電気通信大学
脳科学ライフサポート研究センター特別講演会

平成25年5月14日

脳血流のバイオメカニクス

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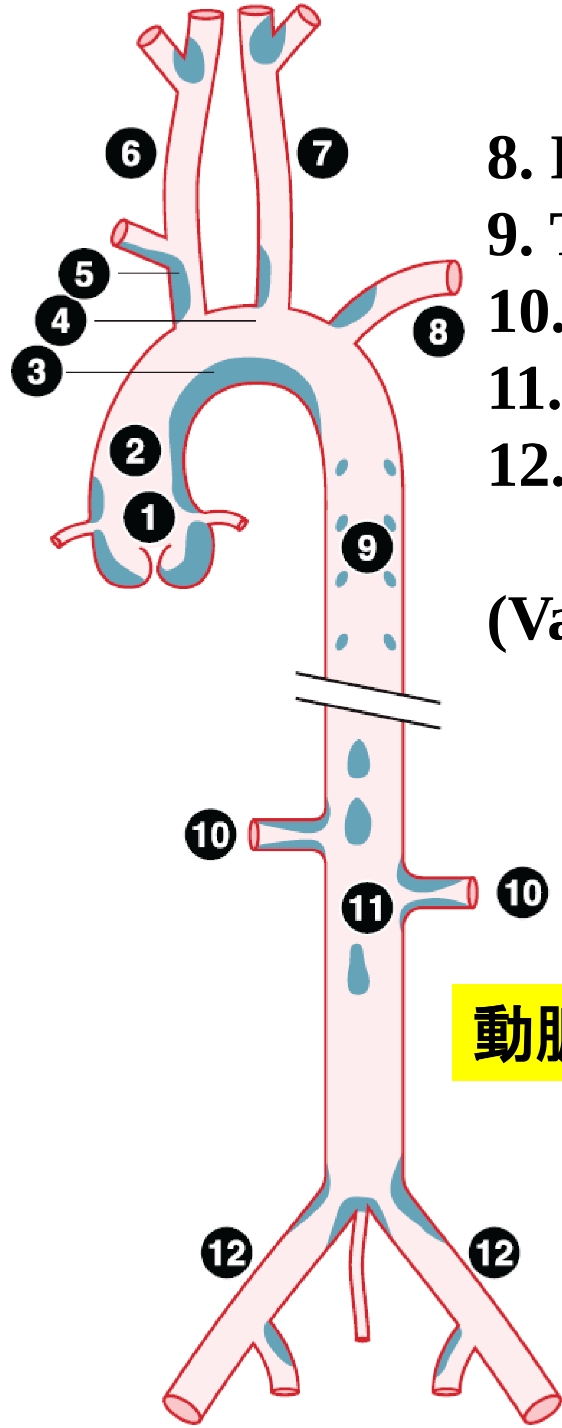
血管は単なるパイプではない

→物理現象である血流との整合性は？

Observed distribution of atherosclerotic plaques (grey shading) in the vasculatures of mice fed a high-fat diet

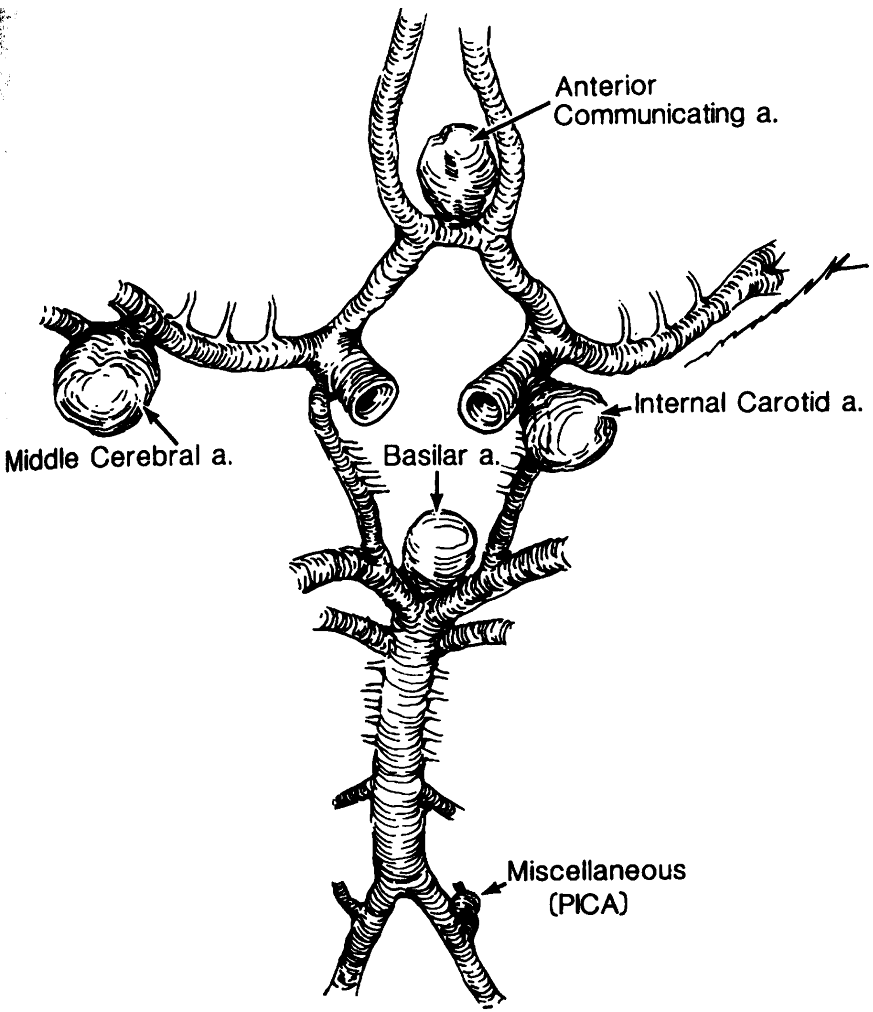
1. Aortic sinus
2. Ascending aorta
3. Inner curvature of aortic arch
4. Outer curvature of aortic arch
5. Innominate artery
6. Right common carotid artery
7. Left common carotid artery
8. Left subcravian artery
9. Thoracic aorta
10. Renal artery
11. Abdominal aorta
12. Iliac artery

(VanderLaan et al.)



動脈硬化病変の局在性

脳動脈瘤発生も好発部位が存在:血流の影響？



Schematic diagram of the frequent appearance of intracranial aneurysms within the circle of Willis.

(A.G. Osborn, 1995)

***Anterior cerebral artery: 40%**

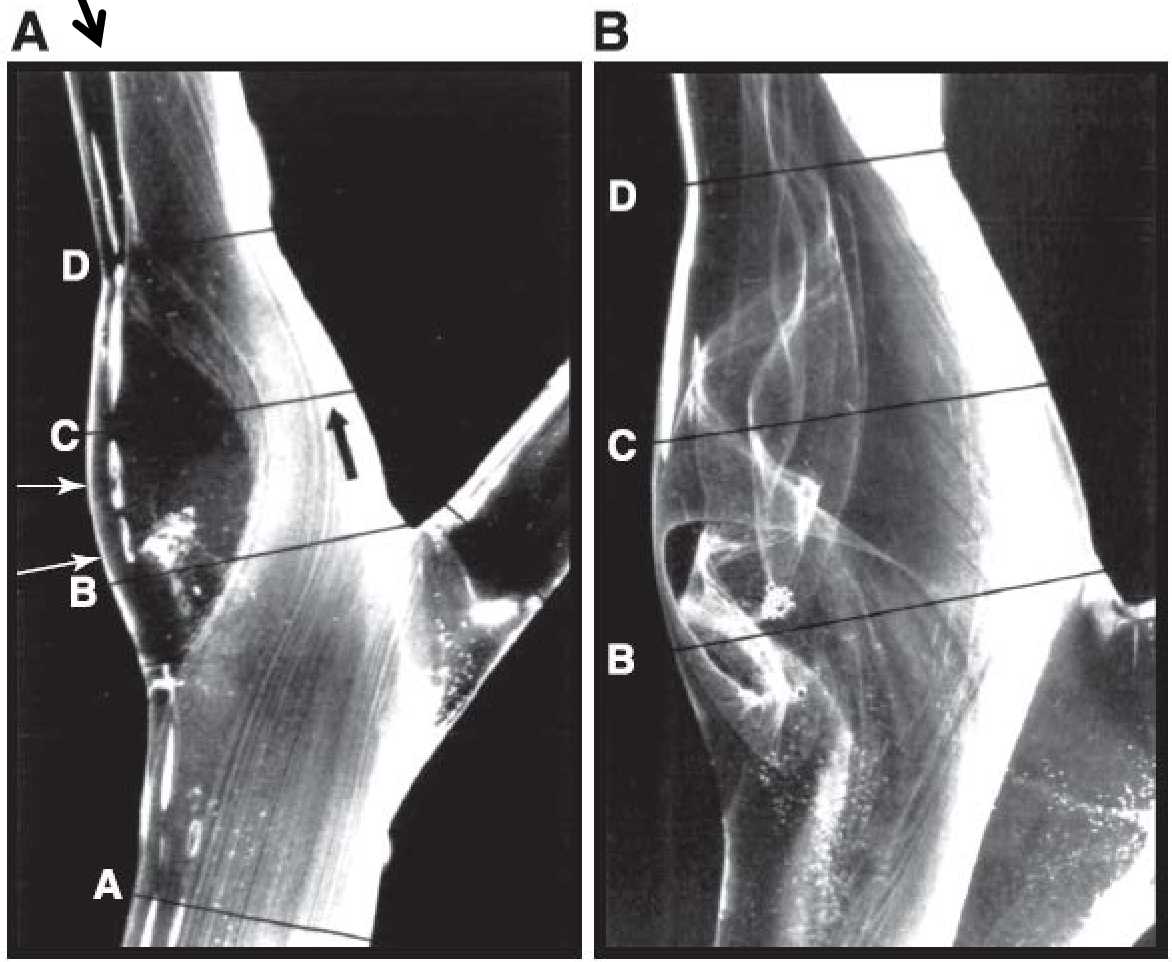
***Internal carotid artery: 30%**

***Middle cerebral artery:20%**

***Basilar artery: 10%**

Internal carotid artery

Flow separation Complex helical flow patterns occupy the separated flow region



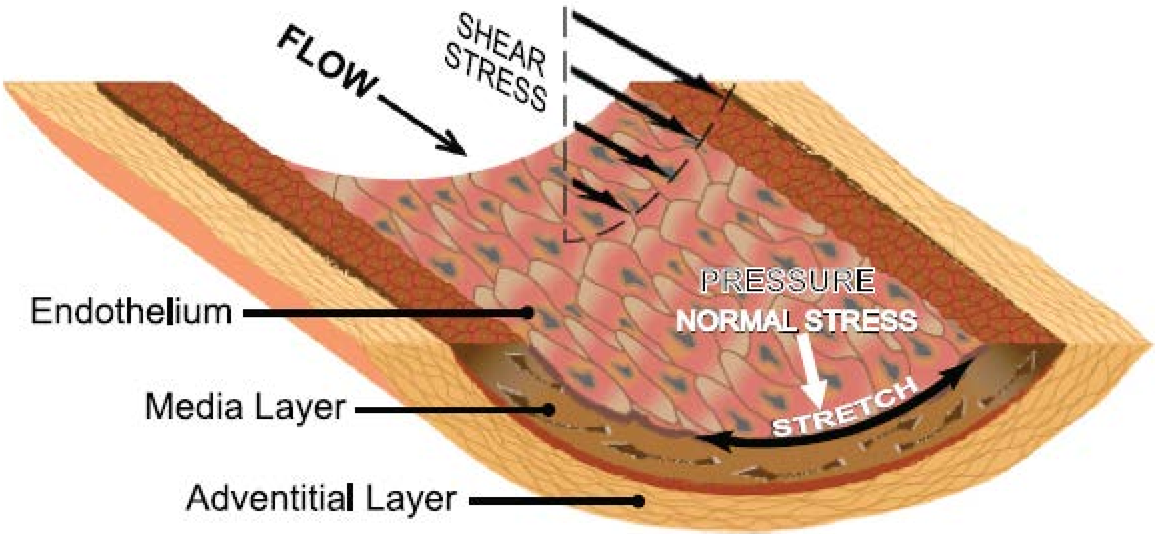
Hydrogen bubble visualization of flow in molds of carotid bifurcation. A. flow is rapid, laminar. Large area of flow separation is formed along the outer wall of the sinus Zarins et al.

Blood flow ⟷ **Pathophysiological events in the blood vessel**

physics

biology

The interface between the physics and biology is the inner surface of blood vessels: endothelial cells



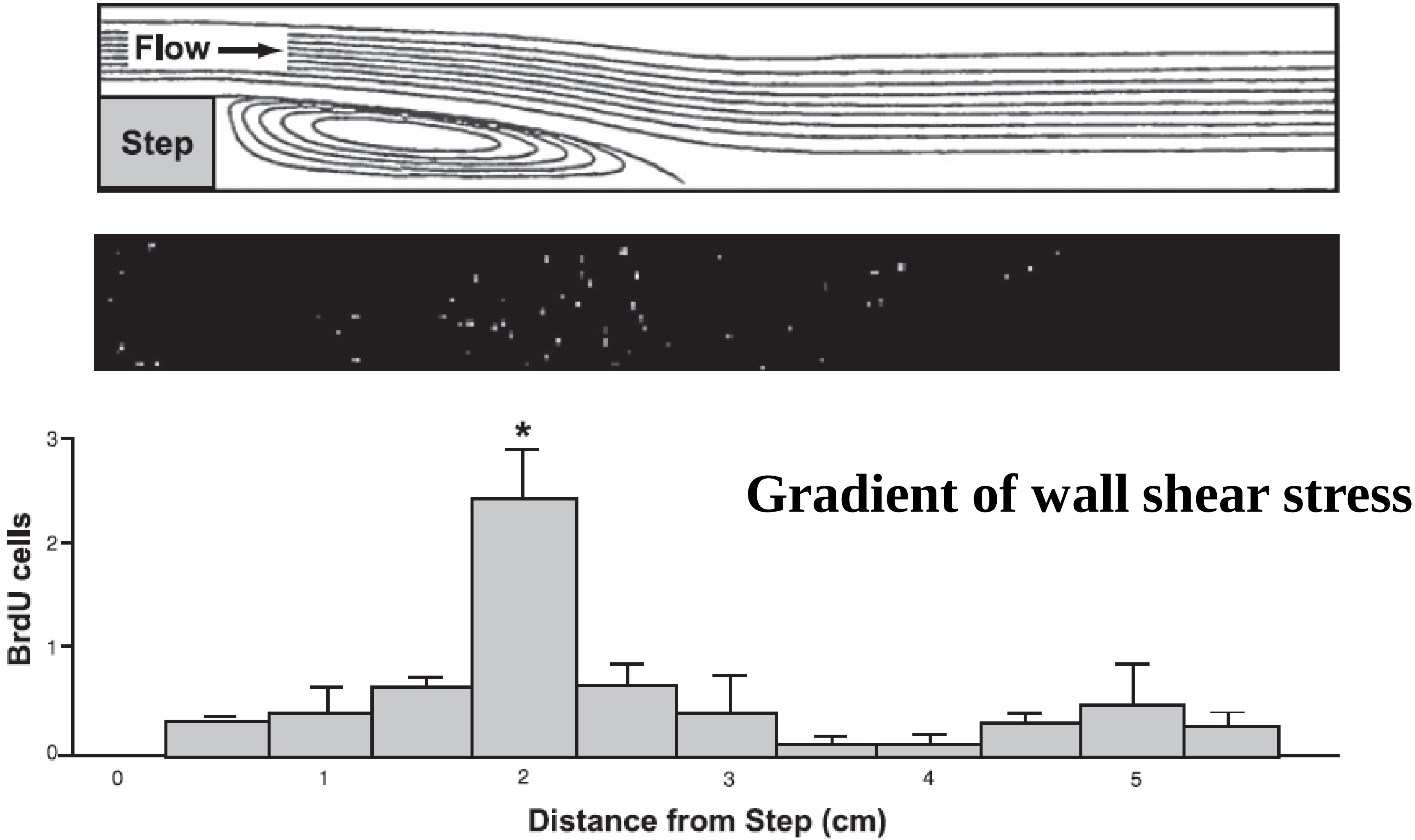
The generation of shear stress by blood flow and generation of normal stress and circumferential stretch due to the action of pressure (Shu Chien)

The plaque-prone hemodynamic flow patterns impair endothelial function in carotid arteries.

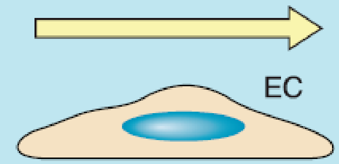
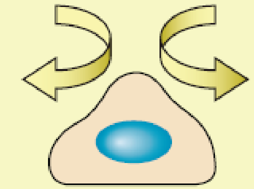
We should elucidate the role of disturbed flow pattern in endothelial function and dysfinction to get insights into mechanisms of pathophysiological processes for the prevention and management of vascular diseases resulting from atherosclrosis and thrombosis.

What is "disturbed flow"?

動脈硬化病変が生じる場所: disturbed flowが生じている？



EC proliferative rate is increased in regions of disturbed flow. The proliferation of cultured bovine aortic ECs assayed by BrdU incorporation assays is markedly elevated in the disturbed flow region near the reattachment point in the step flow channel. (Chien)

	Laminar flow / high shear stress 	Disturbed flow / low or reciprocating shear stress 
Vasoactivity	Vasodilation	Vasoconstriction
Turnover rate	Low	High
Macromolecular permeability & LDL uptake	Low	High
DNA synthesis	Low	High
Morphology	Elongated & aligned	Polygonal
Expression of adhesion molecules, inflammatory & chemokine genes	Low	High
Expression of antioxidant genes	High	Low
WBC adhesion and platelet aggregation	Inhibition	Promotion
Oxidative stress/ROS	Low	High (Sustained)
VSMC activation	Low	High
Wound repair: Endothelization	Promotion	Retardation
Heterogeneity	Low	High
Fibronectin/fibrinogen deposition	Low	High
Atherosclerosis & thrombosis	Prevention	Promotion

Effects of different flow patterns and associated shear stresses on endothelial and vascular biology. (Shu Chien)

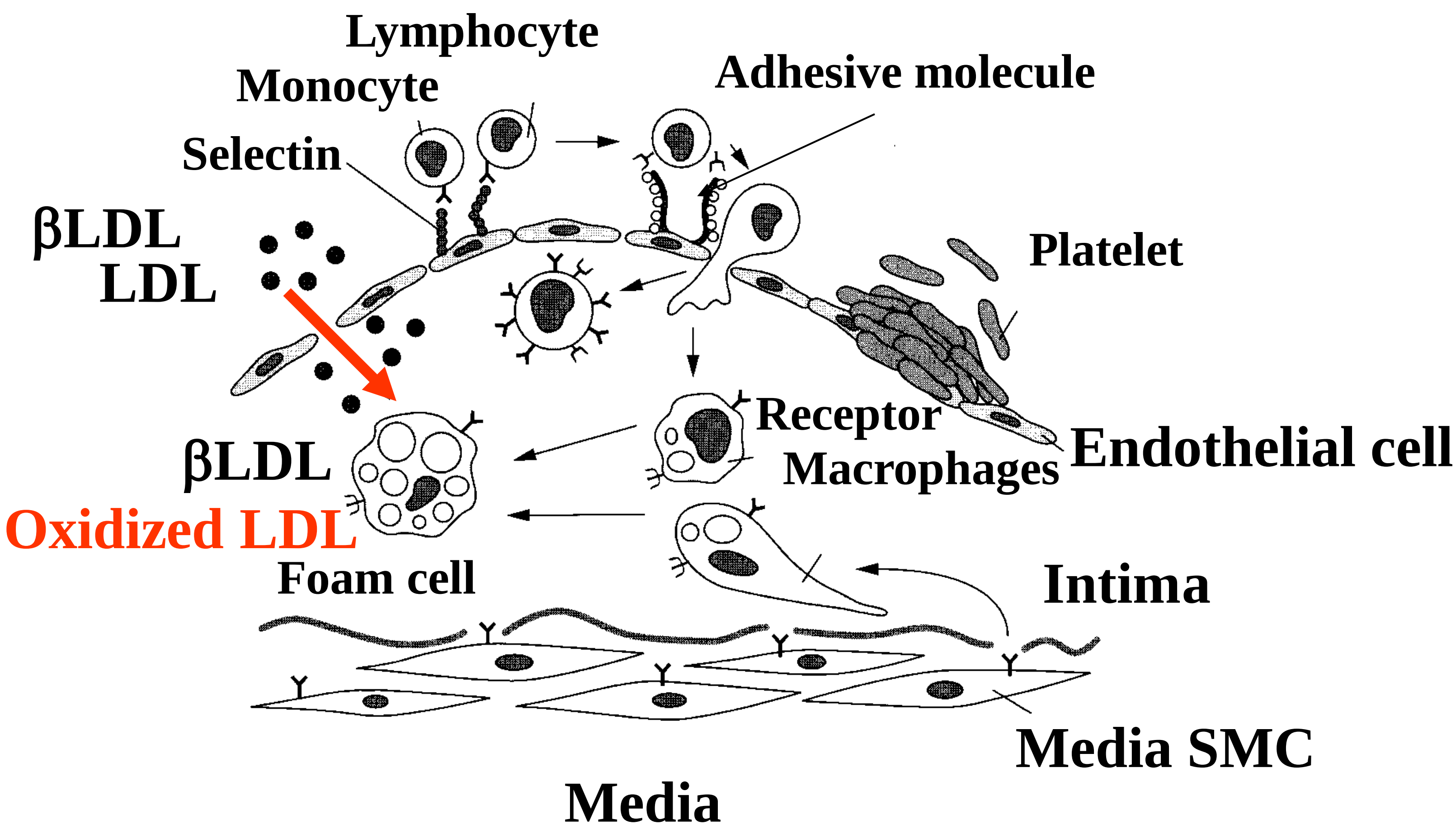
血管は流れの状態を感知している

血行力学説(hemodynamic hypothesis)

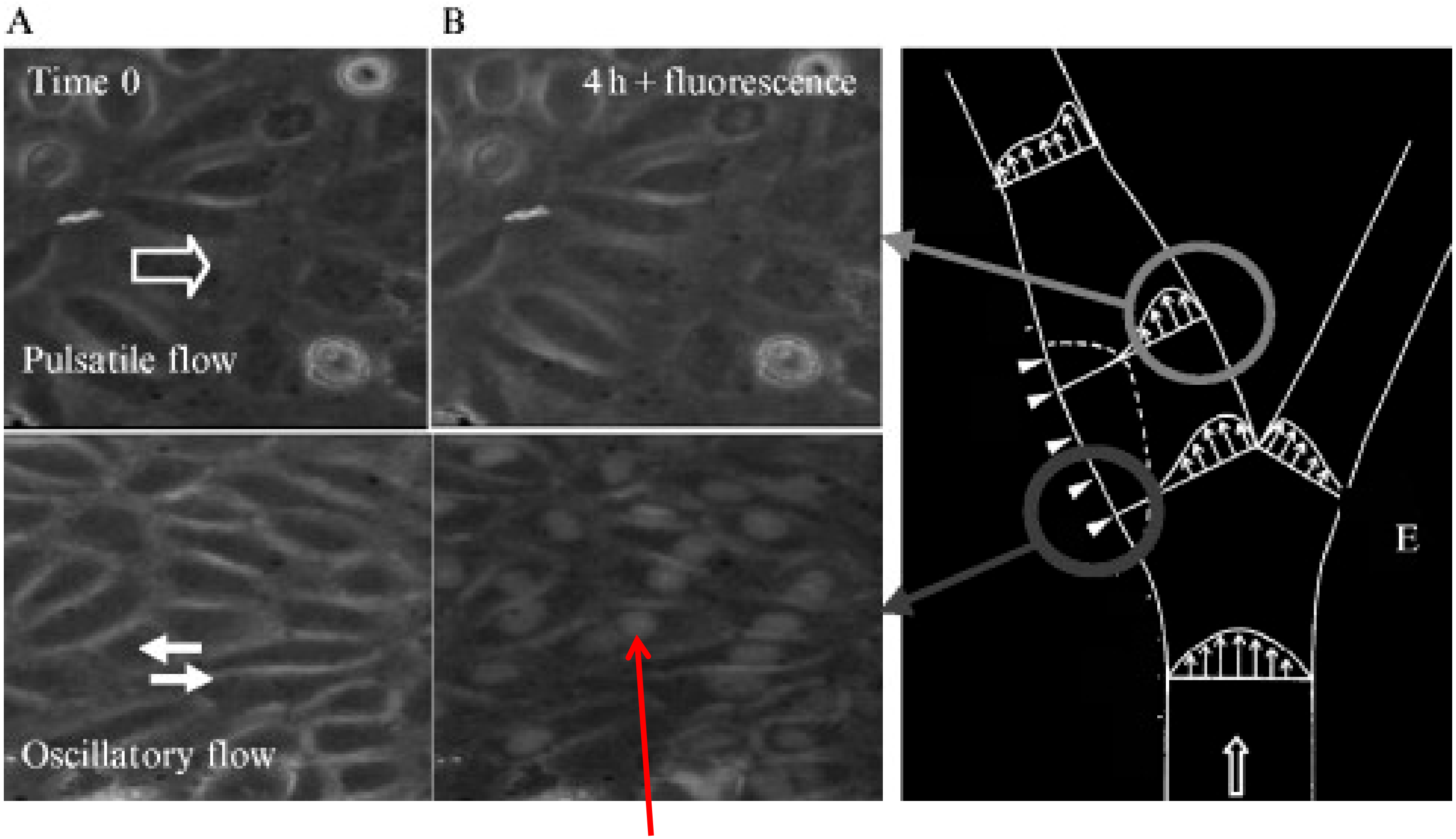
→血流からの流体力とアテロームの発生とを結び付ける考え方

The formation of atheroma is strongly associated with the blood flow. This is referred to as the hemodynamic hypothesis.

Molecular Hypothesis of Atherosclerotic lesion formation (Ross)



Ross, R., Nature (1993)



Real time $O2^-$ production at 4h with oscillatory flow
Mahsa Rouhanizadeh et al. (2008)
振動流において、活性酸素が生じている事を蛍光で同定。
核が白く見える部分が活性酸素が生じている場所。

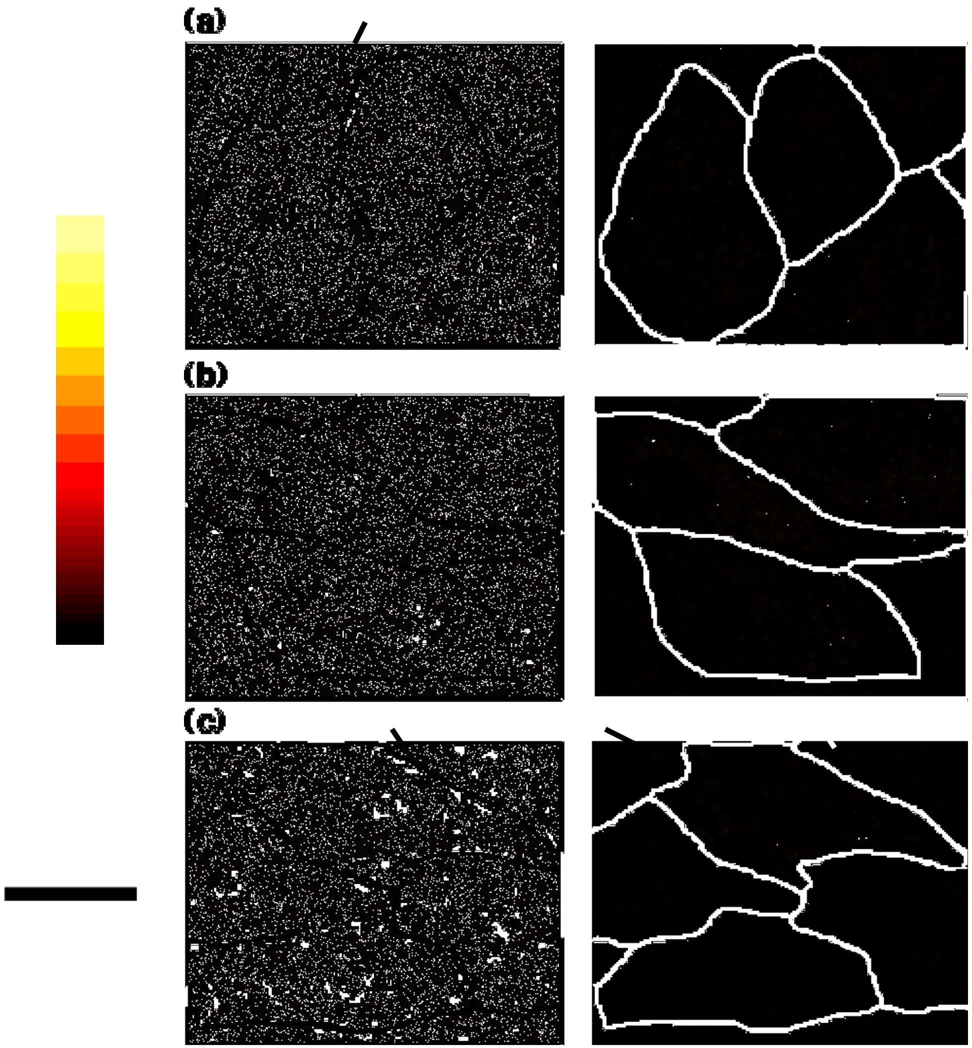
The disturbed flow is the condition of

- **Low shear stress**
- **Oscillating shear**

which is prone to initiate thevascular disease.

Shear stimulus affects the cell functions

Albumin uptake intothe cells depends on the shear stress stimulus



The amount of albumin uptake is determined by the fluorescent intensity in the images

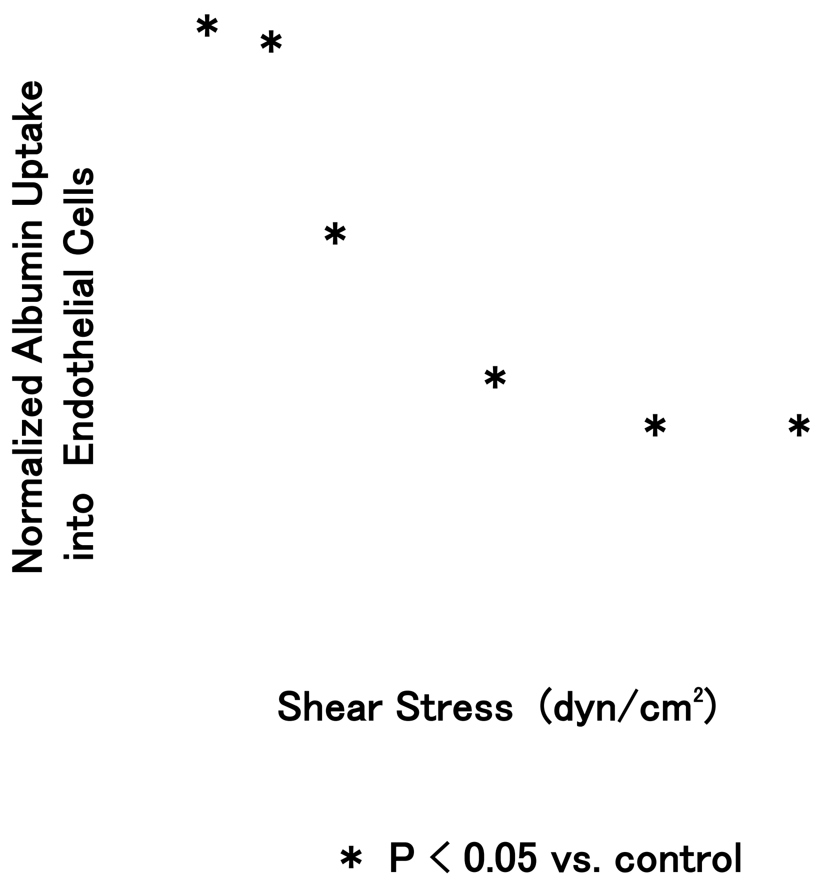
(a) without flow

(b) Shear stress = 1 Pa

(c) Shear stress =6 Pa

Bar = 20 μm

Shear dependency of albumin uptake into the cells



Normalized albumin uptake as a function of imposed shear stress (Kudo, Tanishita et al. Trans. JSME, 1998)

Shear stress effect on mitochondrial membrane potential

JC-1

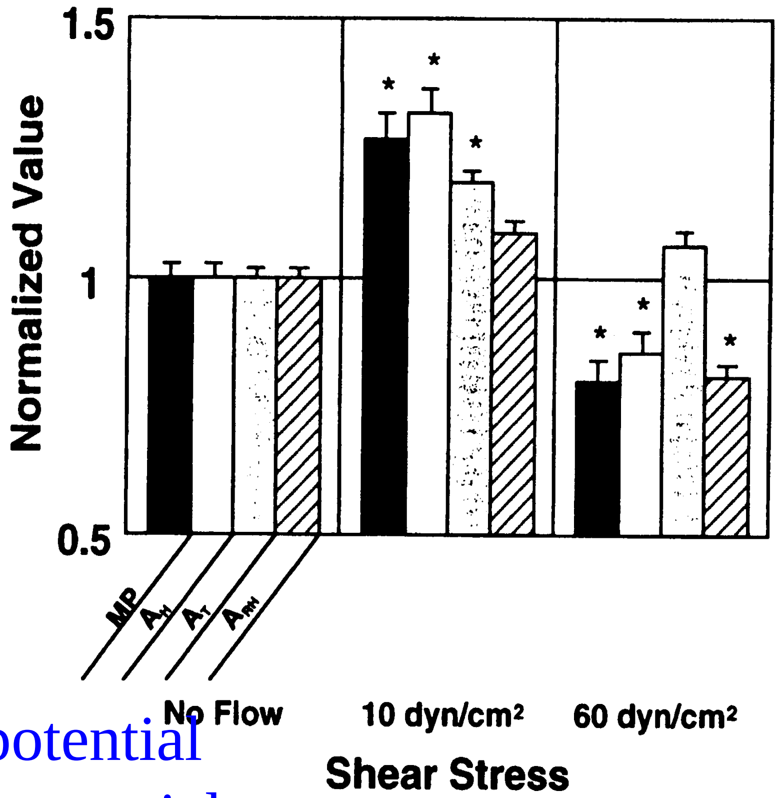
Low membrane potential

: green fluorescence emission

High membrane potential

: red fluorescence emission

Fluorescence was detected by Confocal laser scanning microscope.



MP: Mitochodrial membrane potential

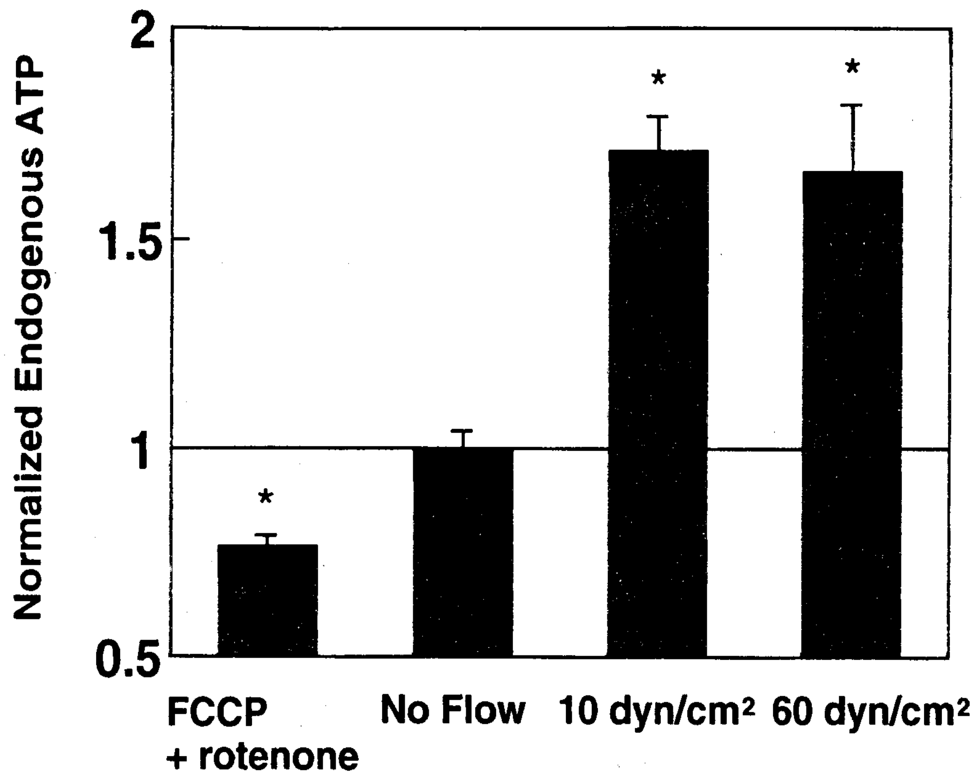
A_H: Area of higher membrane potential

A_T: Total area of mitochondria

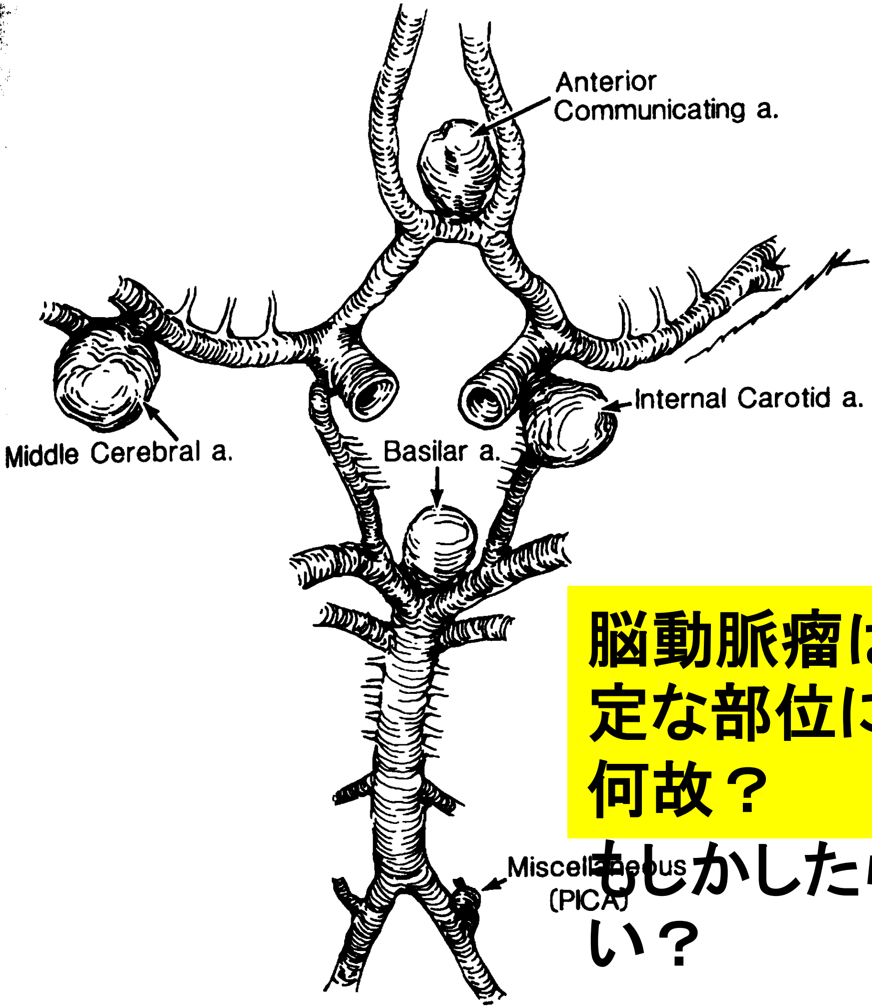
A_R: A_H/A_T

Kudo et al. BBRC (2000)

Endogeneous ATP depends on the imposed shear stress stimulus



The favorite sites of cerebral aneurysm



Schematic diagram of the frequent appearance of intracranial aneurysms within the circle of Willis.

(A.G. Osborn, 1995)

***Anterior cerebral artery: 40%**

脳動脈瘤は局所的に特定な部位に発生している。何故？

もしかしたら血流のせい？

***Basilar arter**

UCLA　Prof. Vi

Possibility of rupture of cerebral aneurysm

Cerebral aneurysm

Rupture（0.05-1%）　　**Unrupture (more than 99 %)**

Observation

Neurosurgical intervention　　**Endovascular embolization**

High morbidity & mortality　　**No long-term efficacy**

Aneurysms without possibility of rupture should not be treated.

What is a predictor (risk factor) for rupture?

N.Engl J Medicine (1998)

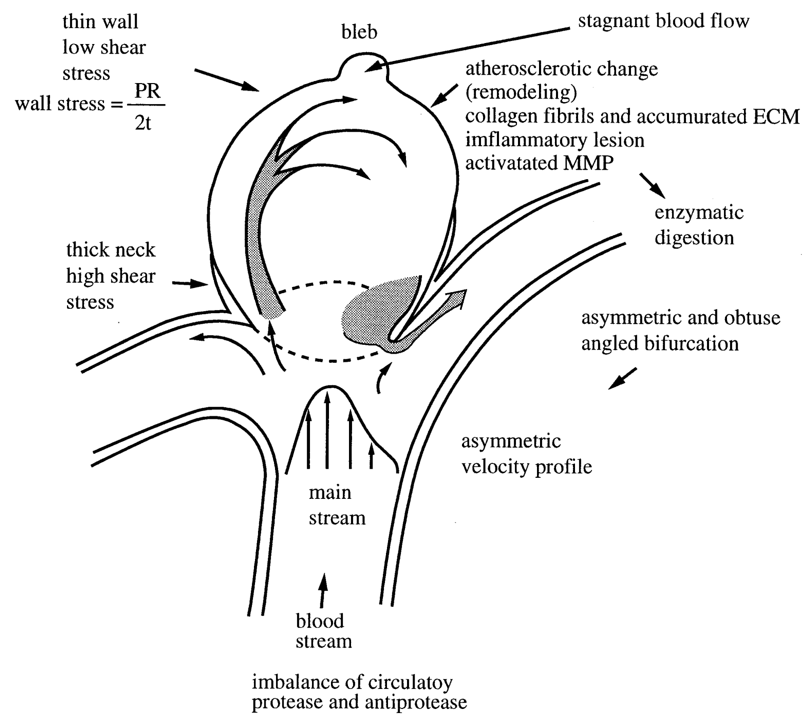
The patterns of intra-aneurysmal flow

The intra-aneurysmal flow consists of

***inflow: position and size of the neck and flow ratio into the distal branches**
***circulating flow: aspect ratio (depth / neck width)**
***outflow: usually nonpulsatile and low velocity**

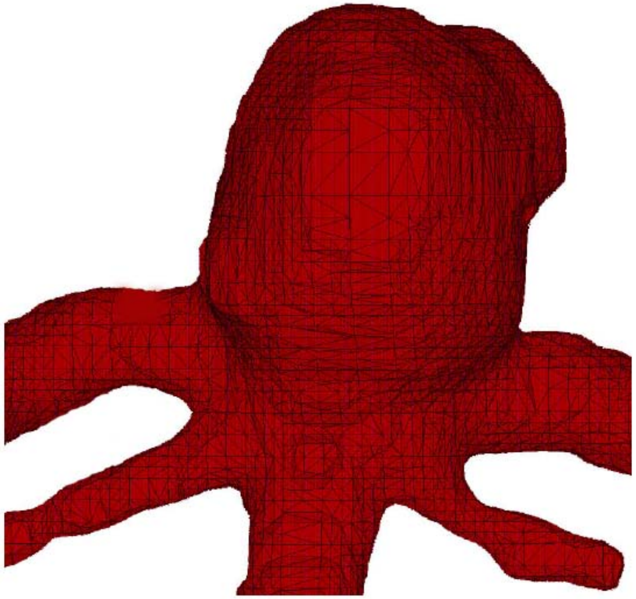
Ujiie et al. recognizes that the intrra-aneurysmal flow is determined by the aspect ratio, rather than the aneurysmal size.

Ujiie et al. Neurosurgery (1999)



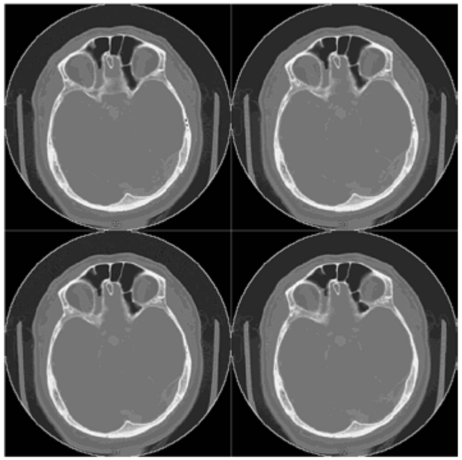
Necessity of prospective study based on the anatomically realistic models

The knowledge of intra-aneurysmal flow in the realistic models are required to ensure the hemodynamic hypothesis

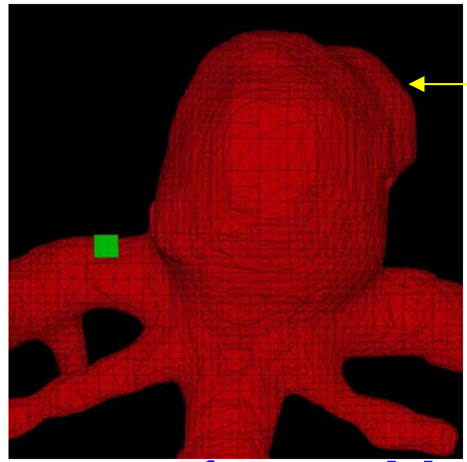


Tateshima et al., J. Neurosurg. (2001)
This study received the award of MAGNA CUM LAUDE CITATION from the American Society of Neuroradiology in 2001.

Reconstruction of Cerebral Aneurysm



CT images



bleb

3D Surface Model

Epoxy Resin Model

- Abstraction of the vessel wall
- Piling up
- Smoothing

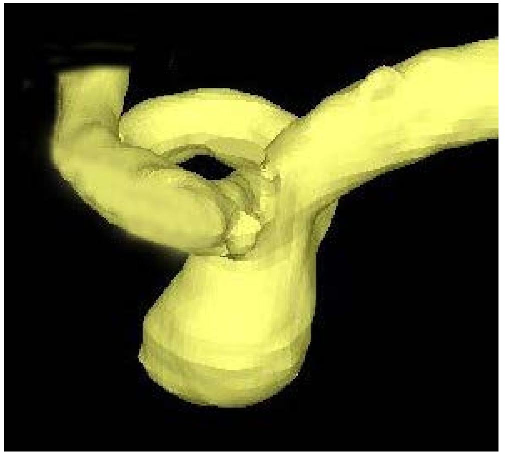
- Photoforming method
- Magnification (×2.6)

<u>Features of the morphology</u>

- Asymmetrical shape of the aneurysm
- Presence of a bleb (daughter aneurysm)

Realistic models of cerebral aneurysm cases

Model 1



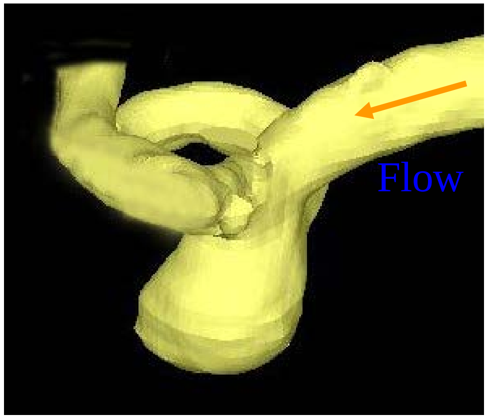
- Unruptured
- Middle cerebral bifurcation aneurysm
- Aneurysm size = 6.3mm
- Neck size = 5.7mm
- With a bleb

Model 2

- Ruptured
- Middle cerebral bifurcation aneurysm
- Aneurysm size = 4.7 – 7.7mm
- Neck size = 4.3mm
- With a bleb

(from Dept. of Radiological Science, UCLA)

Vector diagrams in the middle cerebral artery (unruptured case)



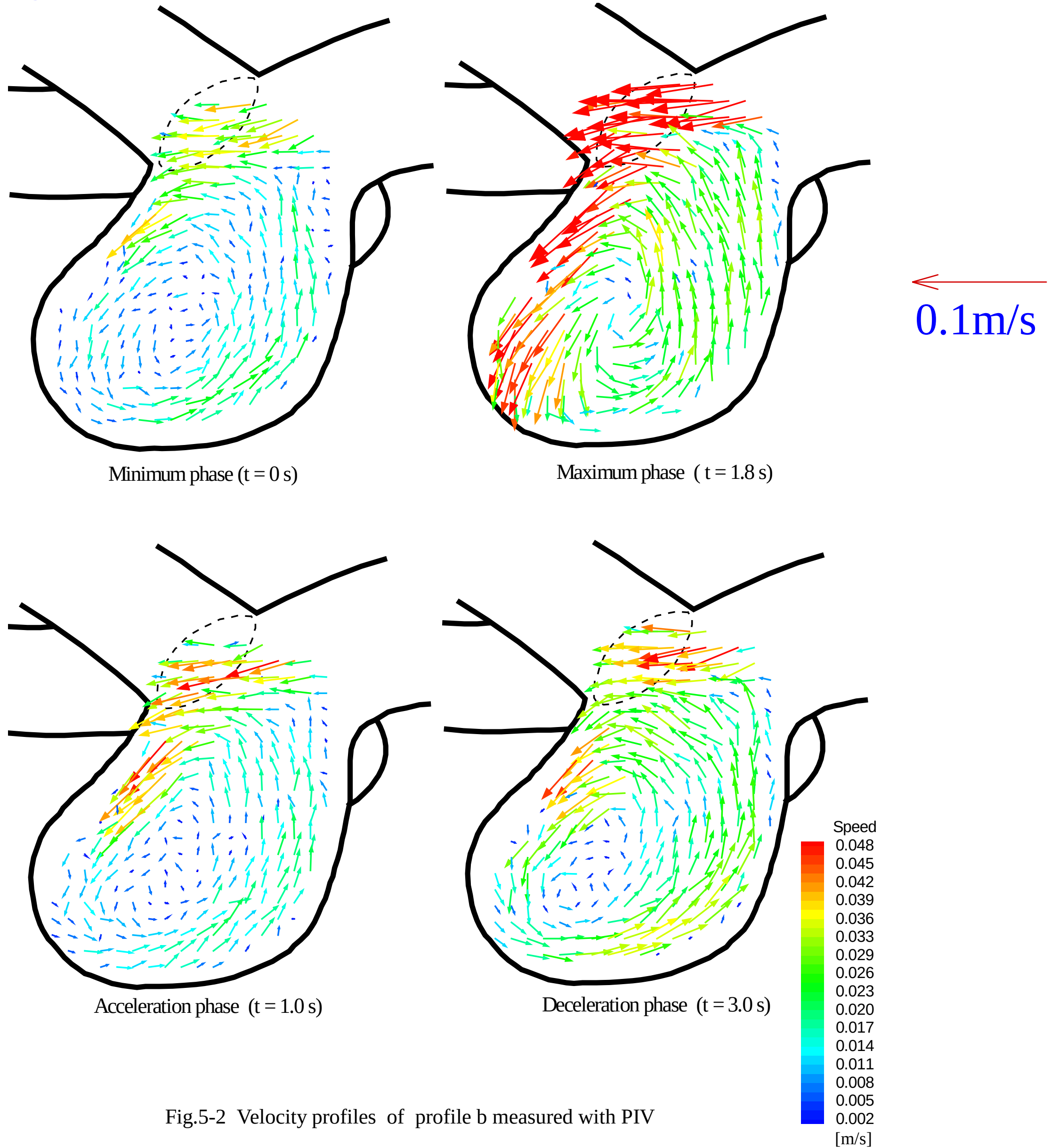
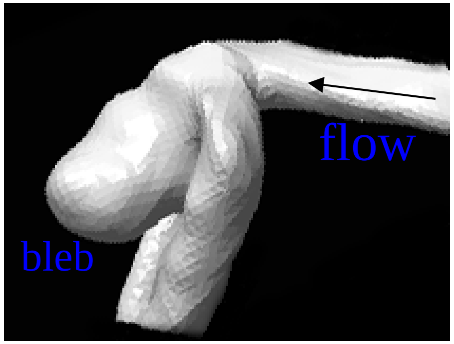
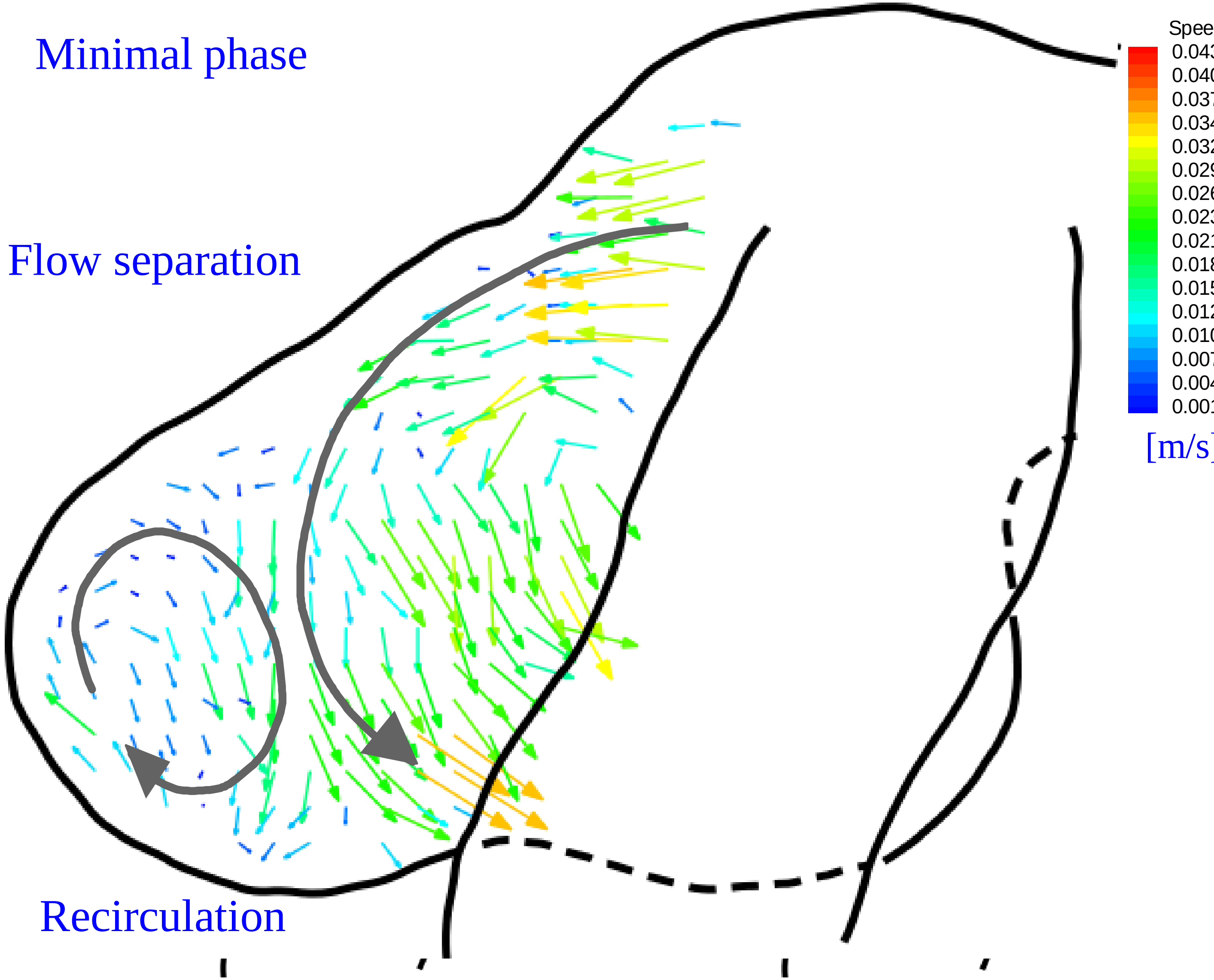


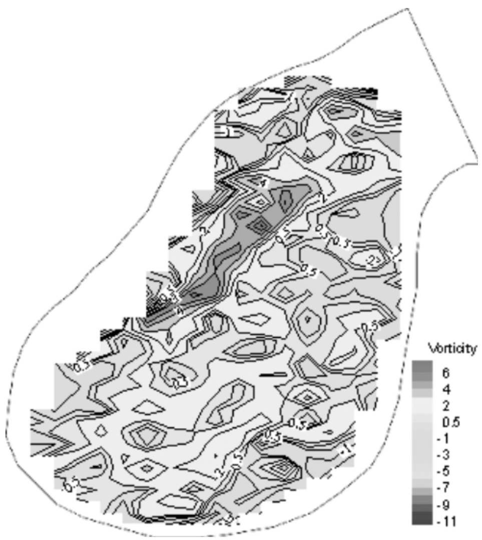
Fig.5-2 Velocity profiles of profile b measured with PIV

Vector diagrams in the middle cerebral artery aneurysm (ruptured case)





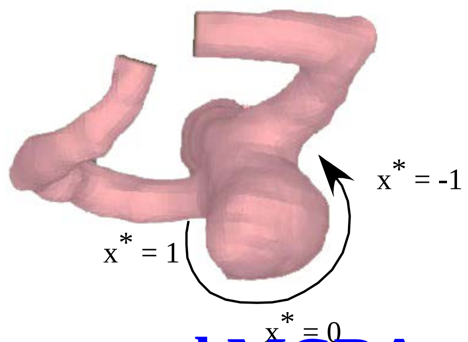
Distribution of vorticity in aneurysm

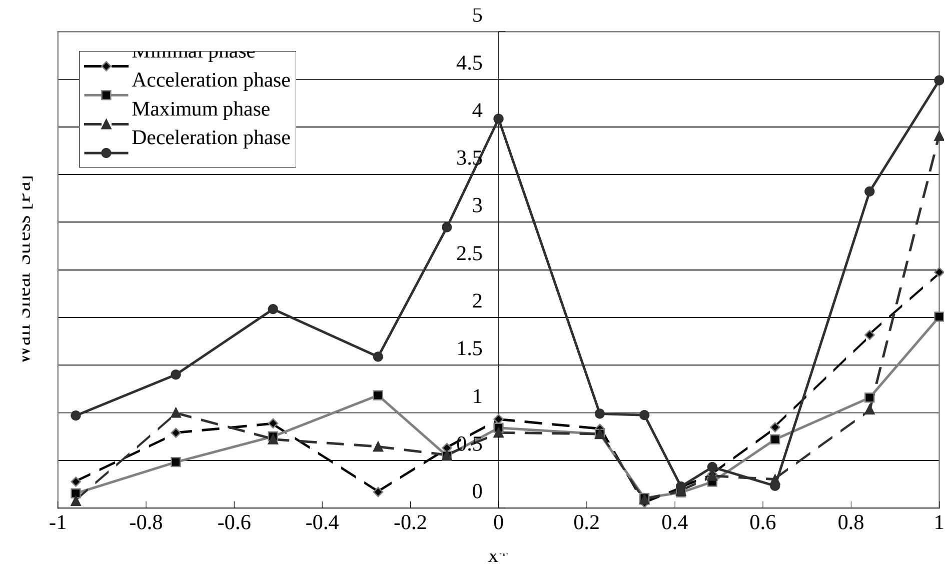


a) Unruptured MCBA

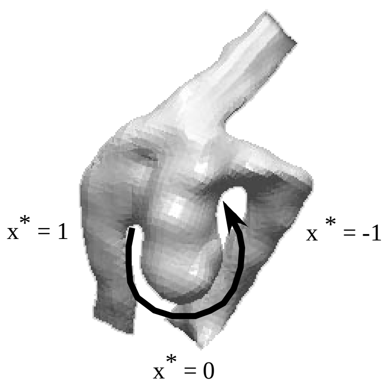
b) Ruptured MCBA

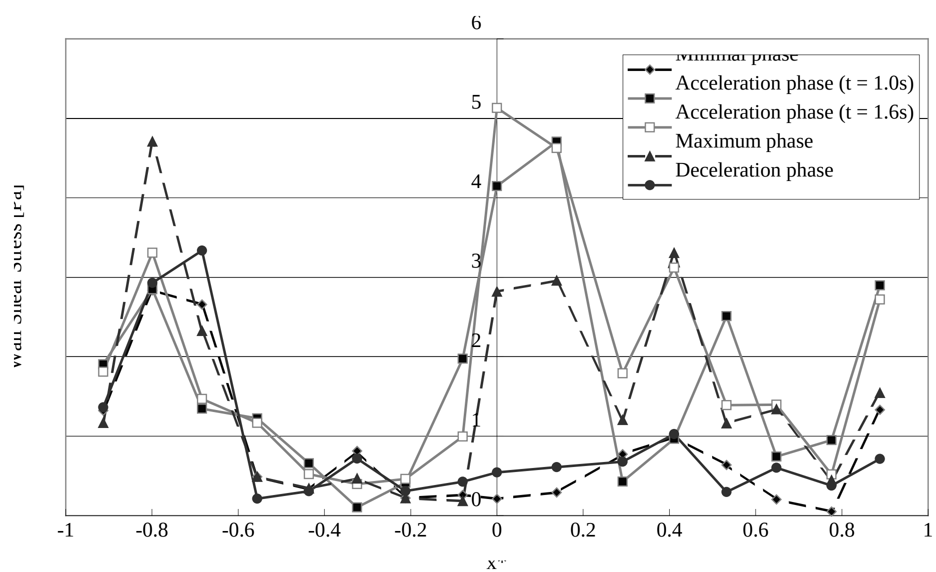
Wall shear stress profiles obtained by LDV





Unruptured MCBA



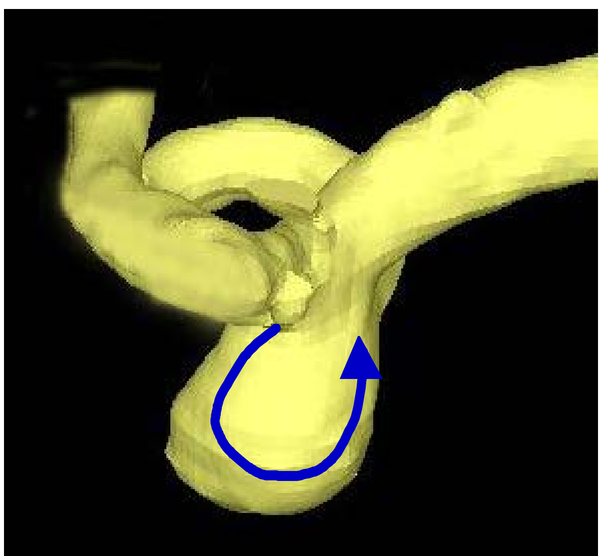


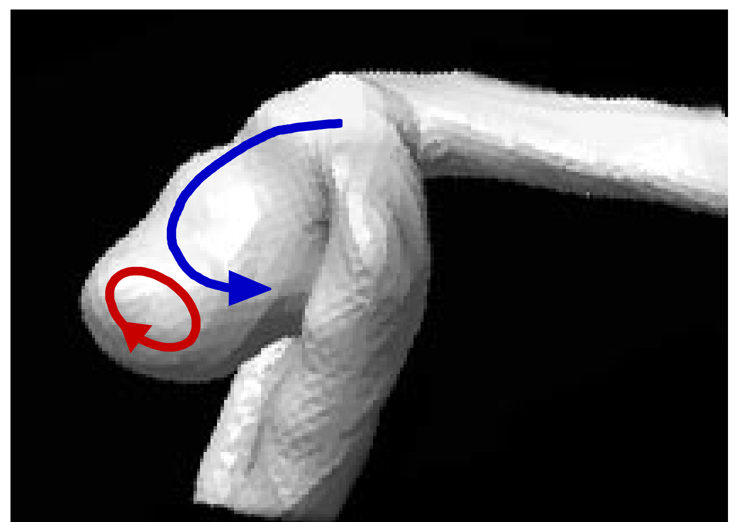
Ruptured MCBA

What is the difference between ruptured and unruptured cases?

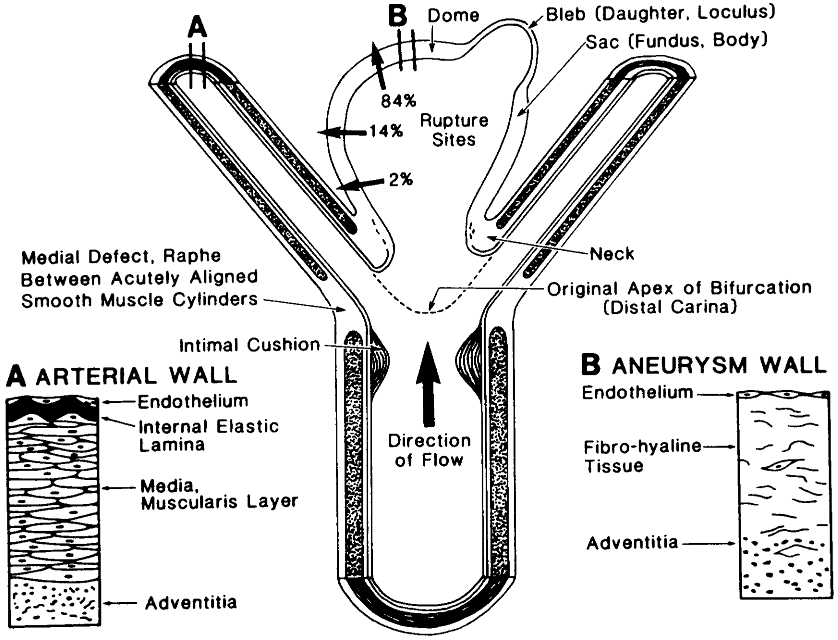
MCBA (unruptured)
V_{inflow} = 80-90% of V_{max}
Aspect ratio = 1.0
Area ratio = 2.0
Single circulation

MCBA (ruptured)
V_{Inflow}: = 70-80% of V_{max}
Aspect ratio = 1.8
Area ratio = 2.1
Bleb:Recirculation
Peaked WSS





The internal elastic lamina is absent.



The pathology of intracranial arterial saccular aneurysms indicates that the aneurysmal sac lacks normal layers. Particularly the internal elastic lamina is usually absent or reduced to fragments.

Weir and Macdonald, in Neurosurgery, 1996, McGraw-Hill

Treatment by intravascular surgery

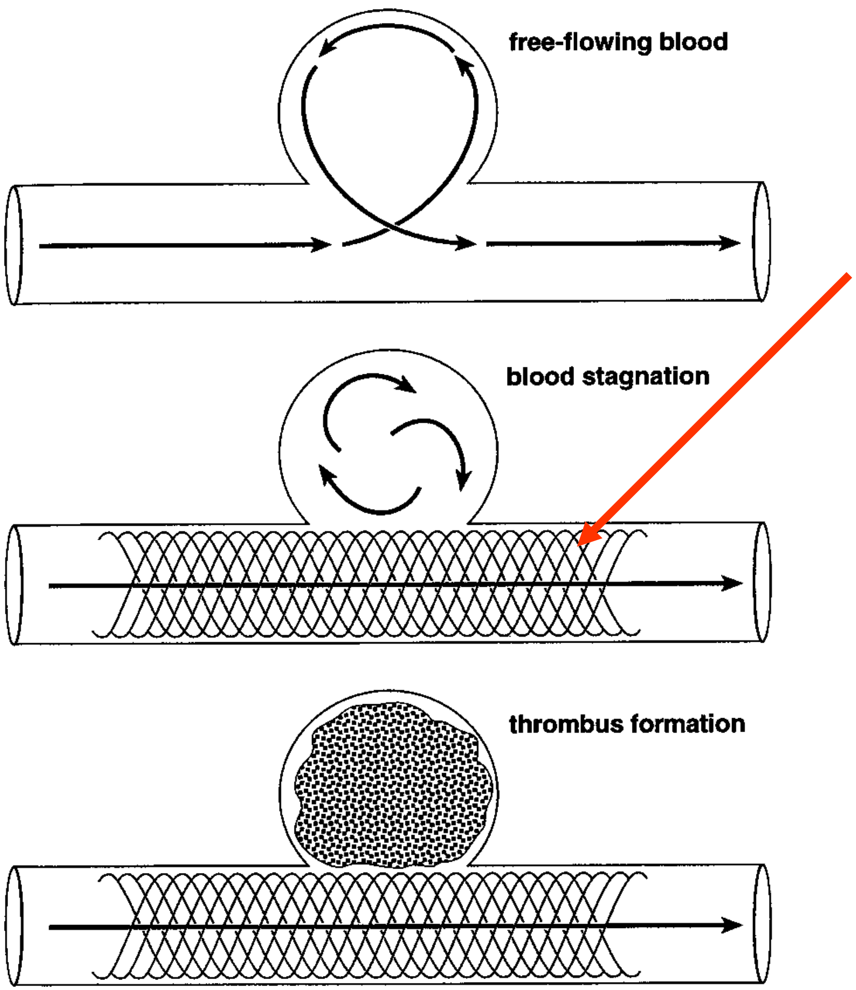


FIGURE 6.19. Schematic diagram representing the general biophysical interactions exerted by an intravascular stent on the hemodynamics.

Use of Intravascular stent

The thrombus formation is induced by making the flow stagnant in the aneurysm.

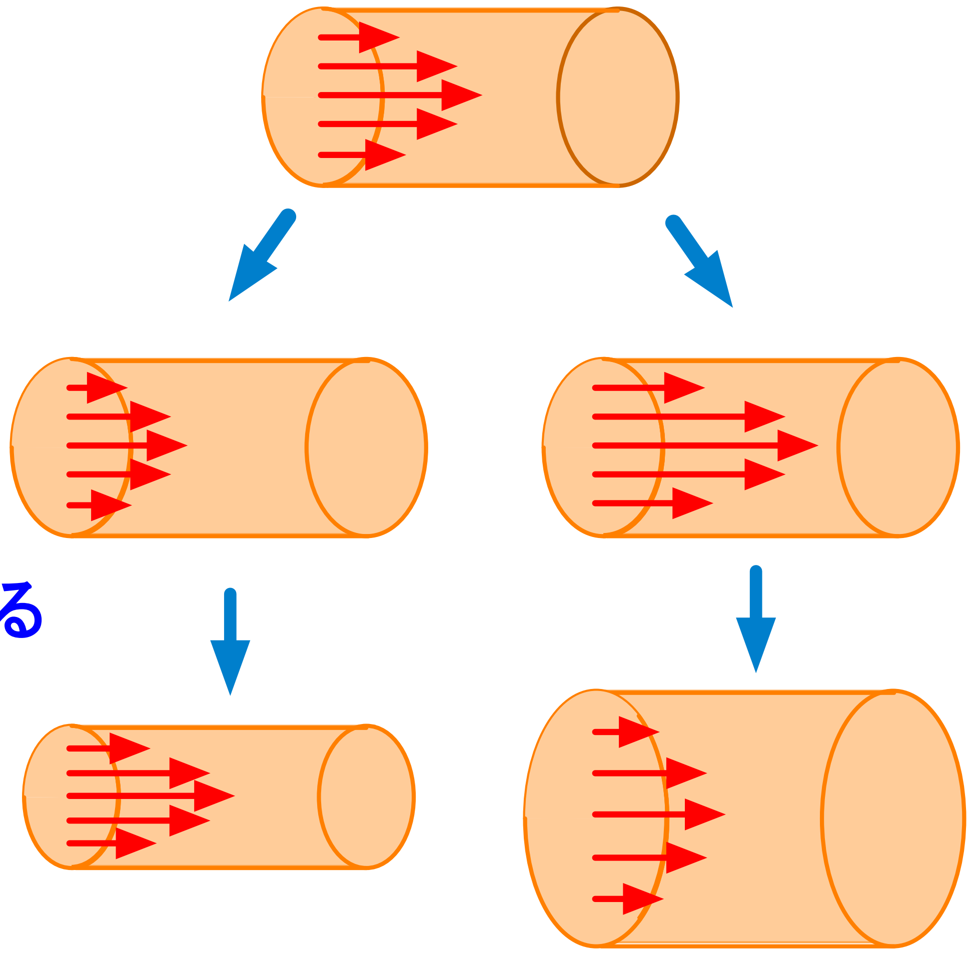
Hademenos, G.J and Mssoud, T.F., (1998)

Intravascular surgery is quite promising and related technology will be developing rapidly.

微小血管内の血流

実際の臓器における検証が重要

細動脈における血管のリモデリング

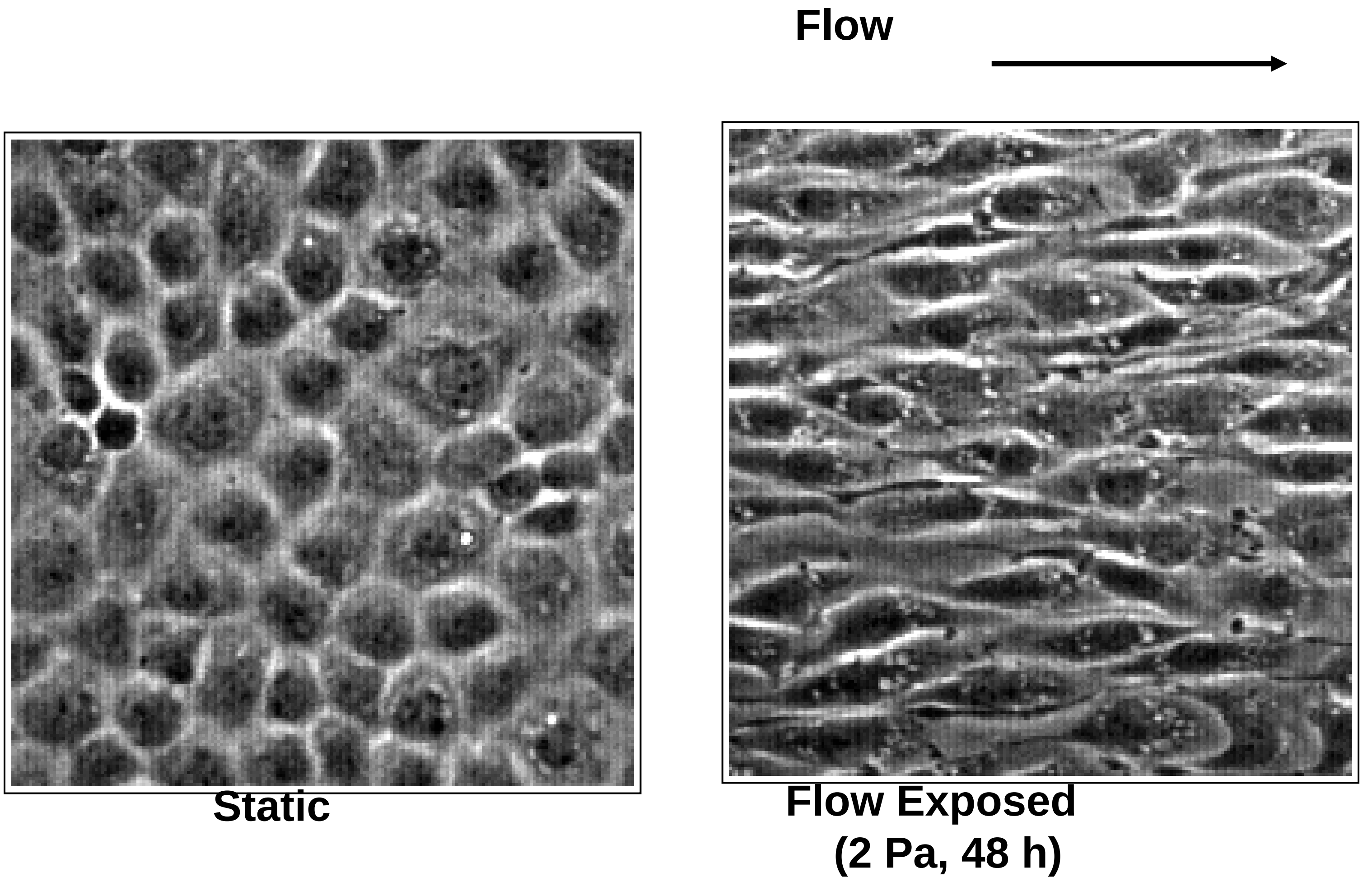


血流が減ると
血管が細くなる

血流が増える
と
血管が太くなる

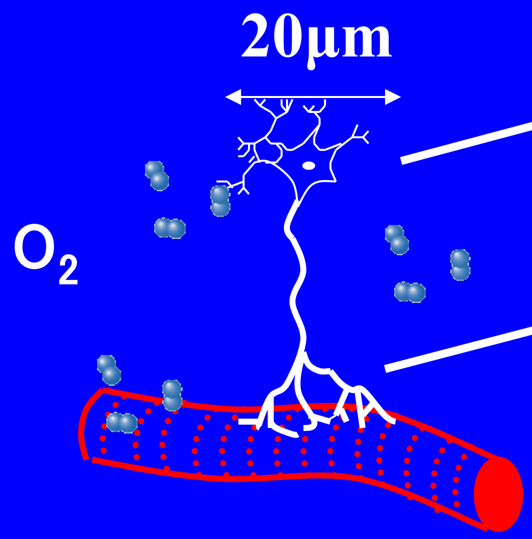
血管の径が血流量の変化によって変わる
⇒血流を感ずるセンサーがあるはず

Shape change of endothelial cell due to shear stress



ブタの内皮細胞を培養して、48時間流れの刺激を与えた

Oxygen is delivered to brain by the blood flow.

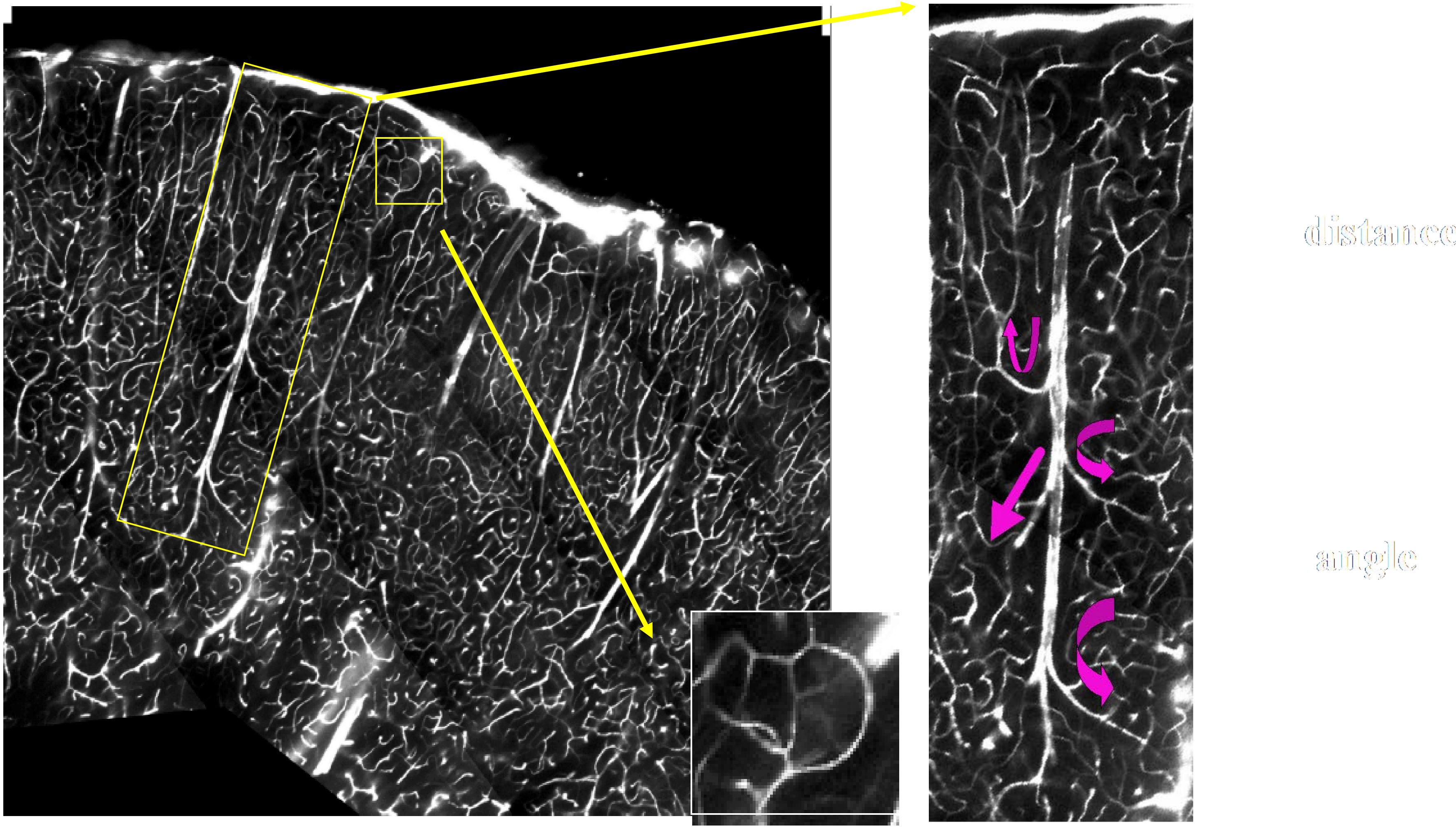


Increase of oxygen consumption due to the increased activity

Increase of oxygen delivery due to the increased blood flow

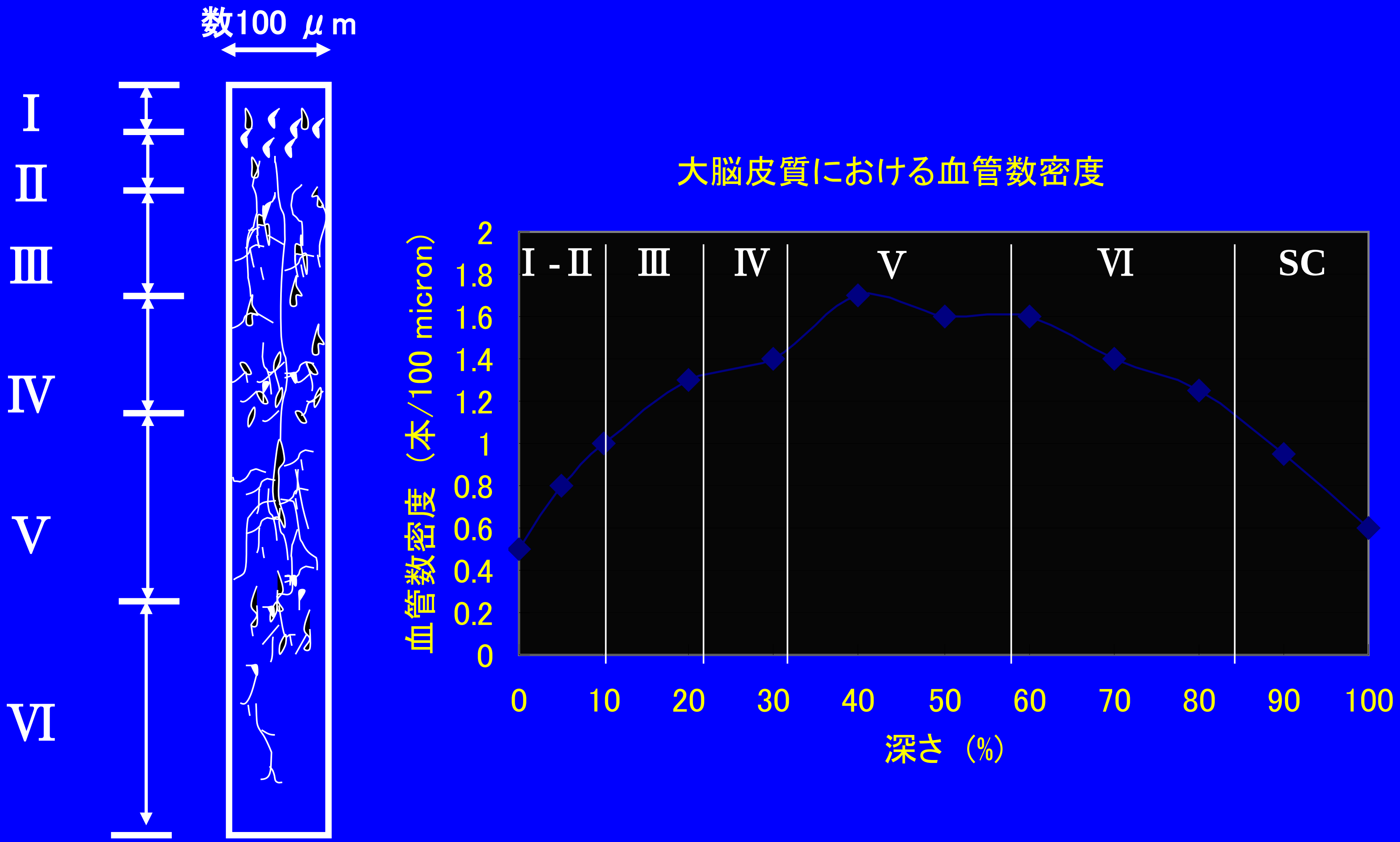
Minimal reserves of oxygen and glucose are stored in the brain, so that failure of delivery of either will quickly result in energy depletion.

That is why we need to know the oxygen transfer related to the hemodynamics in the brain.



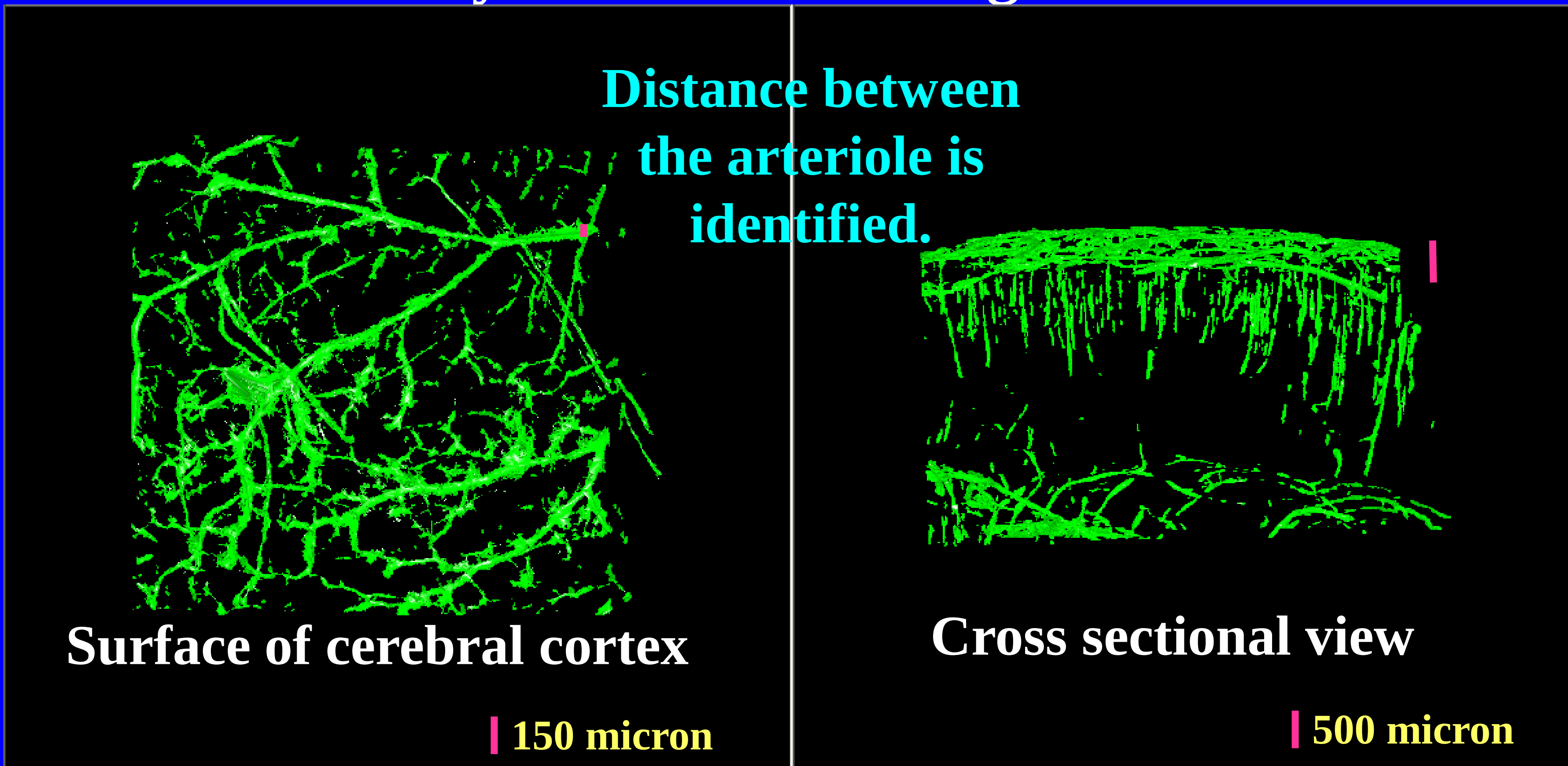
The bifurcating geometry and density of capillary network

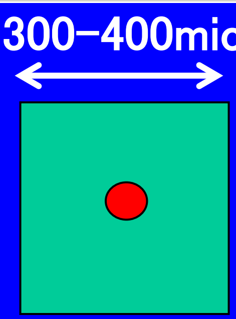
Density of capillary network in the each layer



K. Masamoto, K. Tanishita, et al. *Brain Research* (2004)

Estimate of module unit by 3D structure reconstructed by surface rendering.

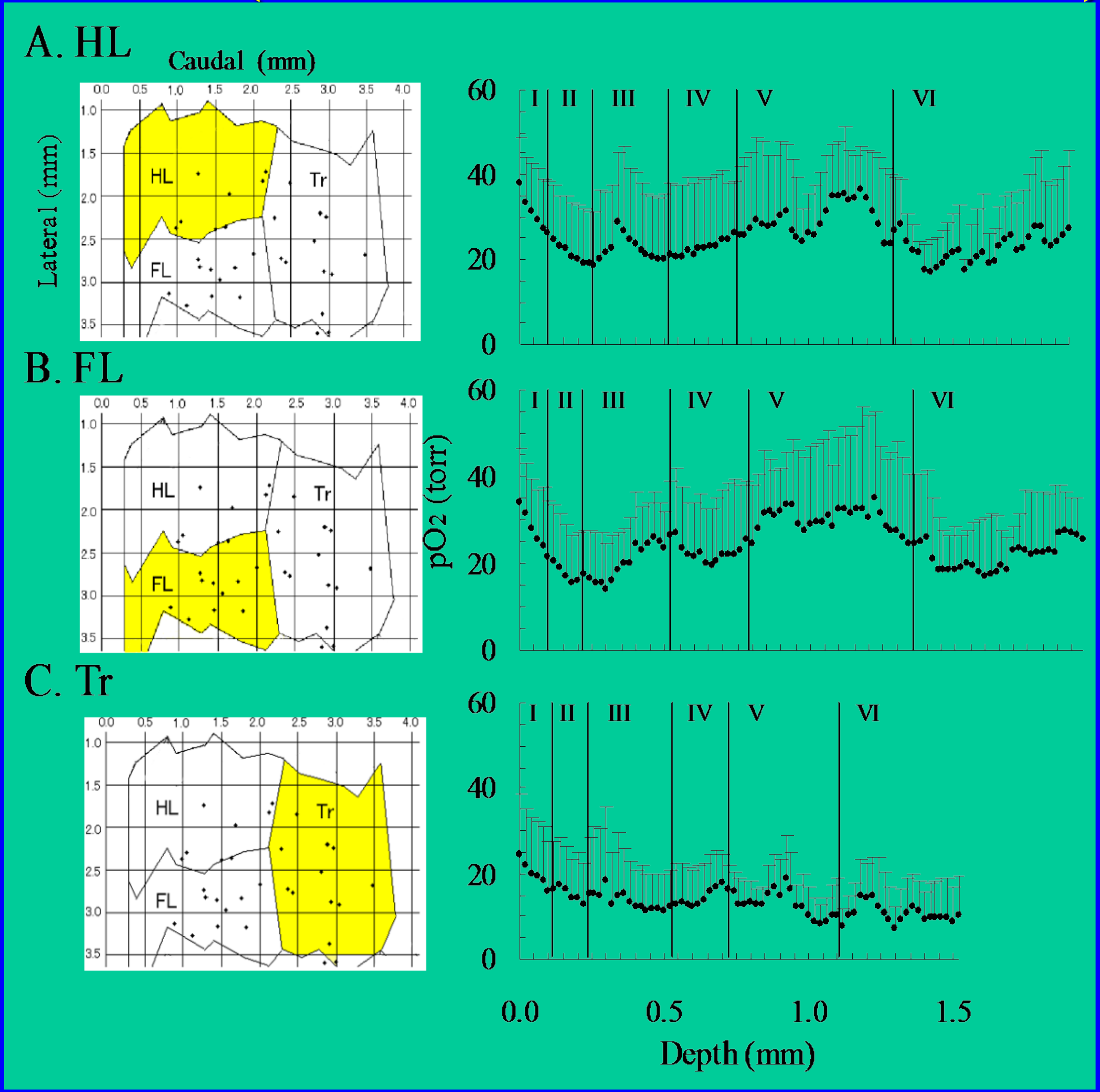




Micro-CT image (Skyscan 1072, Toyo Technica)

(3D-DOCTOR：Able Software Corp.)

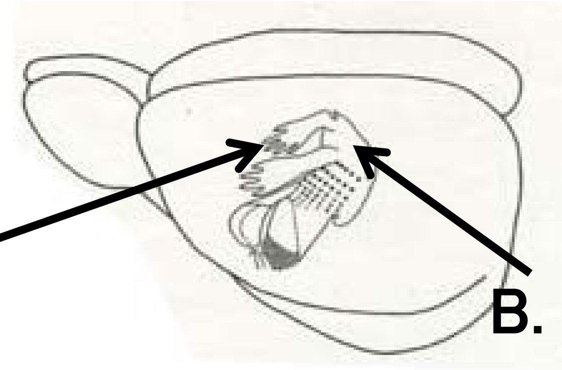
Depth profile of pO2 distribution in the somatosensory areas of rat
(without functional stimulation)



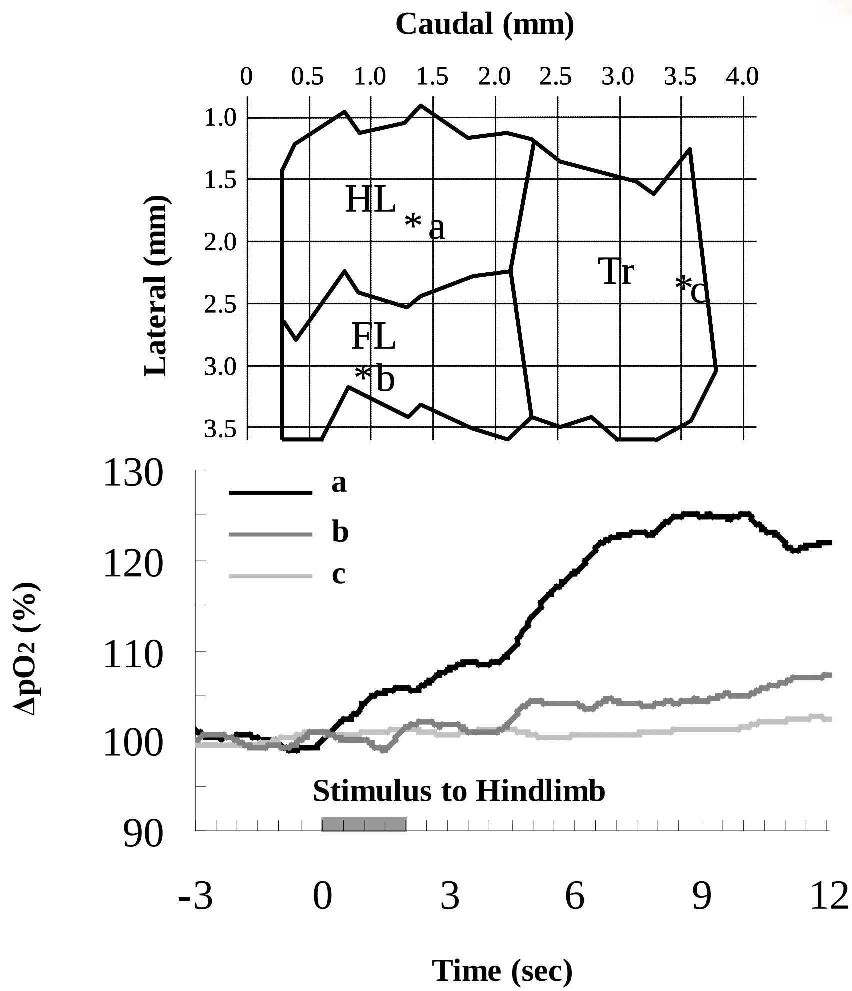
The layers from IV to VI depend on the area.

pO2 change after the functional stimulation

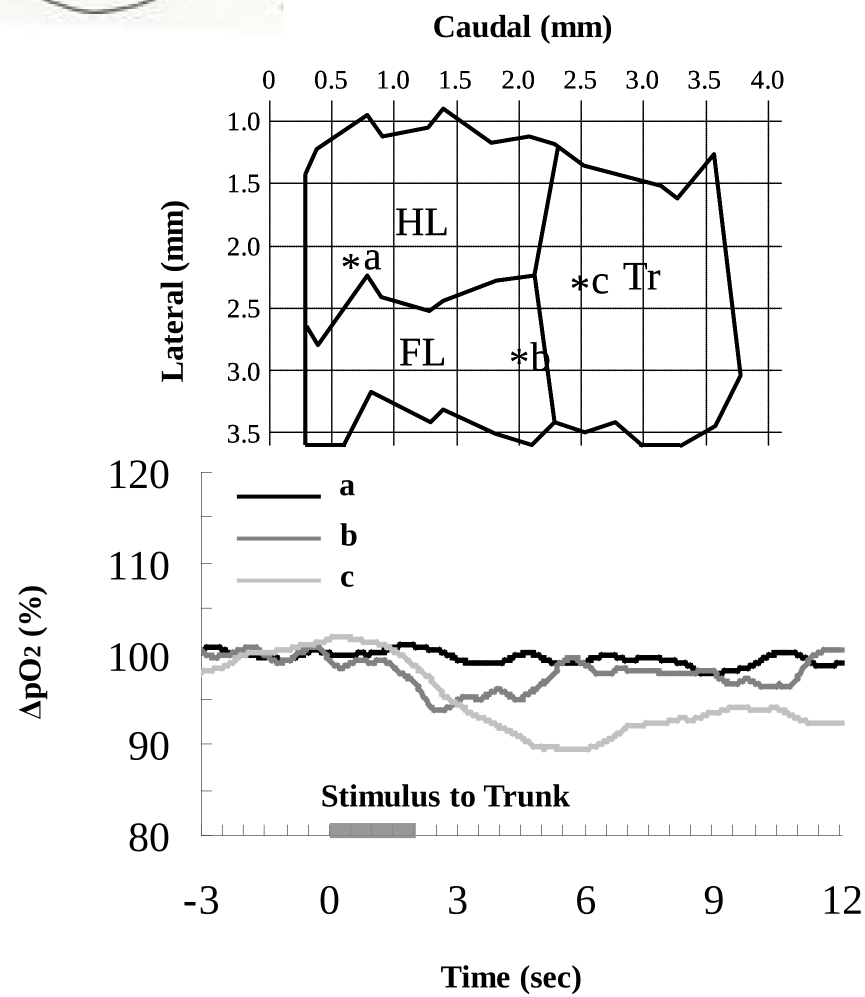
Puzzling results!



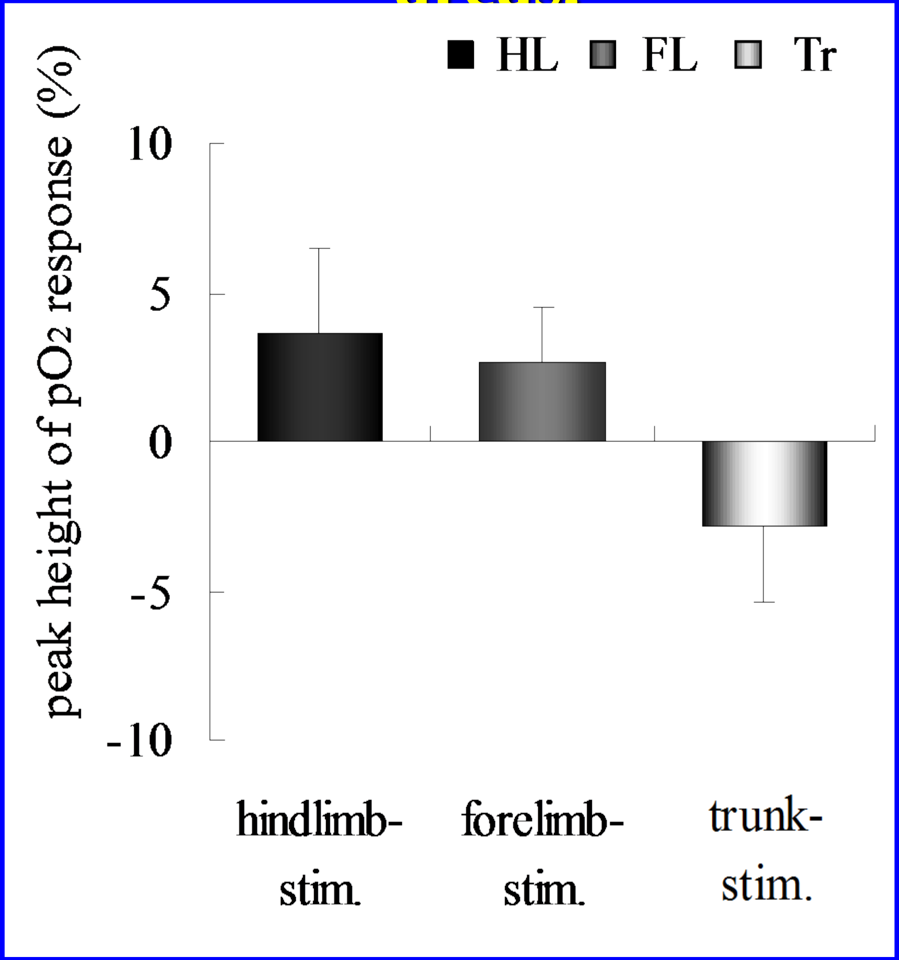
A. Hindlimb stim.



B. Trunk stim.



Dual response of tissue pO2 depending on the cortical areas.

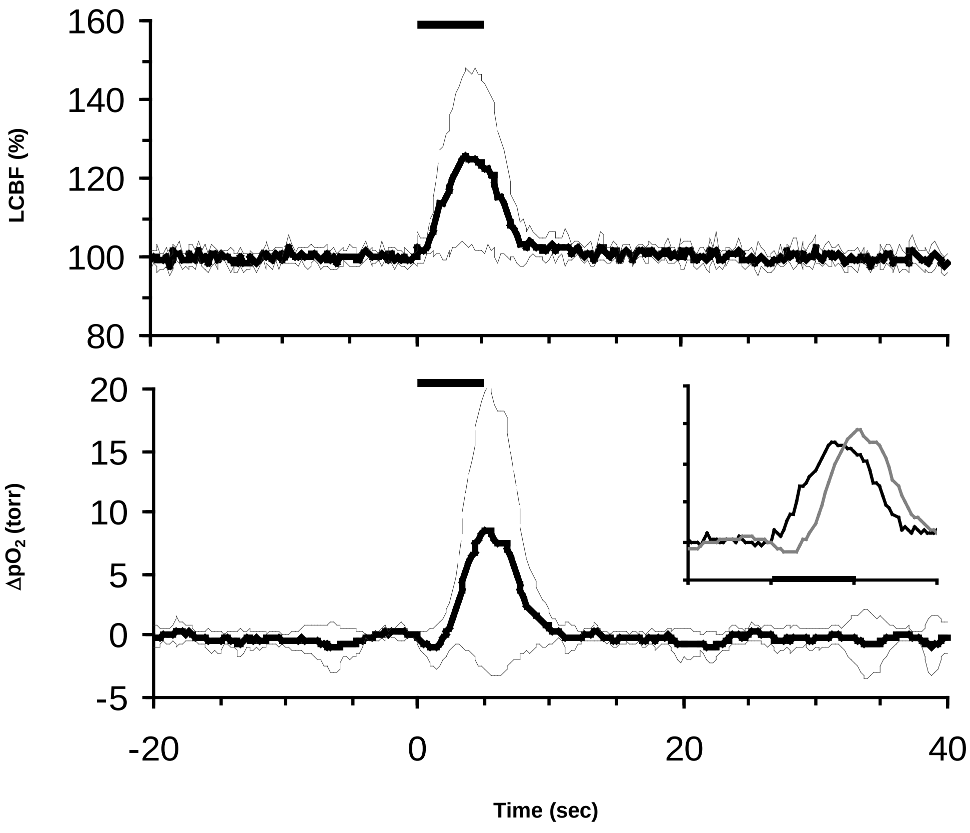


K. Masamoto, K. Tanishita, et al. "*Brain Research.* (2003)

（N=6）

pO2 for HL and FL increases after the stimulation, on the contrary pO2 for Tr decreases after the stimulation. ??

Simultaneous measurements of pO2 and local cerebral blood flow in rat somatosensory cortex (Masamoto et al. J Appl Physiol 2007)

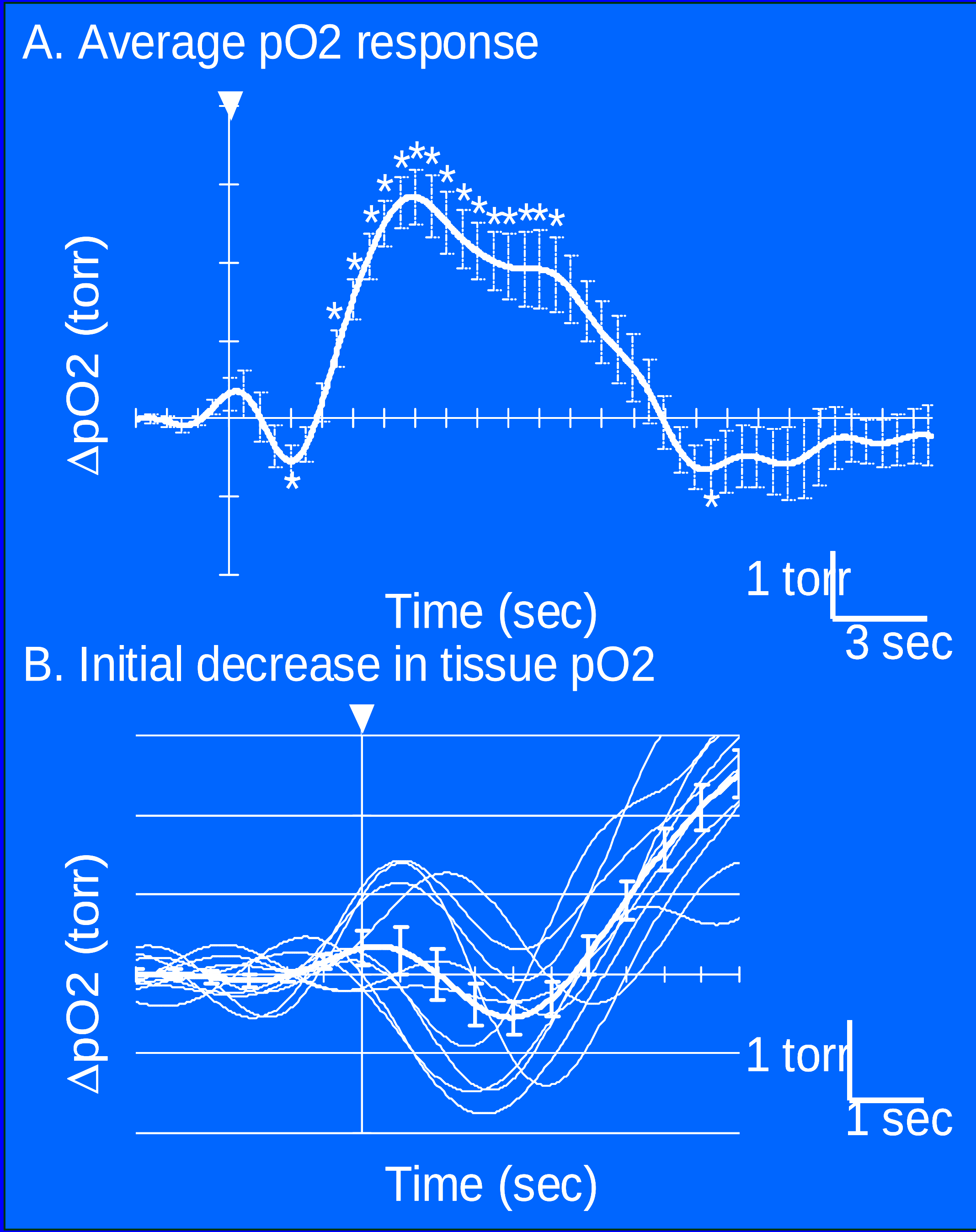


Biphasic changes of pO2

In the activated region, tissue pO2 initially decreased during the 3 seconds after the onset of acoustic stimuli, and then increased during the next seconds.

We should note the presence of **initial dip of pO2**.

K. Masamoto, K. Tanishita, et al. *Journal of Cerebral Blood Flow and Metabolism.* (2003)



Oxygen conservation equation for the cylindrical model

$$(1+m)\left(\frac{\partial p_{O2}}{\partial t}+v_z\frac{\partial p_{O2}}{\partial z}\right)=\frac{1}{r}\left(\frac{\partial}{\partial r}D_B{}^{(r)}\left(r\frac{\partial p_{O2}}{\partial r}\right)\right)+\frac{\partial}{\partial z}D_B{}^{(z)}\frac{\partial p_{O2}}{\partial z} \qquad (0<r<R_1)$$

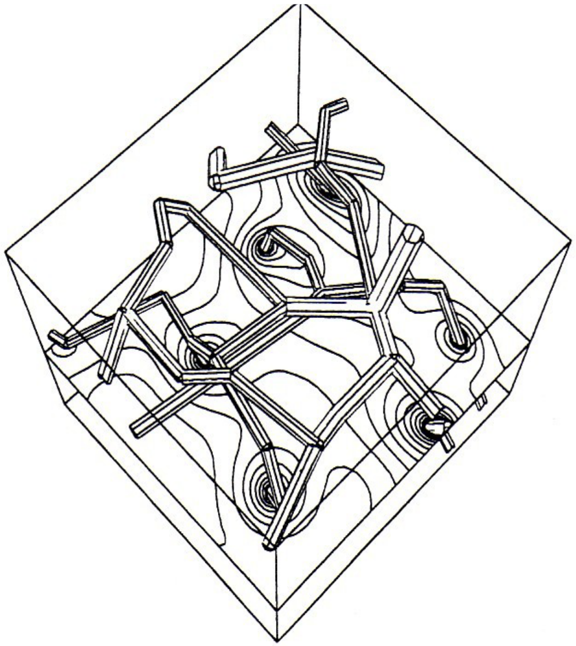
$$\frac{\partial p_{O2}}{\partial t}=\frac{1}{r}\left(\frac{\partial}{\partial r}D_T{}^{(r)}\left(r\frac{\partial p_{O2}}{\partial r}\right)\right)+\frac{\partial}{\partial z}D_T{}^{(z)}\frac{\partial p_{O2}}{\partial z}+R_{O2}K \qquad (R_1<r<R_2)$$

$$m=\frac{dc_{HbO2}}{dc_{O2}}$$

Upper equation represents the oxygen conservation in the vessel.
Lower equation represents the conservation in the tissue.

Oxygen transfer model by Secomb (2000)

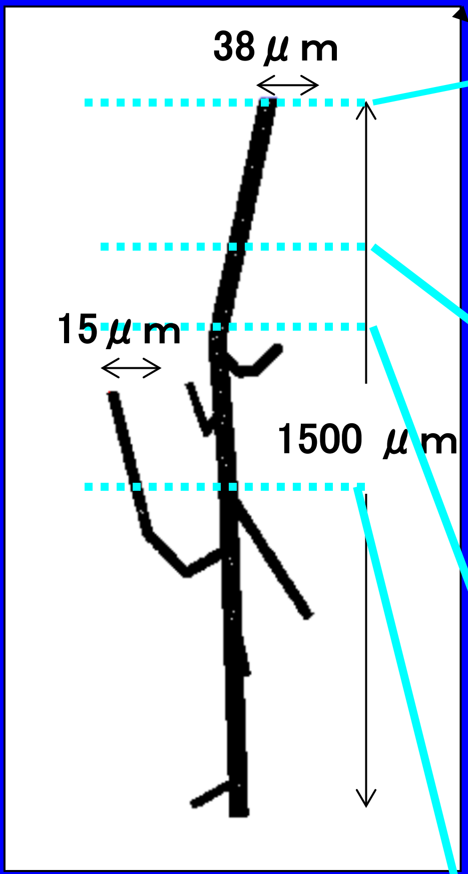
They calculated the pO2 profile in the cerebral tissue based on the SEM imaging for three-dimensional vessel network.



Their result indicates that hypoxic damage is avoided by decreasing the oxygen consumption rate by 31 % for the blood flow decrease by 75%.

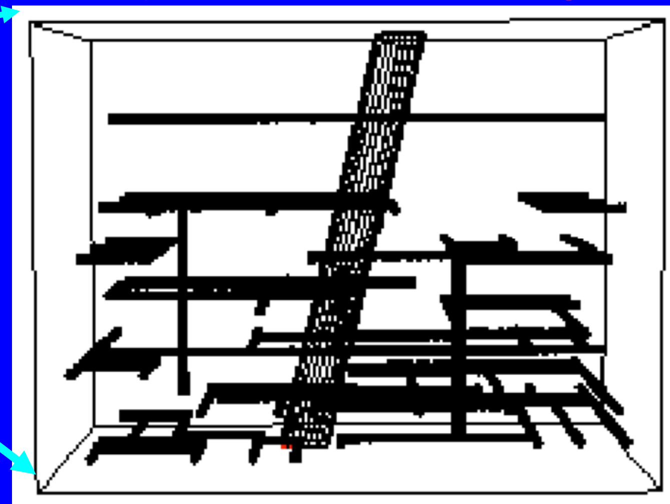
The oxygen transfer model contributes the prediction and avoidance of localized brain damage due to the cerebral ischaemia and hypoxia.

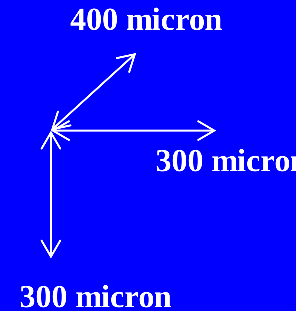
Model for superficial and middle layers



Arteriole geometry

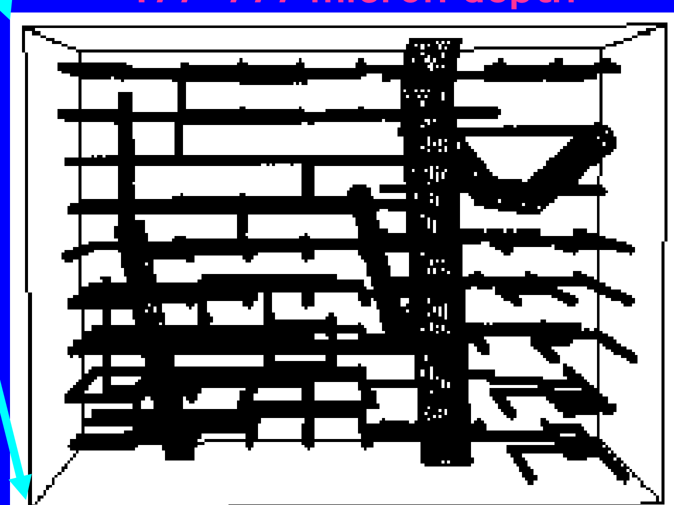
Superficial layer: 0–300 micron depth





Middle layer

477–777 micron depth



中間層/表層の比

arteriole surface

2.01

capillary networks surface

1.63

total vessels’ surface

1.69

Mesh size
arteriole tissue– 5 micron
capillary– 2 micron

Governing equations

Arteriole

Navier–Stokes equation

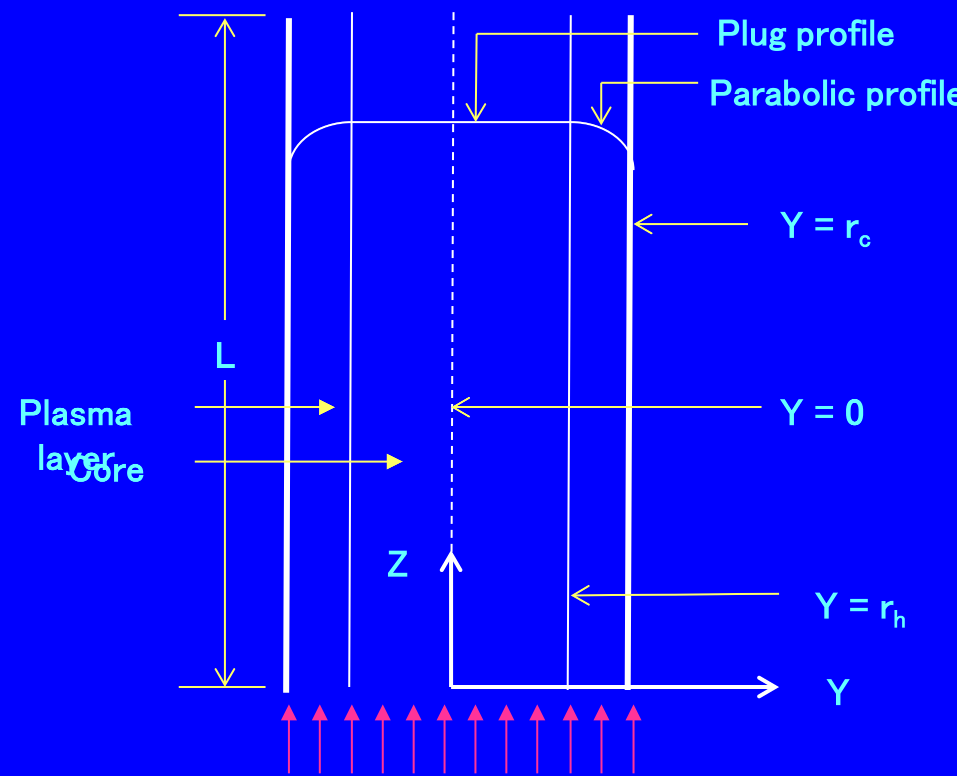
$$\frac{\partial \mathbf{U}}{\partial t} + (\mathrm{grad}\,\mathbf{U})\mathbf{U} = -\frac{1}{\rho}\mathrm{grad}P + \mu\nabla^2\mathbf{U}$$

ρ : density of blood ; 1.05g/ml

μ : viscosity of blood ; 4mPa/s

Re = 10^{-2}

Capillary



Core

$$U_h = \frac{\Delta P r_c^2}{2\mu_p L}\left(1-\gamma^2\right)$$

Plasma layer

$$U(Y) = \frac{\Delta P r_c^2}{2\mu_p L}\left(1-\chi^2\right)$$

$\gamma = r_h / r_c$ $\quad$ $\chi = Y / r_c$,

Re = 10^{-3}

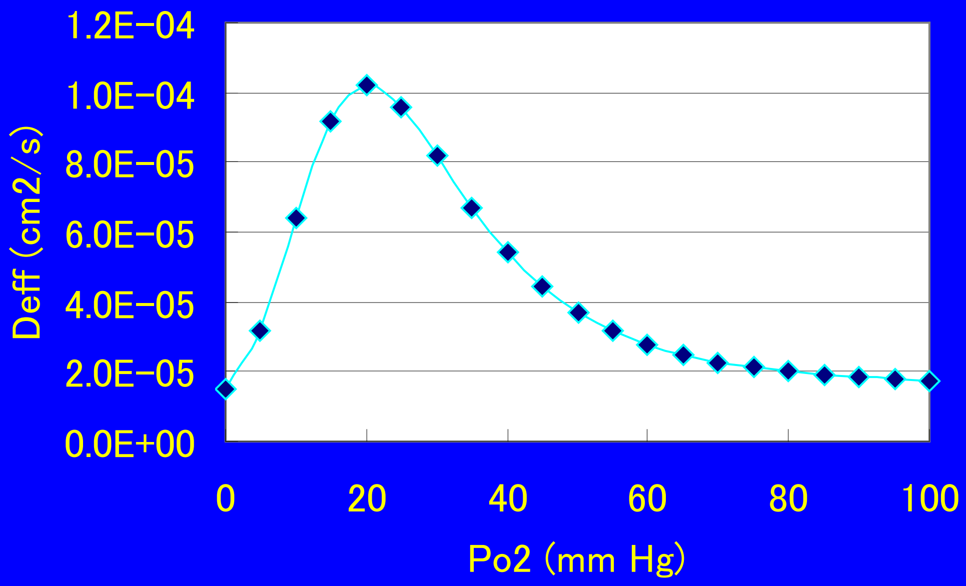
Oxygen transport

Within the vessel

$$u_i \frac{\partial [O2]}{\partial x_i} = D_{eff}\, \alpha \frac{\partial^2 PO2}{\partial^2 x_i}$$

Deff : O2 effective diffusion coefficient

α : O2 solubility ; 3e-05 ml/ml/mmHg



Within the tissue

$$D\alpha\left(\frac{\partial^2 Po2}{\partial^2 x} + \frac{\partial^2 Po2}{\partial^2 y} + \frac{\partial^2 Po2}{\partial^2 z}\right) - M = 0$$

M : O2 consumption

D : O2 diffusion coefficient ; 1.5e-5 cm^2/s

α : O2 solubility ; 3e-05 ml/ml/mmHg

Algorithm SIMPLE

Solver Fluent 5 : Fluent

Assumptions for the calculation

- **Matching flux at the vessel wall**
- **The oxygen gradient at the edge of module unit is zero**
- **The oxygen consumption rate is zero in the superficial layer up to 100 μm depth.**

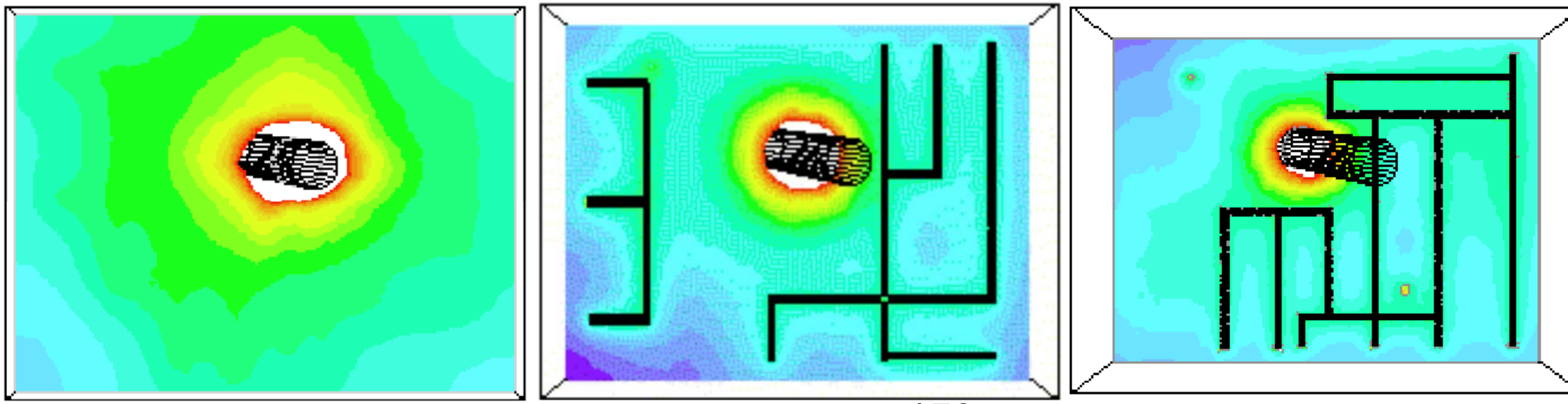
	Superficial layer	Middle layer
arteriole inlet Po_2	100 mm Hg	85 mm Hg
capillary inlet Po_2	50 mm Hg	50 mm Hg

normal condition

CBF (cm^3/100g/min)	153	247

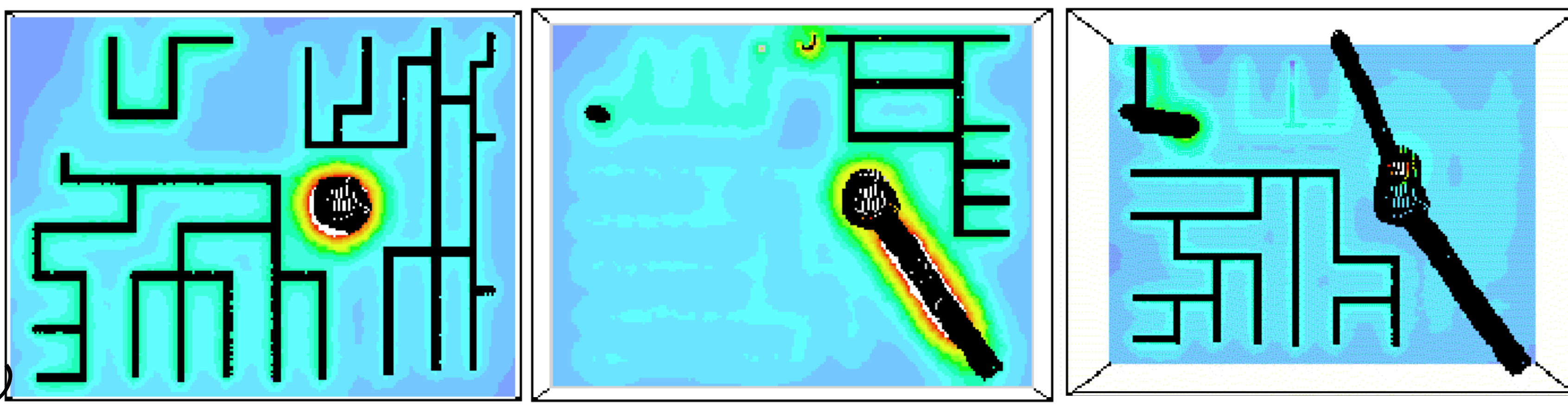
control flow

Superficial layer pO2 profile

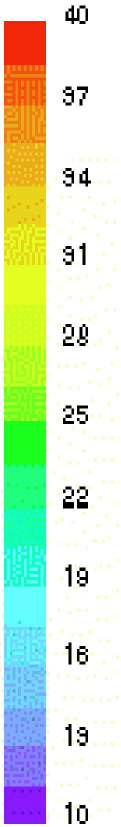


50micron 150micron 250micron

Middle layer pO2 profile



500micron 600micron 700micron

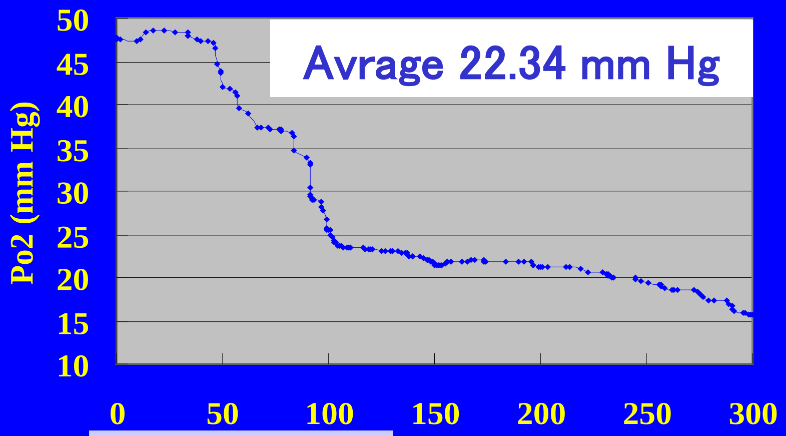


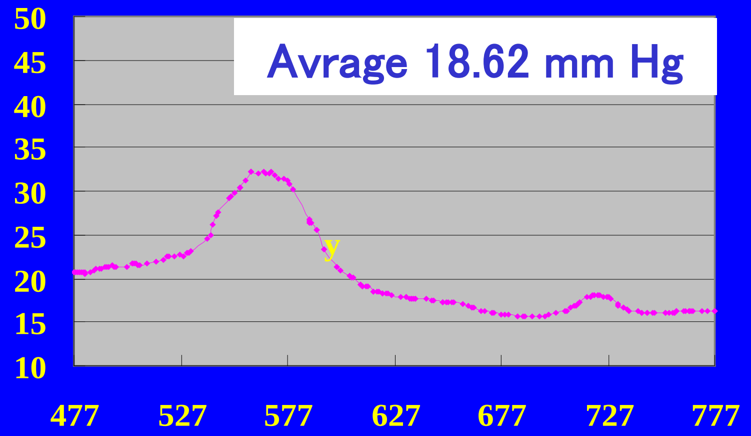
Po2 (mm Hg)

Comparison between the calculation and measured pO2

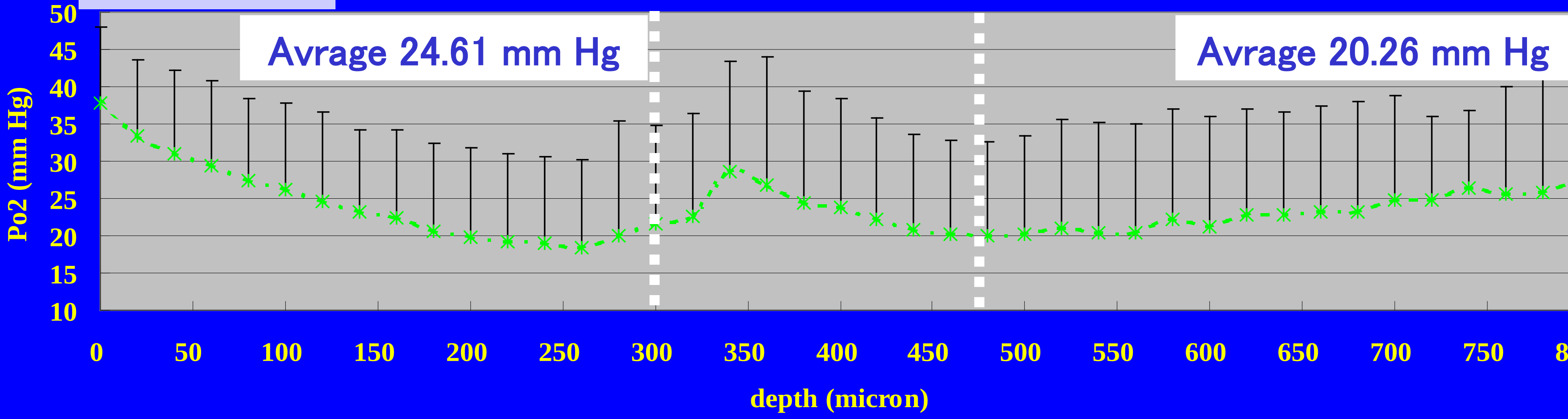
Calculated

Near arteriole





Measured



The increase of oxygen delivery due to the increase of blood flow

CBF parameter

Change of blood flow

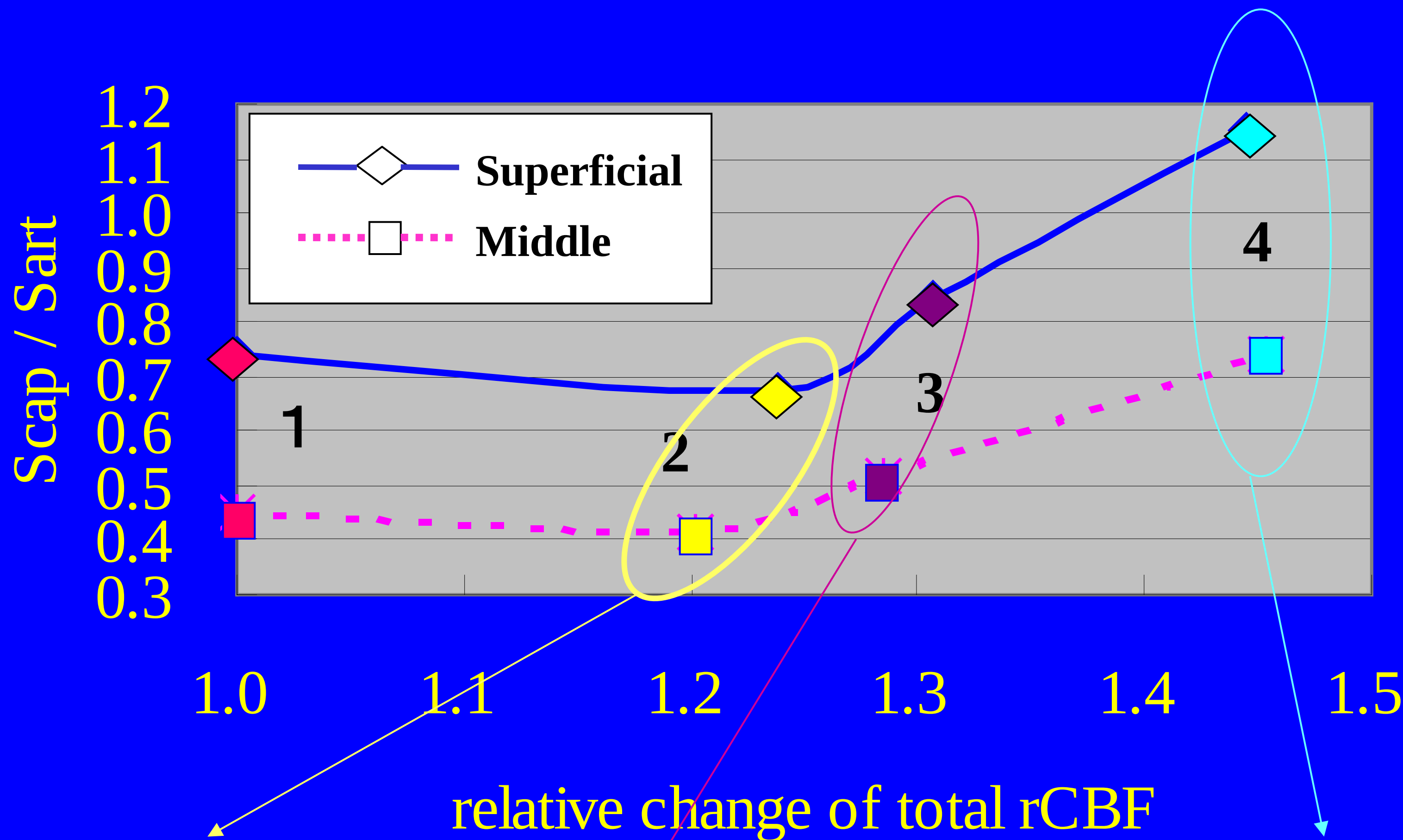
		CBF (cm3/100g/min) Superficial		CBF (cm3/100g/min) Middle	
1	Control flow	153	(0)	247	(0)
2	Art_CBF 30% up	189	(24)	297	(20)
3	Art_CBF 30% up + cap_CBF 33% up[a]	200	(31)	318	(29)
4	Art_CBF 30% up + cap_CBF 100% up[b]	221	(45)	360	(45)

全体の増加率（%）

(a) David et al（1998）

(b) Afonst et al (2000)

Ratio of the oxygen supply from capillary to that from arteriole is affected by the blood flow rate.



Sart 10 % Up

Scap 26 % UP (Sup)

Scap 33 % UP (Mid)

Scap 71 % UP (Sup)

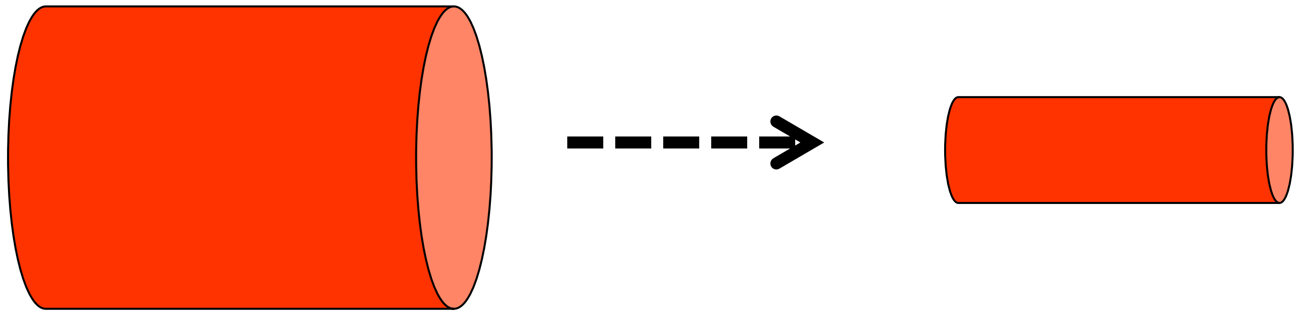
Scap 76 % UP (Mid)

The oxygen transfer plays an important role in the brain function.

Blood flow ↔ Oxygen delivery ↔ Neural activity

↕

Brain science

	太い血管	微小血管
		
壁面せん断応力	低い	高い
内皮細胞から血管壁へ	血管病変の進行	能動的な血流制御によるリモデリング、適合性
	血管壁の機能が問題	臓器機能が問題

Viewpoints from biology and physics

Importance of biology in the mechanics: biomechanics

Importance of mechanics in the biology: mechanobiology

Vascular Biology & Medicine Vol.11/No.4 2010.11

血管医学

特集

血管のメカノバイオロジー

バイオメカニクスでなくて、

メカノバイオロジー？？

物理的な環境・刺激が、生物反応・機能・現象を制御するメカニズムの解明を目指す領域。

特集：血管のメカノバイオロジー

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三俣昌子

◆学生・技術者待望のテキスト――――――――2012年3月刊行！

生物流体力学

谷下一夫・山口隆美 = 編集

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……本書では，最新の研究の進展を紹介することが目的ではなく，生物流体力学の基本から流れが関わる生物機能までを分かりやすく解説する事に重点を置いている．今後，生物流体力学が大きく進展しても，本書に書かれている基本の重要性は変わらない．生物流体力学に取り組む院生や研究者・技術者が長く参照して頂ける内容となっており，本書の発刊は，我が国の生物流体力学の発展に大きく貢献すると思われる．理工学分野のみならず，医学生物学分野の医学者や研究者にも参照して頂きたい．

――「序」より（谷下一夫）

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（朝倉書店にて発刊）

御清聴有難う御座いました。

Acknowledgements