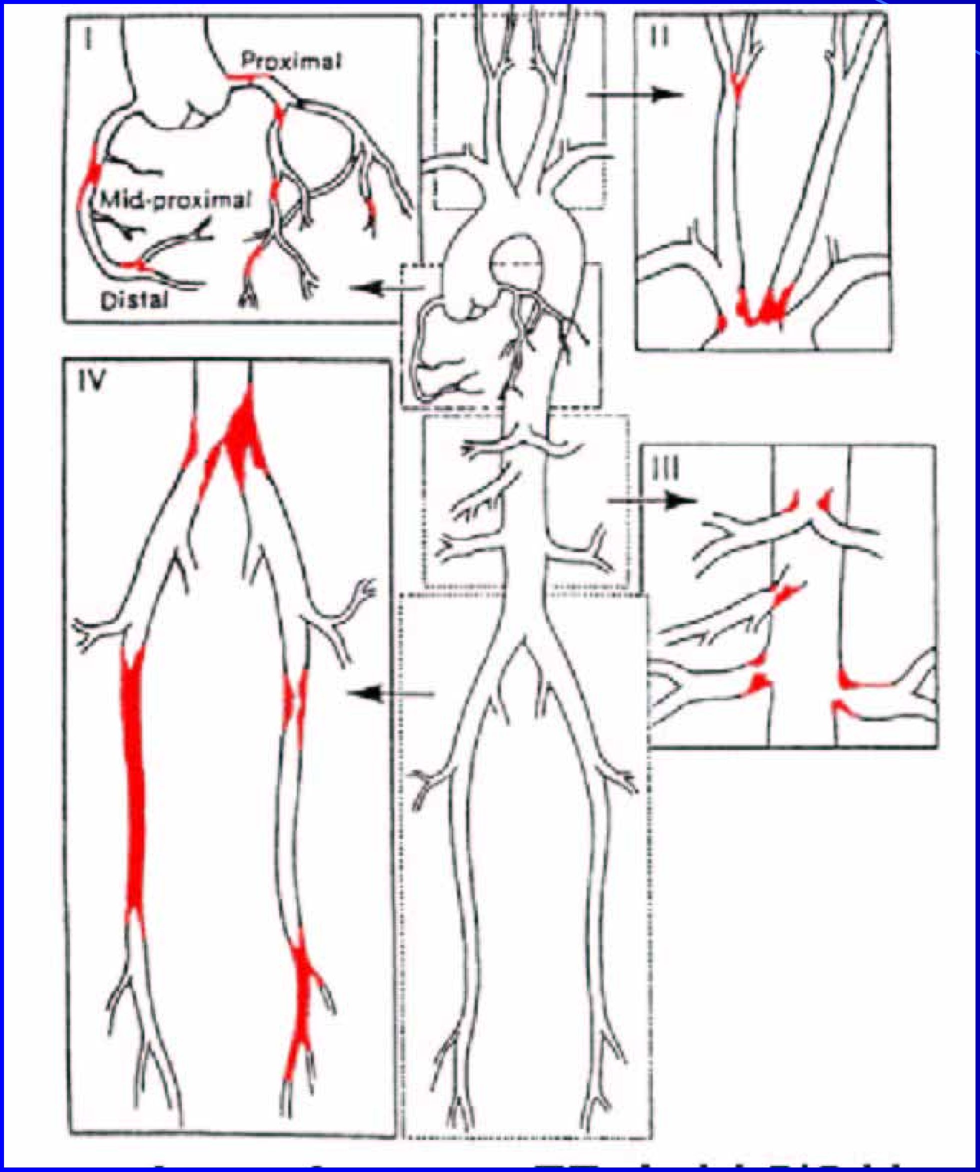
- **Water**
  - Embryo (2 Months) 95%
  - Baby 80%
  - Adult 65%



心血管流体力学倍受关注

- 心血管疾病死亡率
  - ✓日本 30%
  - ✓美国 51-52%
- 中国高血压病的患病率 1970s 8-12% → 17-22%，已超过1亿人，冠心病、脑卒中的发病率每年都在增加

Atherosclerosis (AS，动脉粥样硬化)



- 一种以大动脉内膜粥样化损害为特征的血管疾病（血细胞被胆固醇和脂质包裹）
- 血管狭窄和闭塞，导致心肌梗死、脑中风和外周器官如肝、肾和胰的功能不良

动脉粥样硬化(AS)的机理

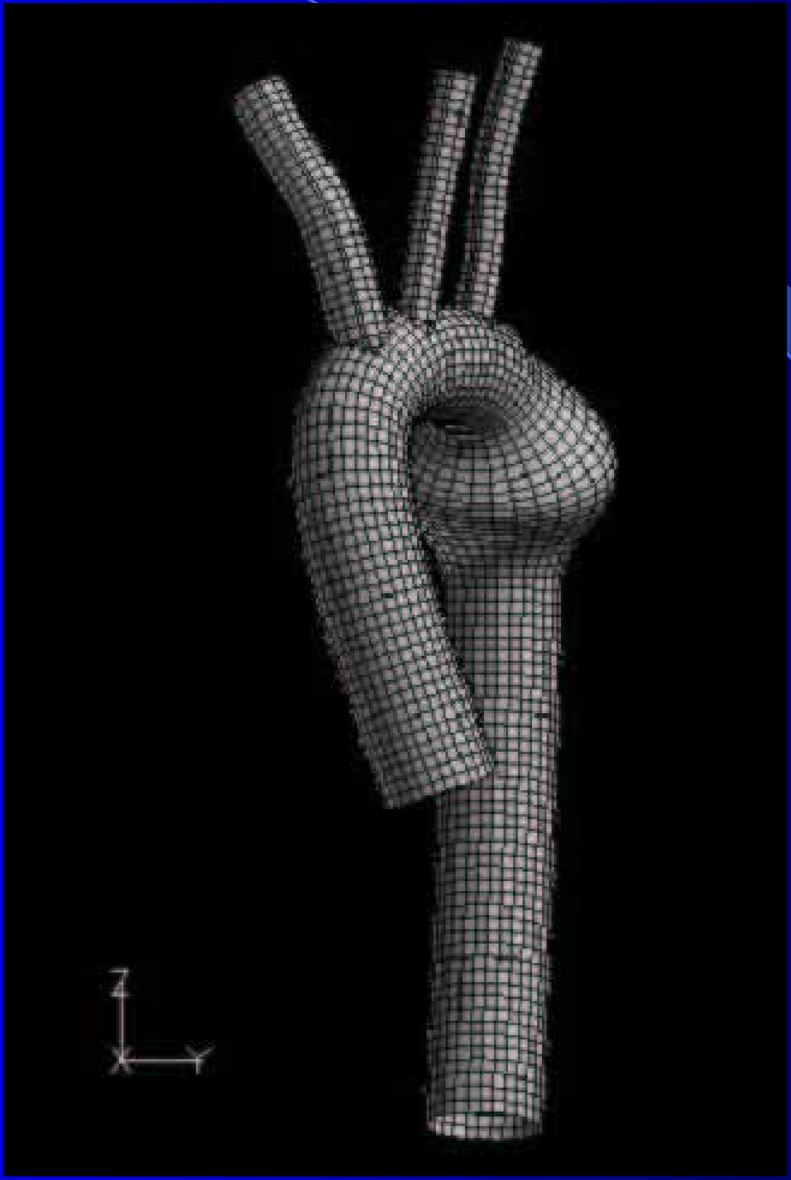
- “ response-to-injury hypothesis ” (Ross, 1973): 血管壁对内皮细胞损伤的一系列炎症反应的结果
- 导致内皮细胞和血管炎症反应的因素
  - 生化因素（细胞因子和生长因子）
  - 微生物因素（病毒和细菌）
  - 力学因素（血管应力和流体切应力）

AS *vs* Hemodynamics

- Fry (1968): High Shear Stress Hypothesis
- Caro (1969): Low Shear Stress Hypothesis
- Ku (1985): Low Oscillatory Shear Stress Hypothesis

- Circumferential stress, flow separation, secondary flow, turbulent flow(?), mass transfer
  - Medline > 40,000 Papers Related to Atherosclerosis

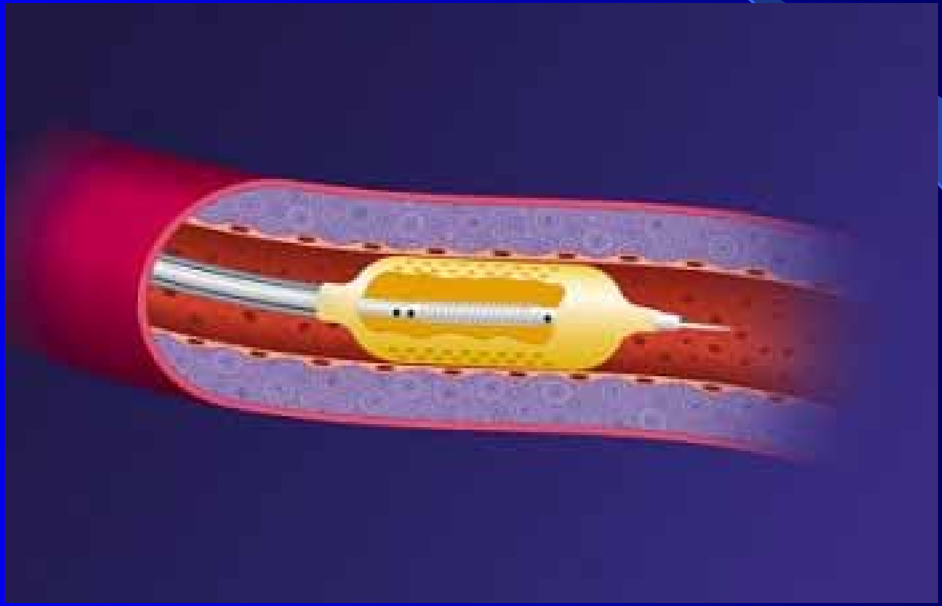
Aneurysm(动脉瘤） *vs* Hemodynamics



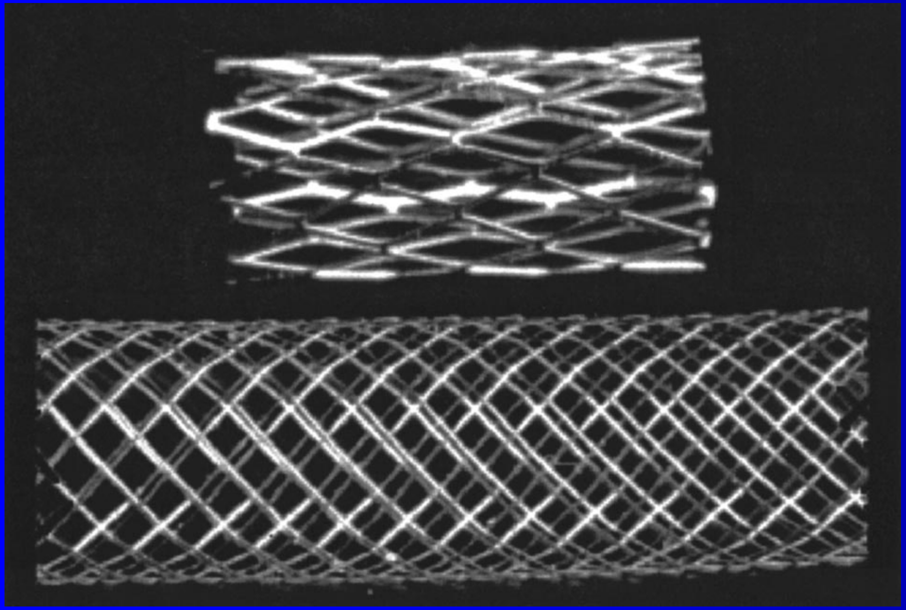
AS预防和治疗的常规方法

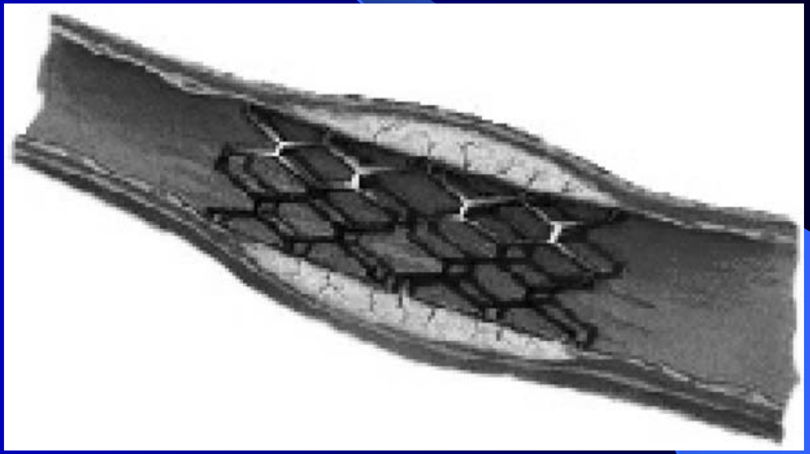
- 预防和延缓AS的方法
  - 运动-->增加血流切应力
  - 控制饮食（低胆固醇和低脂质饮食）
  - 抗氧化剂的使用（VE, VC和胡萝卜素）
- 晚期AS: 狭窄和闭塞-->不可逆转
  - 血管成形术(angioplasty)
  - 血管和支架(stenting)
  - 血管移植(grafting)

血管成形术(angioplasty)

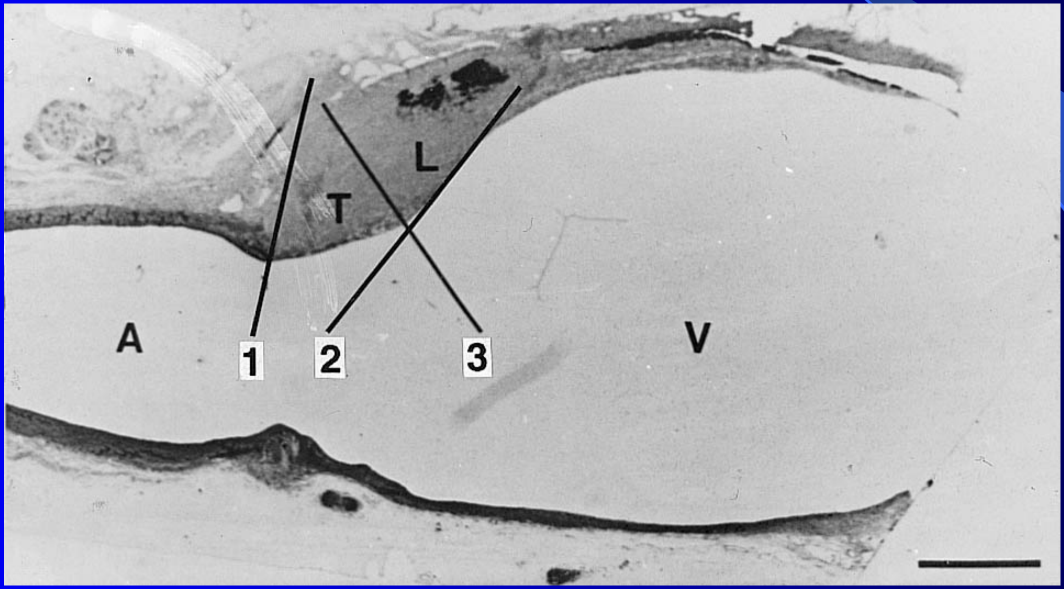


血管支架(stent/drug-coated stent)





静脉移植(Vein Grafting)



血管移植物(Vascular Grafts)

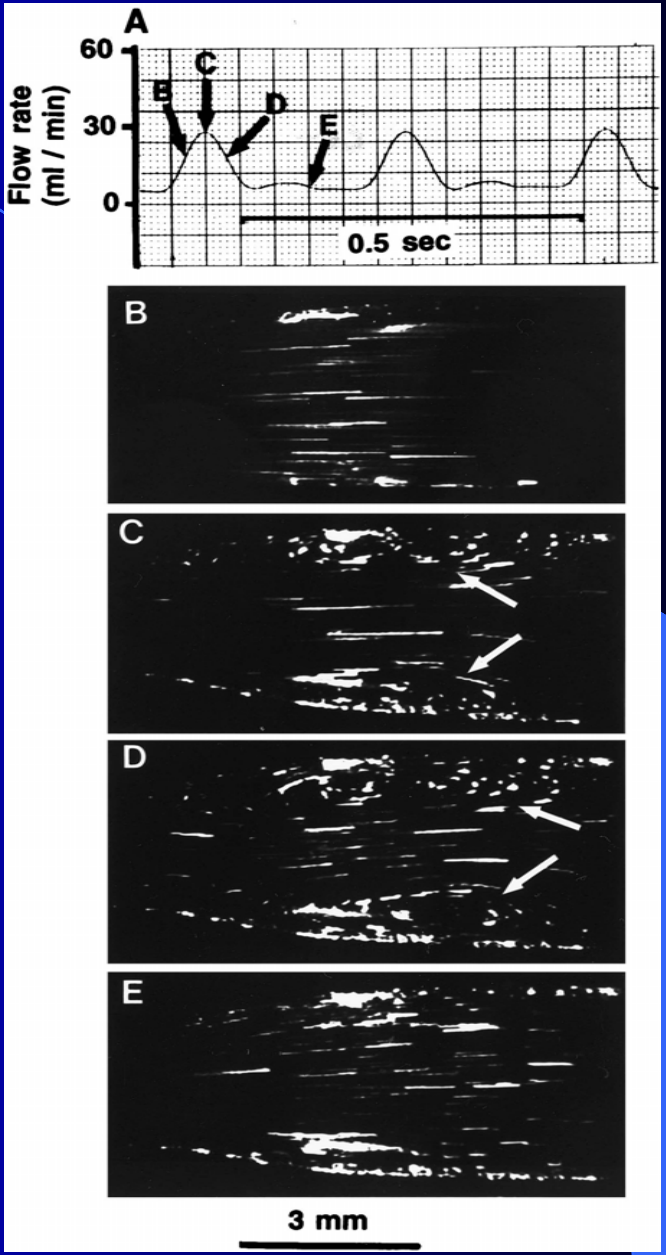
- 聚四氟乙烯和涤纶移植物
- 自体静脉和动脉(金标准移植物）
  - 再狭窄率：

1M	1Y	3Y	10Y
10.9%	18.9%	36.8%	49.9%

  - 几乎没有一个静脉移植物能活到20年

Restenosis (再狹窄) v.s. Hemodynamics

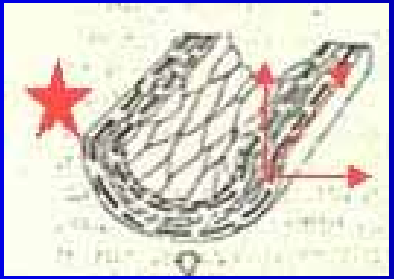
- ✓ Shear stress (steady / pulsatile / turbulent)
- ✓ Shear stress gradient (flow separation / secondary flow)
- ✓ Circumferential stress
- ✓ Mass transfer (steady / pulsatile / turbulent)

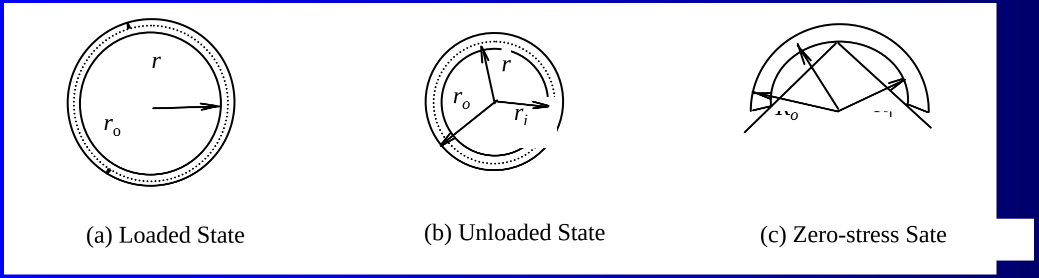


Vascular Biomechanics

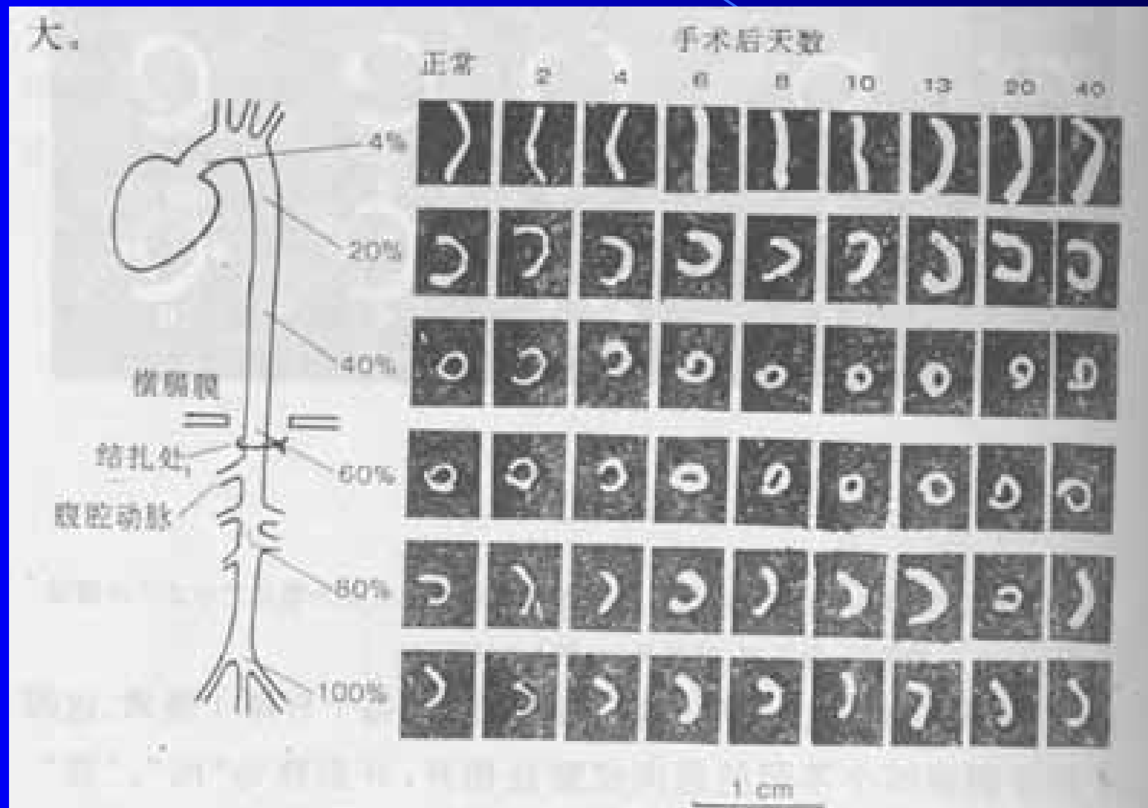
血管壁应力

- 均匀直圆管模型
  - 2个张应力：周向应力/轴向应力
  - 1个压应力：径向应力





血管的零应力状态



Fung YC冯元桢

血管承受动载荷，血管材料是非线性粘弹材料

$$\frac{\partial \sigma_r}{\partial r} + \frac{\sigma_r - \sigma_\theta}{r} = \rho \frac{d^2 r}{dt^2}$$

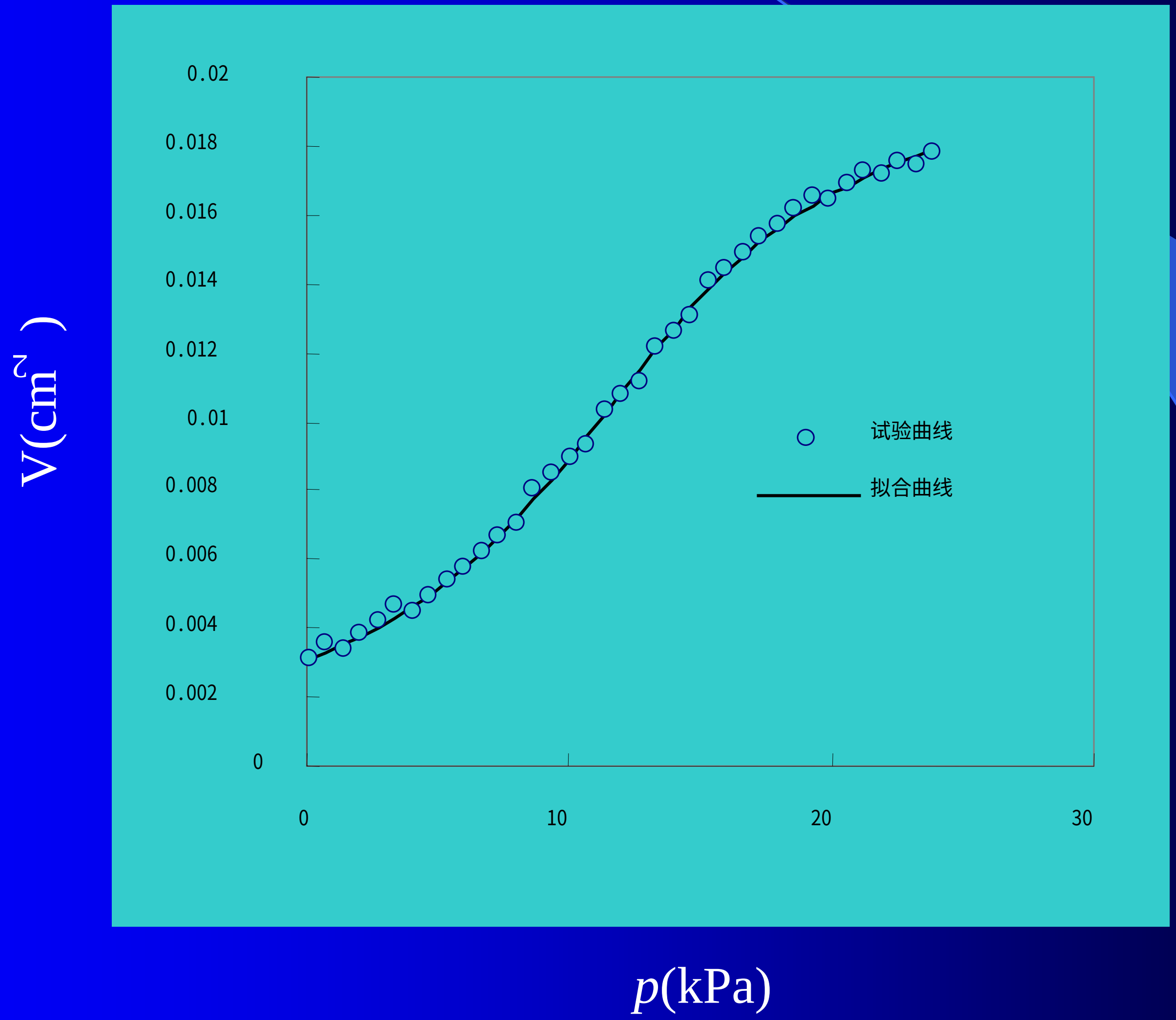
$$\sigma_i = \lambda_i^2 \frac{\partial W}{\partial E_i} + q_i \qquad (i = r, \theta, z)$$

$$W = 0.5c\exp(b_1 E_\theta^2 + b_2 E_z^2 + b_3 E_r^2 + 2b_4 E_\theta E_z + 2b_5 E_z E_r + 2b_6 E_\theta E_r)$$

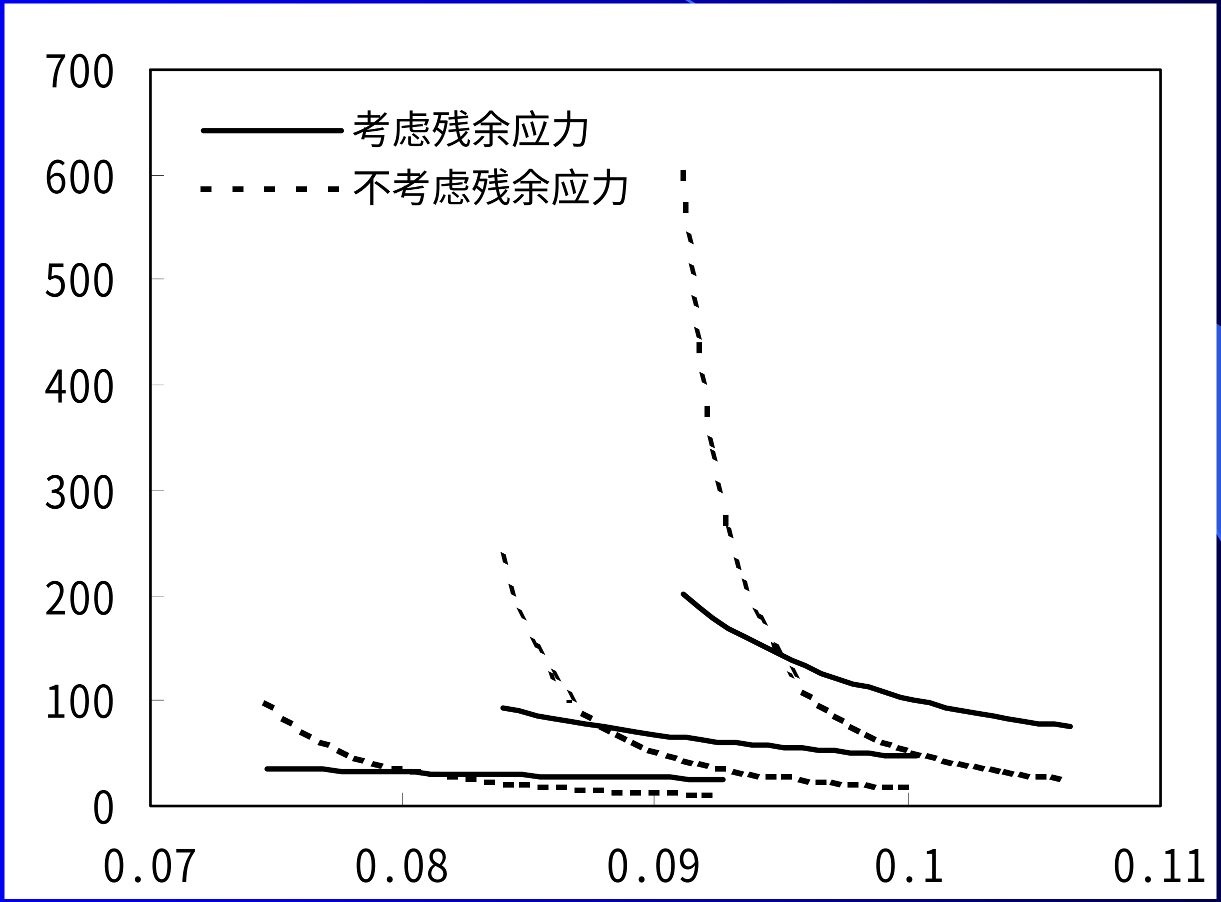
$$E_i = \frac{1}{2}(\lambda_i^2 - 1)$$

$$\lambda_r = \frac{\partial r}{\partial R}, \qquad \lambda_\theta = \frac{\pi}{\pi - \alpha} \quad \frac{r}{R}, \qquad \lambda_z = \frac{\partial z}{\partial Z}$$

p—V Relationship of the Rat's Carotid Artery



血管壁周向应力分布



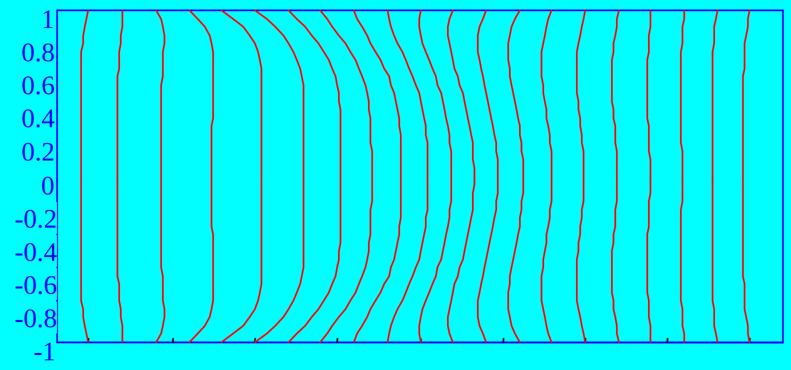
血流切应力(Fluid Shear Stress)

- 刚性直圆管中的Hagen-Poiseuille公式

$$u = \frac{1}{4\eta}(R^2 - r^2)(-\frac{dp}{dx})$$

$$\tau = \eta \frac{du}{dr}$$

- 刚性直圆管中的Pulsatile Flow (Womersley,1957)



非均匀血管的血液流?

→Fluid-Solid Coupling Problem

→FEM + CFD

Vascular Mechanobiology

张应力与血管重建(器官和组织水平)

- 肾动脉和/或主动脉缩狭引起体循环高血压
- 乏氧引起的肺循环高血压

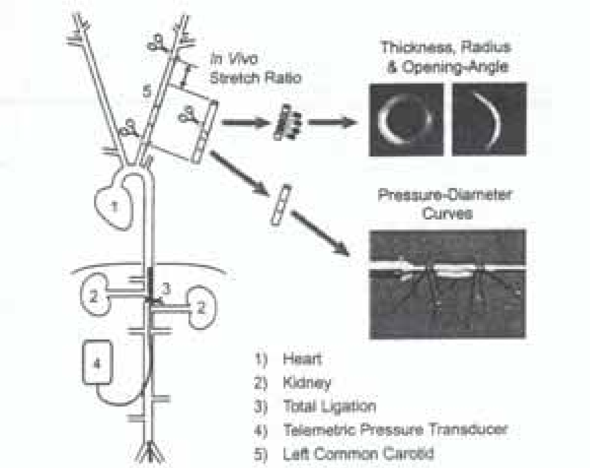
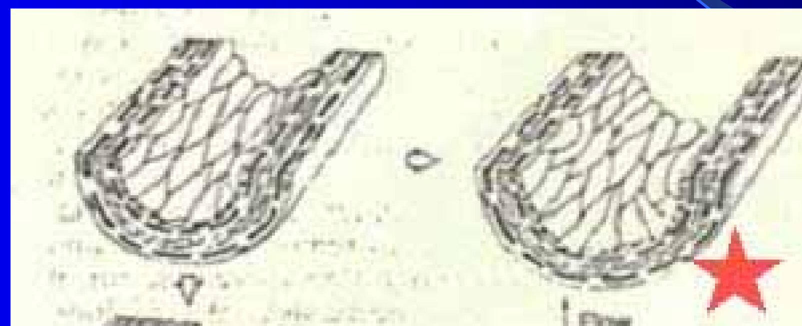


FIGURE 1. Schematic diagram of the experimental procedures showing the placement of the telemetric pressure transducer (4), the site of total aortic ligation (3), and the segments of the LCC used for the inflation/extension tests and for geometrical analysis.

- 壁厚增加
- 周向应力改变

血流切应力与血管重建(器官和组织水平)

- 发育过程中，血流快的血管成为大动脉



- Kamiya (东大)关于狗的动静脉吻合实验

$$\tau = \frac{4\eta Q}{\pi r^3} = const$$

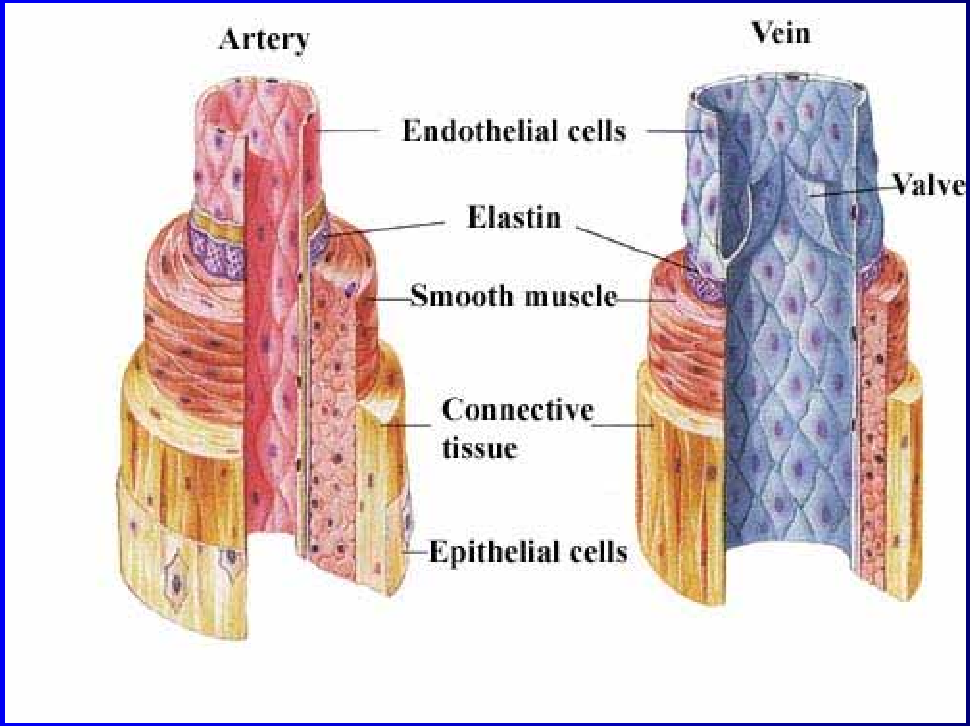
η黏度

Q流量

r半径

参与血管重建的细胞类型

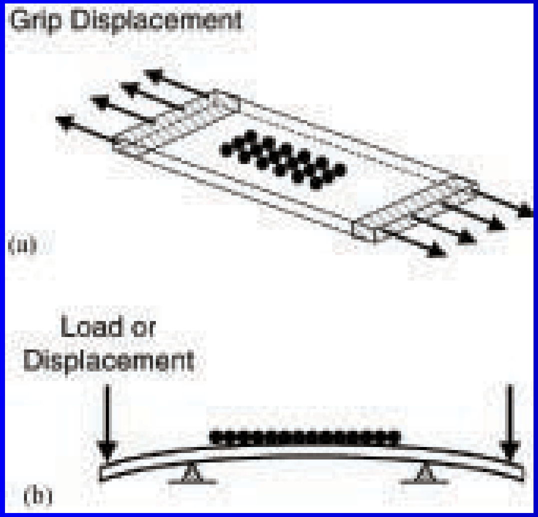
- 内皮细胞（血管）
- 平滑肌细胞（血管）
- 白细胞和血小板（血液）

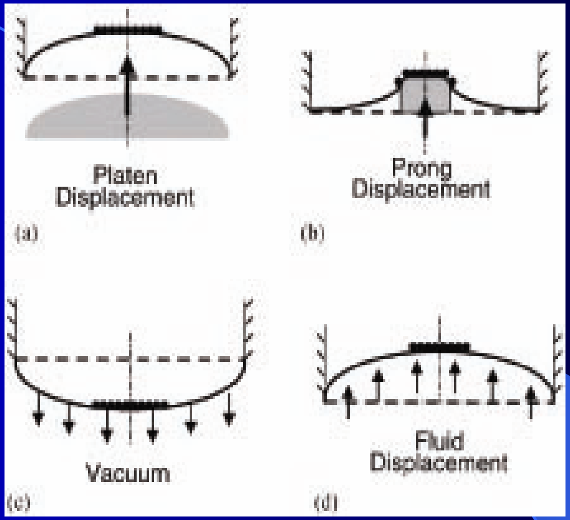


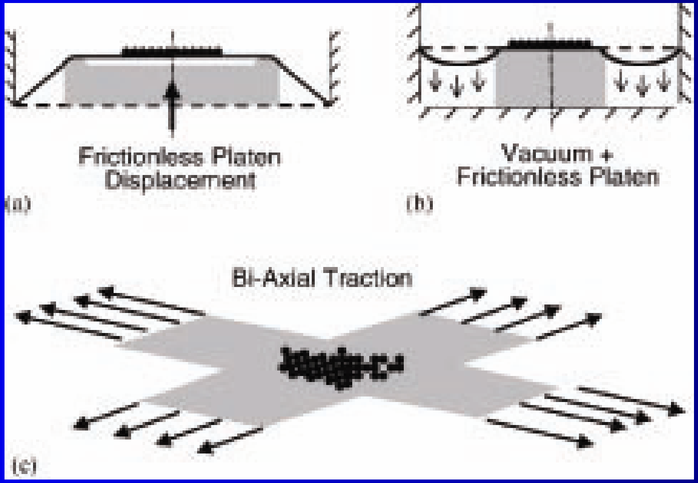
细胞重建的基本过程

- 细胞增殖(Cell Proliferation)
- 细胞死亡(Cell Death)
  - 坏死(necrosis) vs 凋亡(apoptotic)
- 细胞间相互作用(Cell-to-Cell Interaction)
- 细胞外基质的产生(Production of Extracellular Matrix)

Tensile Stress and ECs



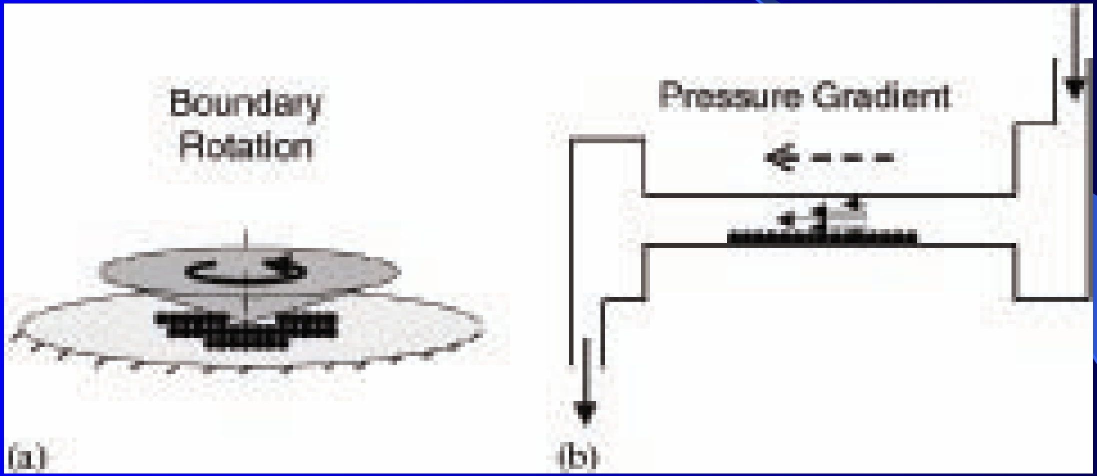




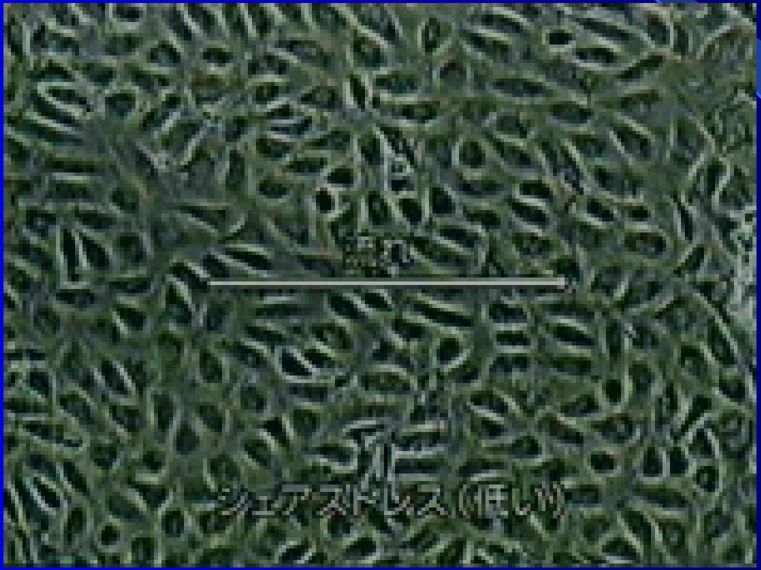
张应力/应变升高引起的细胞重建

- 引发内皮和平滑肌细胞DNA合成和增殖
- 促进细胞骨架蛋白、肌浆球蛋白以及平滑肌细胞外基质合成
- 调节平滑肌细胞的排向
- 加强平滑肌细胞中angiotensin II的有丝分裂活动
- 引发生长因子基因的上调
- 引发细胞凋亡

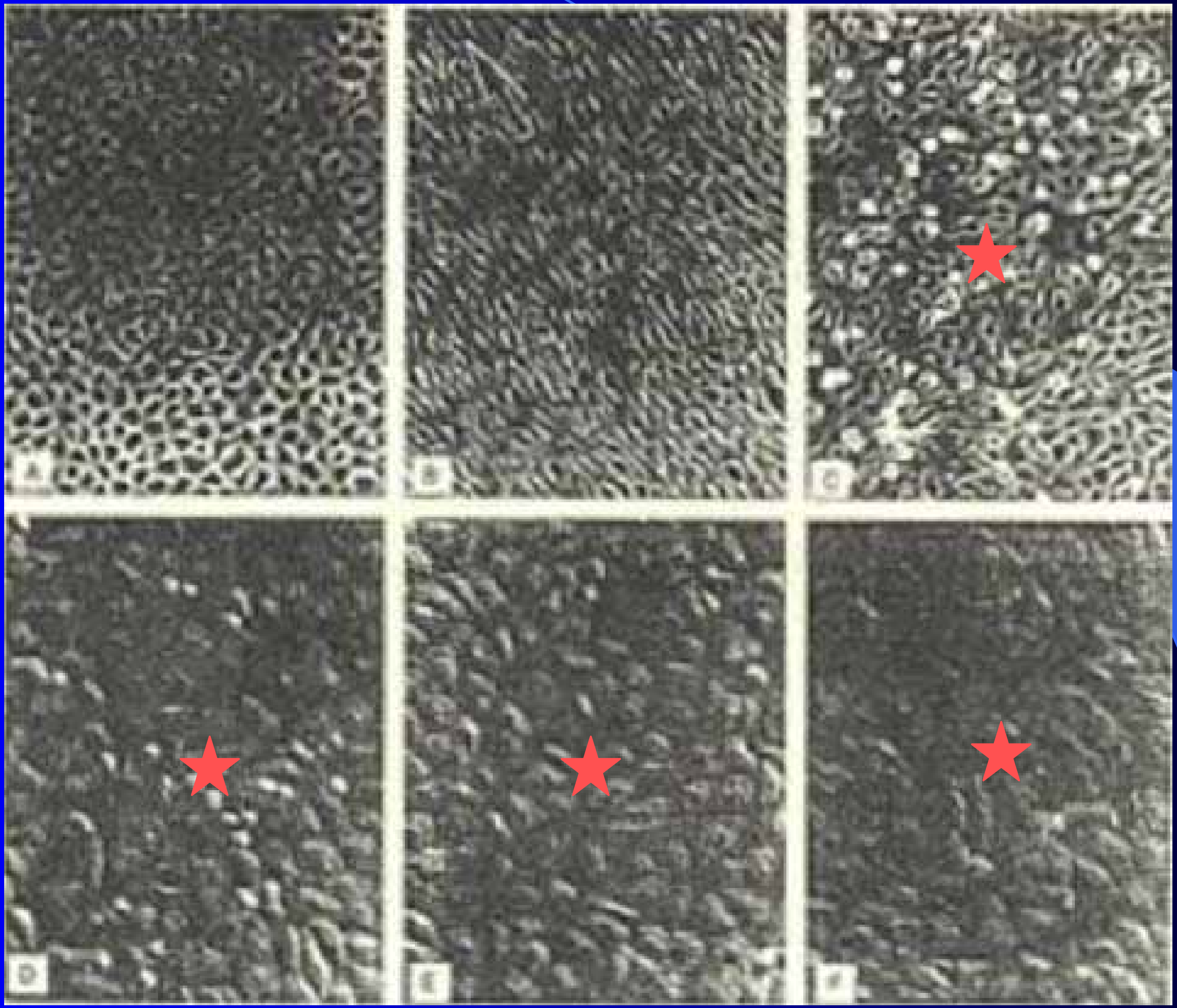
Fluid Shear Stress and ECs



Morphological response of ECs to Laminar Shear Stress



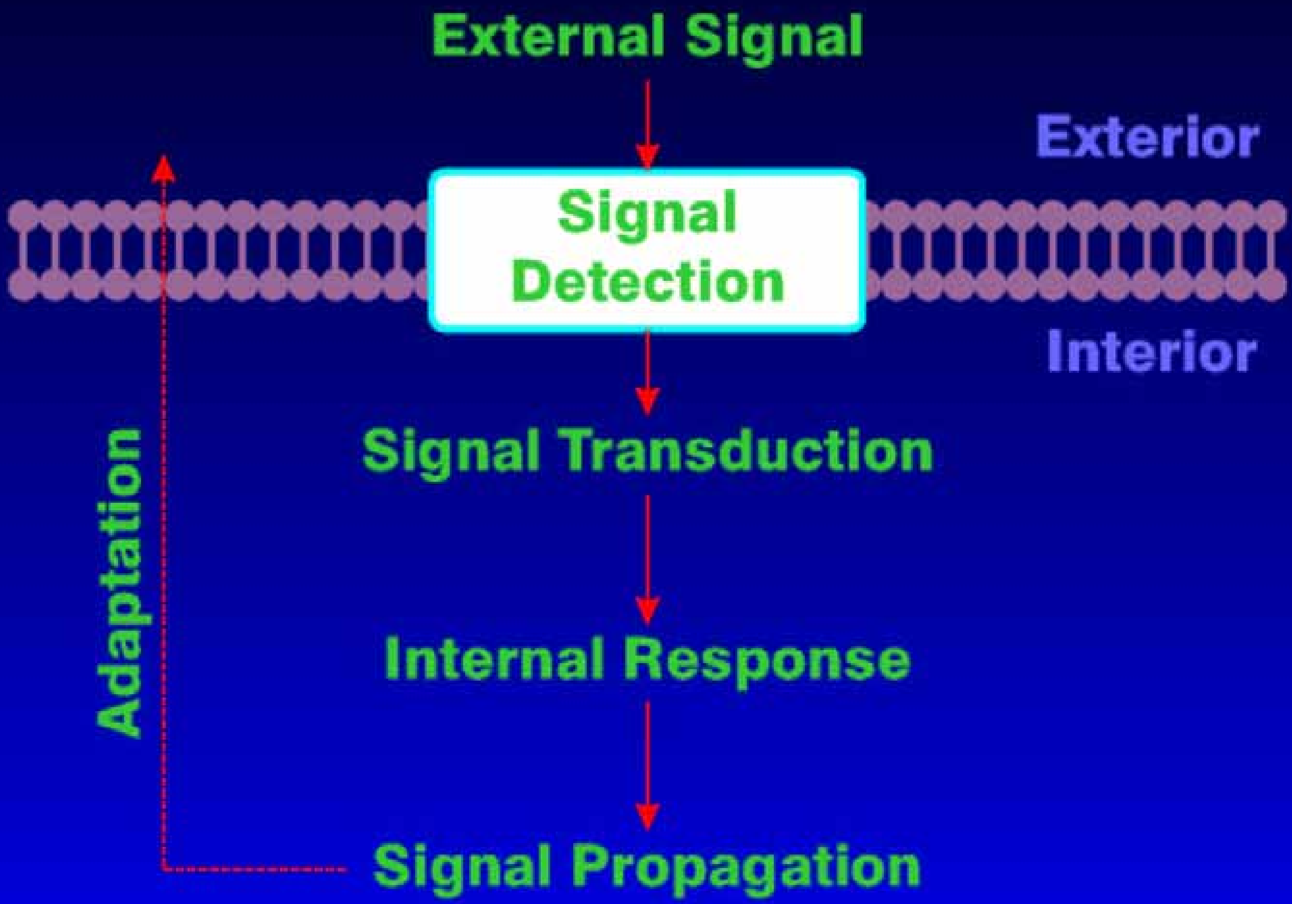
Morphological response of ECs to Turbulent Shear Stress



Endothelial Responses to Shear Stress

- Cell-shape modifications
- Cell-orientation modifications
- Cytoskeletal organization
- Mechanical stiffness modifications
- Cell proliferation
- Secretion of vasoactive substances
- Transendothelial transport
- Intracellular signaling

Signal transduction cascade



Signal Transduction Cascade

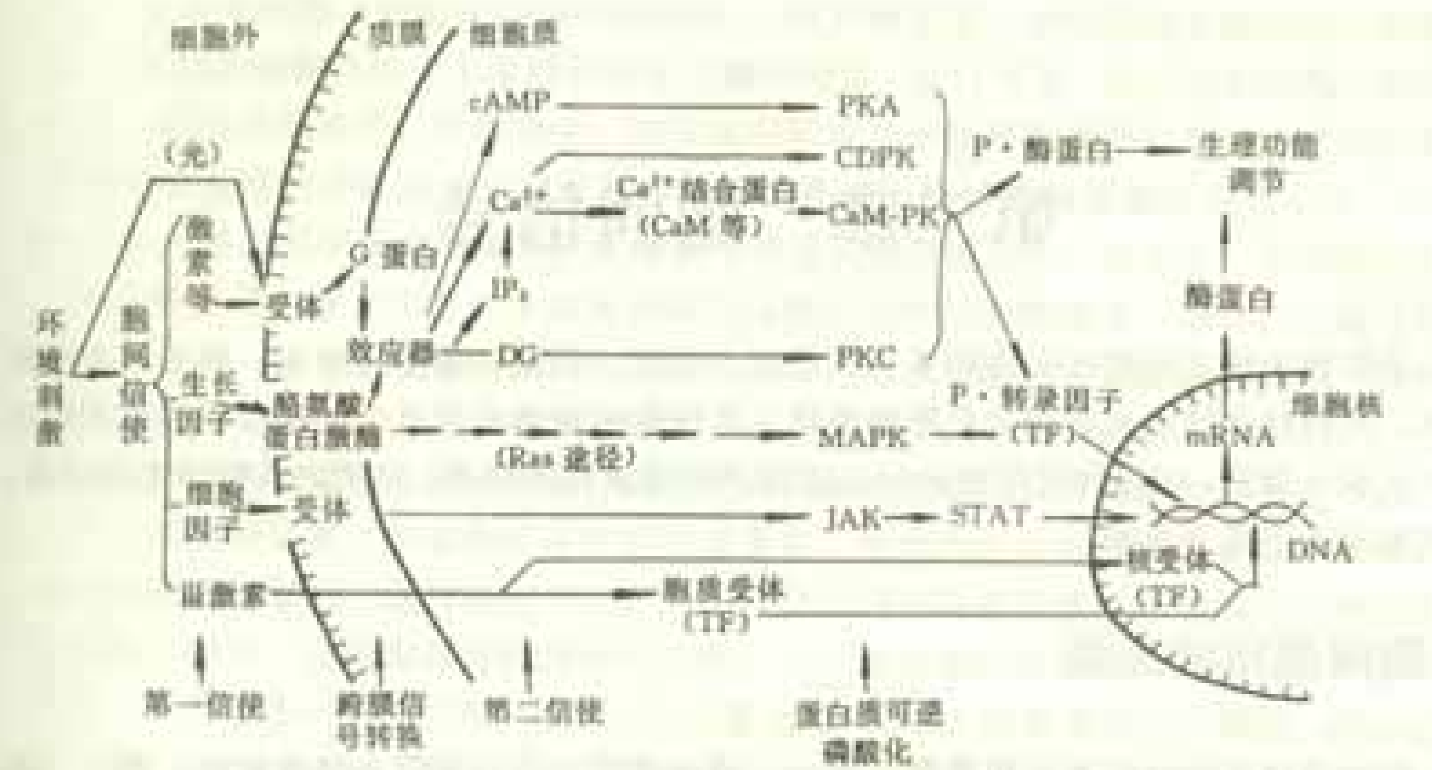
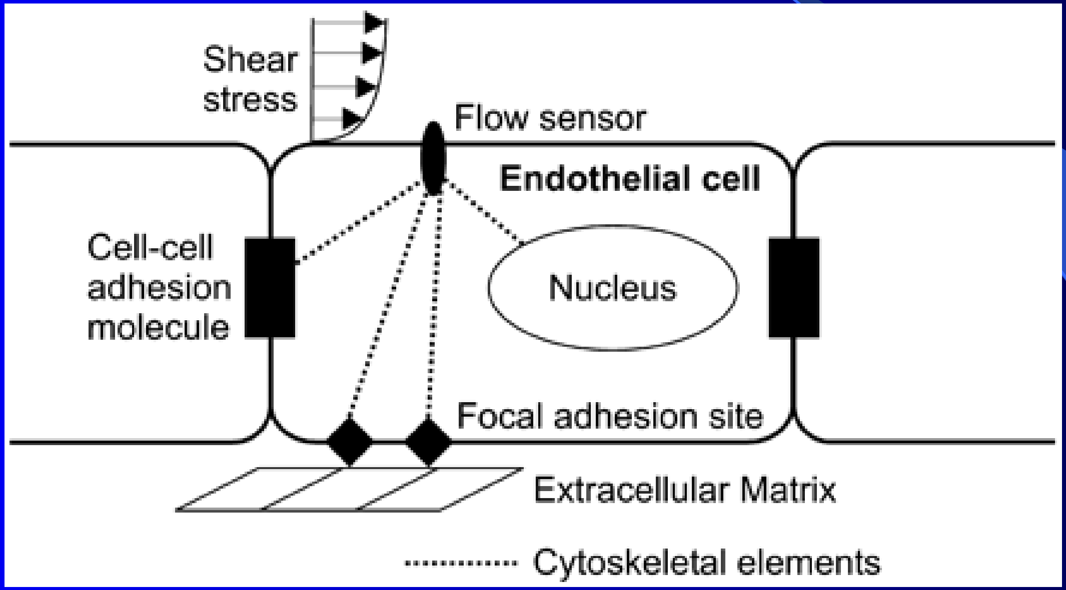


图 1.6　细胞信号转导主要途径模式图

IP_3：三磷酸肌醇；DG：二酰甘油；PKA：依赖cAMP的蛋白激酶；　PKC：依赖Ca^{2+}与磷脂的蛋白激酶；CaM·PK：依赖Ca^{2+}·CaM的蛋白激酶；CDPK：依赖Ca^{2+}的蛋白激酶；MAPK：有丝分裂原蛋白激酶；JAK：另一种蛋白激酶；TF：转录因子

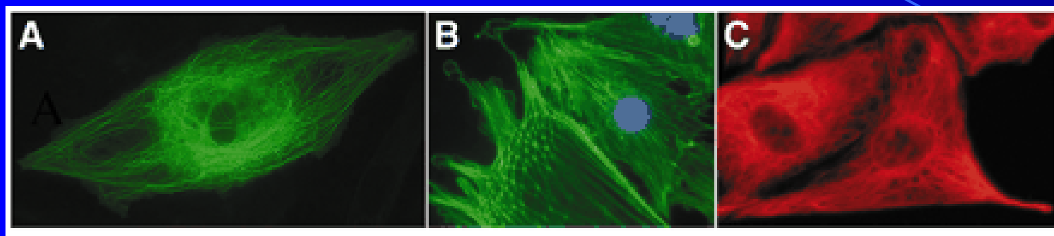
Decentralization Model of Mechanotransduction

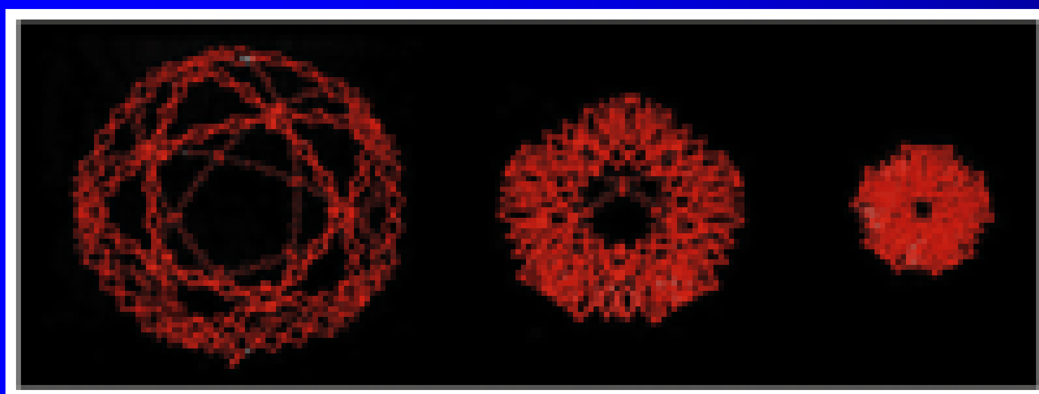
(Davies PF. ,1995)

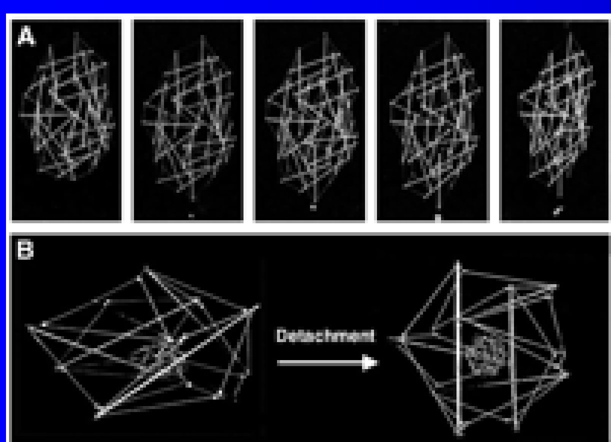


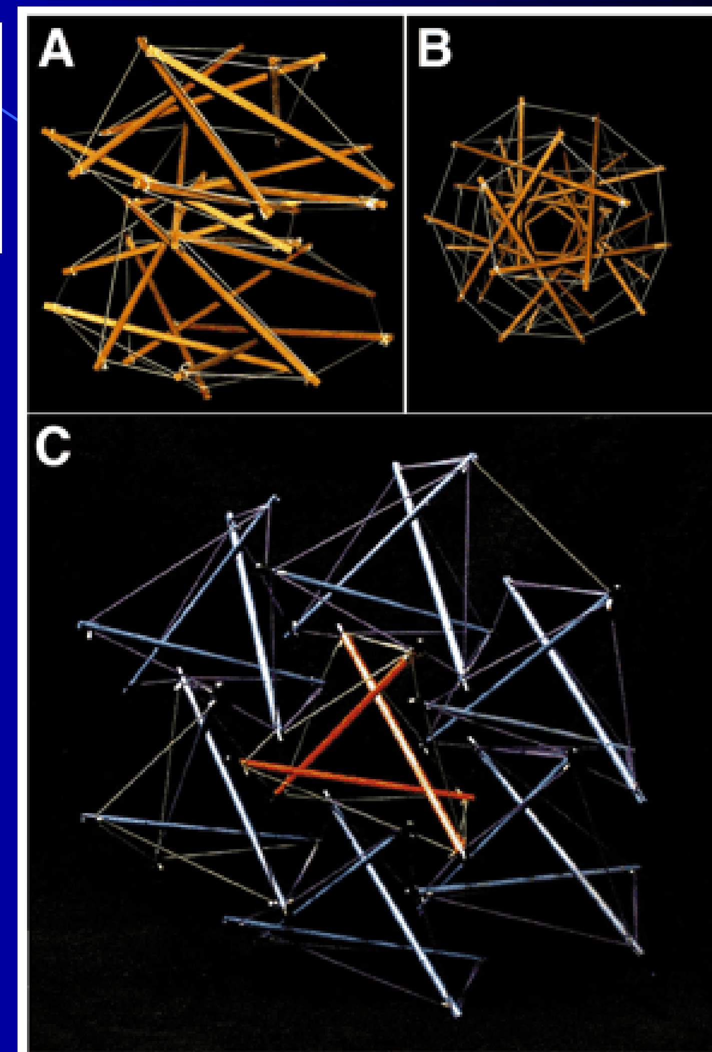
Tensegrity Model of Mechanotransduction

(Ingber DE. *J. Cell Sci.* 116,1157-1173, 2003)









Brief Summary

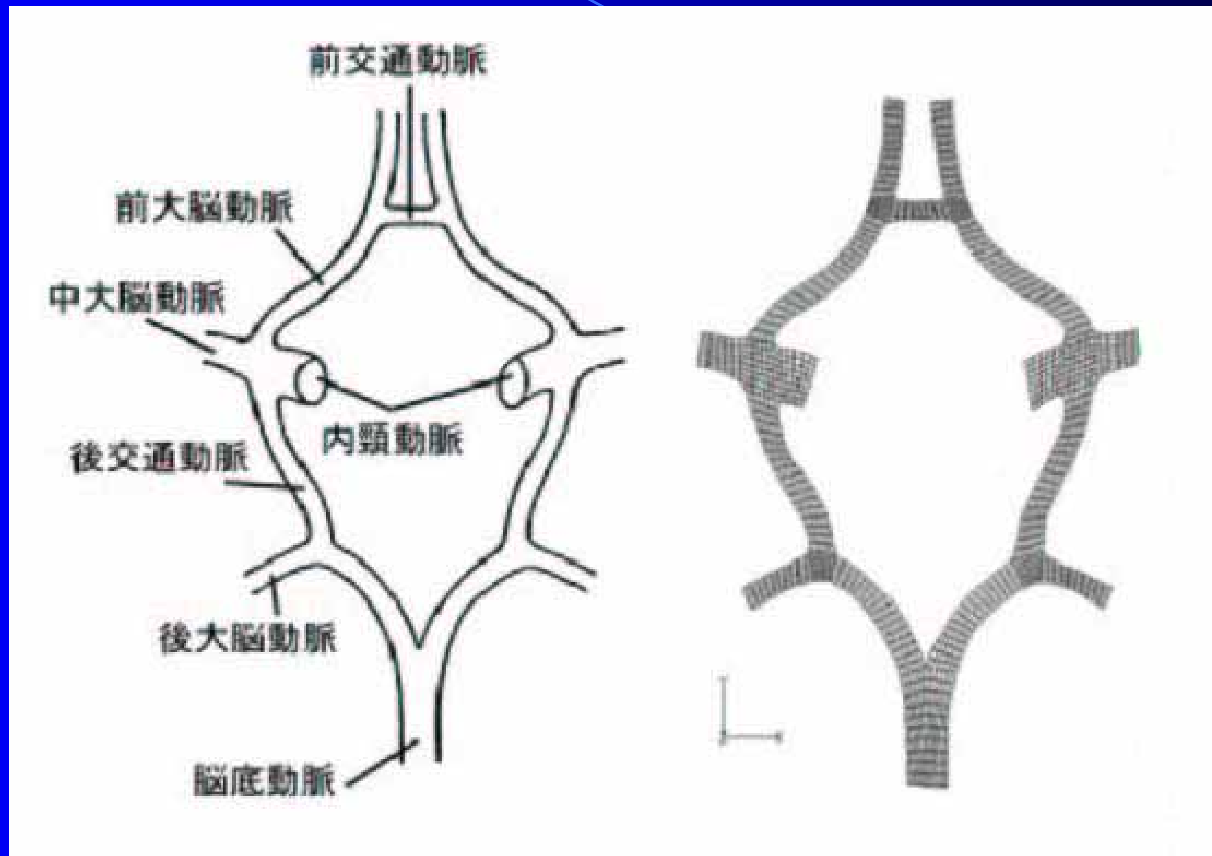
- Background
- Biomechanics *vs* Mechanobiology

Applications of CFD in the Diagnosis and Therapy of Cardiovascular Diseases

Diagnosis of Cerebral Vascular Diseases

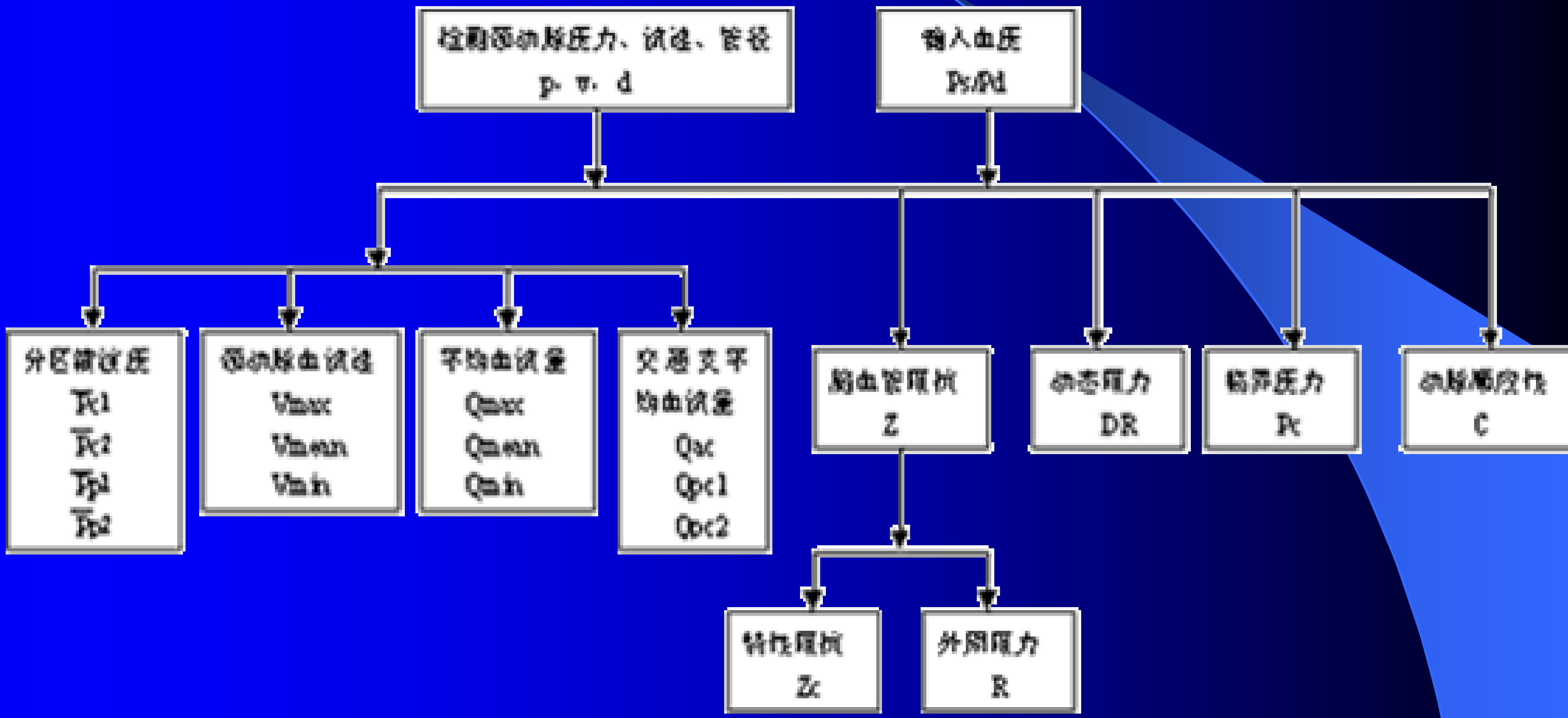
- 脑血管疾病是我国死亡率最高的疾病。每年中国新发病人140多万，死亡90多万，累积的500多万存活者中一般遗有轻重不等的偏瘫、失语和痴呆等后遗症

Cerebral Vascular Hemodynamics



脑血管血液动力学参数的改变往往早于
影象学(CT/MRI)参数的改变

Inverse Problem



Cerebral Vascular Hemodynamics Analyzer

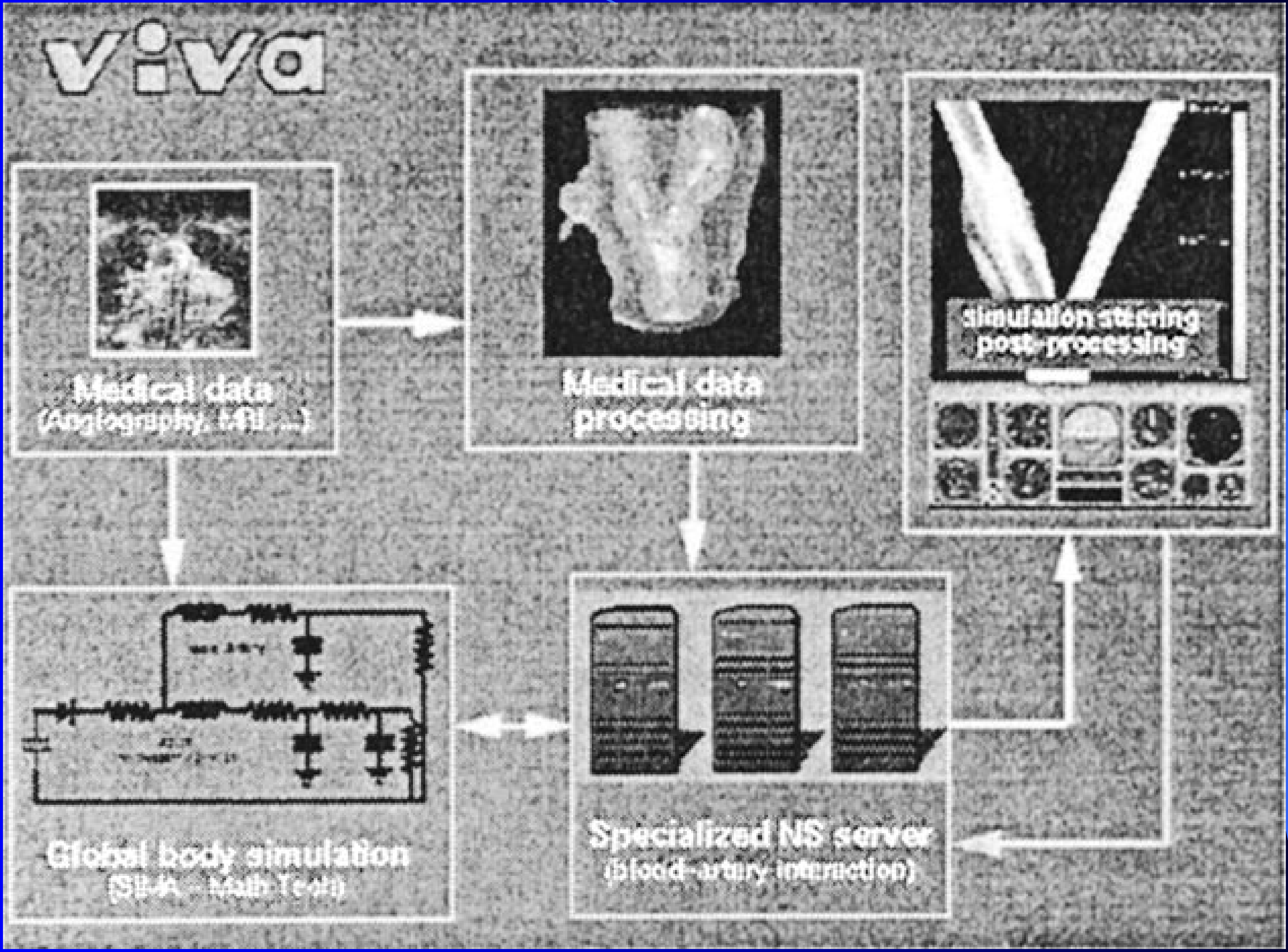
ViVa: The Virtual Vascular Project

- Initial Applications: Clinical research and training
- Later Stage: Surgical planning

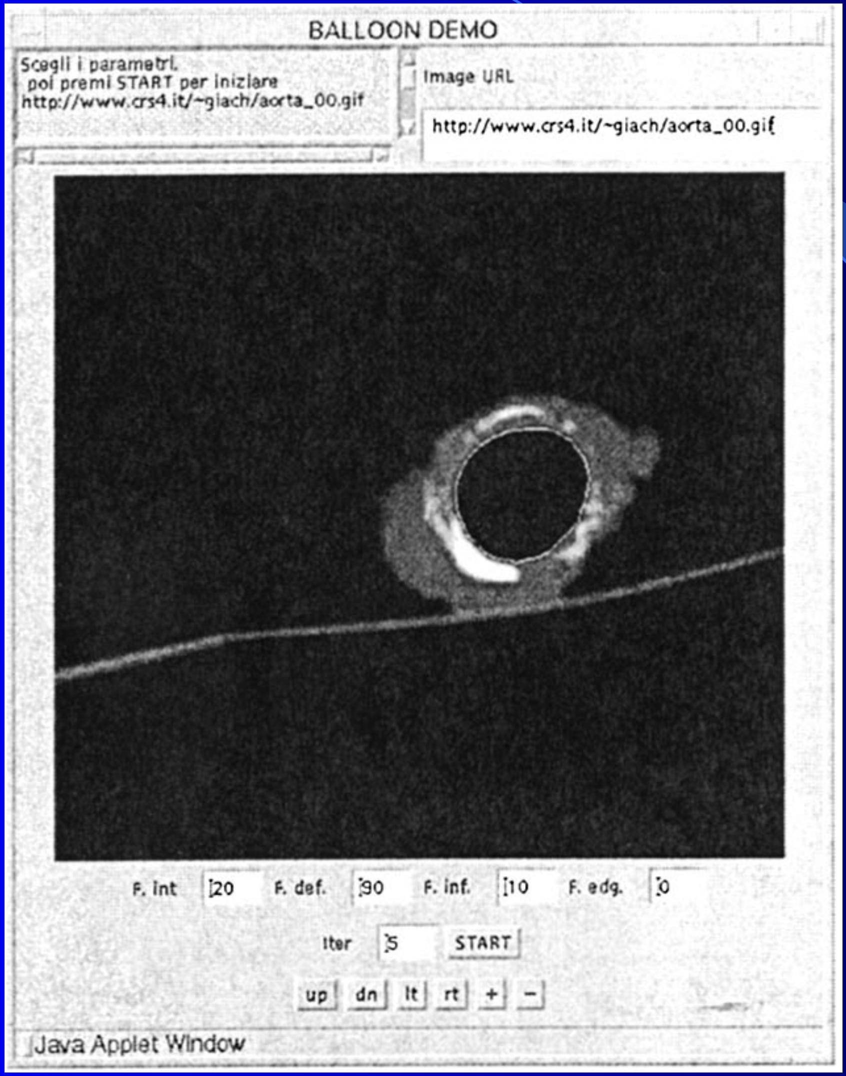
ViVa

- Data Acquisition
- Image Processing and Segmentation
- Real-time 3-D Volume Visualization
- 3-D Geometry Reconstruction
- 3-D Mesh Generation
- Blood Flow Simulation and Visualization

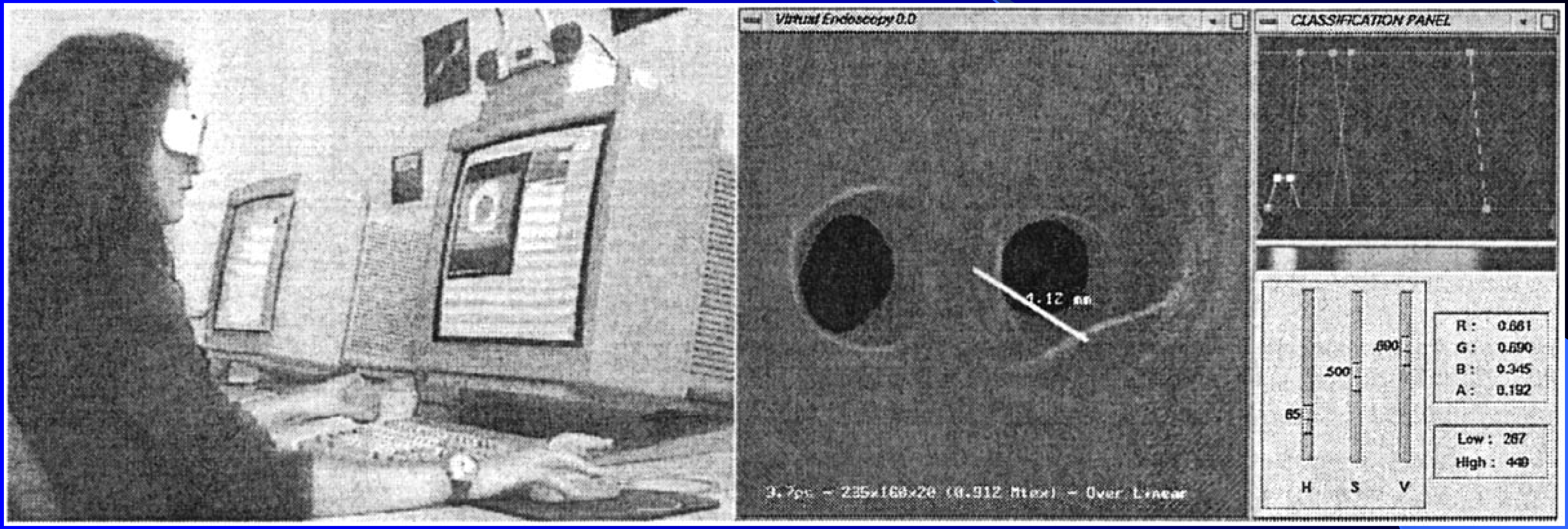
ViVa: Overview



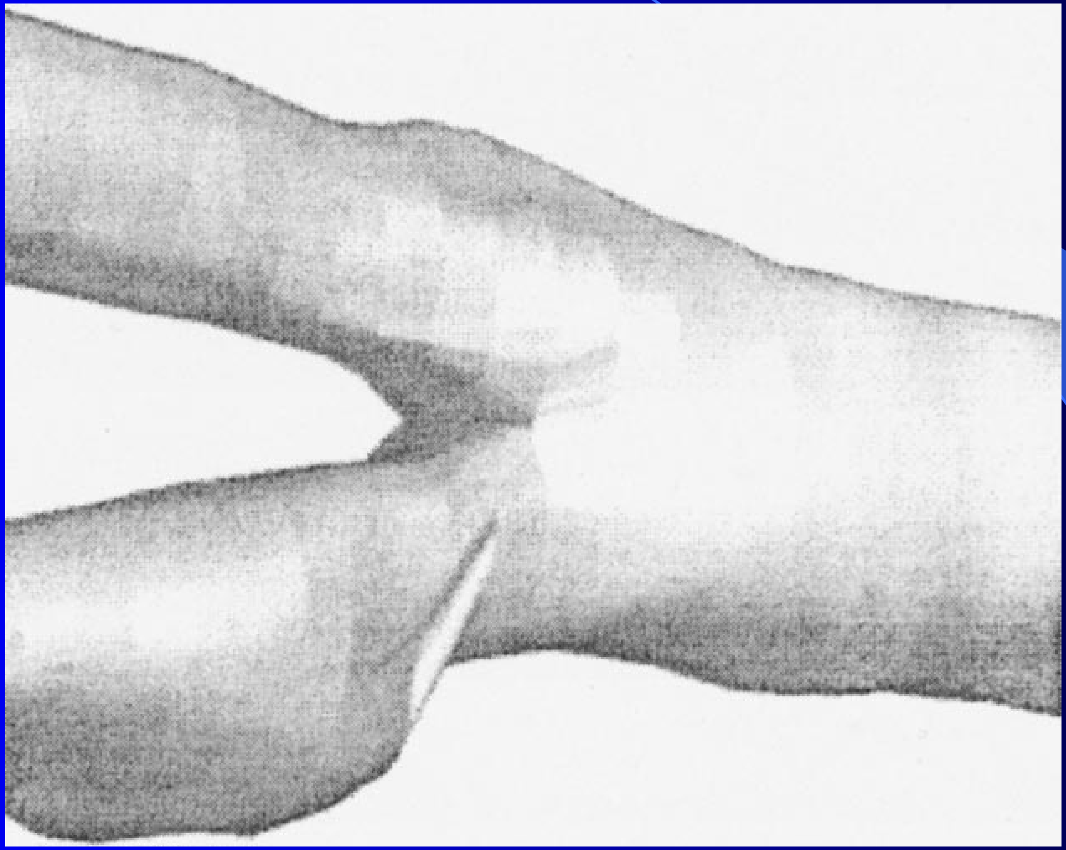
ViVa: User interface of the image processing and segmentation subsystem



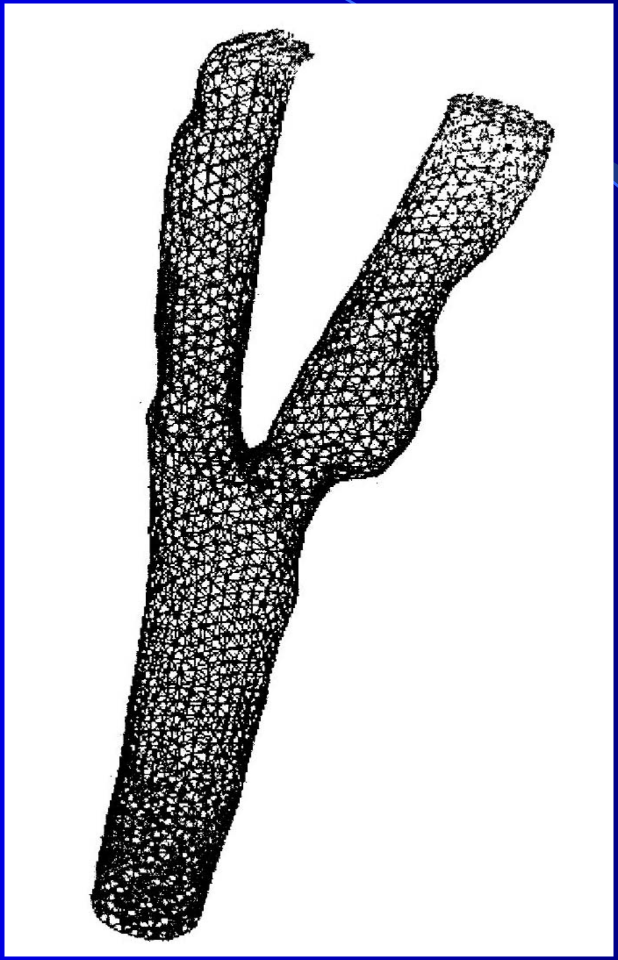
ViVa: Real-time 3-D Volume Visualization



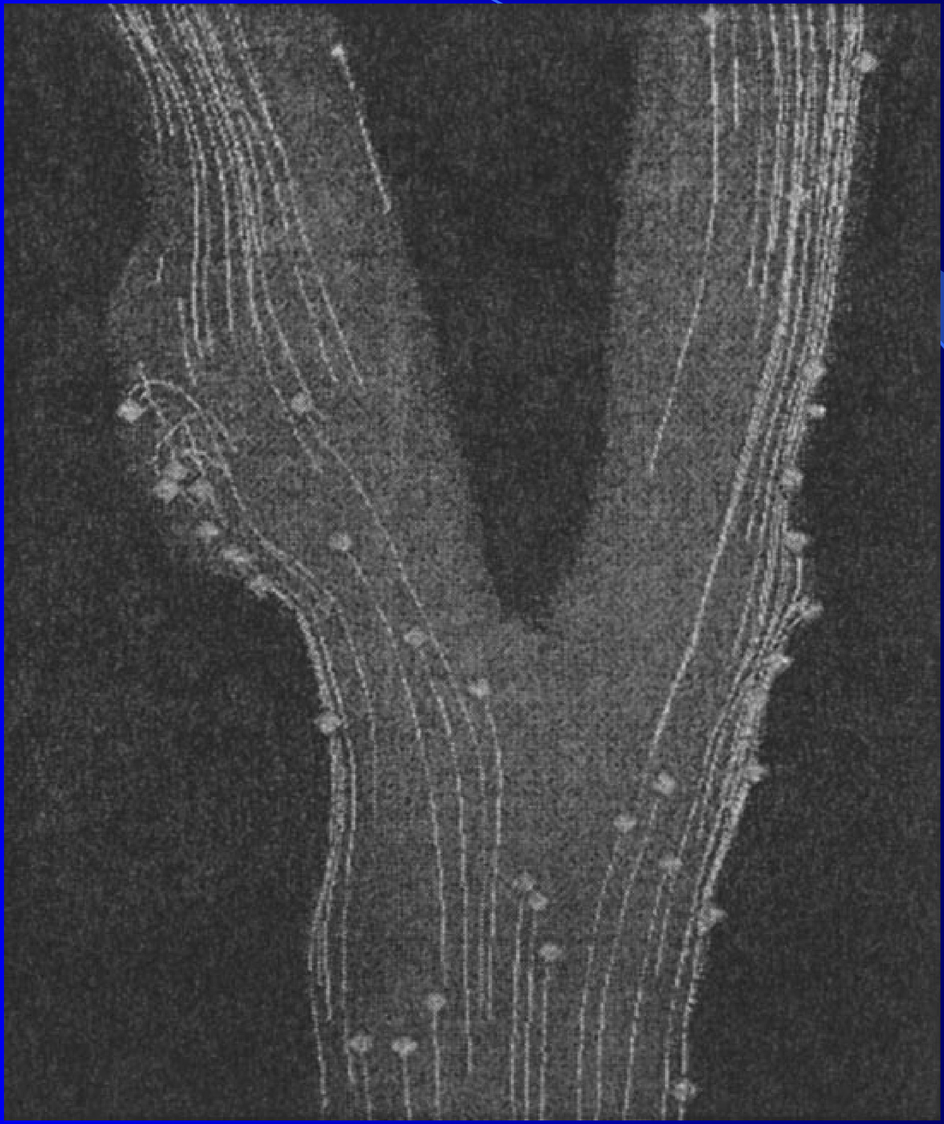
ViVa: 3-D Geometry Reconstruction



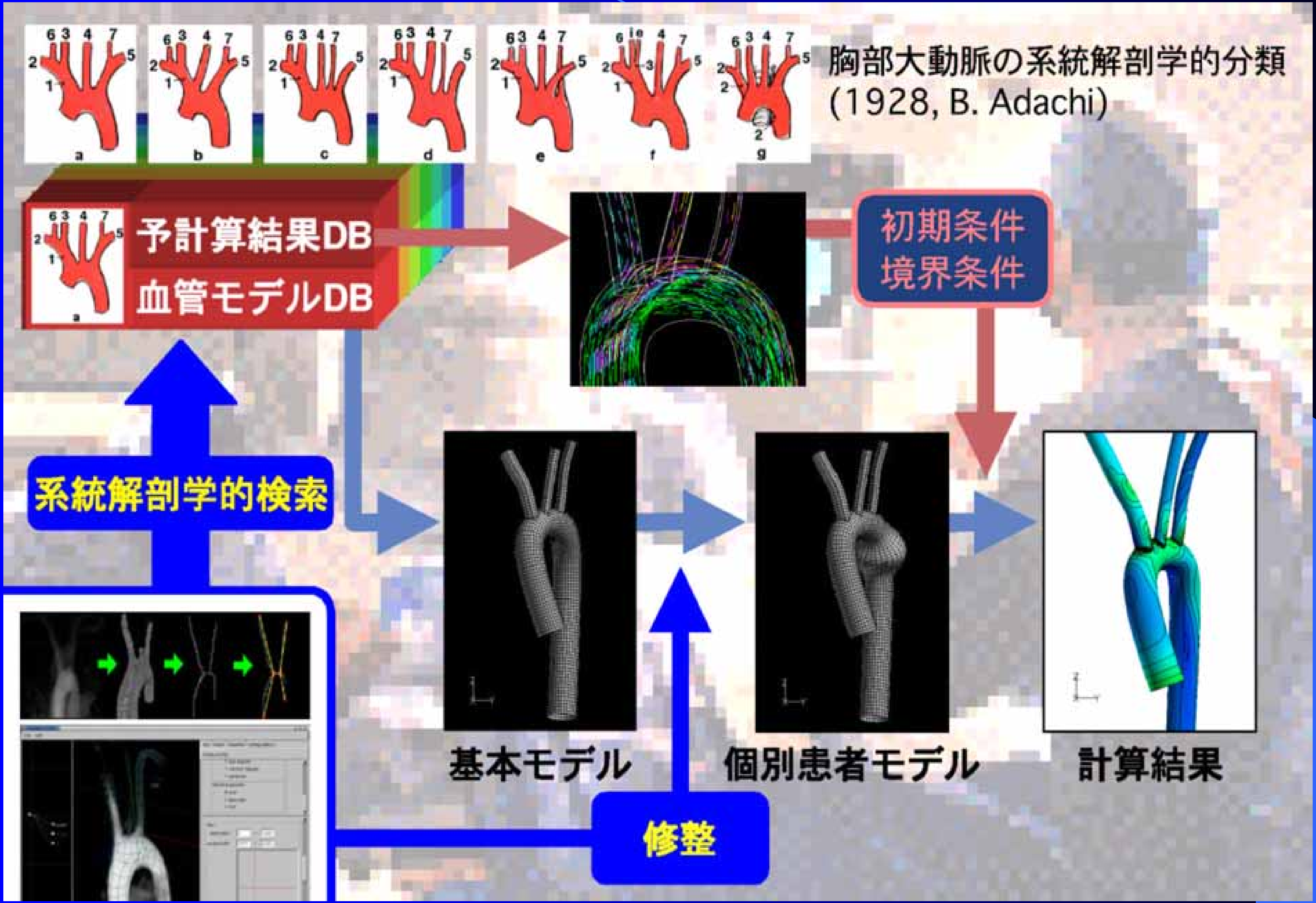
ViVa: 3-D Mesh Generation



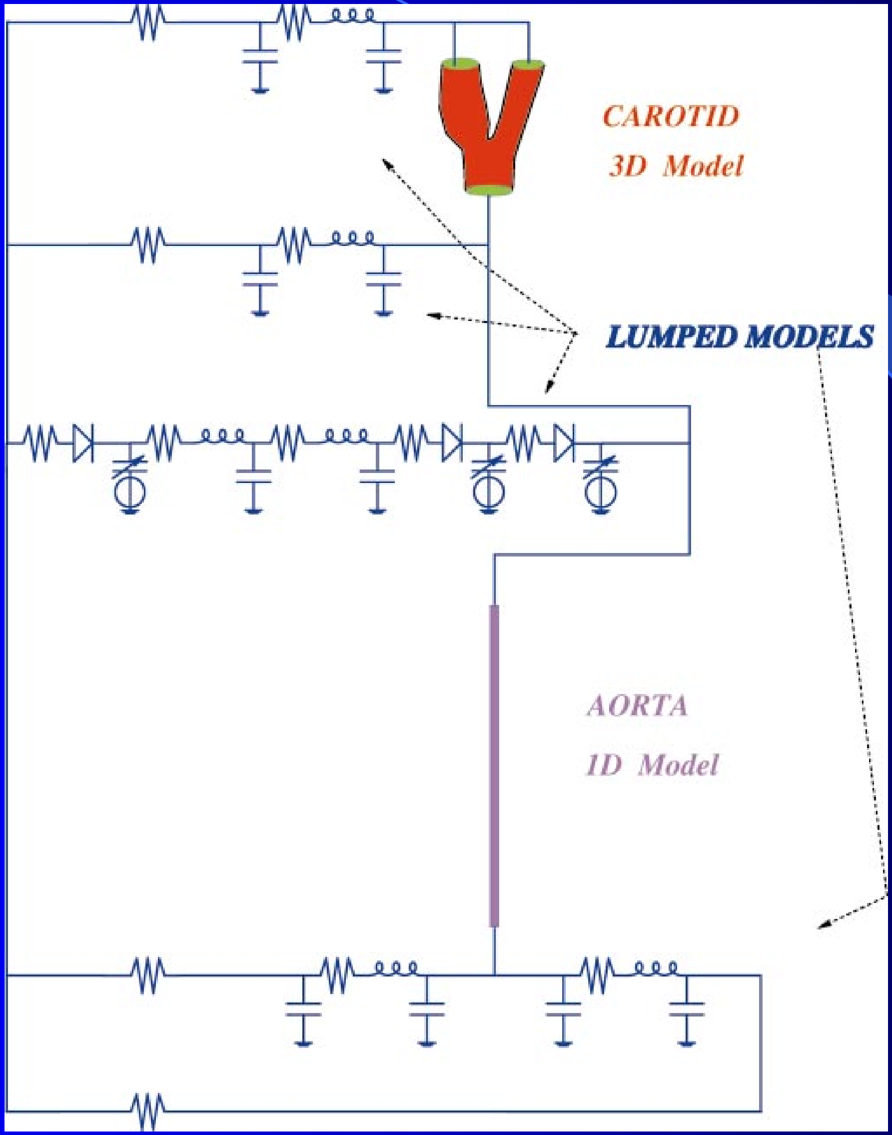
ViVa: Blood Flow Simulation and Visualization



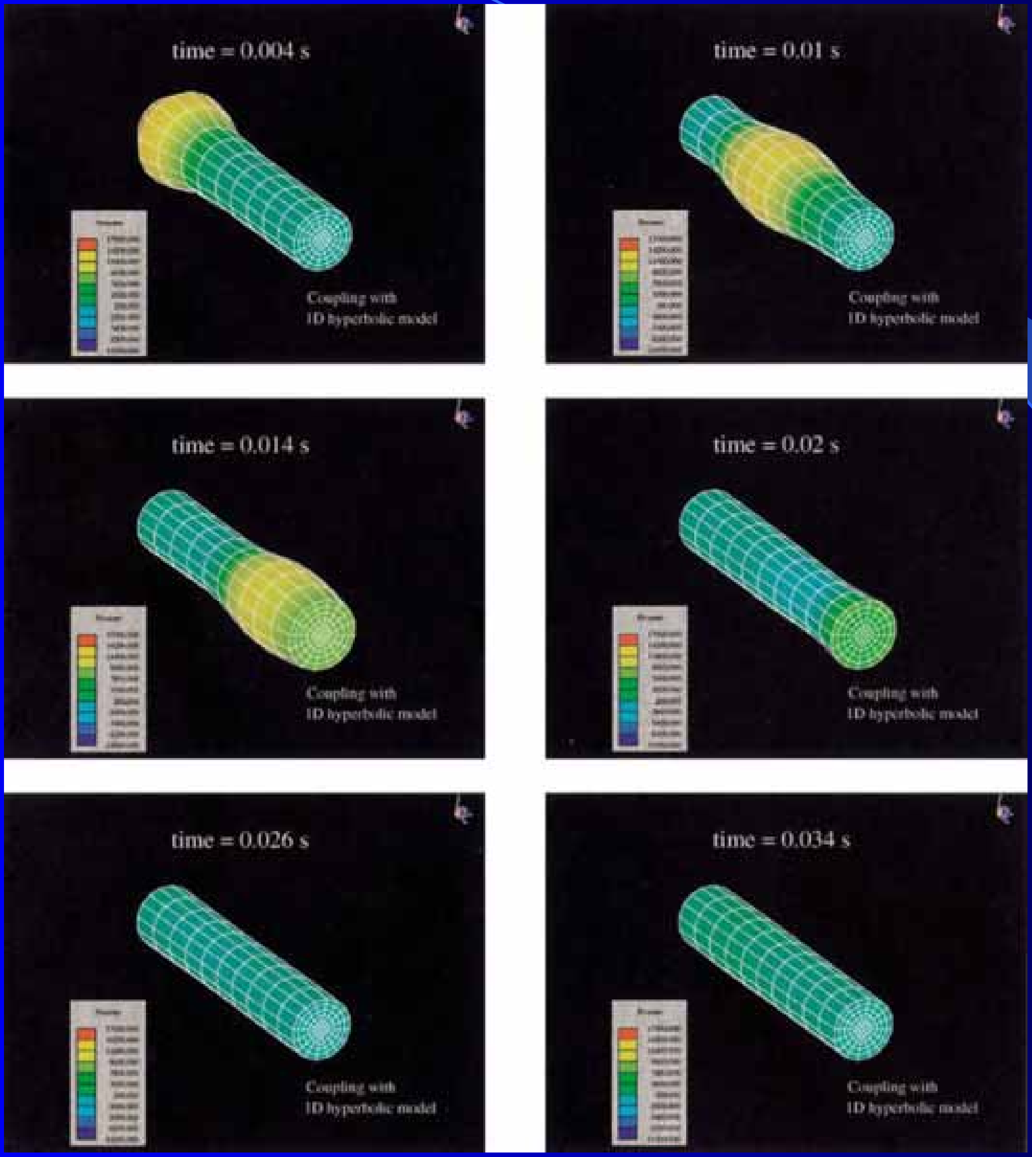
ViVa in Japan (山口隆美，刘浩)



Multiscale Approach



Coupling of 1D and 3D N-S Equation

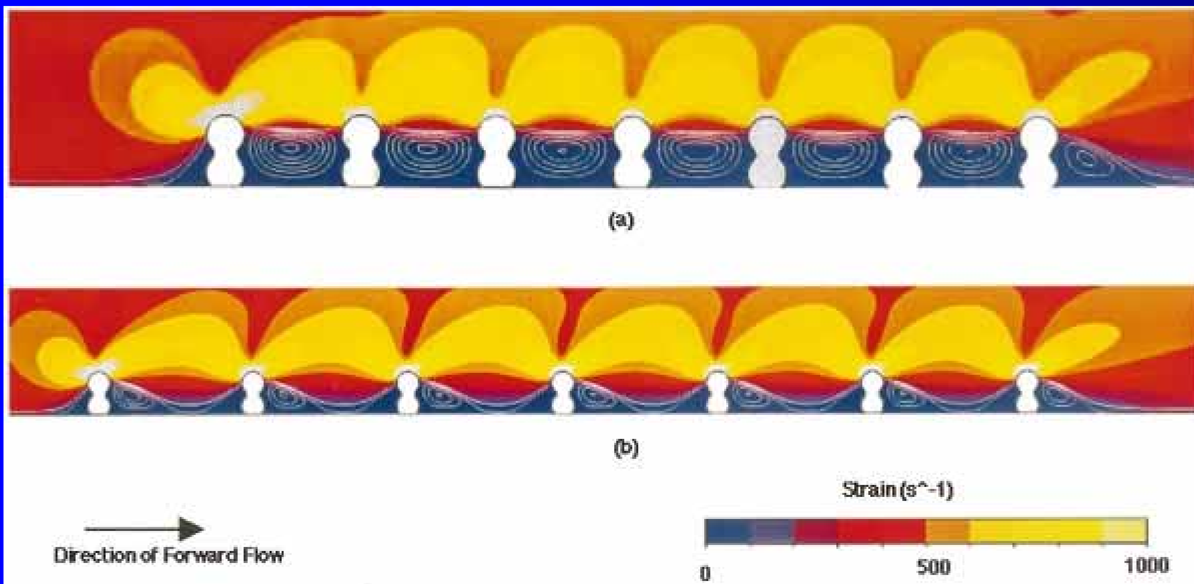


Applications of CFD in Vascular Tissue Engineering

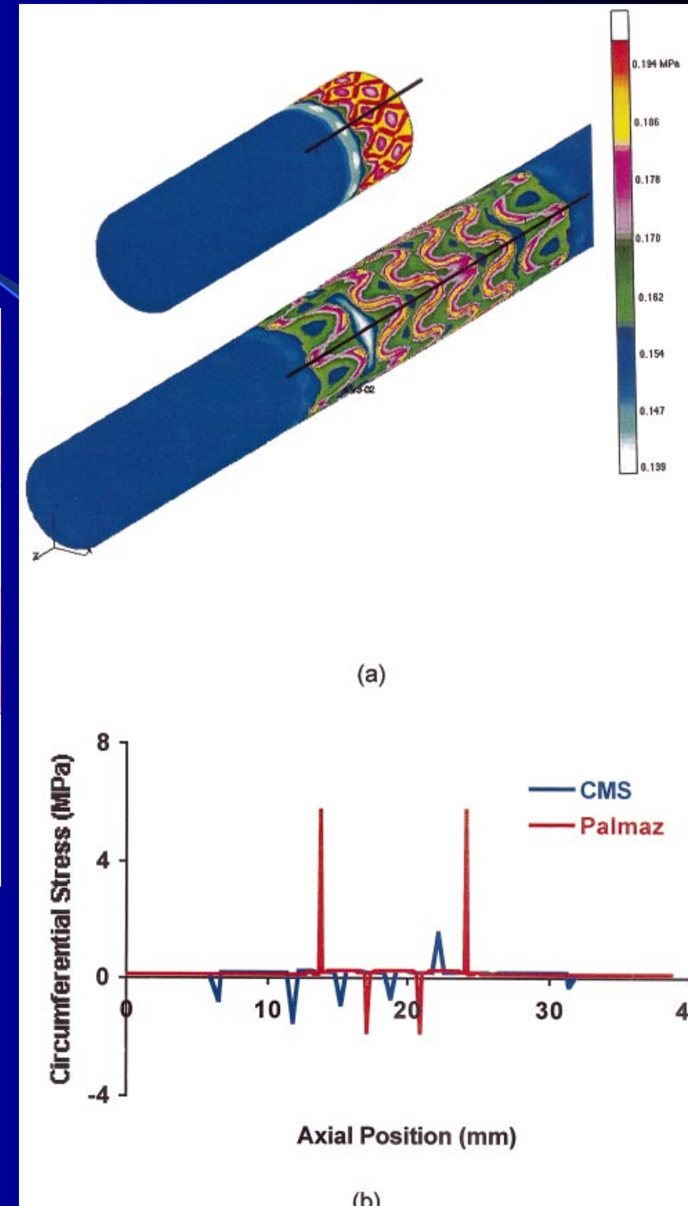
血管组织工程 Vascular Tissue Engineering

- 用工程学的原理和方法，修复发生病变血管的分子、细胞和组织的结构和功能
  - 基因转入血管(gene therapy)
  - 血管内支架(stenting)
  - 血管成形术(angioplasty)
  - 自体、多聚物和生物合成血管移植物(grafting)

Stenting

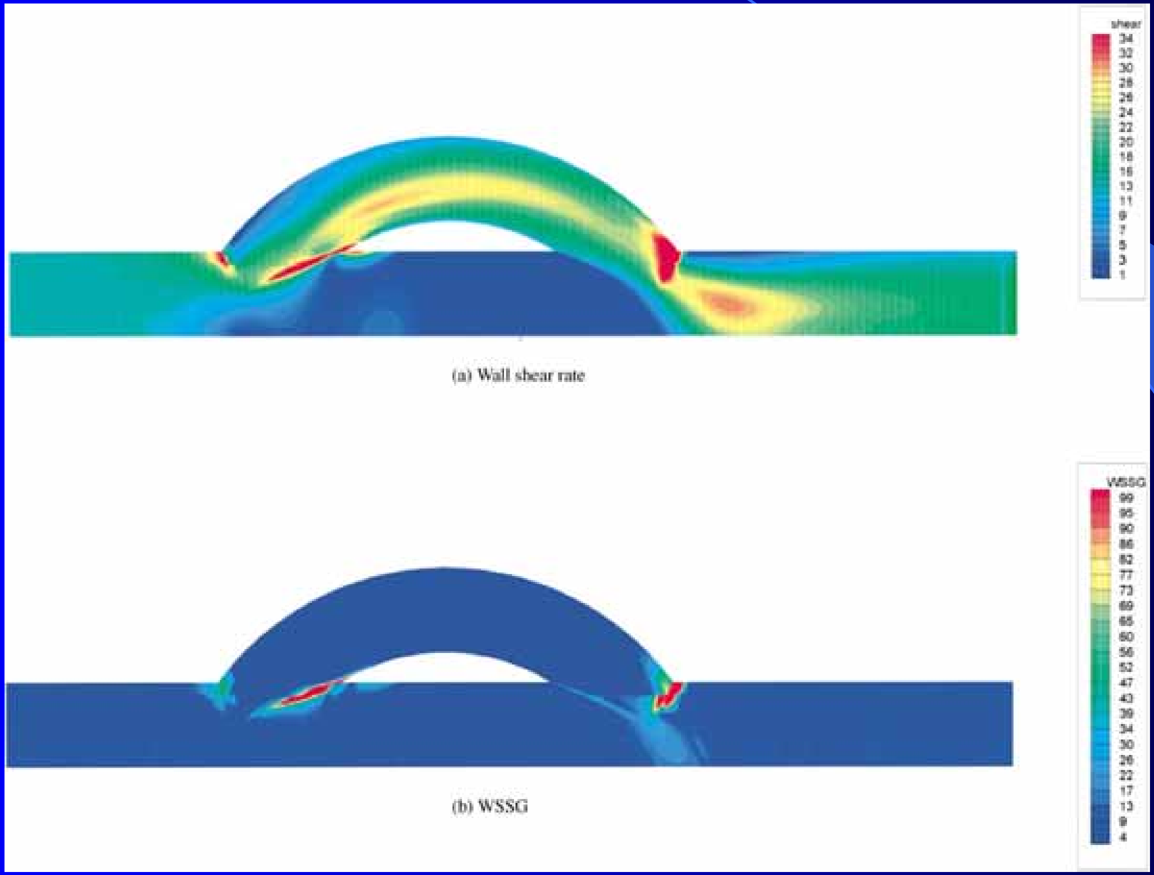


(a)
(b)
Strain (s^-1)
0
500
1000
Direction of Forward Flow



0.194 MPa
0.186
0.178
0.170
0.162
0.154
0.147
0.139
(a)
Circumferential Stress (MPa)
8
4
0
-4
0
10
20
30
40
Axial Position (mm)
CMS
Palmaz
(b)

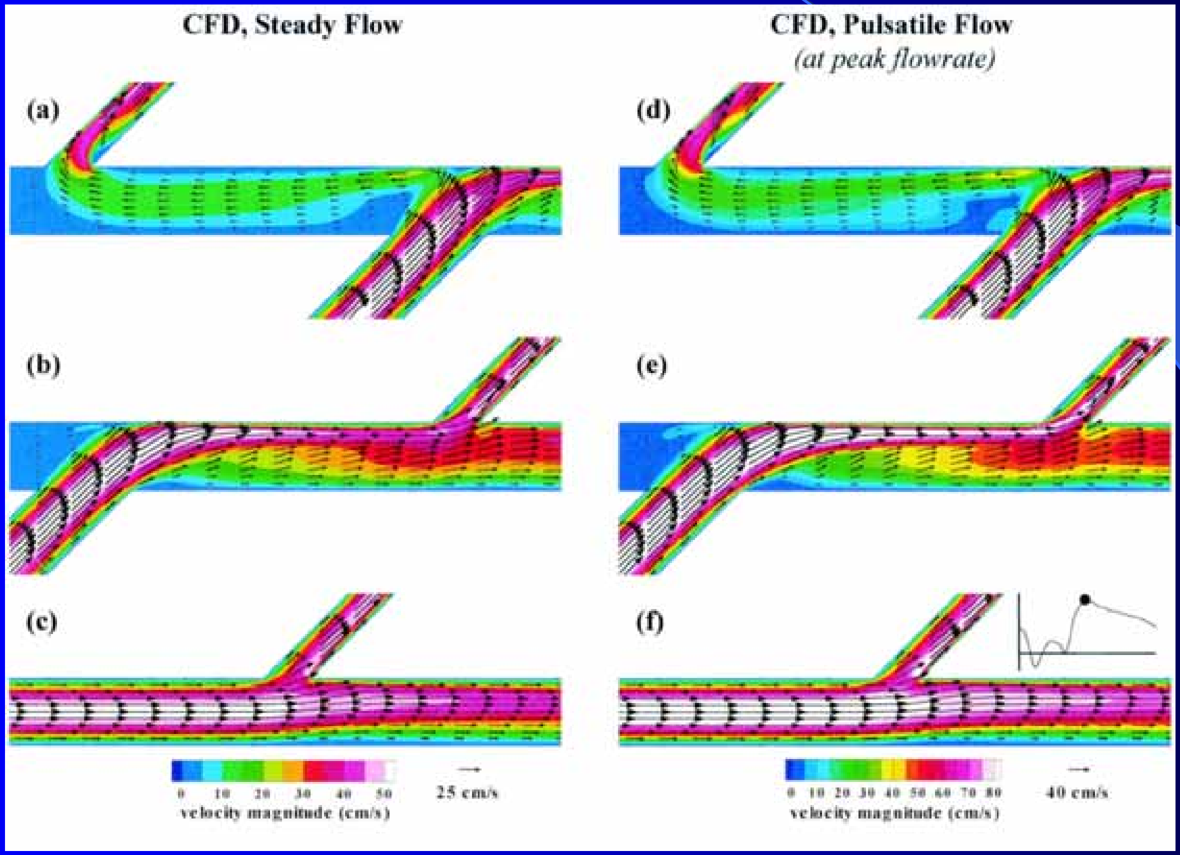
Bypass grafting (side-to-side)



(a) Wall shear rate

(b) WSSG

Grafting (end-to-side)



血管组织工程中的几条力学原则

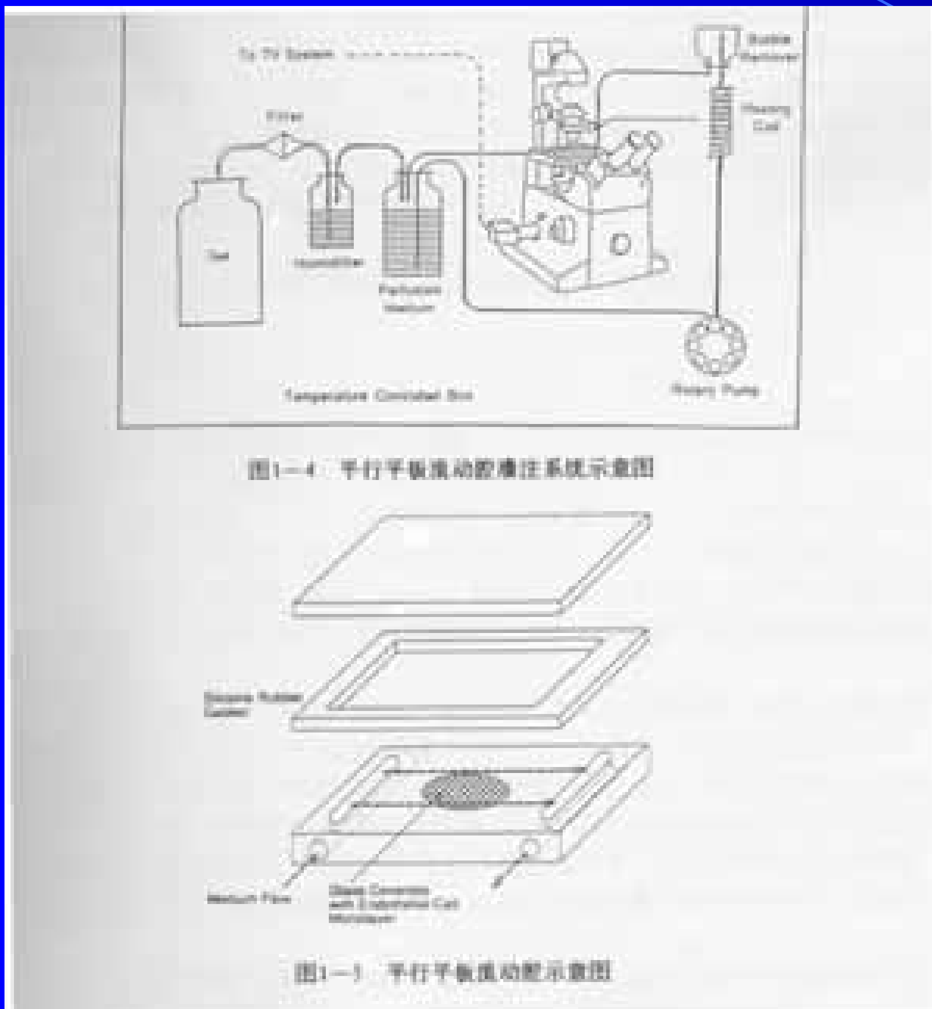
- 尽可能使得手术后的流体力学（固体力学）环境与正常的一致
  - 减少eddy/votex
  - 减少low oscillatory shear stress
  - 减小circumferential stress

Applications of CFD in Cell Mechanics

- Design and Construction of Parallel-plate Flow Chambers with Shear Stress Gradients

Rectangular Parallel-plate Flow Chamber

Rectangular Parallel-plate Flow Chamber

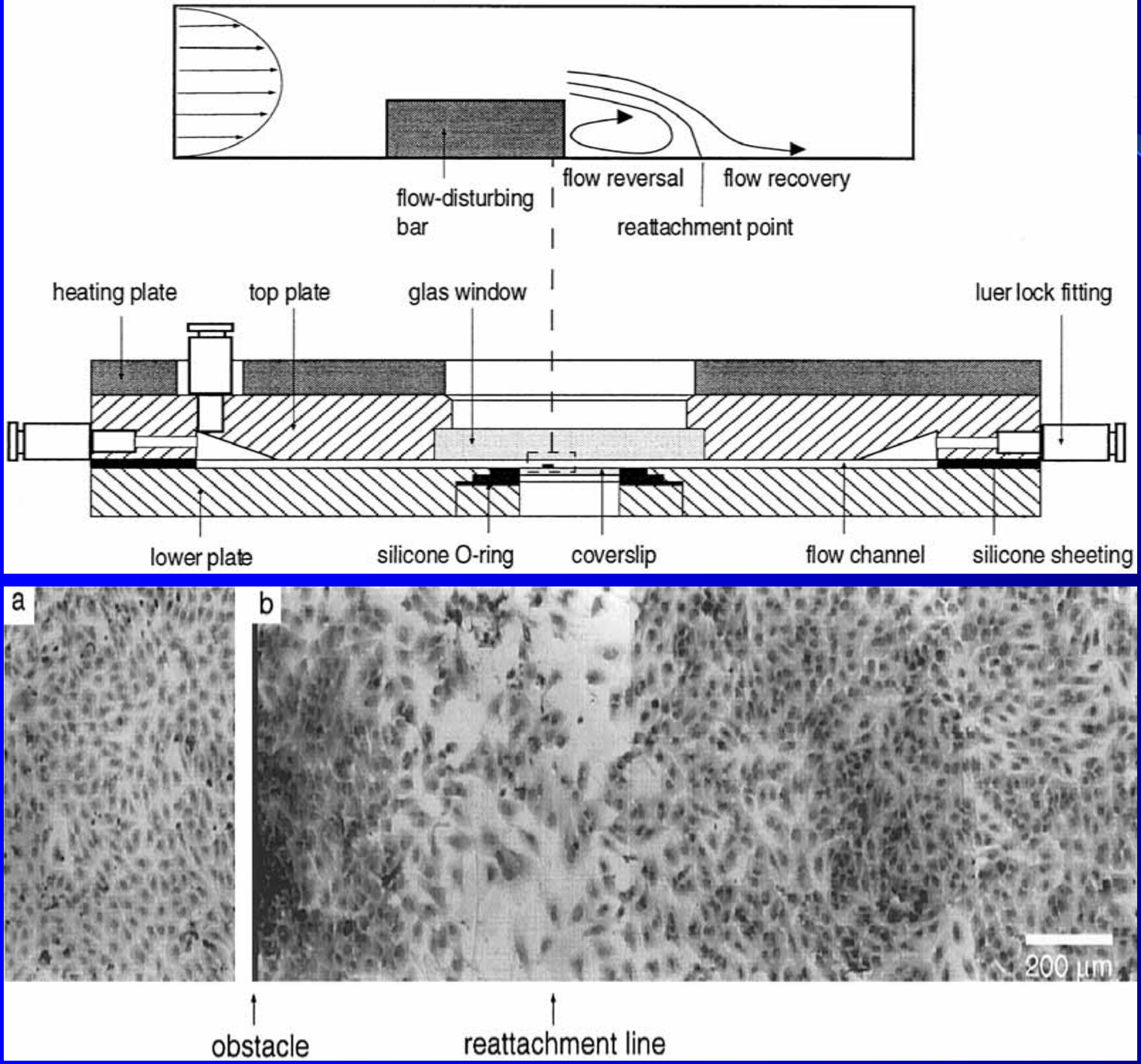


- **Advantage**
  - Uniform Flow Field
  - Single shear stress

$$\left|\vec{\tau}\right| = \frac{6\mu Q}{bh^2}$$

- **Disadvantage**
  - Time Consuming

Flow Chamber with Shear Stress Gradients

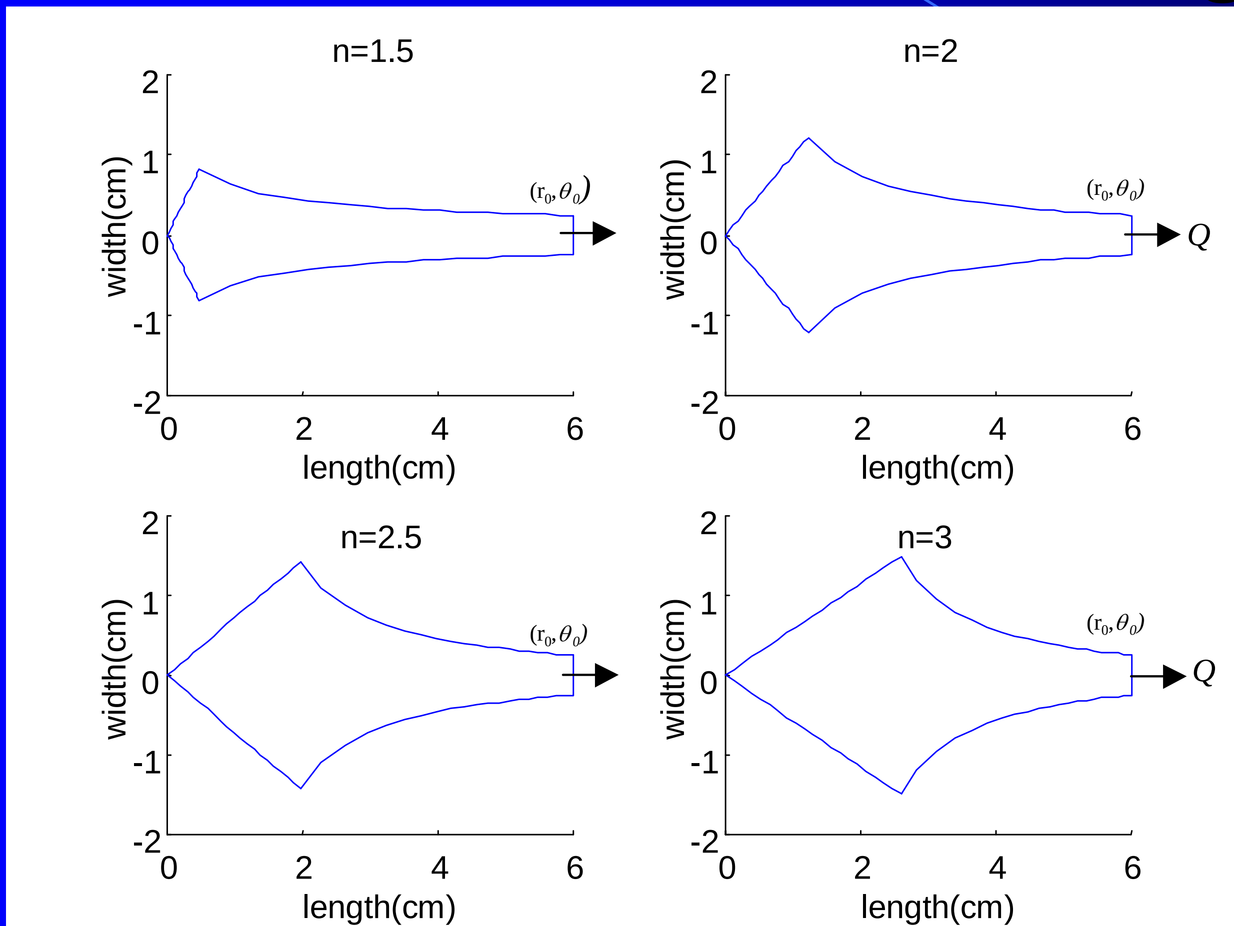


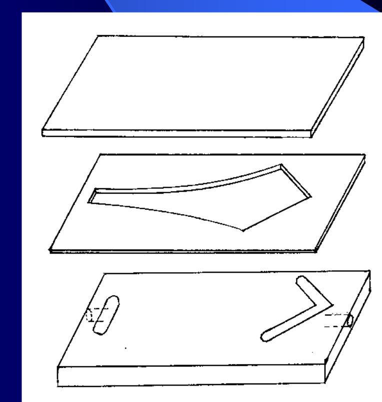
- Advantage
  - Eddy Flow
  - Shear Gradient
- Disadvantage
  - Complicated

Objectives

- Design and construct new type flow chambers with shear stress gradients
- Convenient and Time saving

Planforms of the parallel-plate flow chambers with shear stress gradients





Formulas

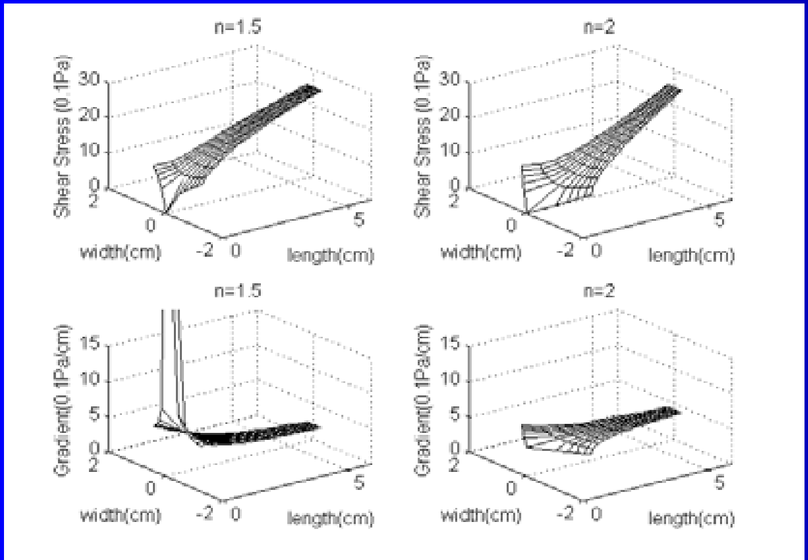
- Shear Stress

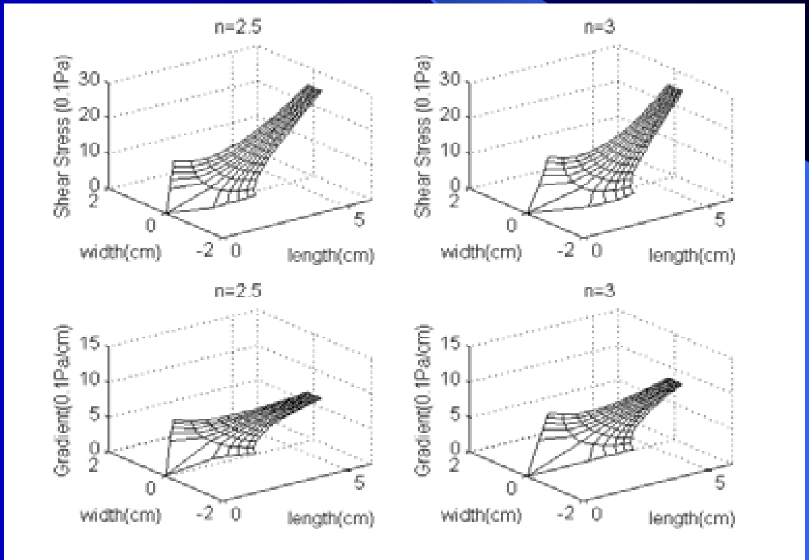
$$\left|\vec{\tau}\right| = \frac{6\mu Q}{bh^2} \cdot \left(\frac{r}{L}\right)^{n-1}$$

- Shear Stress Gradient

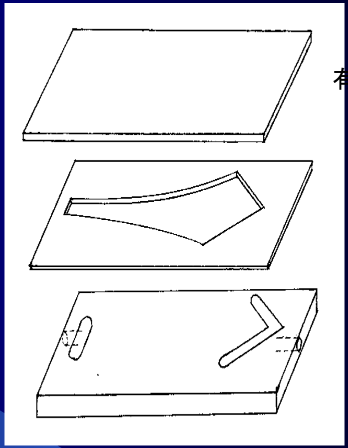
$$\frac{d\left|\vec{\tau}\right|}{dr} = \frac{6\mu Q}{bh^2} \cdot \frac{(n-1)r^{n-2}}{L^{n-1}}$$

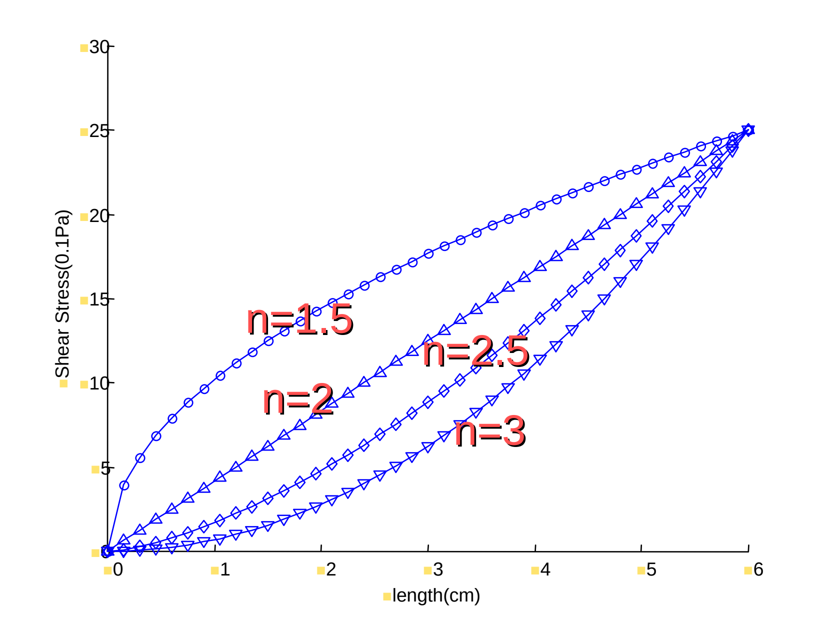
Distribution of shear stresses and shear stress gradients on the bottom of the flow chamber

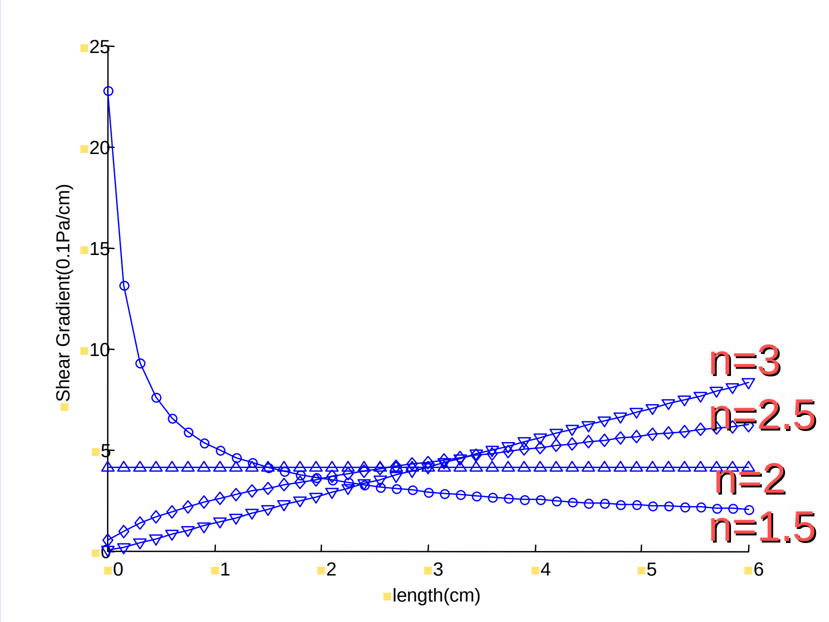




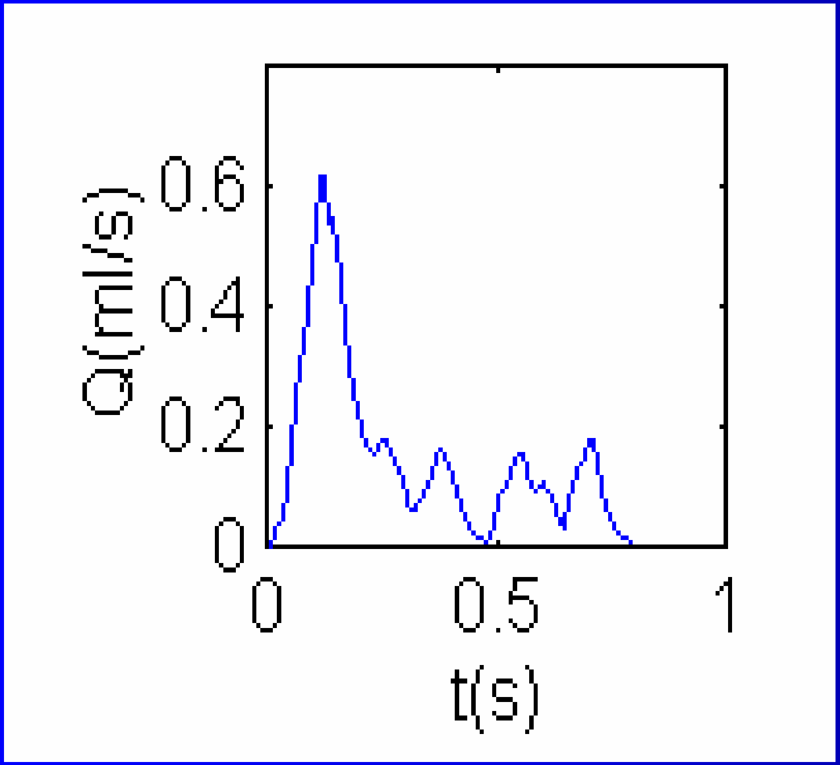
Variation of shear stresses and shear stress gradients along the axis of the flow chamber

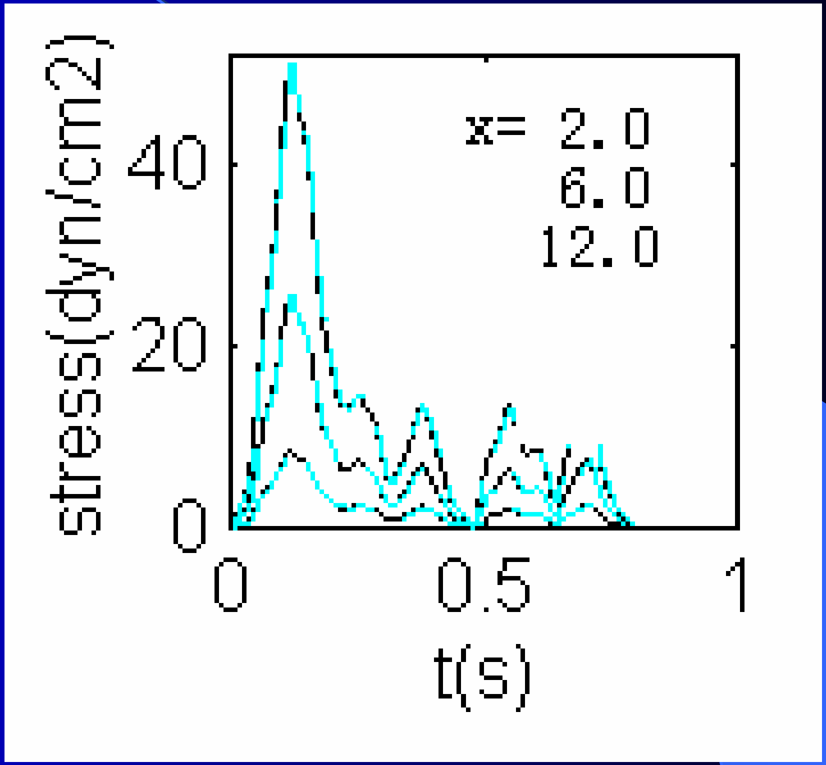




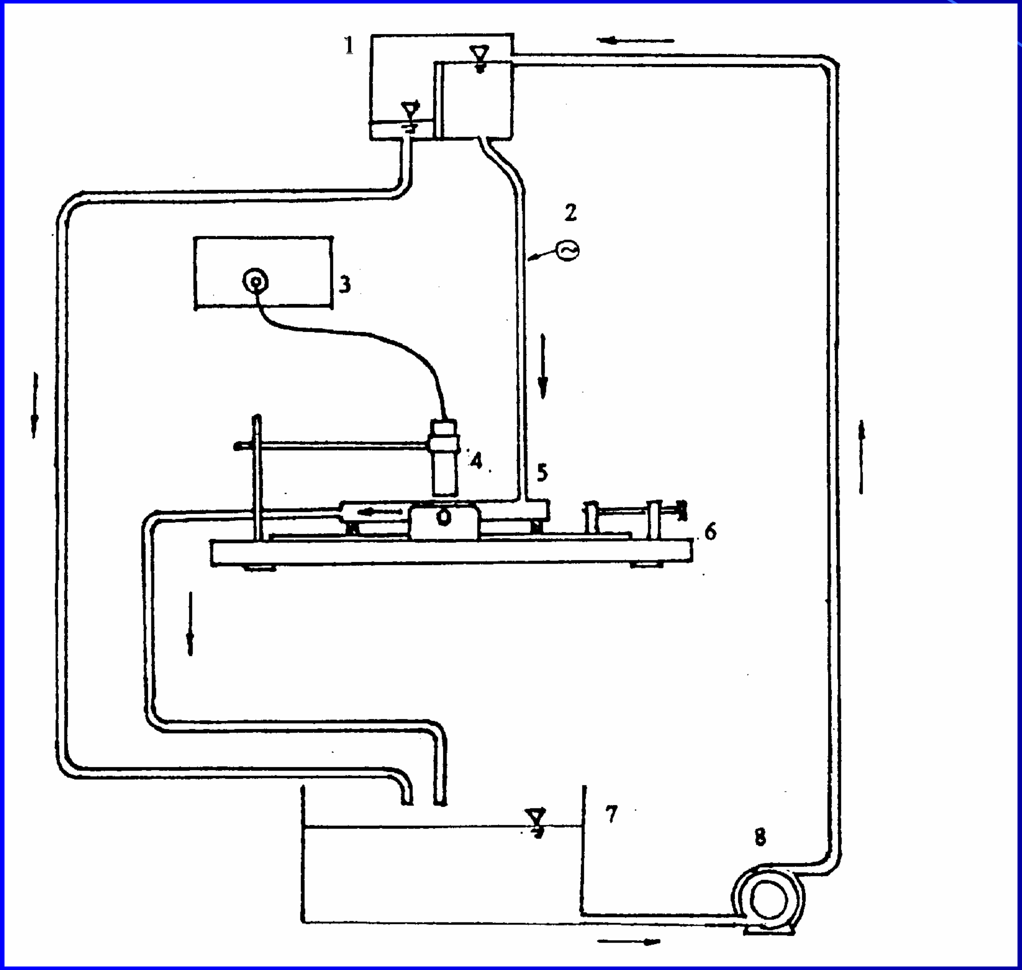


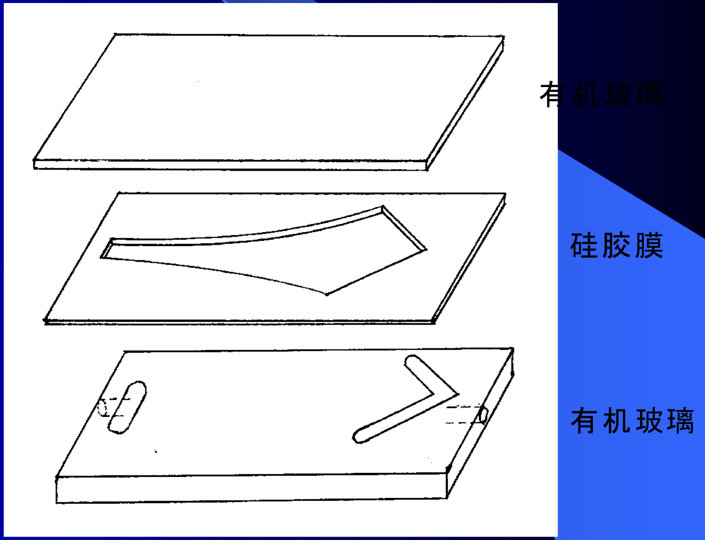
Pulsatile Flow (Theoretical Results)



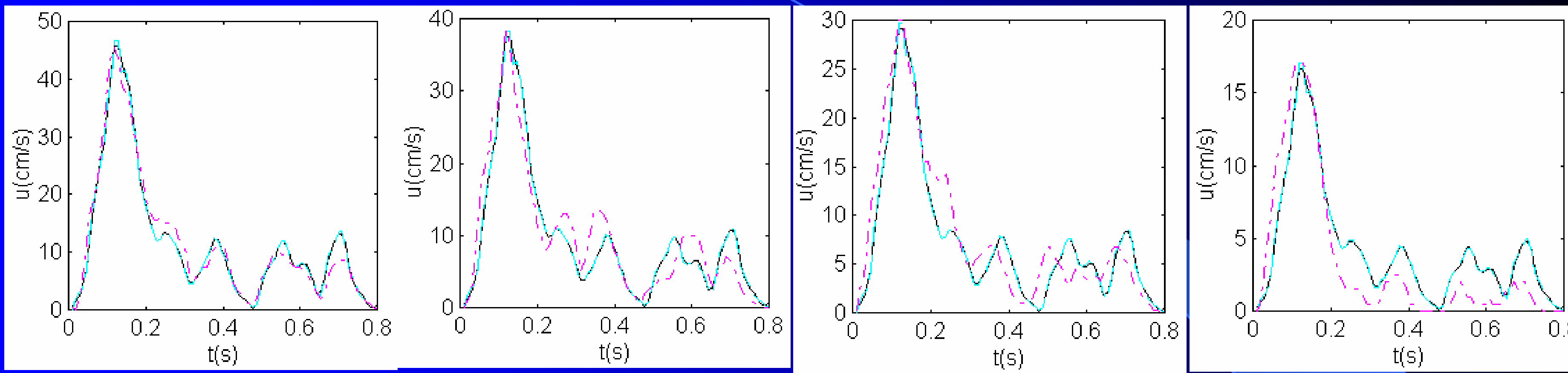


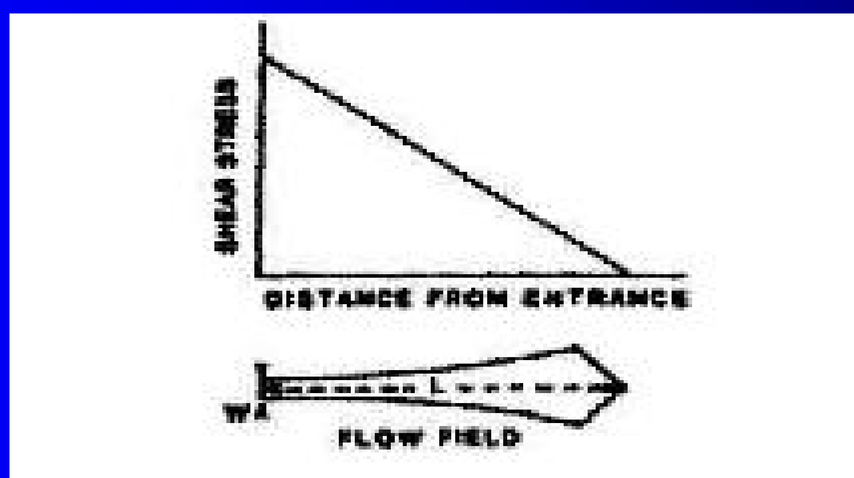
Measurement System of Flow Fields





Theoretical and Experimental Velocities

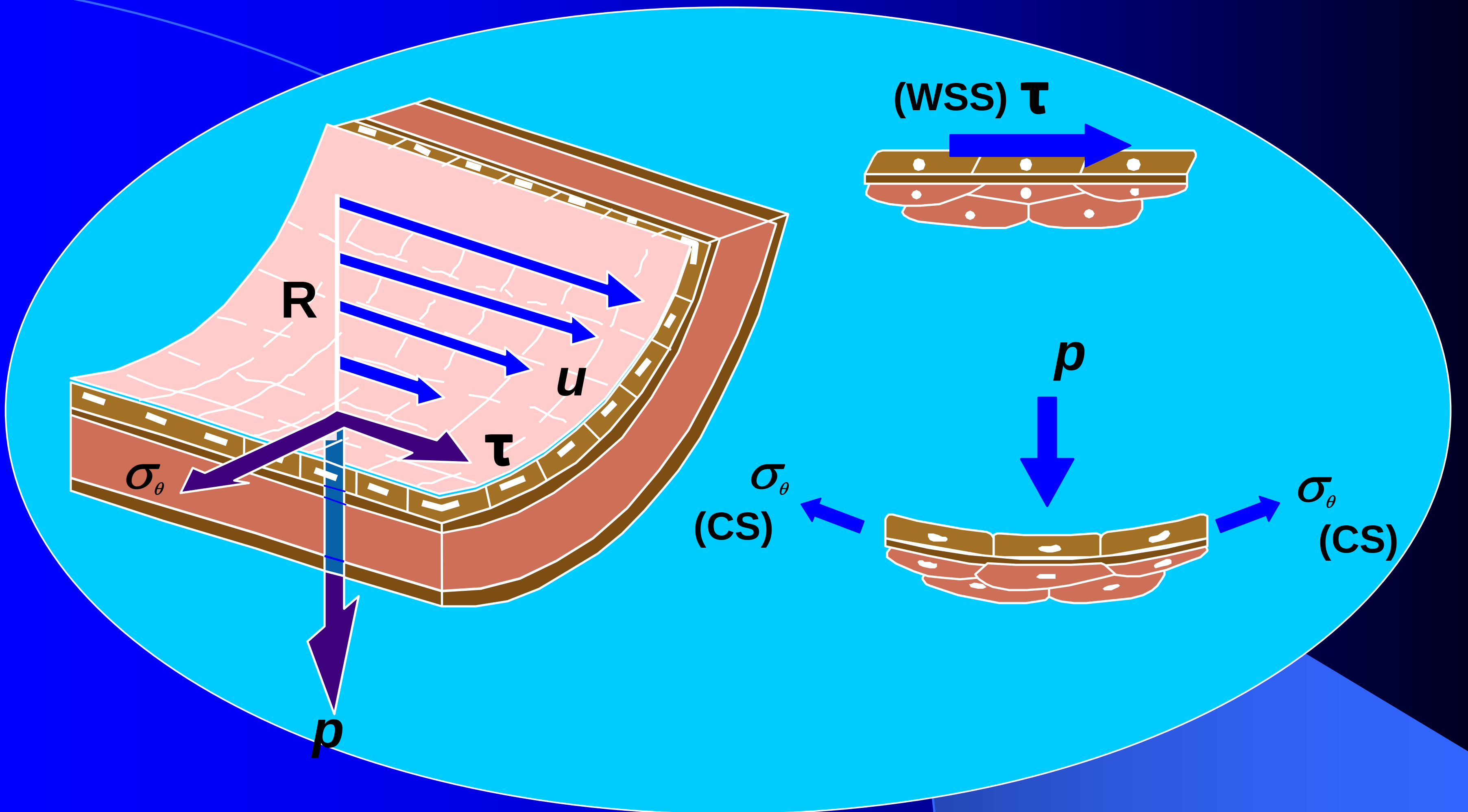




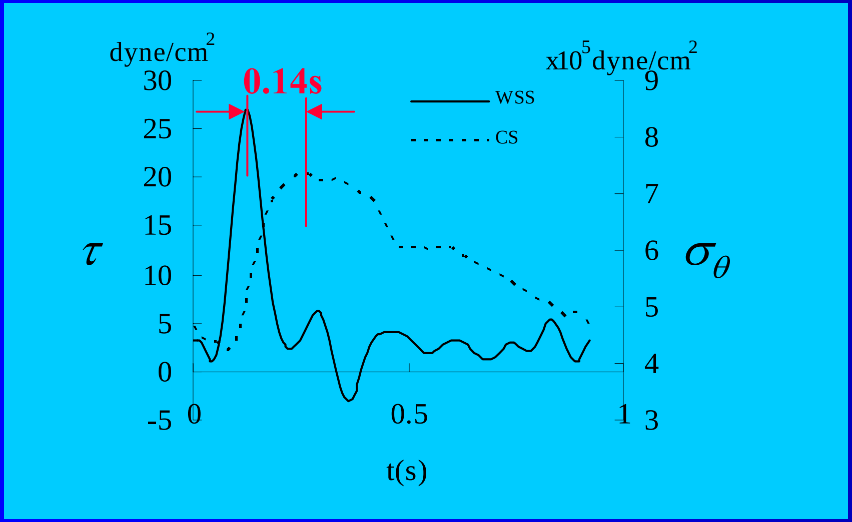
Cone-plate Flow Chamber

Responses of ECs Simultaneously Exposed to Wall Shear Stress and Circumferential Stress

Wall Shear Stress (WSS) & Circumferential Stress (CS)



Synergy of CS & WSS *in Vivo*



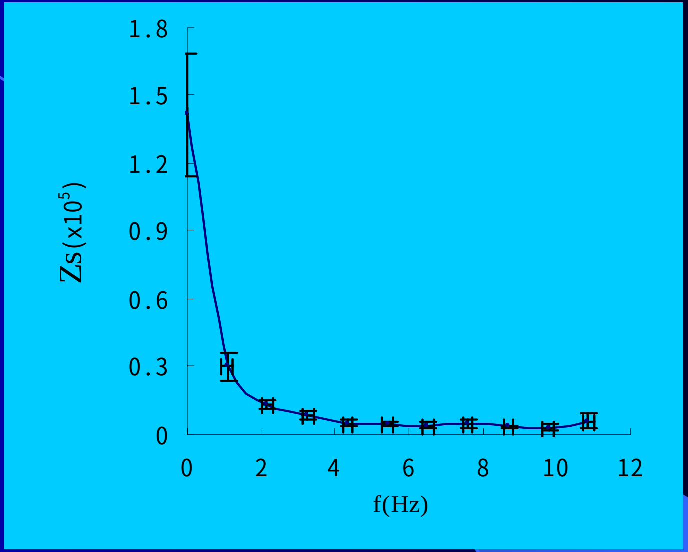
CS & WSS in the Normal Human Common Carotid Artery versus Time

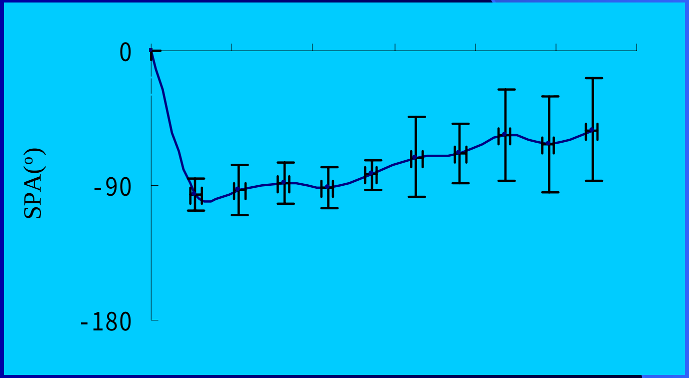
$$\sigma_\theta(t) = \sum_{n=-\infty}^{+\infty} \sigma_n e^{j(n\omega t + \varphi_{\sigma_n})}$$

$$\tau(t) = \sum_{n=-\infty}^{+\infty} \tau_n e^{j(n\omega t + \varphi_{\tau_n})}$$

$$Zs(\omega_n) = \frac{\sigma_n}{\tau_n}$$

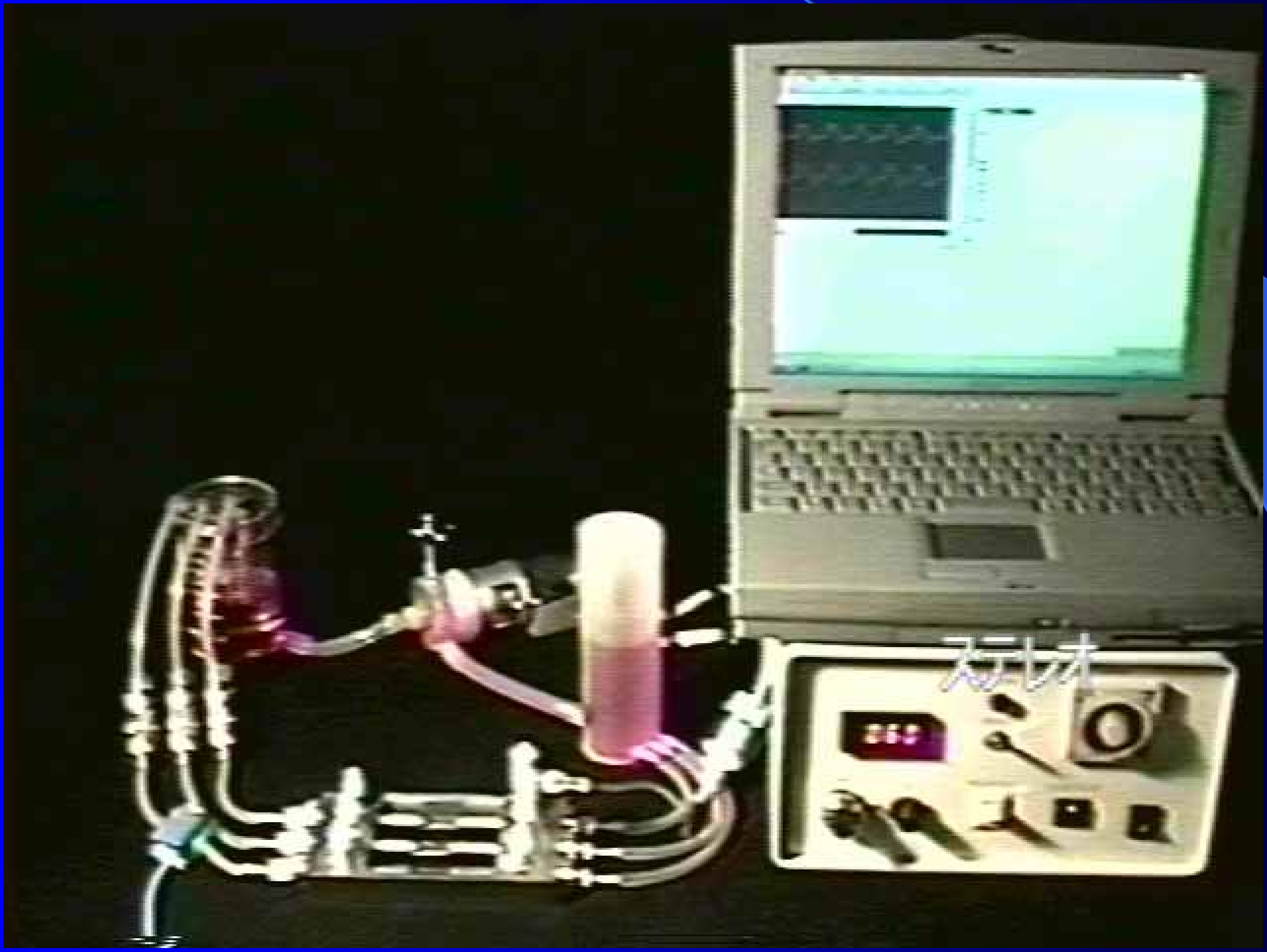
$$SPA(\omega_n) = \varphi_{\sigma_n} - \varphi_{\tau_n}$$





Zs and SPA versus Frequency (n=6)

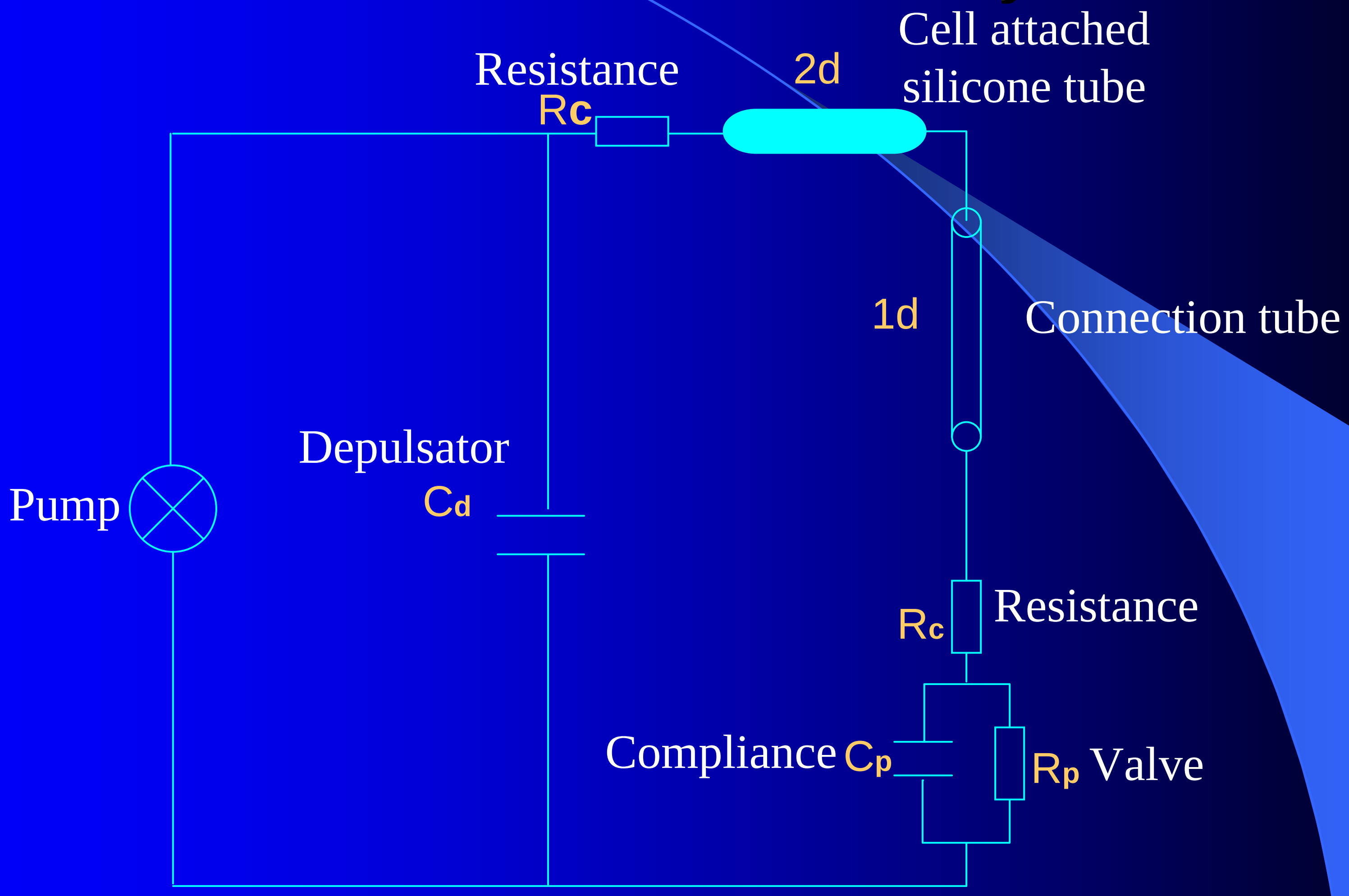
In Vitro Apparatus



Objectives

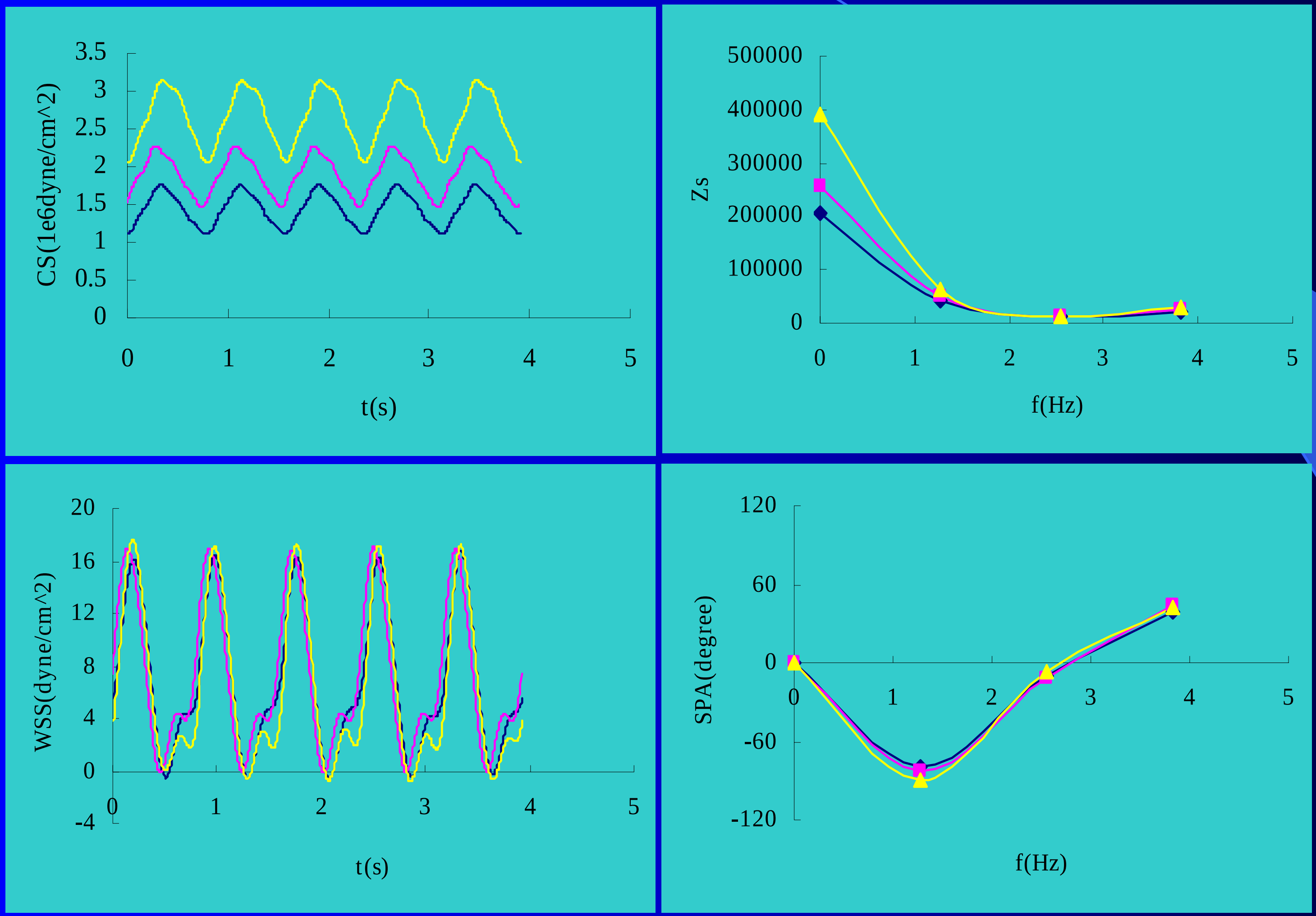
- To establish a silicone tube flow system that can mimic *in vivo* hemodynamic conditions in blood vessels
- To examine Ca^{2+} responses of ECs simultaneously exposed to CS and WSS

Numerical Device: Multi-scale Model for a Silicone Tube Flow System



2D: PDE (N-S Eq.)   1D: PDE   0D: ODE

Numerical Device: Effects of Pump Output (Preload)

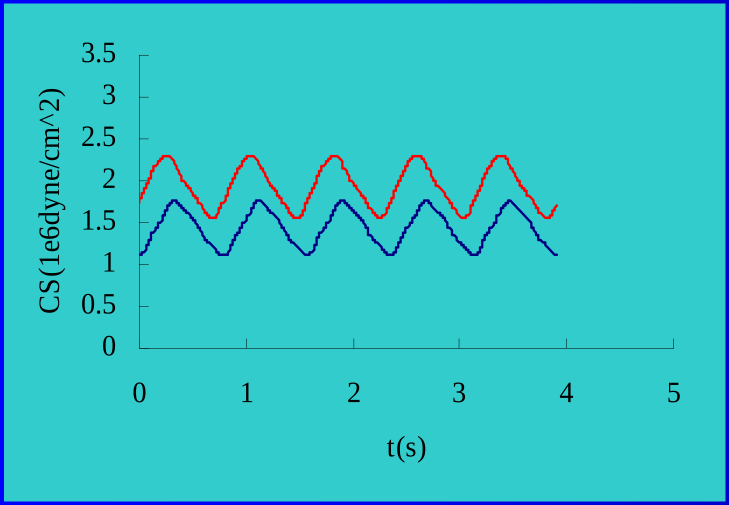


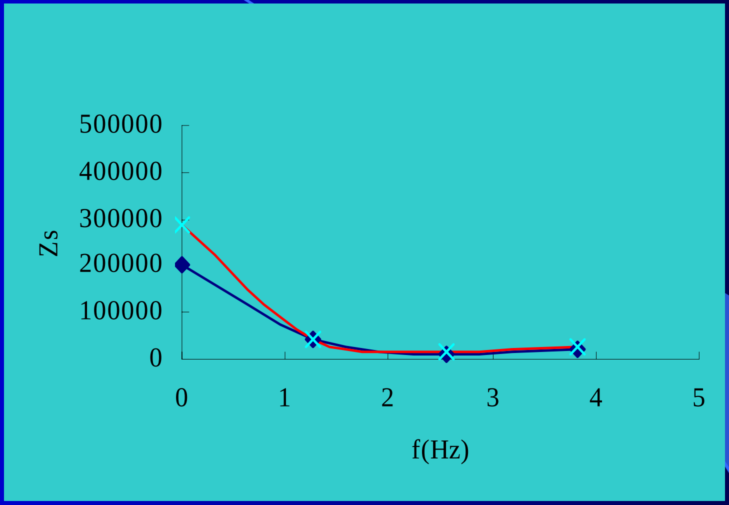
Yellow: Strong

Red: Moderate

Blue: Weak

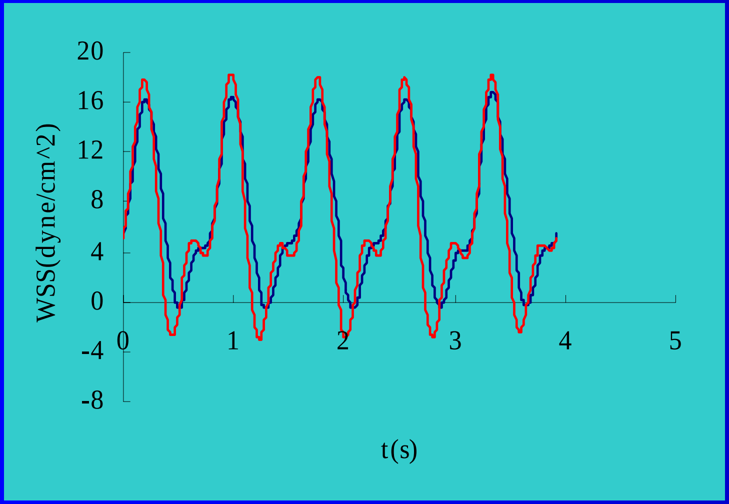
Numerical Device: Effects of the Cp (After-load)

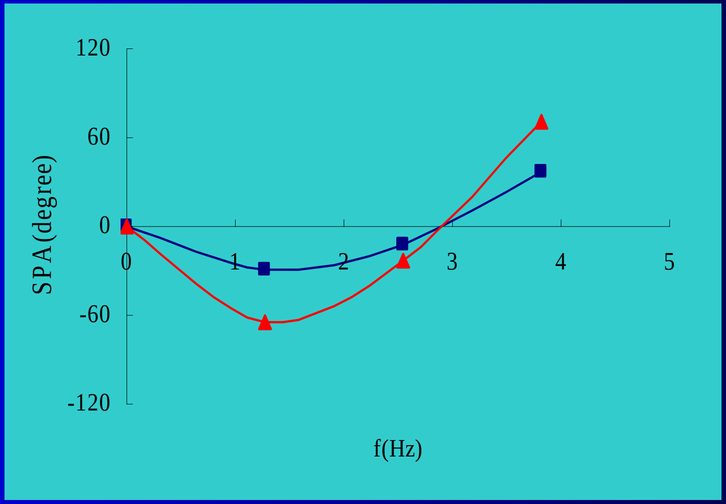




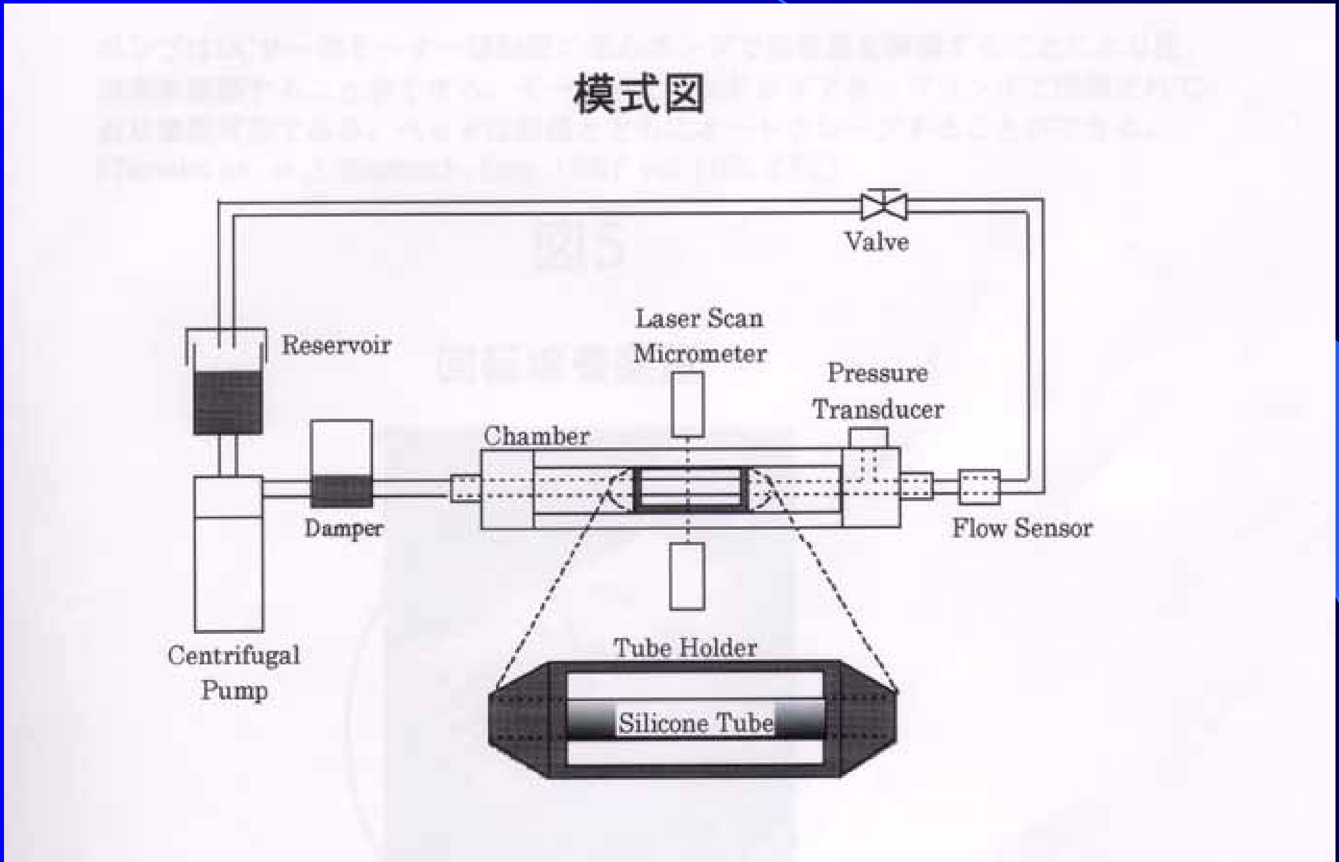
Blue: Larger Cp

Red: Smaller Cp





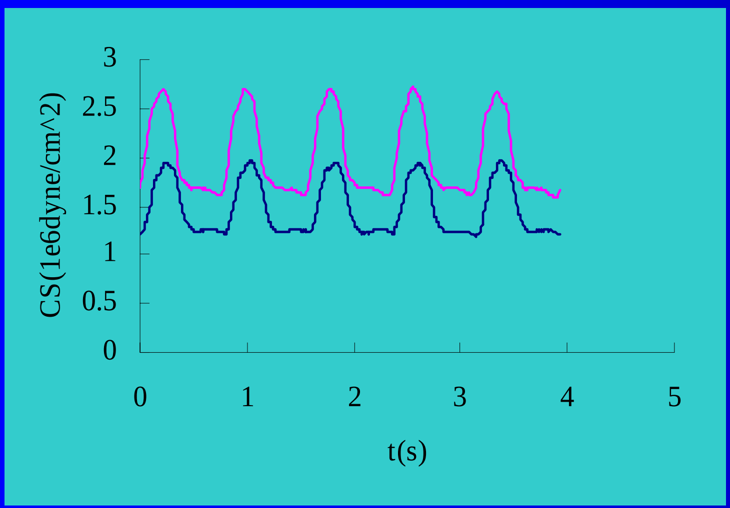
Actual Device

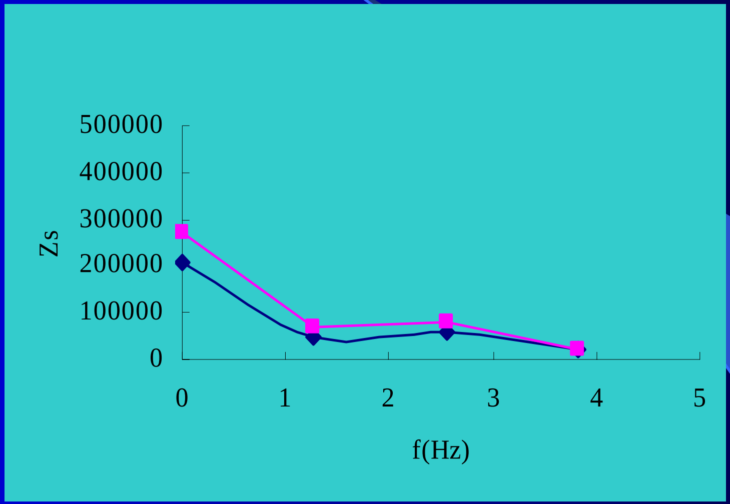


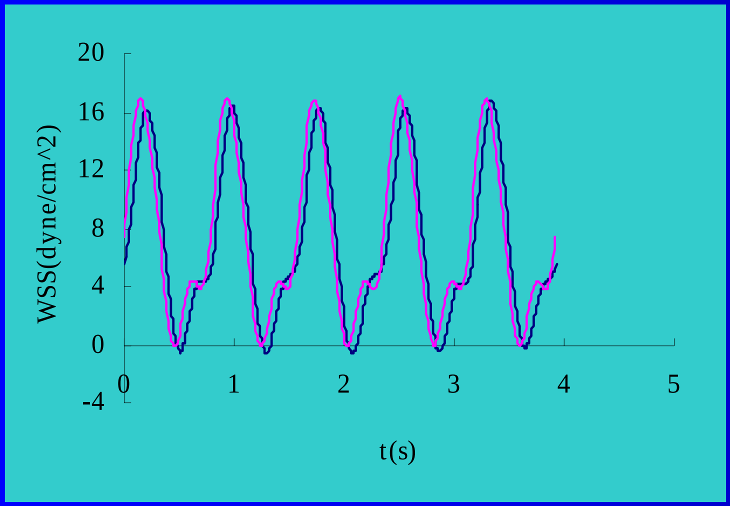
Actual Device: Effects of the Pump Output (Preload)

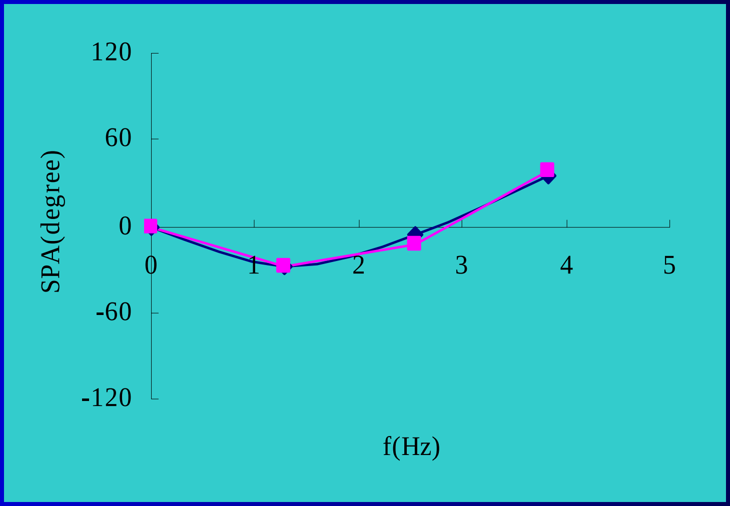
Blue: Weaker

Red: Stronger

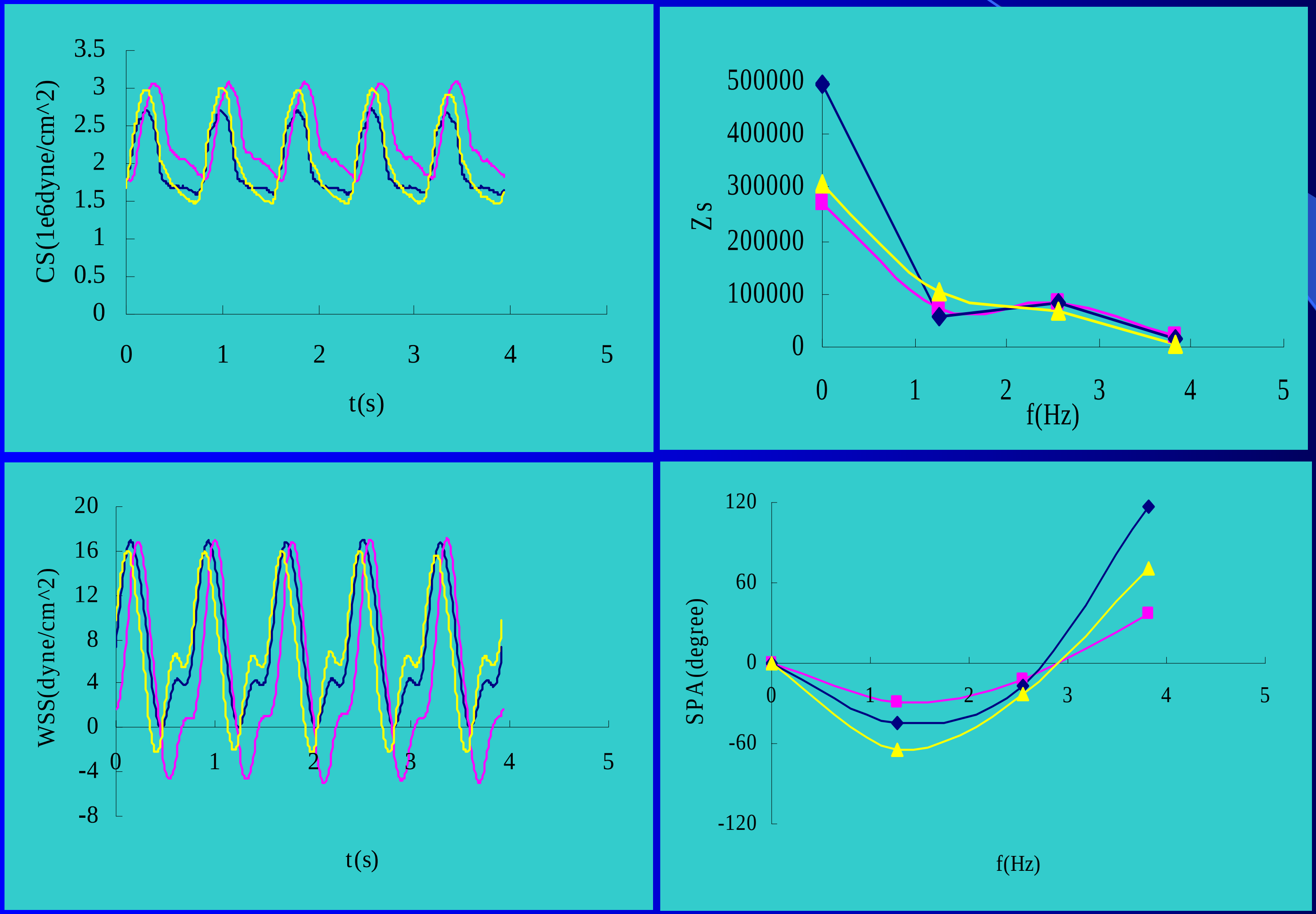








Actual Device: Effects of the Cp & Rp (After-loads)



Red: Large Cp & Small Rp

Blue: Moderate Cp & Moderate Rp

Yellow: Small Cp & Large Rp

Synergistic Effects of CS & WSS on ECs

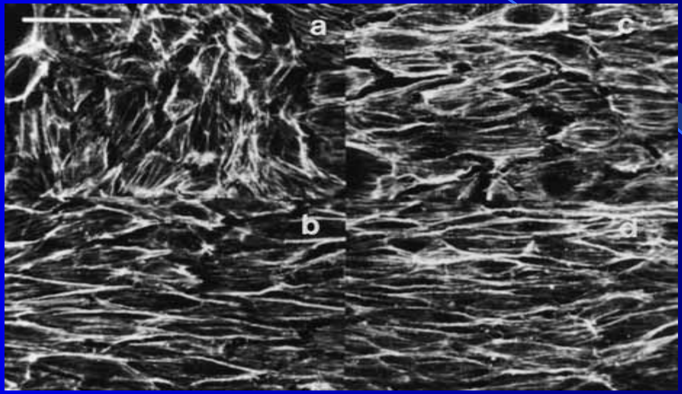
- Morphological responses

Static

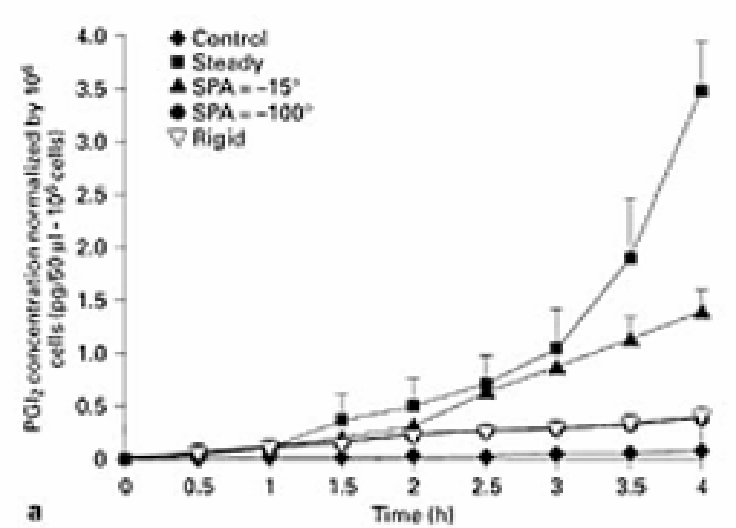
CS alone

WSS alone

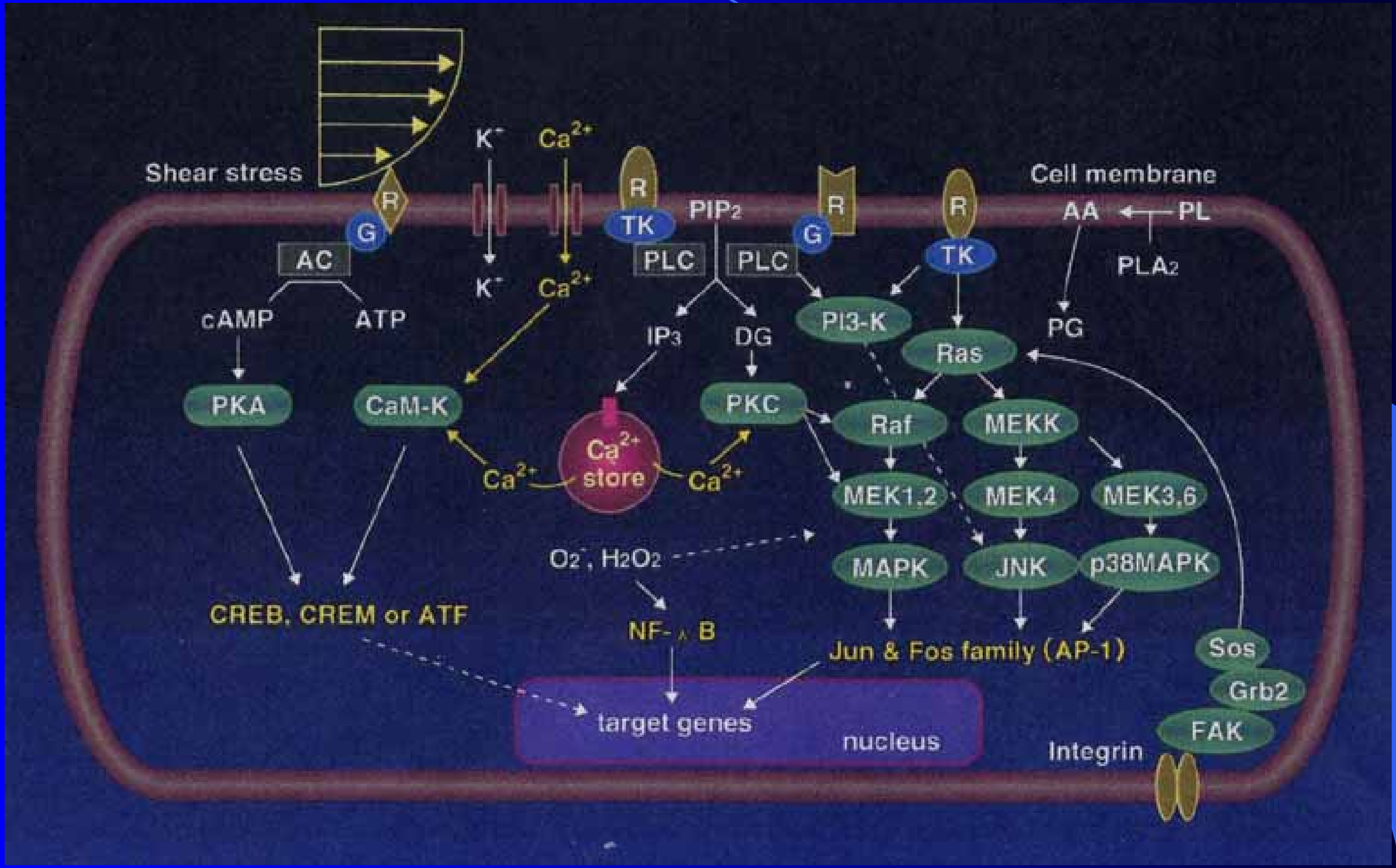
CS + WSS



- Biochemical responses (PGI_2, ET-1) are dependent on Stress Phase Angle (SPA)



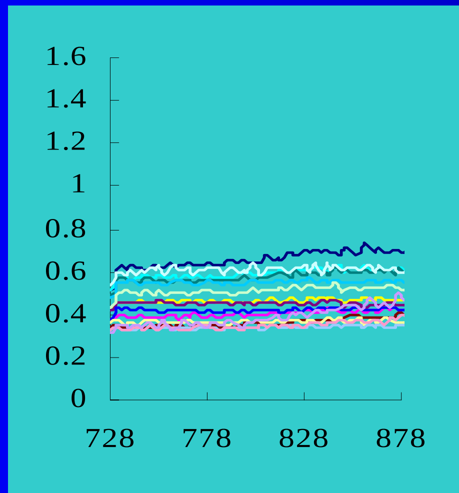
Calcium Signaling



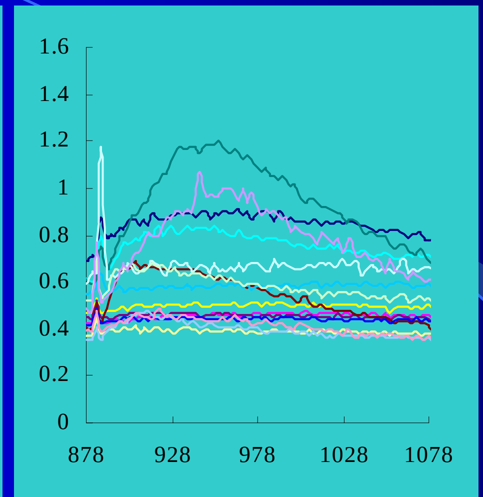
Ca^{2+} Responses to WSS Alone

Glass Tube

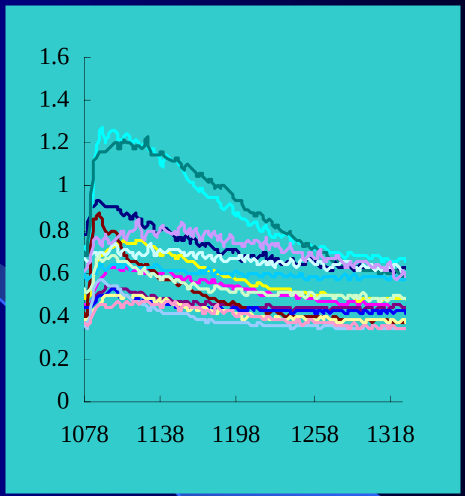
Ca^{2+} + HBSS + 500nM ATP



1dyne/cm^2

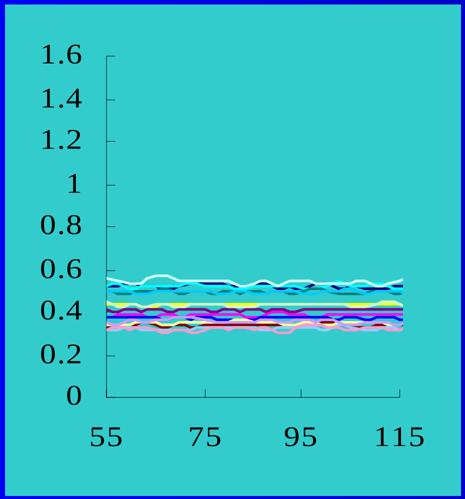


5dyne/cm^2

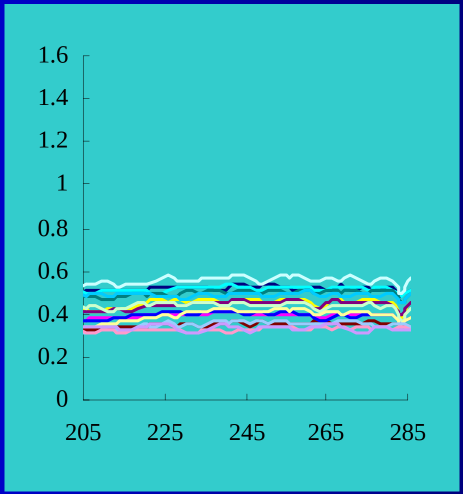


9dyne/cm^2

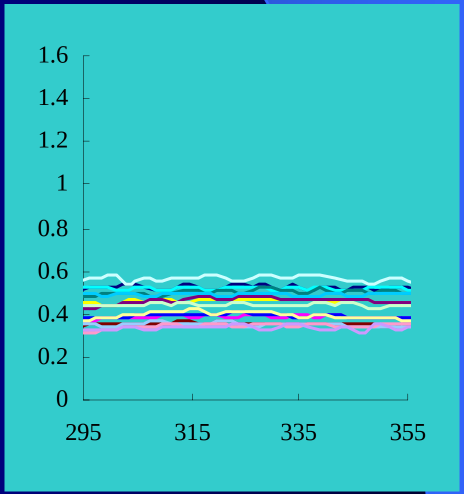
Ca^{2+} free HBSS + 2mM EGTA+ 500nM ATP



1dyne/cm^2



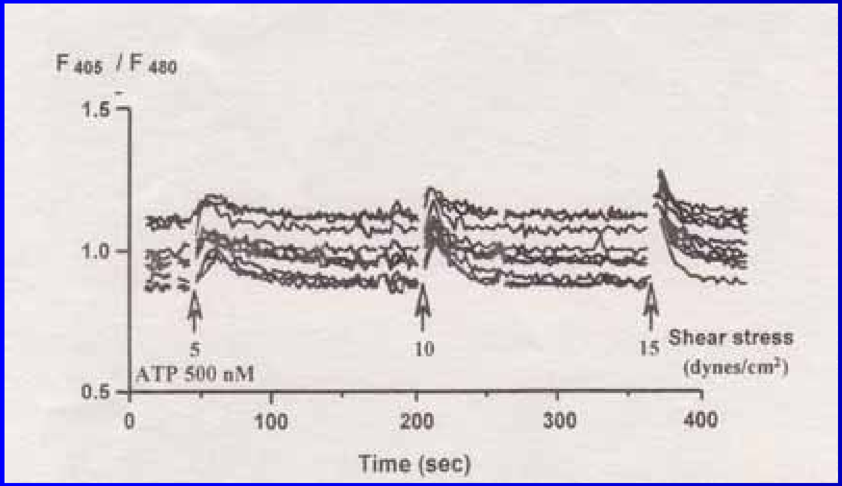
5dyne/cm^2

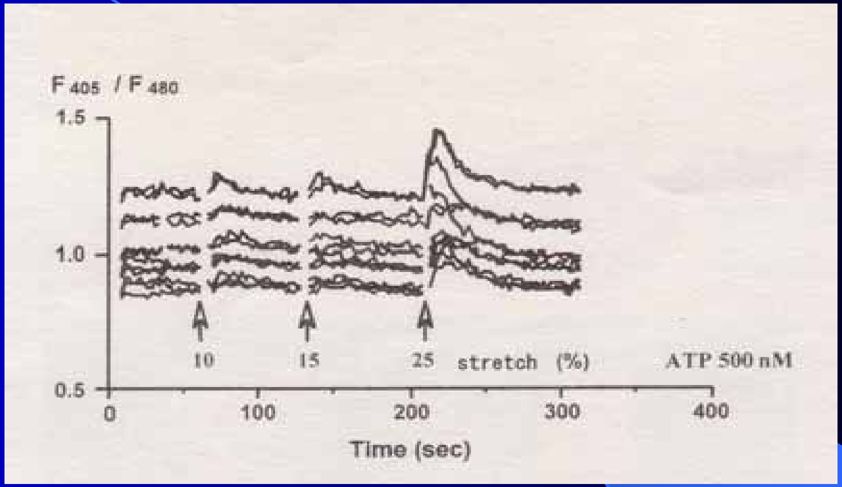


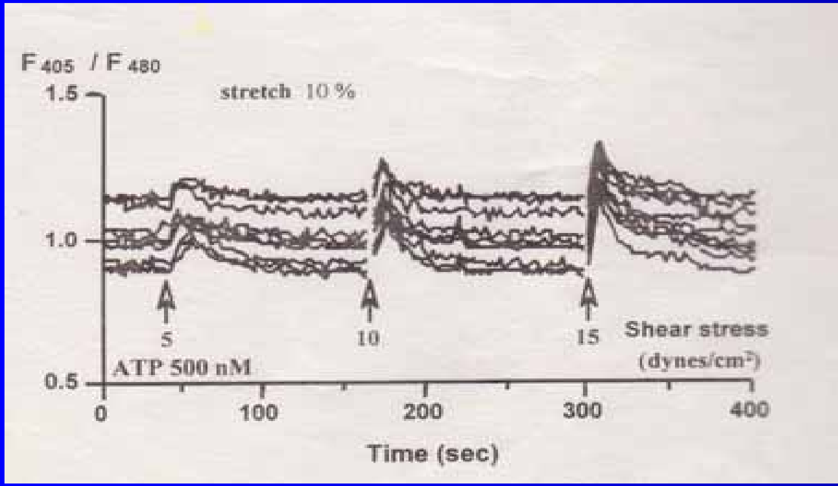
9dyne/cm^2

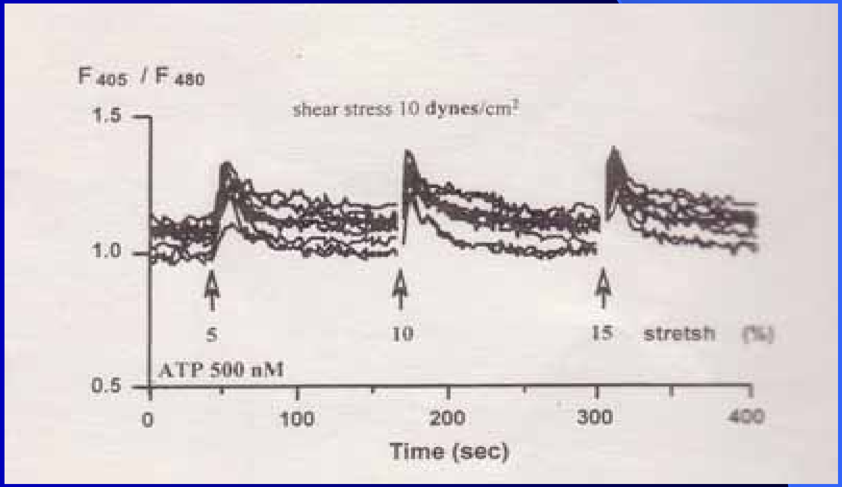
Ca^{2+} Responses to CS & WSS

Silicone Tube



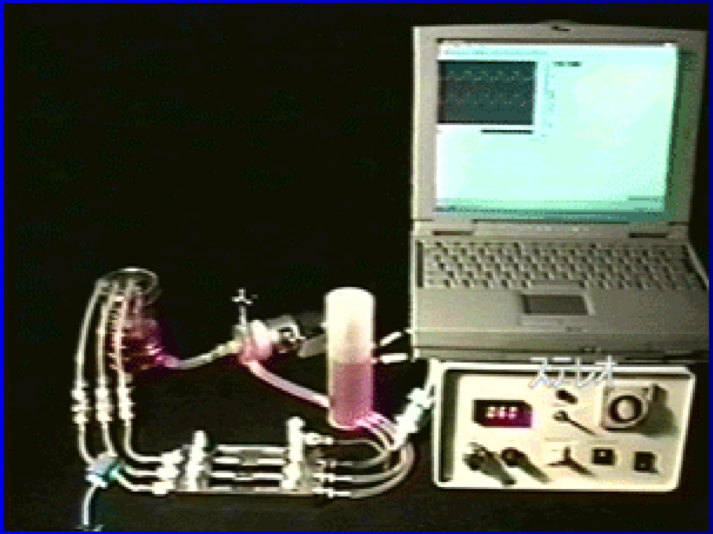




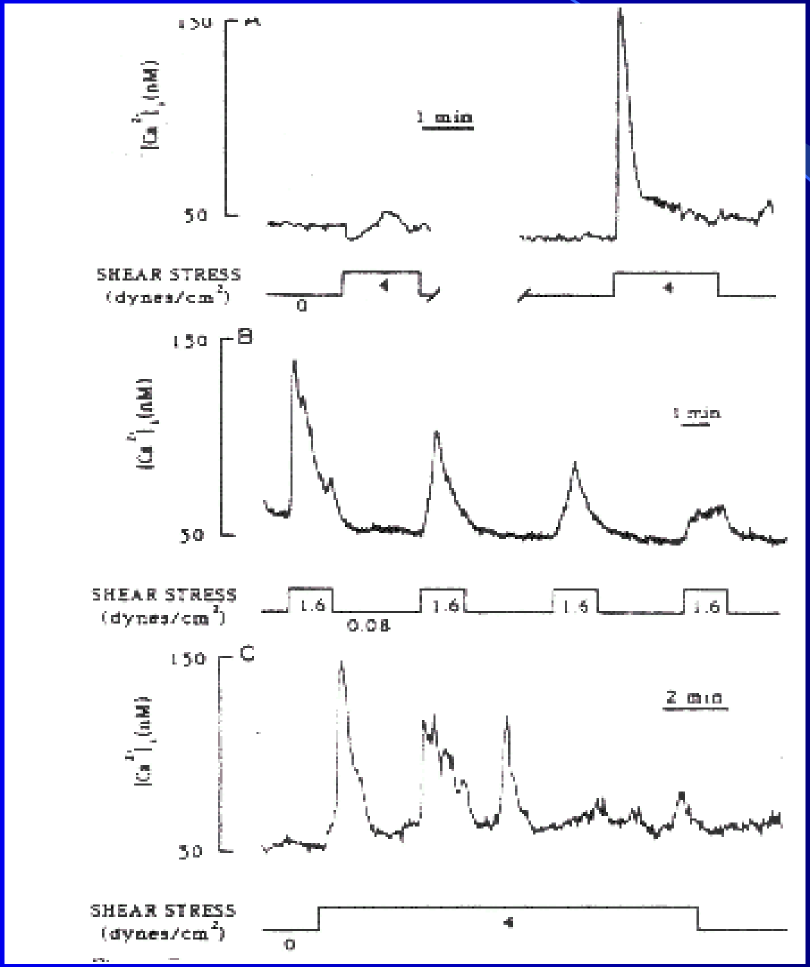


Conclusion

- The silicone tube flow system can mimic *in vivo* hemodynamic conditions in blood vessels
- Ca^{2+} responses of ECs are dependent on WSS rather than CS under physiological conditions



Ca^{2++} Oscillation



Ca^{2++} Wave

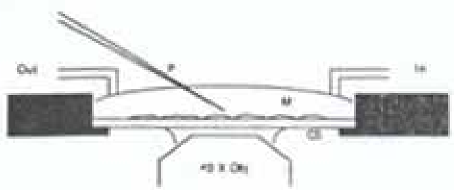
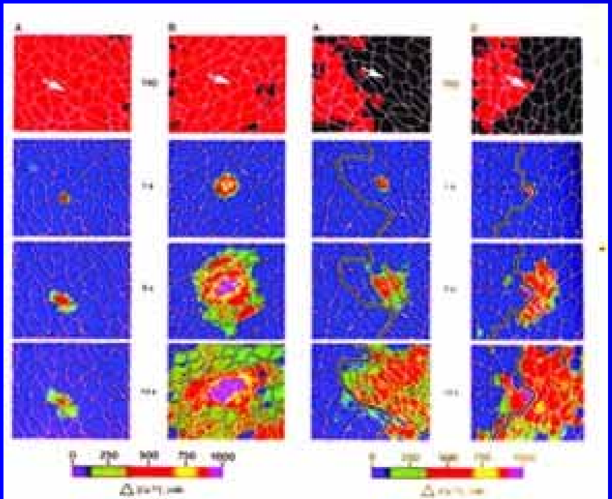
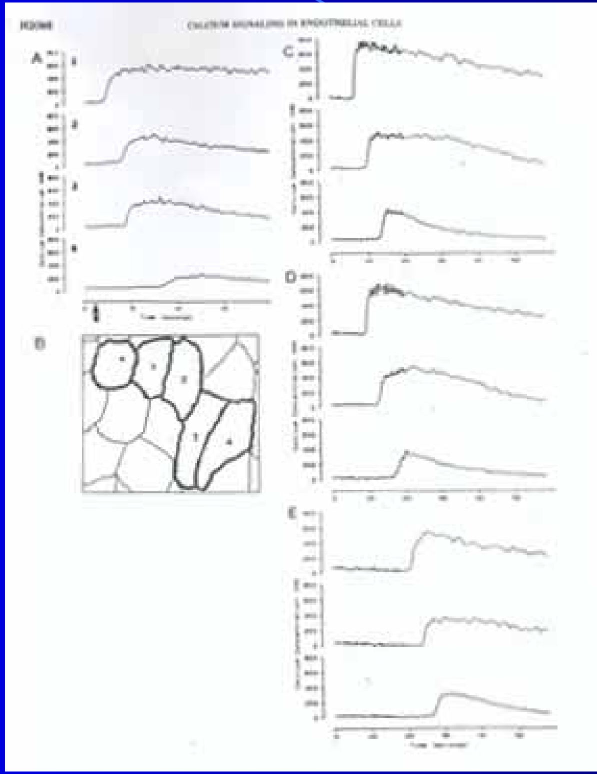
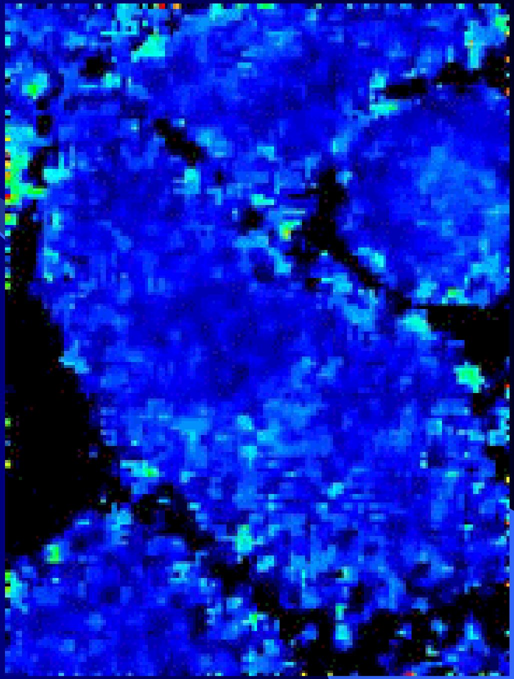


Fig. 1. Apparatus for mechanical stimulation of endothelial cells. Microscope stage was modified to permit mounting of glass cover slips immediately above ×40 objective. Bovine aortic endothelial cells grown on a collagen-coated glass cover slip (CS) were transferred to stage and covered with a meniscus (M) of buffered salt solution. A microprobe (P; 1-μm tip) was displaced downward on apical surface of a single cell. Initial location of probe was adjusted using a micromanipulator, and vertical displacement was controlled electronically. Small inlet (In) and outlet (Out) tubes permitted exchange of bathing solution.







CFD in Calcium Signaling (?)

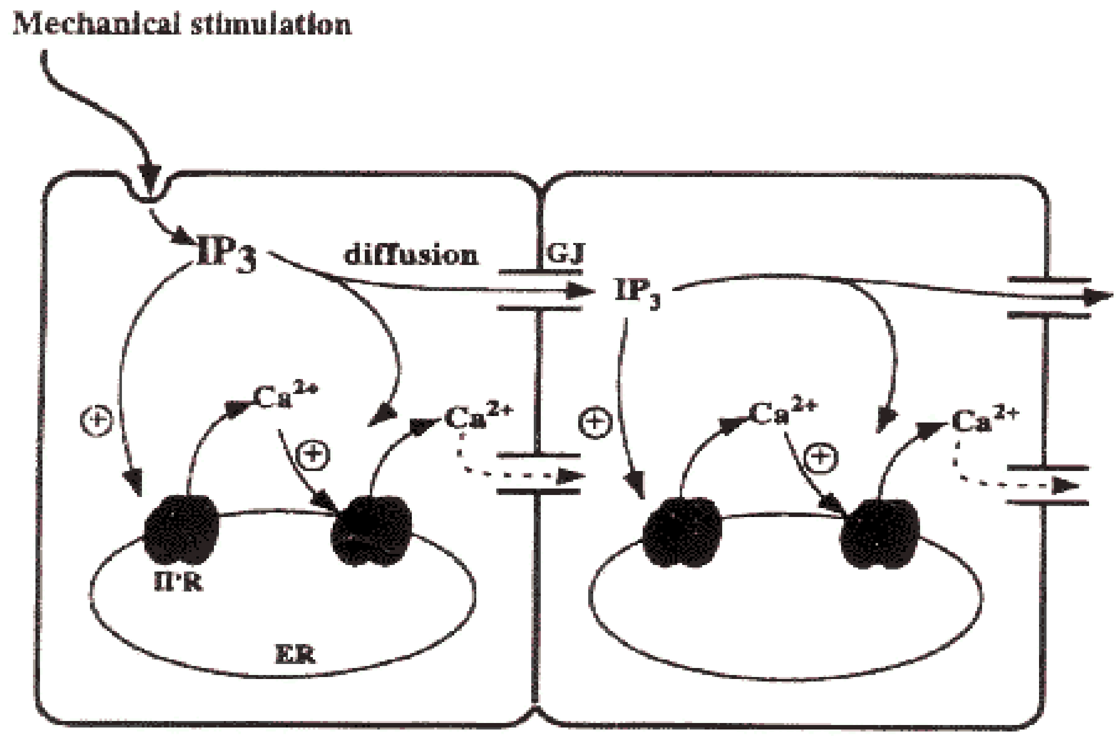
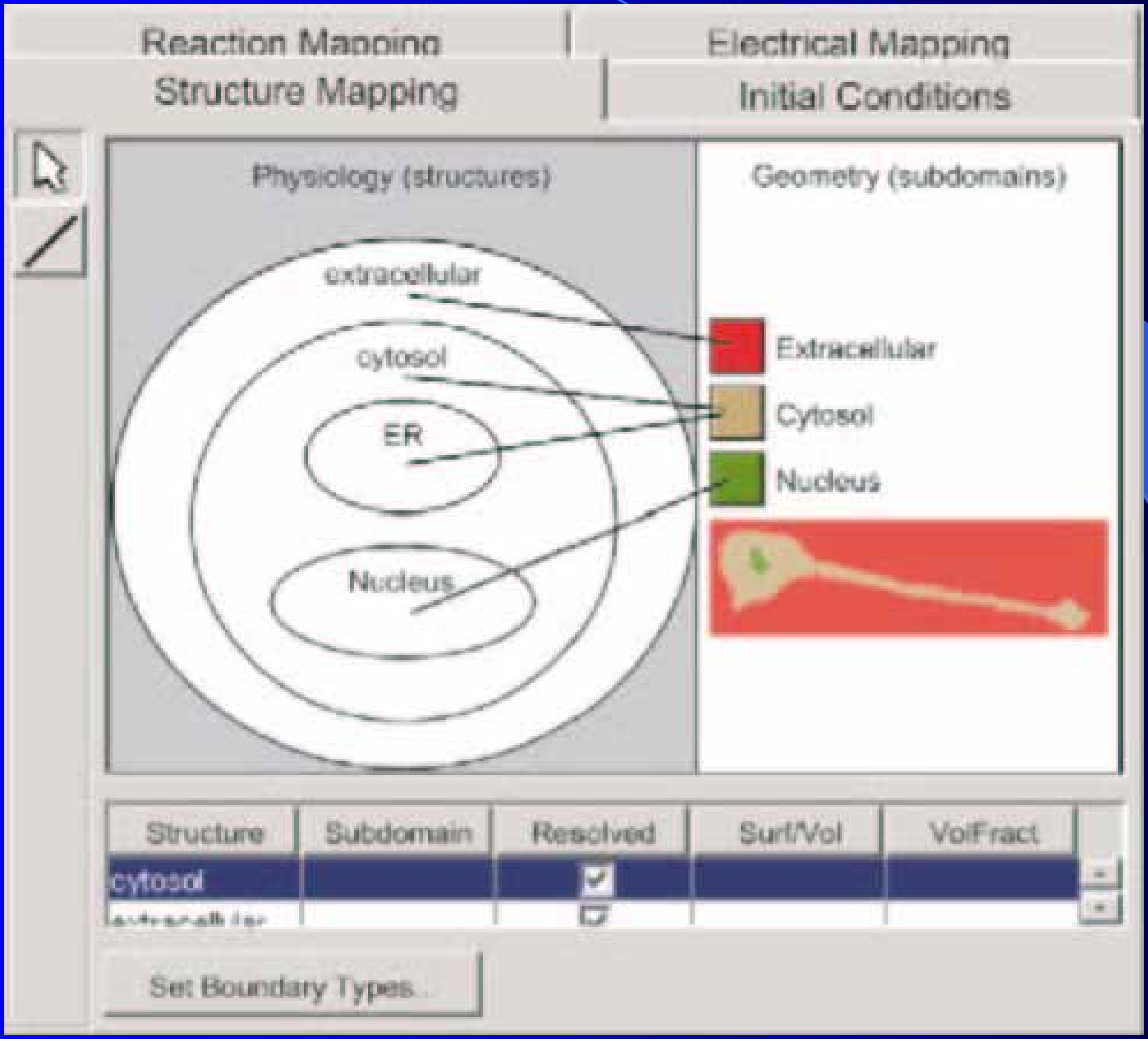


Fig. 1. Schematic diagram of the passive diffusion hypothesis for the propagation of intercellular Ca^{2+} waves. IPR, IP_3 receptor/Ca^{2+} channel; ER, endoplasmic reticulum; GJ, gap junction. The + sign denotes Ca^{2+}-induced Ca^{2+} release.

Virtual Cell (or E-Cell)



Applications of CFD in Traditional Chinese Medicine

黄帝内经（2500B.C.)

- “经脉者，人之所以生，病之所以成，人之所以治，病之所以起”
- “决生死，处百病，调虚实，不可不通”
- 经络的功能：运行气血，平衡阴阳，濡养筋骨，滑利关节，联络脏腑，表里上下，传递病邪

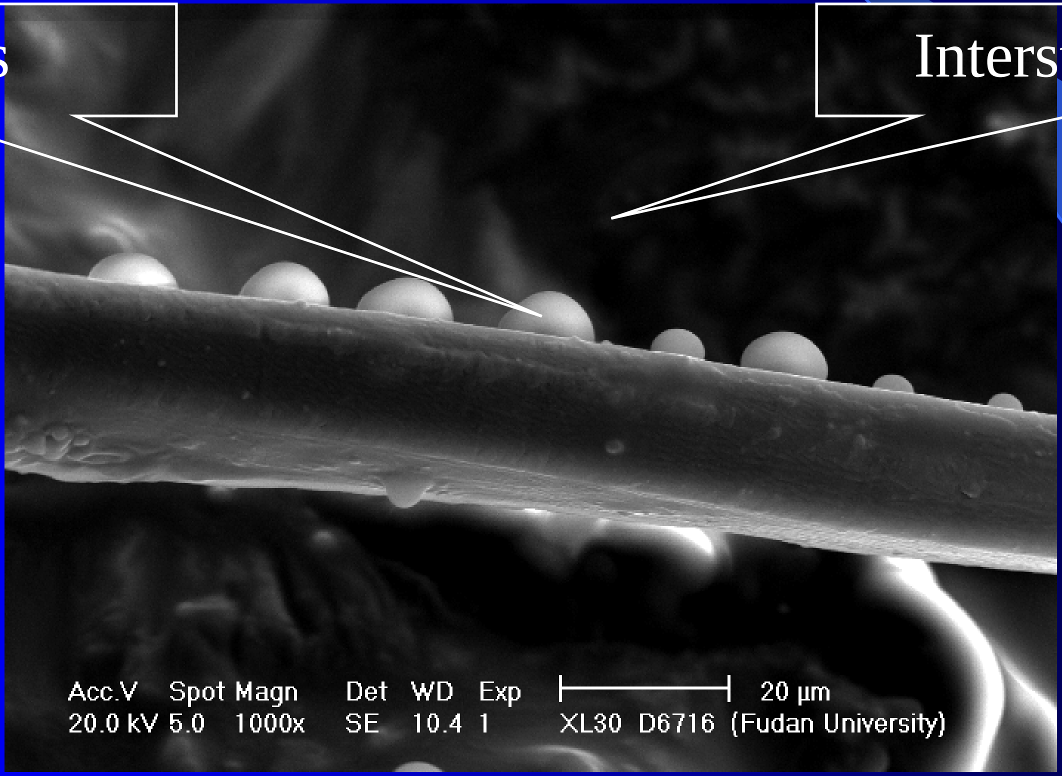
The Interstitial Fluid Flow in Connective Tissue : The Mechanism of Meridians in Traditional Chinese Medicine

Ding Guanghong

Department of Mechanics and Engineering Science
Fudan University
Shanghai, China
Ghding@fudan.edu.cn

Background: Cells Environment

Interstitial fluid is the surroundings that organism cells reside

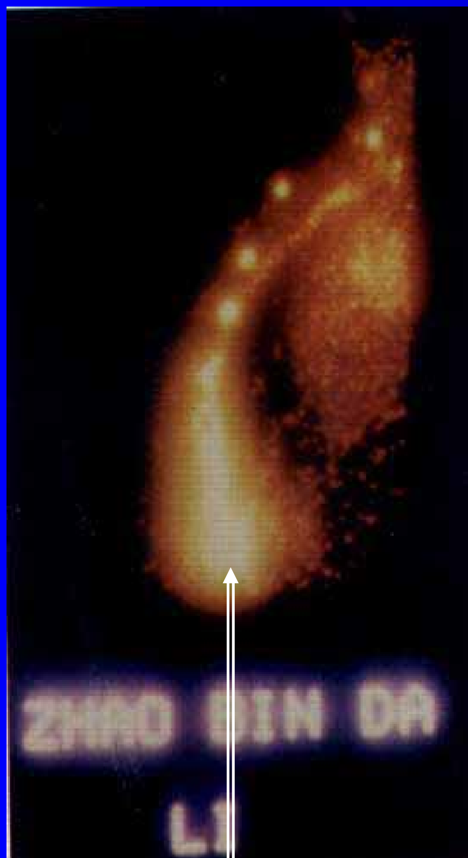


Electronic Microscope image of connective tissue in human ligament

Background: Traditional Chinese Medicine (TCM)

Meridians: TCM Theory

Background: Experiment Results



Move velocity: 1-10cm/min.

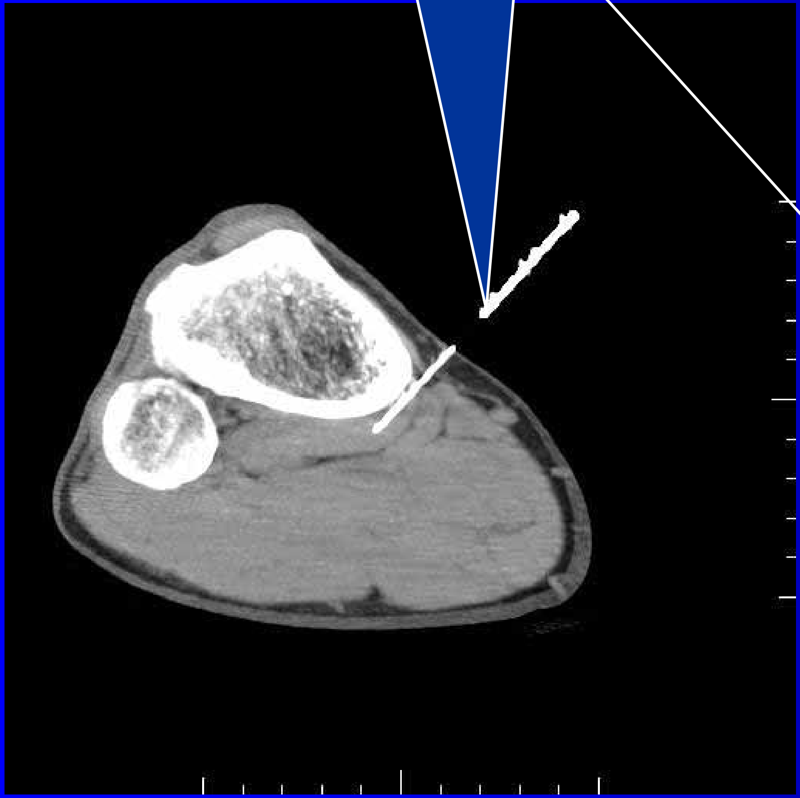
And 30cm/min in acupuncture statement

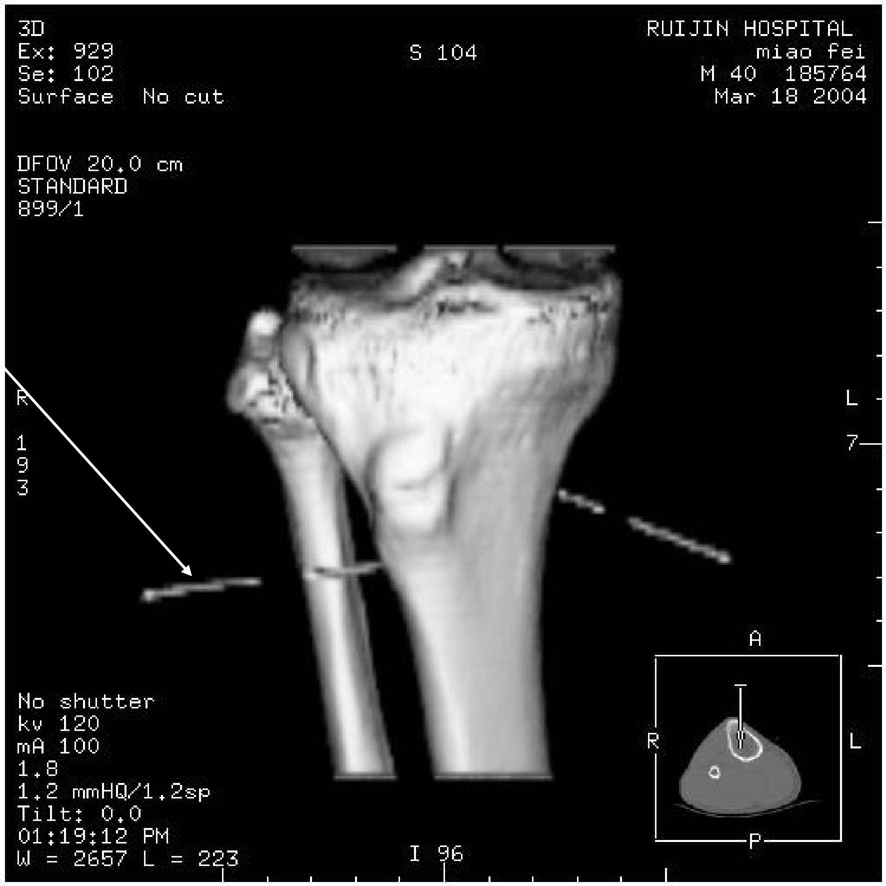
Inject radioactive isotope elements at acupoints

Physical Base of Meridians

Physical Base of Meridians

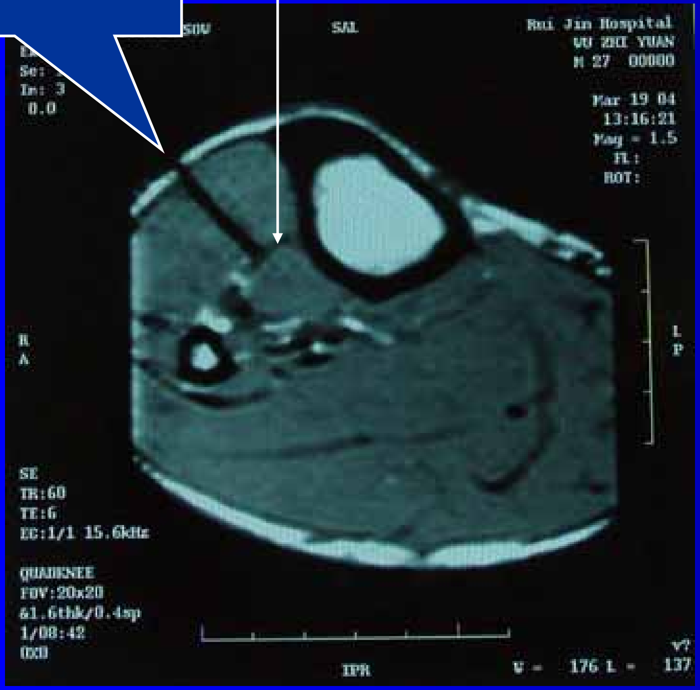
Acupuncture needle





CT of human lower limb

Physical Base of Meridians



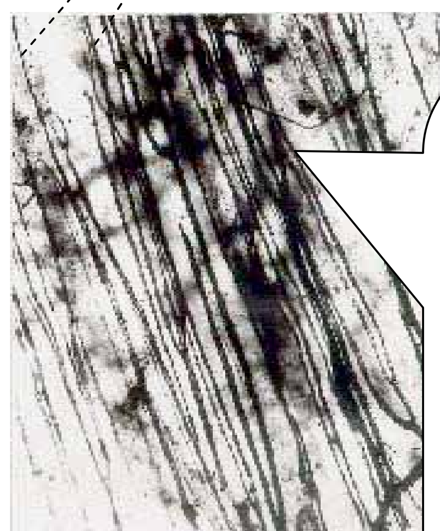
MRI of human lower limb

Physical Base of Meridians

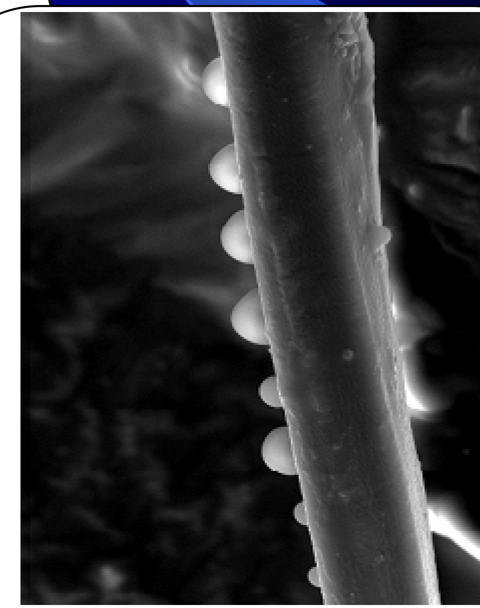
Blood vessel at the interosseous membrane

acupoint

microscope



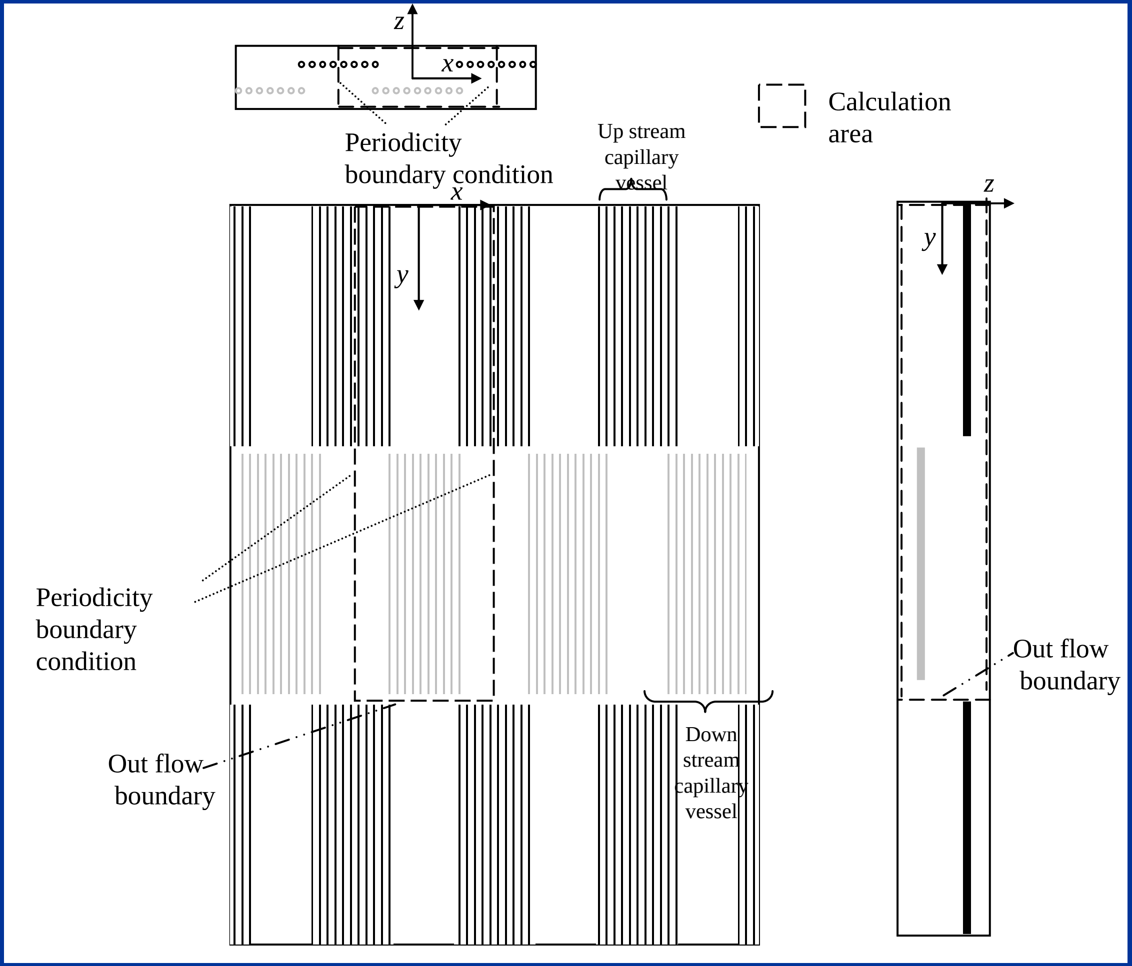
Electronics microscope



Capillary vessel with parallel arrange in acupoints

Biomechanics model of

Interstitial fluid flow with parallel capillary vessel



Calculation Method

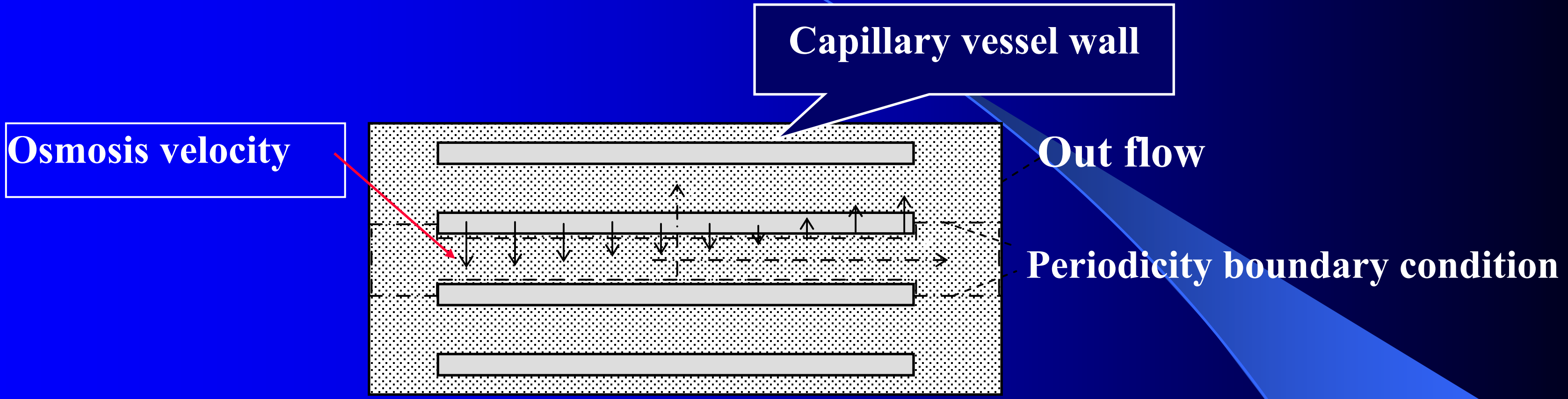
The control equations in the porous medium are Brinkman Equations:

$$\nabla \boldsymbol{p} = \mu \Delta \boldsymbol{u} - \frac{\mu}{\boldsymbol{k}_p} \boldsymbol{u}$$

$$\nabla \cdot \boldsymbol{u} = \mathbf{0}$$

Where ∇ is grads operator， Δ is Laplace operator, u is velocity, P is pressure, Kp is Darcy osmosis.

Boundary condition



The flow velocity in the capillary vessel wall is:

$$v = \frac{\lambda_1 R \Delta p}{\mu_c}\left(\frac{\Delta \alpha}{\Delta p} - \xi\right)$$

Where:

$\Delta\alpha = p_a - p_*$ $\Delta p = p_a - p_v$ $\lambda_1 = \frac{\mu_c \cdot k_c}{R}$

Physiological Parameters

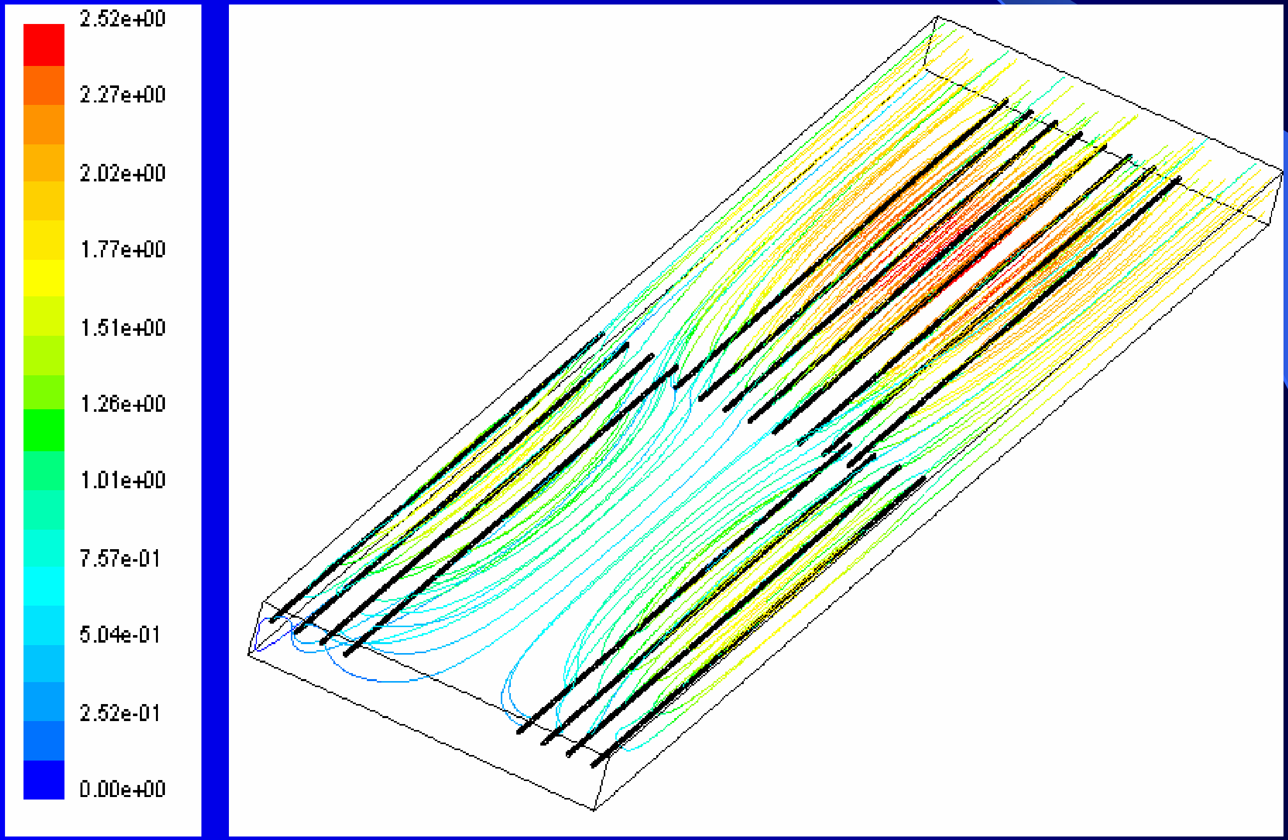
	Parameters	Physiological range
Blood in capillary vessel	Viscosity (cp)	2
Osmosis of capillary vessel wall	k_c	5×10^{-9}
Pressure	Tissue p_o (mmHg)	-2～-5
	Small artery p_a (mmHg)	30～35
	Small venous p_v (mmHg)	10～15
	Tissue osmosis Π_o (mmHg)	4～6
	Plasma osmosis Π_i (mmHg)	28
Geometry parameters of capillary vessel	Diameter D (μm)	8.3± 3.6
	Space between (μm)	37.3± 27.4
	Length L (μm)	750～1950
Tissue interstitial	Density of tissue fluid (kg/m^3)	1000
	Viscosity of tissue fluid (cp)	3.5
	Porous rate φ	0.32～0.42

Numerical Simulation

- **Software calculating velocity field is** FLUENT
- **Software dispersing space grid is** AMBIT
- **Calculation method is** DIFFERENCE

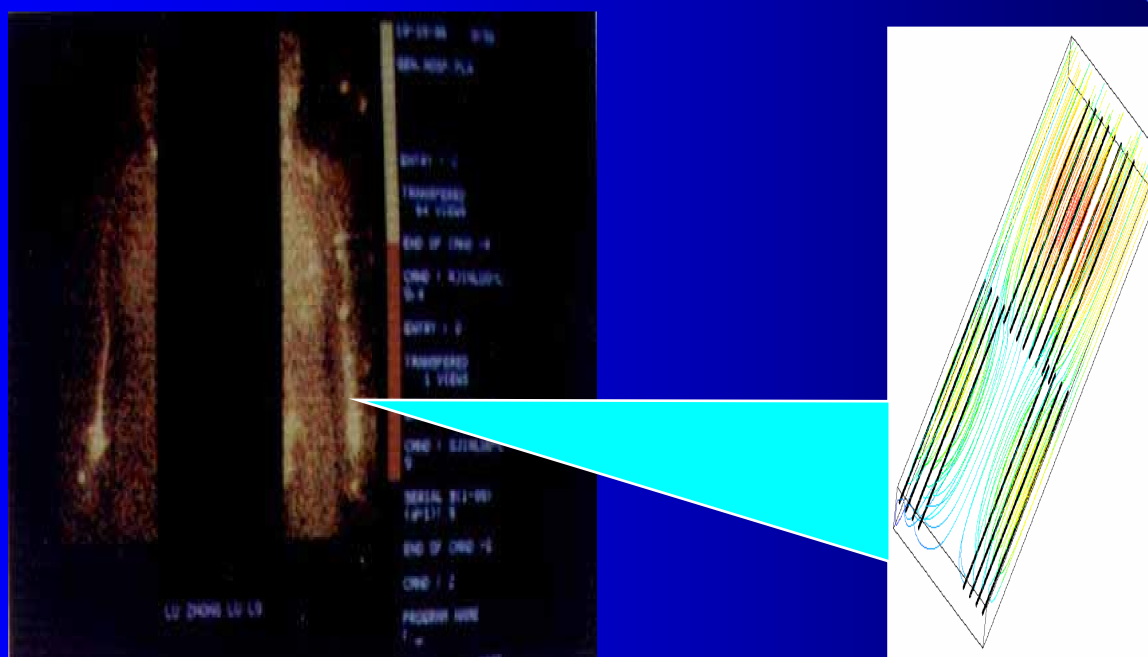
Numerical Simulation Result

3-D velocity field of the tissue interstitial fluid in the interosseous membrane



Results and Discussion

- The interstitial fluid flow in some tissue have a certain direction along the meridians



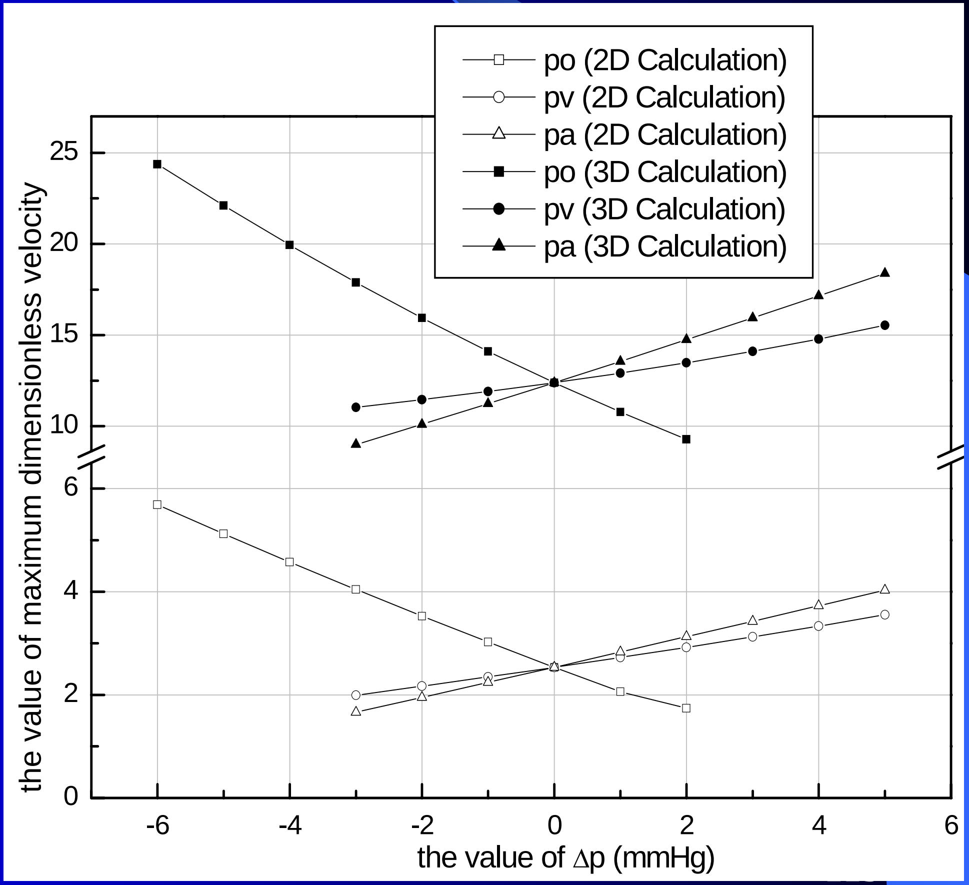
Results and Discussion

- flow velocity is influenced by the vessel and tissue pressure

❖Increasing Vessel pressure cause fluid velocity up

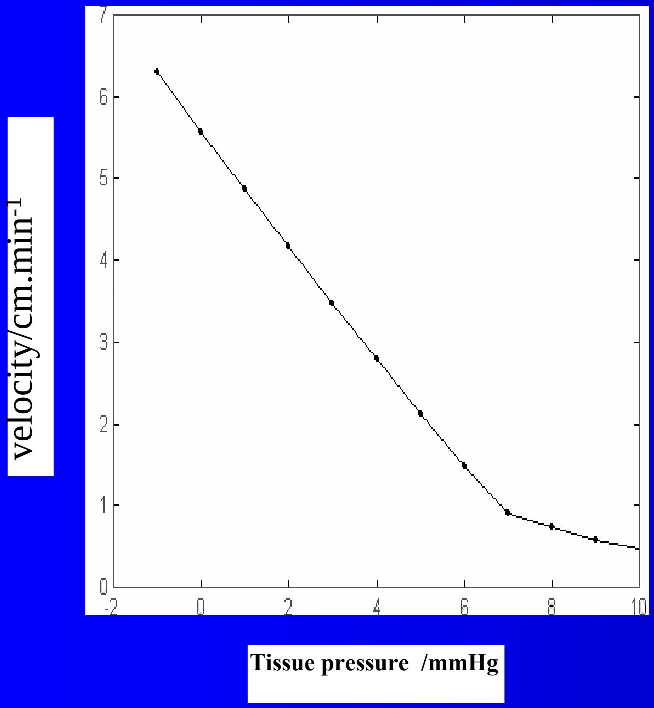
❖Increasing tissue pressure cause fluid velocity down insensitively

❖ The meridians can be blockaded by exterior pressure in clinical



Results and Discussion

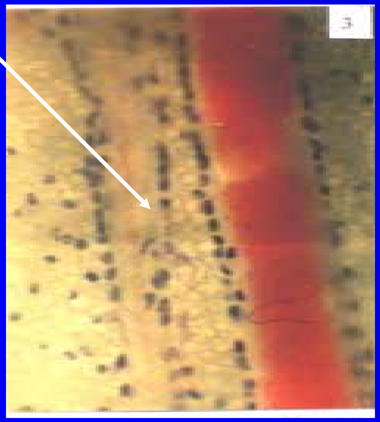
- The negative tissue pressure will increase the interstitial fluid flow, this is the mechanism of cupping treatment in TCM clinical

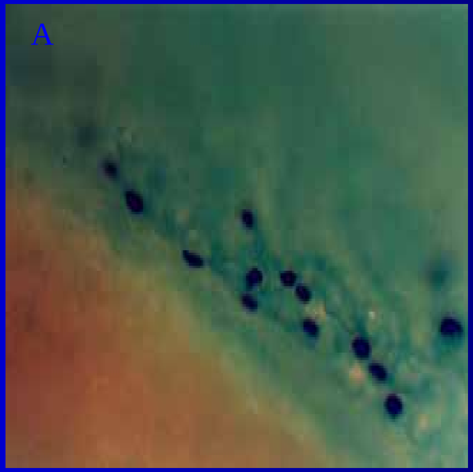


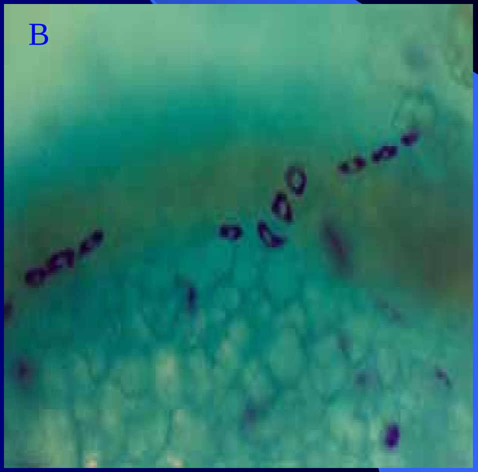
Results and Discussion

- In the tissue interstitial there are many cells such as mast cells
- The acupuncture cause mast cells degranulation

Mast Cells





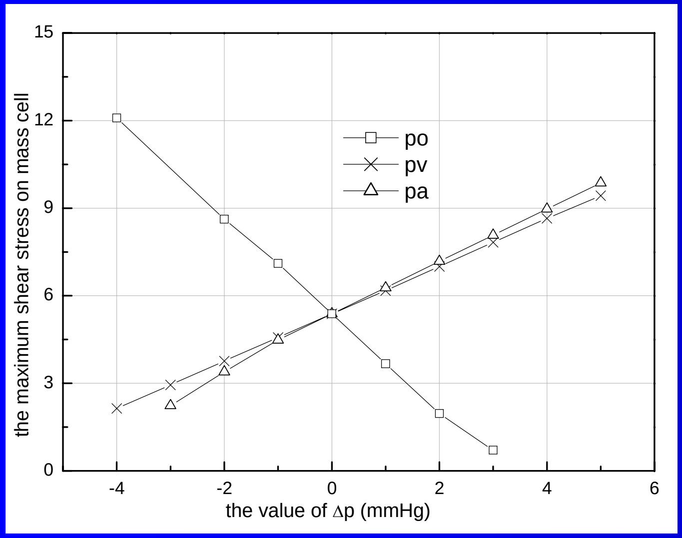


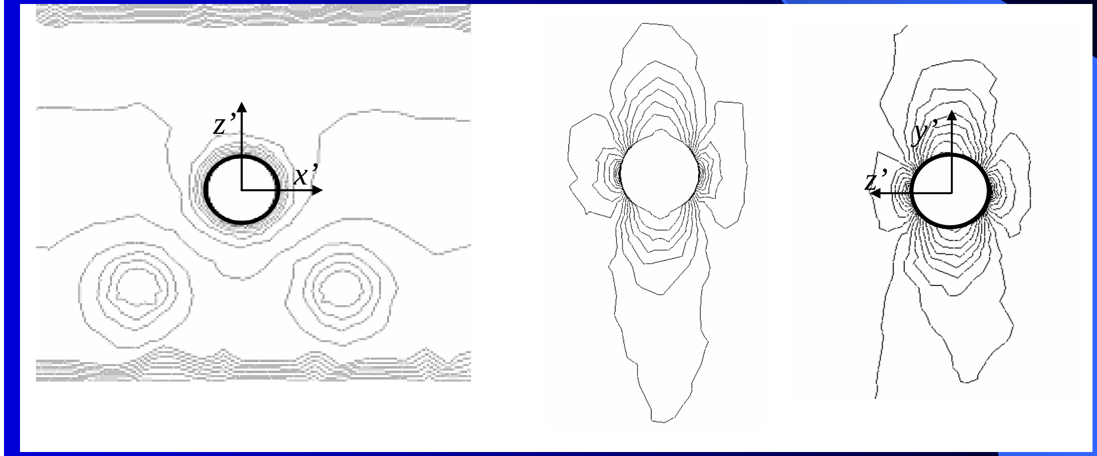
Before acupuncture

After acupuncture

Results and Discussion

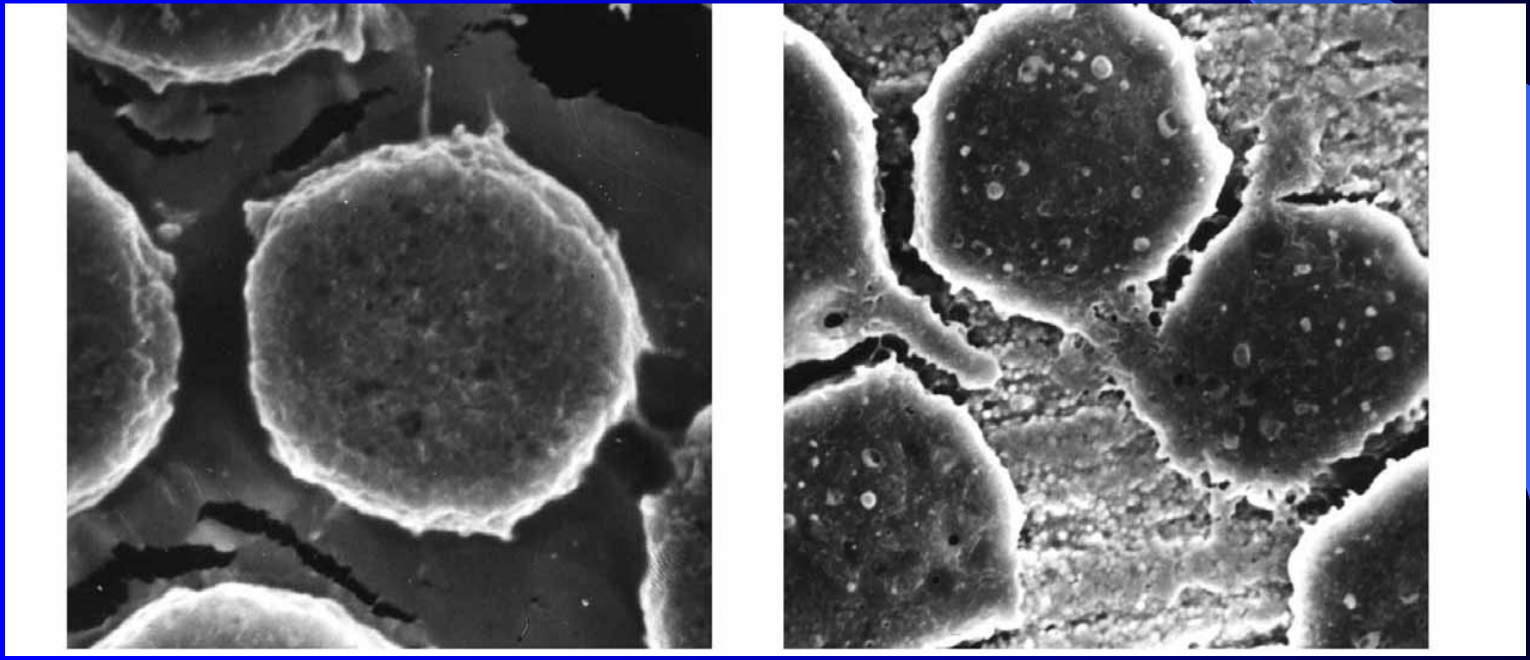
The interstitial fluid flow will generate a wall shear stress in the surface of mast cells



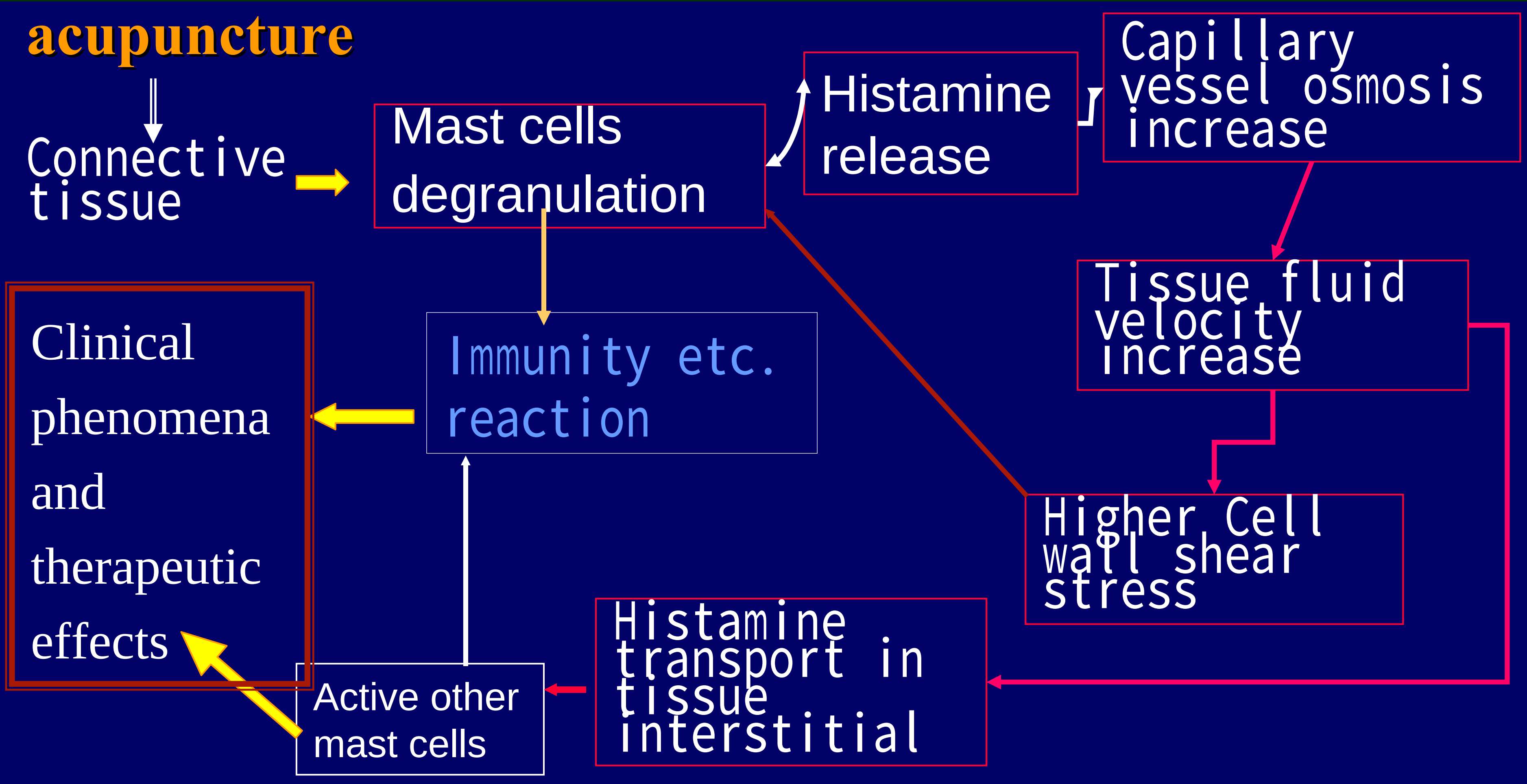


Results and Discussion

- Wall shear stress will cause mast cells degranulation



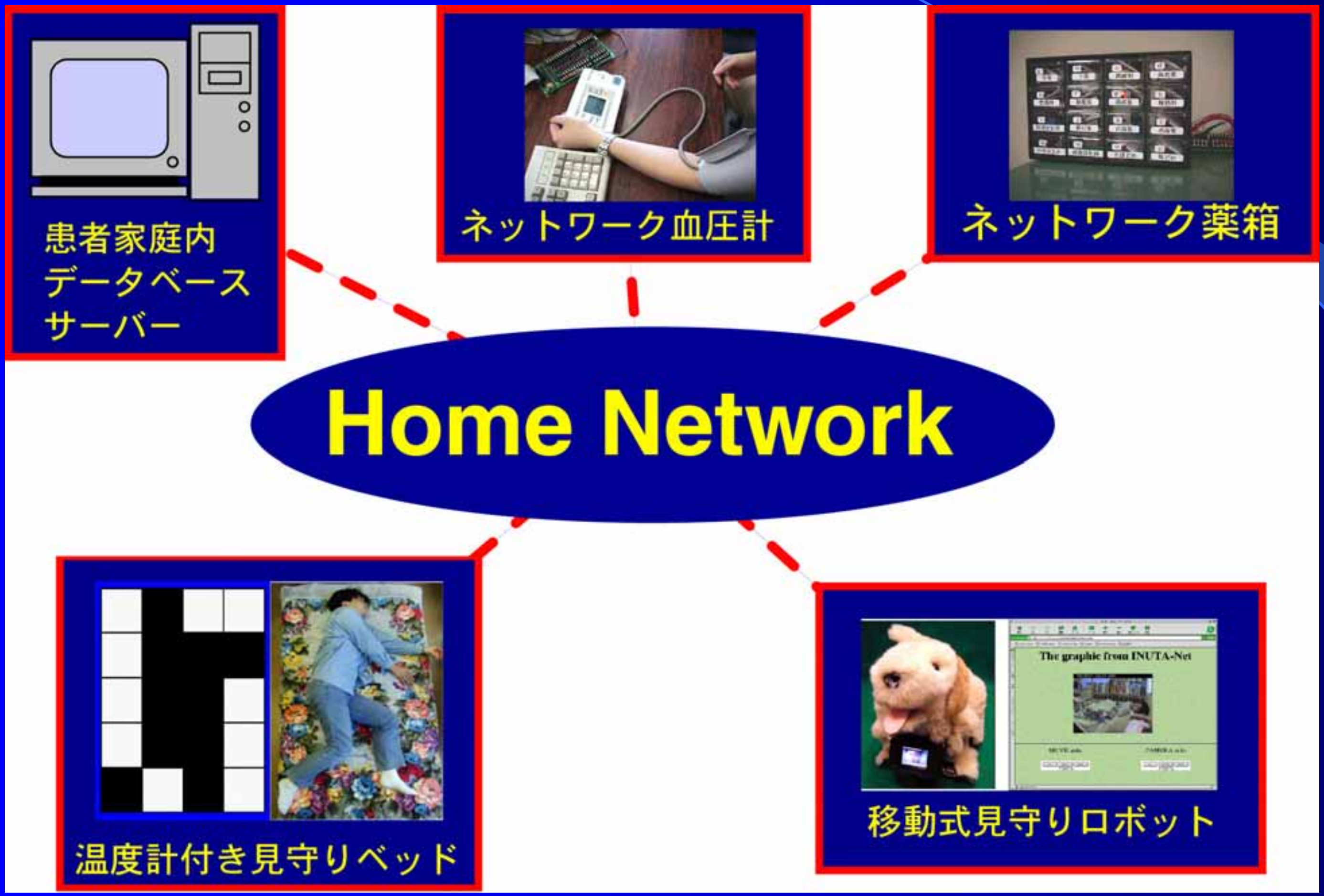
Possible Mechanism of acupuncture and meridians

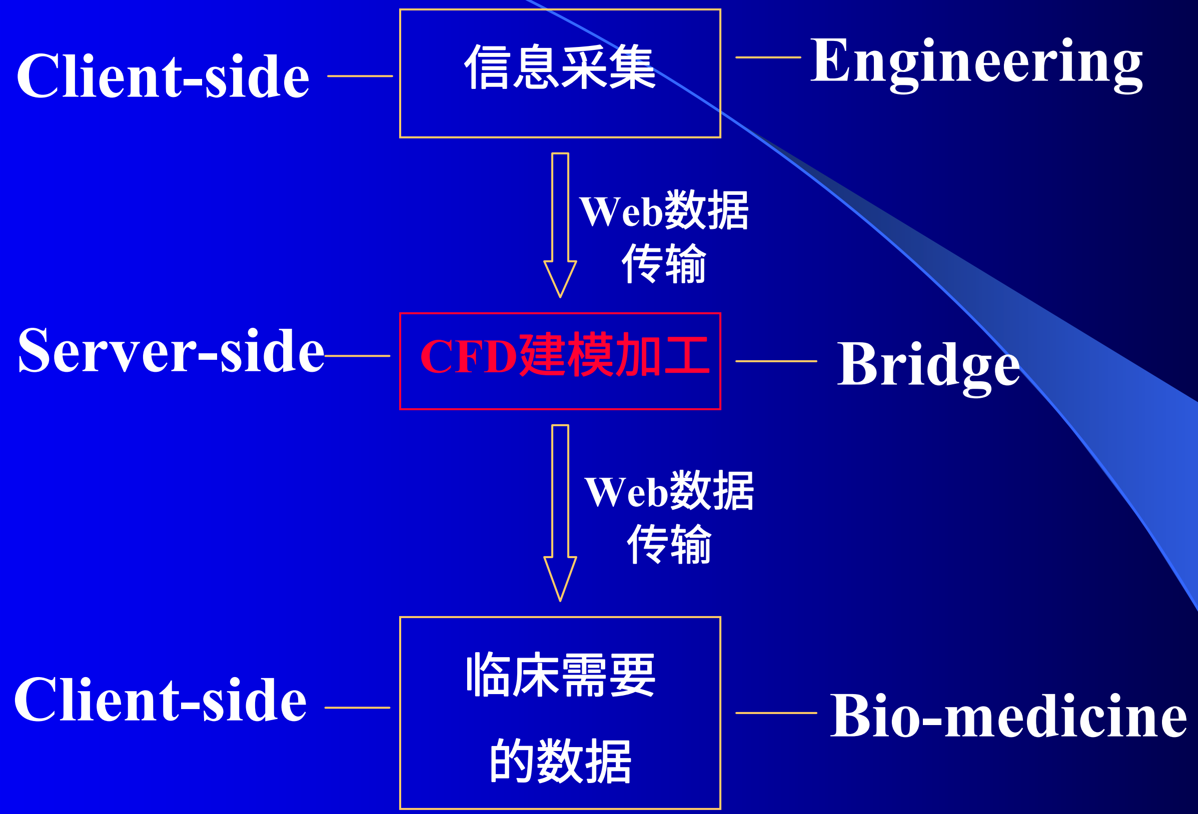


Summary

- Background
- Biomechanics *vs* Mechanobiology
- CFD in diagnosis and therapy of vascular diseases
- CFD in vascular tissue engineering
- CFD in cell mechanics
- CFD in TCM

CFD + Web


患者家庭内
データベース
サーバー
ネットワーク血圧計
ネットワーク薬箱
Home Network
温度計付き見守りベッド
The graphic from INUTA-Net
移動式見守りロボット


Client-side
信息采集
Engineering
Web数据传输
Server-side
CFD建模加工
Bridge
Web数据传输
Client-side
临床需要的数据
Bio-medicine

Thank you!