Microbubbles and Brain Tissue Perfusion Imaging

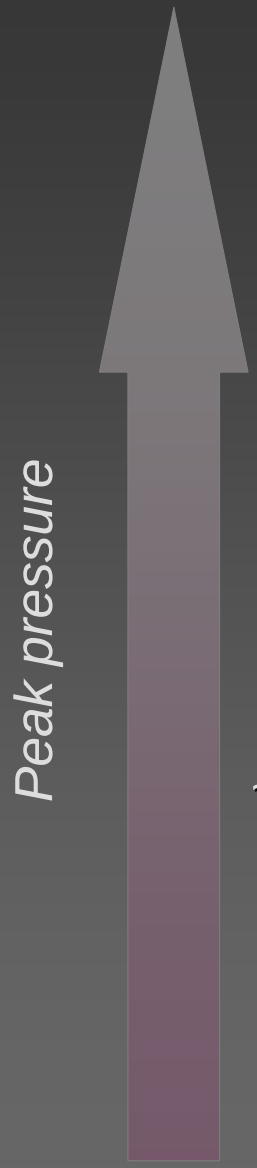
Shiogai T, Matsumoto M, Ikeda K
Mariana A, Nag Kane Y[1)], Mizuno T[1)]
Nakagawa M[1)], Fortunate H[2)]

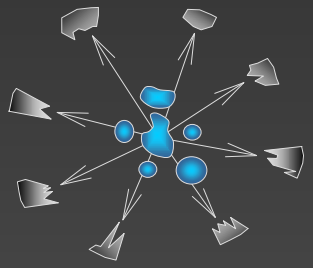
Department of Clinical Neurosciences
Kyoto Takeda Hospital
Department of Neurology
Kyoto Prefecture University of Medicine[1)]
ME lab, Tokyo Jake University School of Medicine[2)]

Problems with Transcranial Ultrasound Perfusion Imaging

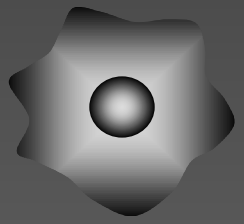
1) Bone- and depth-dependent attenuation of the ultrasound signals
2) Ultrasound systems
    a. insufficient resolution and sensitivity (low signal-to-noise ratio)
    b. optimal signal processing and imaging procedures
        1. imaging parameters
        2. transmitting and receiving frequencies
    c. inhomogeneous acoustic pressures in sector scans
3) Ultrasound contrast agents
    a. size and instability of microbubbles
    b. absorption and scattering (shadowing)
    c. non-linear relation between microbubble concentration and image intensity (bubble saturation)
4) Low data reproducibility (transducer fixation, data analysis, etc)

Ultrasound Interaction with Microbubbles

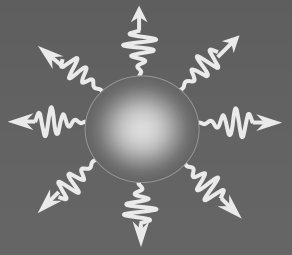




bubble destruction



resonant oscillation



Transient scattering

Stimulated Acoustic Emission (SAE)

Loss of correlation (LOC)

Non-linear backscatter

Harmonic imaging

Linear backscatter

Conventional imaging

Ultrasound Perfusion Imaging of the Brain

a) Harmonic Imaging (HI)- transcranial

1) Gray-scale HI

1. Integrated backscatter (IBS);SONOS5500; Levovist, Optison, BY963, BR14, SonoVue

Second harmonic imaging

Human (Postert et al 1998, 1999, 2001, Seidel et al 1999, 2000, 2001, 2002, 2003, 2004, 2006, Wiesmann et al 2000, 2004, Harrer et al 2002, 2003, 2004, 2008, Meyer et al 2002, 2003, 2007, Shiogai et al 2002, 2003, 2004, 2005, Caruso et al 2005)

Dogs (Claassen et al 2001, Seidel et al 2001)

Ultraharmonic imaging Human (Shiogai et al 2004)

2. B-mode; SONOS5500; Levovist (Federlein et al 2000, Shiogai et al 2005)

3. Pulse (Phase)-inversion HI; HDI5000, Sonoline Elegra, Sequia512; Levovist, Sonazoid, Optison, SonoVue

Human (Meairs et al 2000, Postert et al 2000, Nakaoka et al 2001, Eyding et al 2003, 2004, 2005, 2006, 2007, Holscher et al 2003, Krogias et al 2005, Nolte et al 2005; Engelhardt et al 2007, Holscher et al 2007, Wang et al 2007 - via a skull defect), Jungehulsing et al 2008

Dogs (Rim et al 2001)

2) Power HI (PHI):

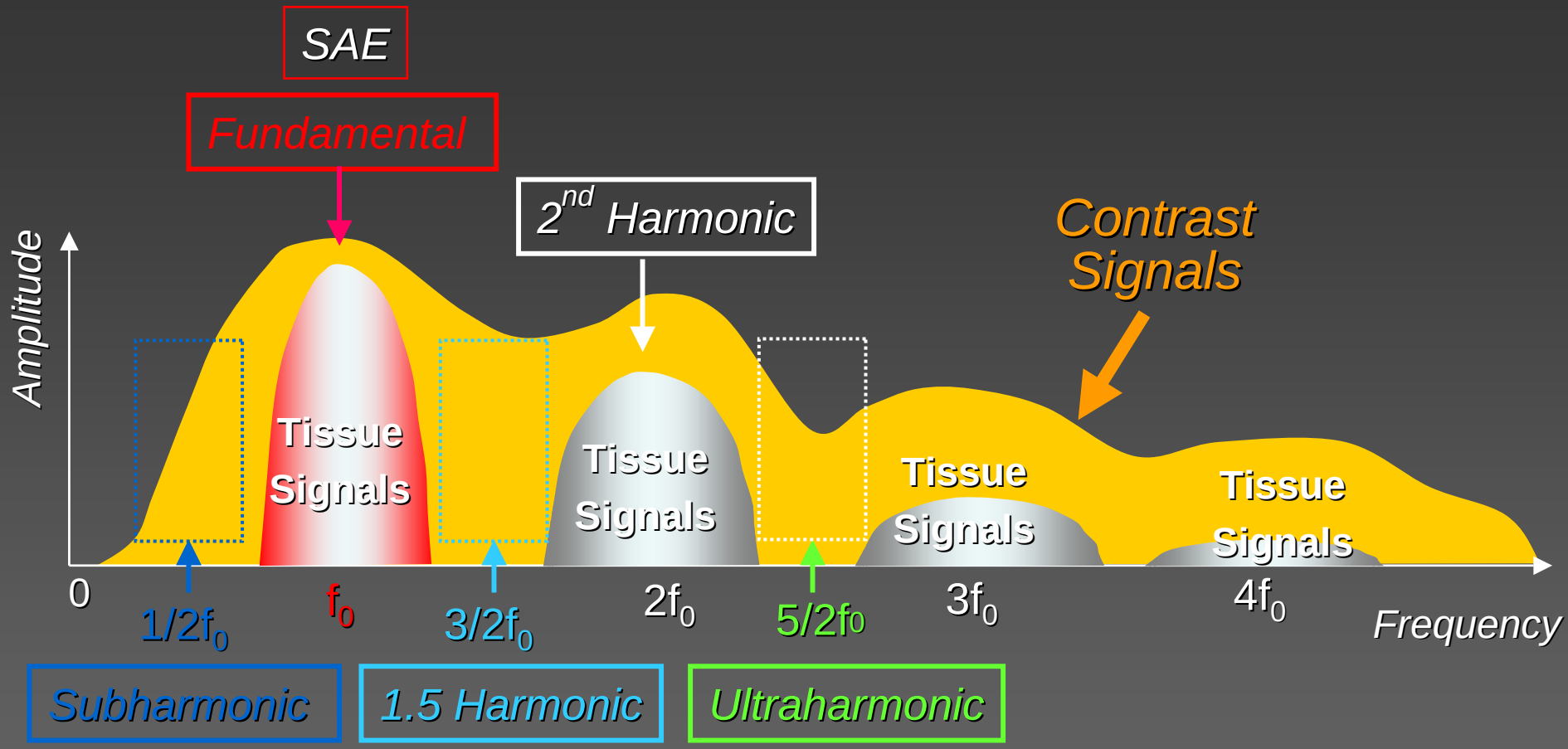
1. Harmonic Power Doppler Imaging (PDI); SONOS5500; Levovist, Optison, Sonazoid

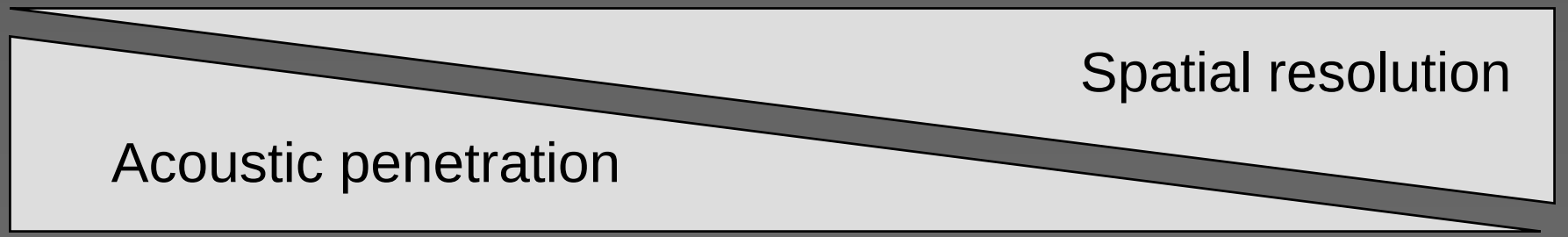
Human (Shiogai et al 2000, 2004, 2006, 2008)

Dogs (Seidel et al 2000, Meyer et al 2002)

2. Power Pulse-inversion HI; HDI5000; SonoVue: Human (Kern et al 2004)

Frequency Distribution of the Receiving Signals





Quantitative Measurements of Brain Tissue Perfusion I

a) Bolus Injection of UCA (Bolus kinetics)

1) Central Volume Principle (Meier and Zieler 1954)

Cerebral blood flow (CBF, ml/min/g) = Cerebral blood volume (CBV, ml/g)/ Mean transit time (MTT)

CBV = AUC (brain tissue)/ AUC (artery)

2) Contrast Burst Depletion Imaging (Eyding et al 2003, 2004)

perfusion coefficient (p), destruction coefficient (d)

$C(n) = C_0(X^{n-1}+Y*X^{n-1}-1/X-1)$

$X = e^{-d}*e^{-p\Delta t}$, $Y = (1-e^{-p\Delta t})$

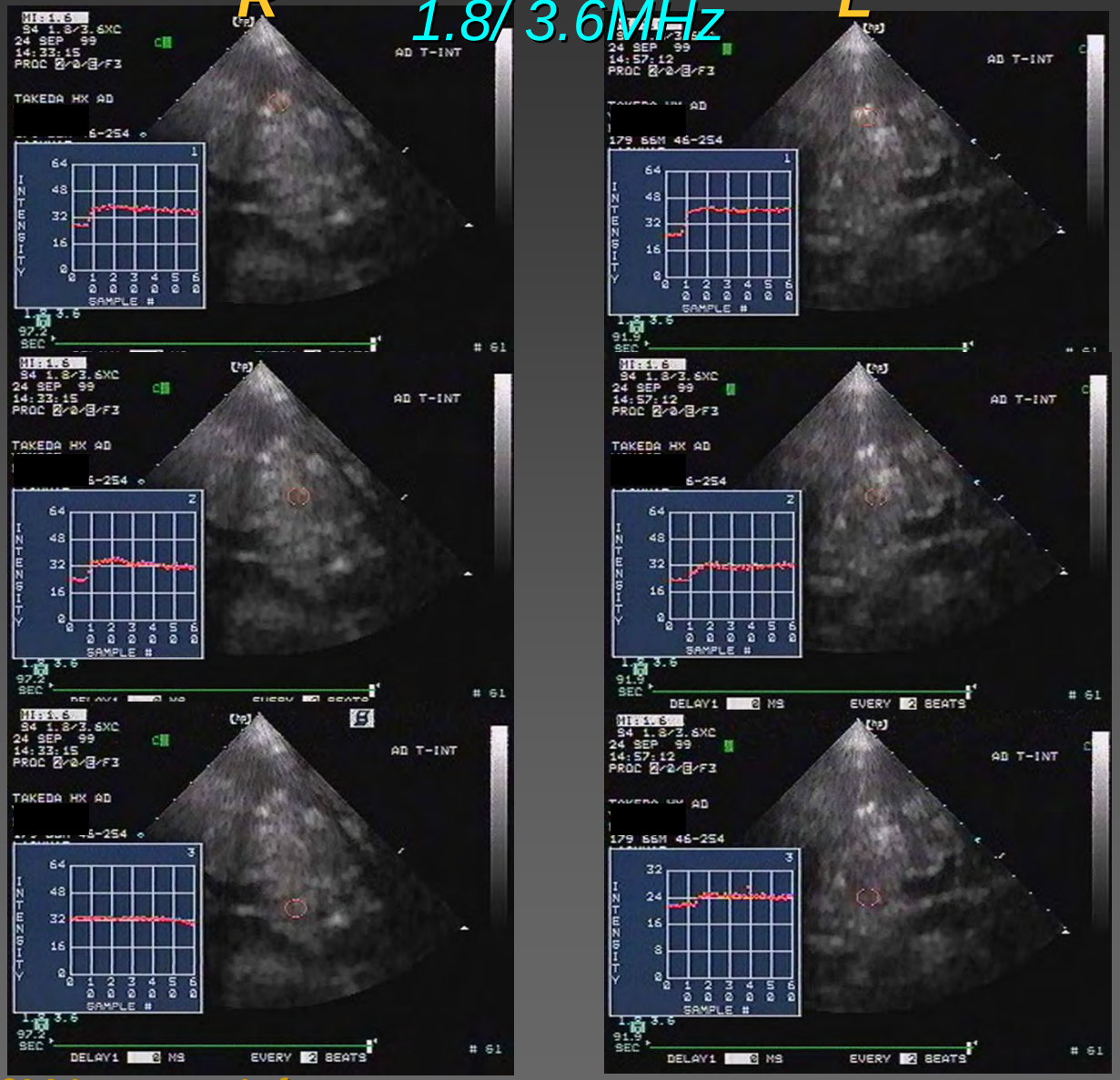
3) Microbubble Destruction Imaging (Power PIHI) (Kern et al 2004)

$\Delta I = I(t_0) - I(t_{baseline})$

Bolus Kinetics

SHI (IBS)

R 1.8/ 3.6MHz L



Time-Intensity Curve (TIC)

Temporal Lobe (TL)

Basal ganglia (BG)

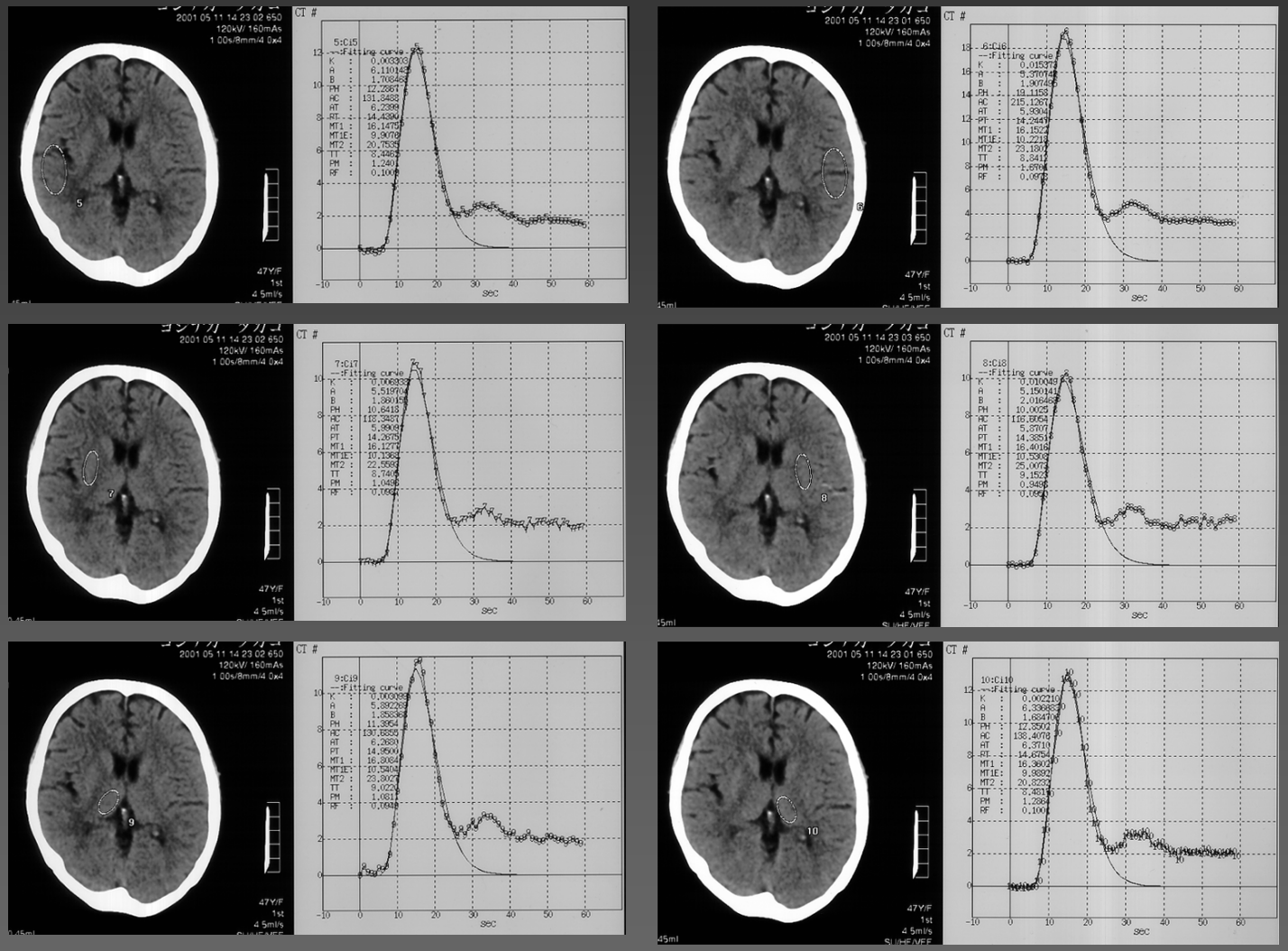
Thalamus (Th)

Shiogai et al Neurotrauma 24:77-82, 2001

KY 66M Lacunar Infarct

Dynamic CT Perfusion

Time-Density Curve (TDC)



Temporal Lobe (TL)

Basal ganglia (BG)

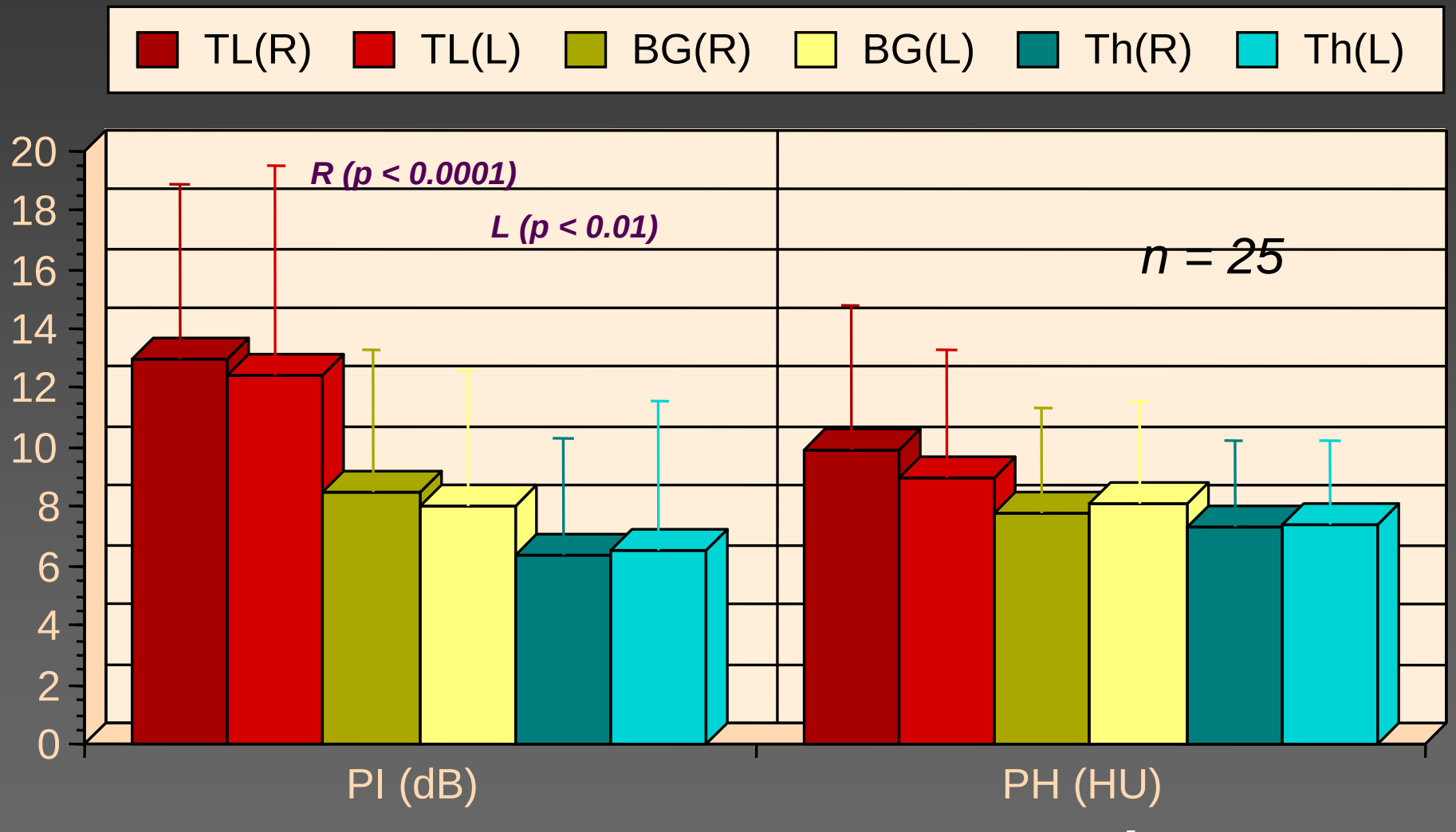
Thalamus (Th)

R

L

TY47 F Traumatic SAH

PI (PH) between Transcranial Ultrasound Perfusion Imaging (TPI) and Dynamic CT



Ultrasound Perfusion Imaging of the Brain

b) Stimulated Acoustic Emission (SAE)- transcranial

1) PDI and Color Velocity Imaging

   HDI5000, Sequoia512; Levovist

   Human (Pohl et al 2000, *Schlachetzki et al 2001*- via a skull defect)

2) Contrast Burst (Depletion) Imaging/ Time Variance Imaging

   Sonoline Elegra; Levovist, SonoVue

   Human (Postert et al 2000, Meves et al 2002, Eyding et al 2003, 2004, Holscher 2005, Ickenstein et al 2008)

3) Contrast Pulse Sequencing (CPS)

   Sequoia512; SonoVue

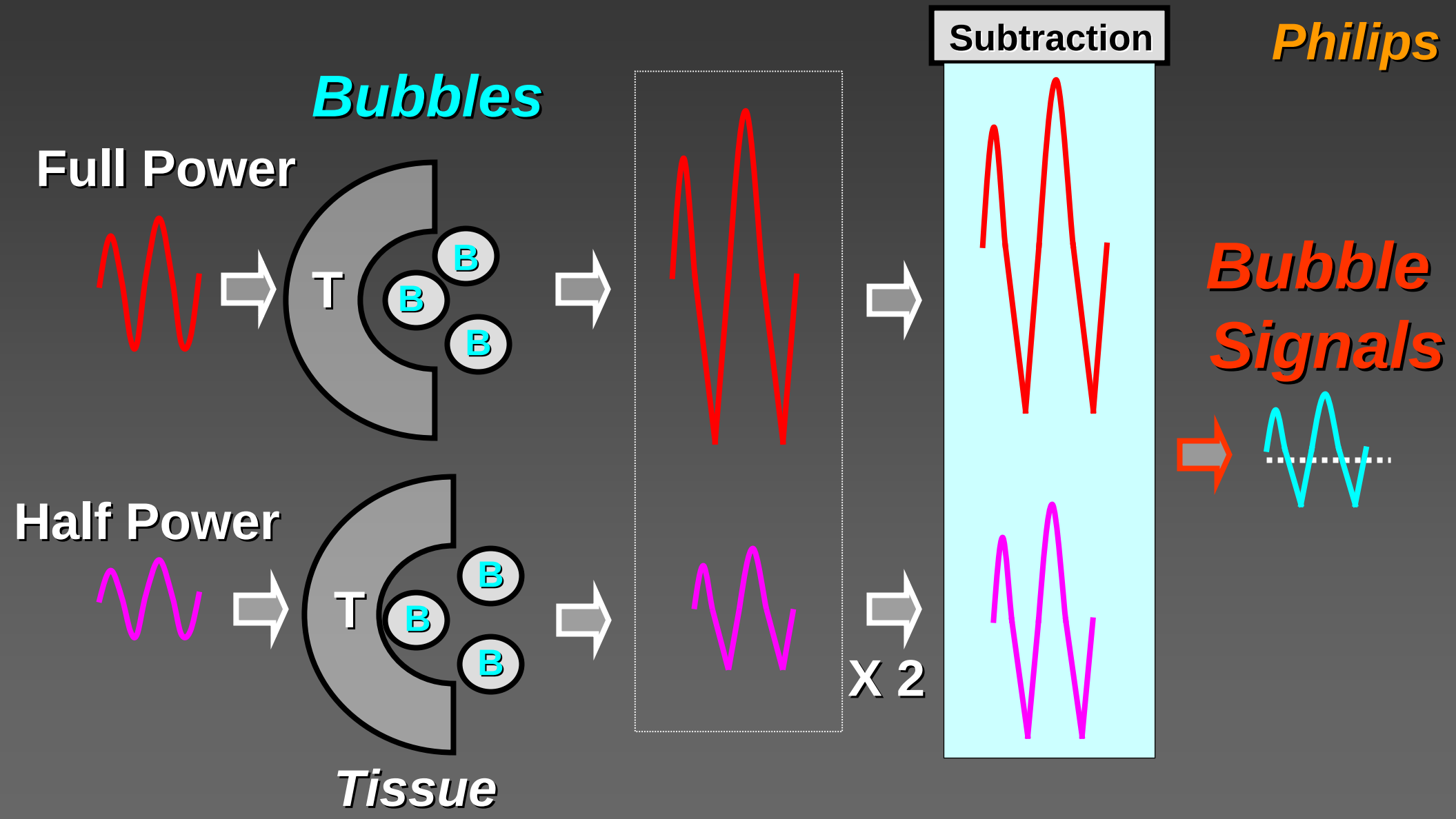
   Human (*Bartels et al 2004* - via a skull defect*, 2005, 2006*)

4) Power Modulation Imaging (PMI)

   Sonos5500; Levovist

   Human (Shiogai et al 2007)

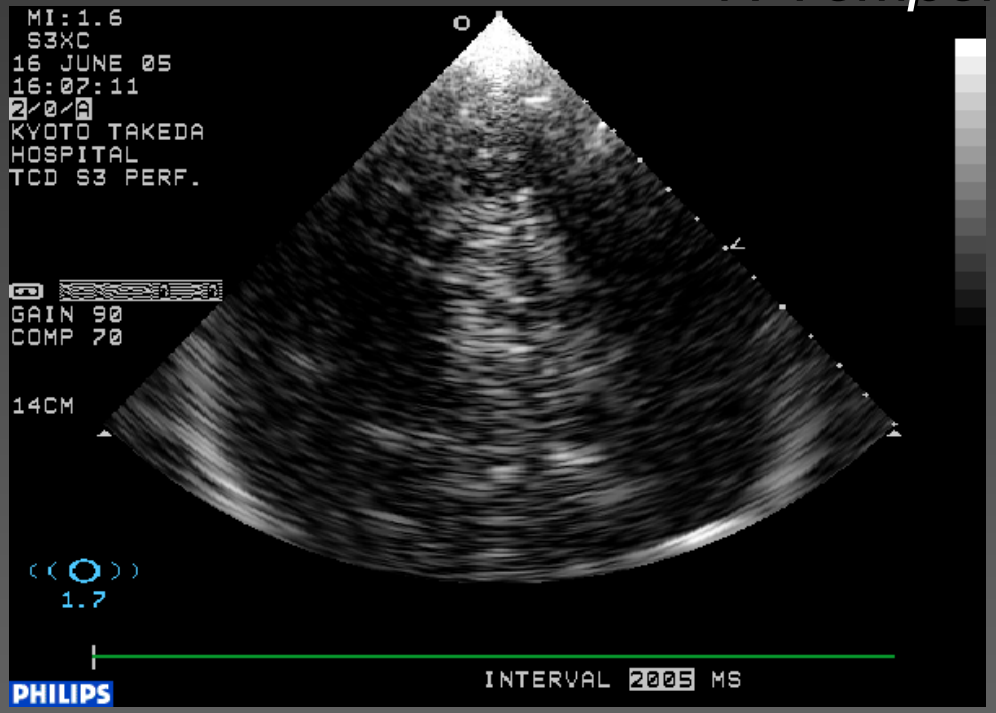
Power Modulation (Bubbles and Tissue)

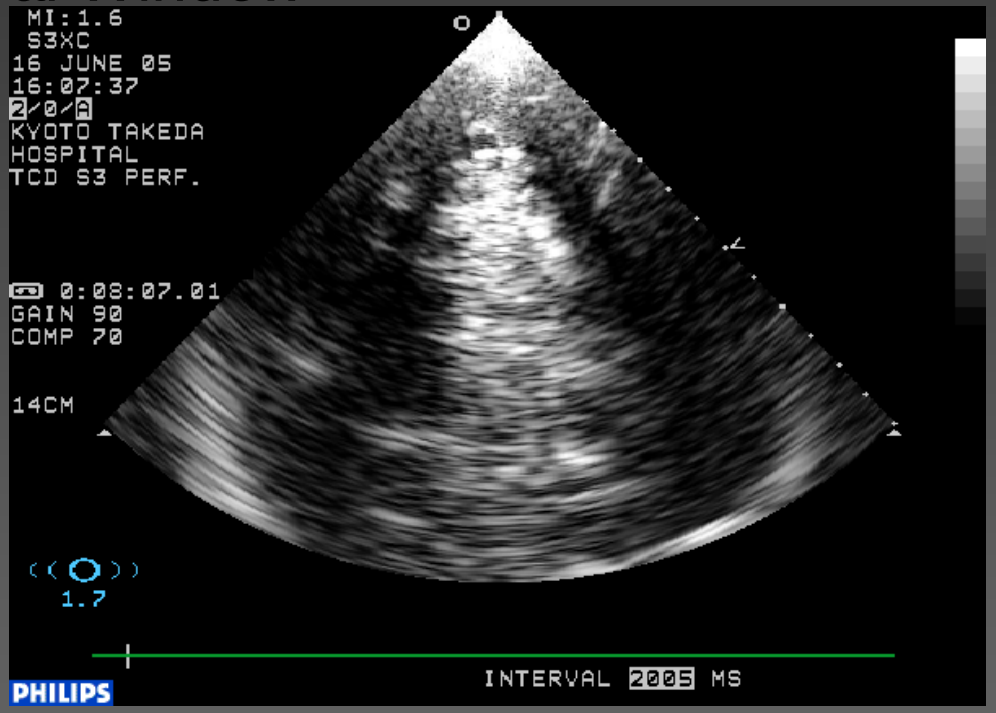


Power Modulation Imaging (PMI)

SONOS5500

R Temporal Window





before

Levovist
(400mg/ml 2.5g)
Bolus Injection

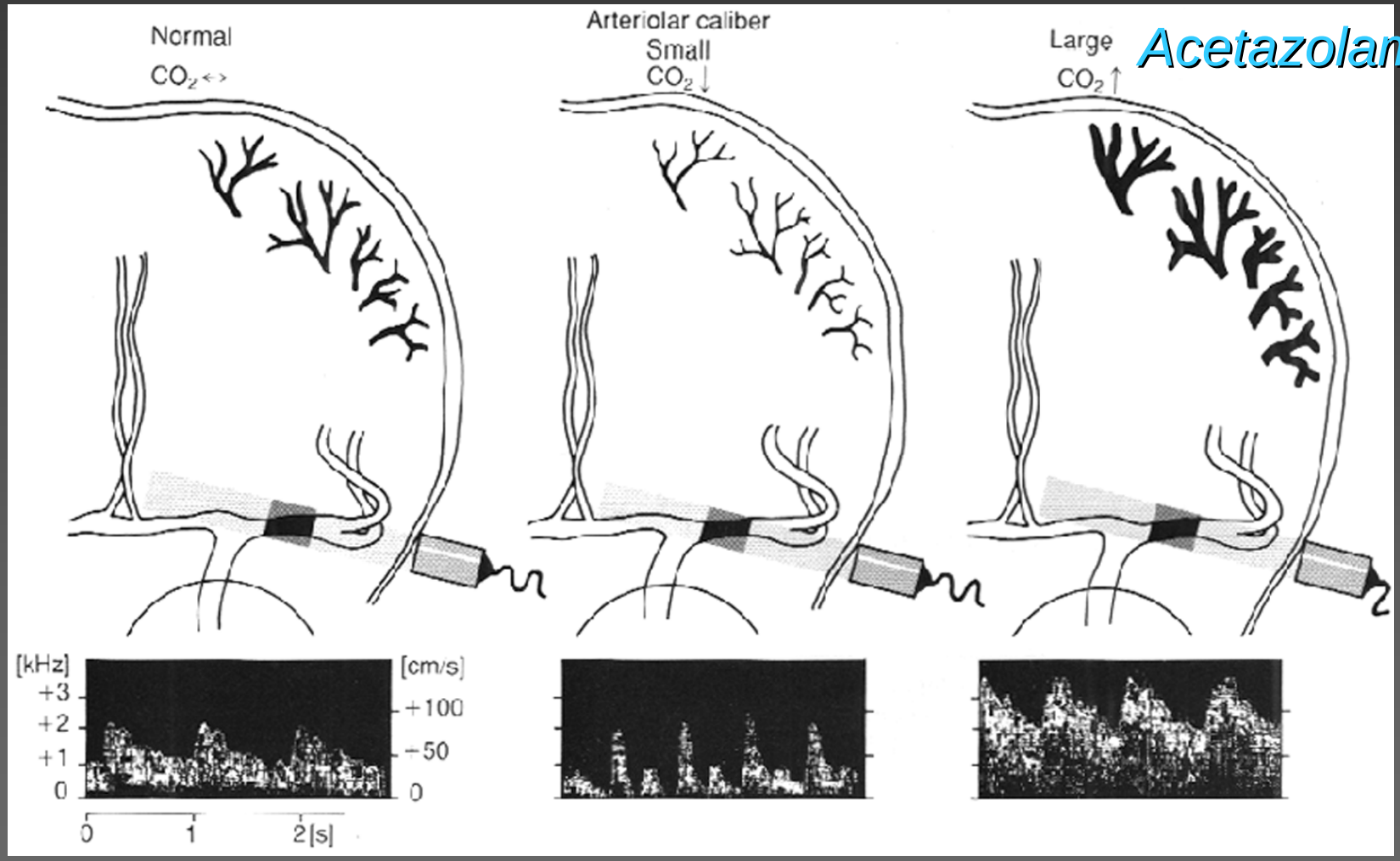
after

PM (1.7MHz)
PI = 2S

KT 75M RICAO

Vasc Lab 3:88-95, 2006

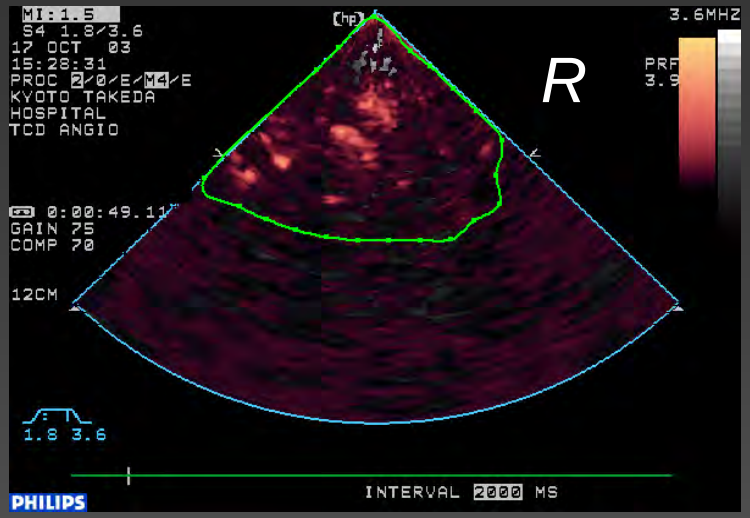
Vasomotor Reactivity (CO_2 and Acetazolamide)

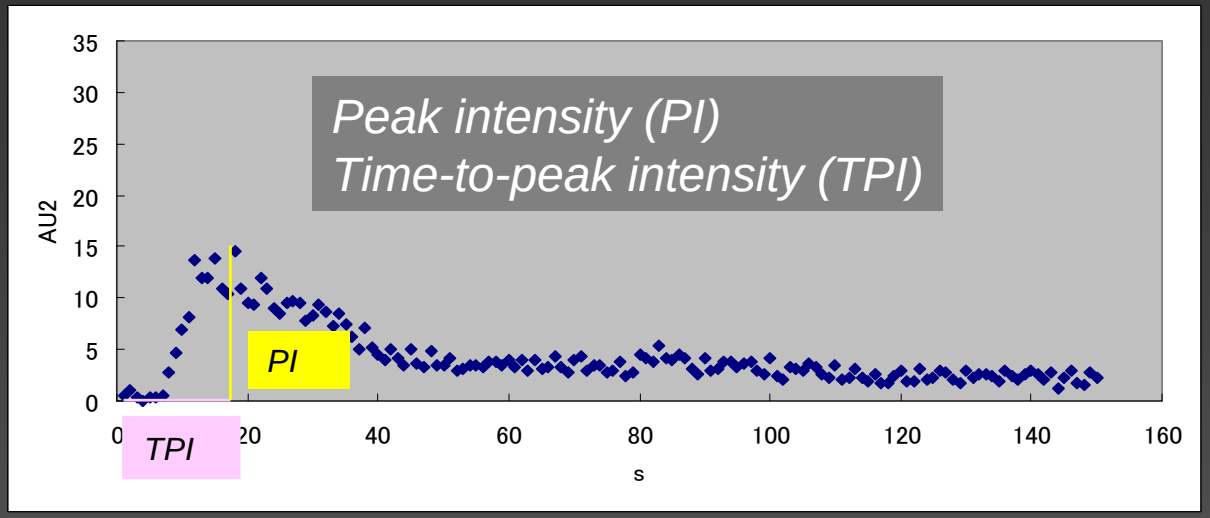


von Reutern and von Budingen 1993

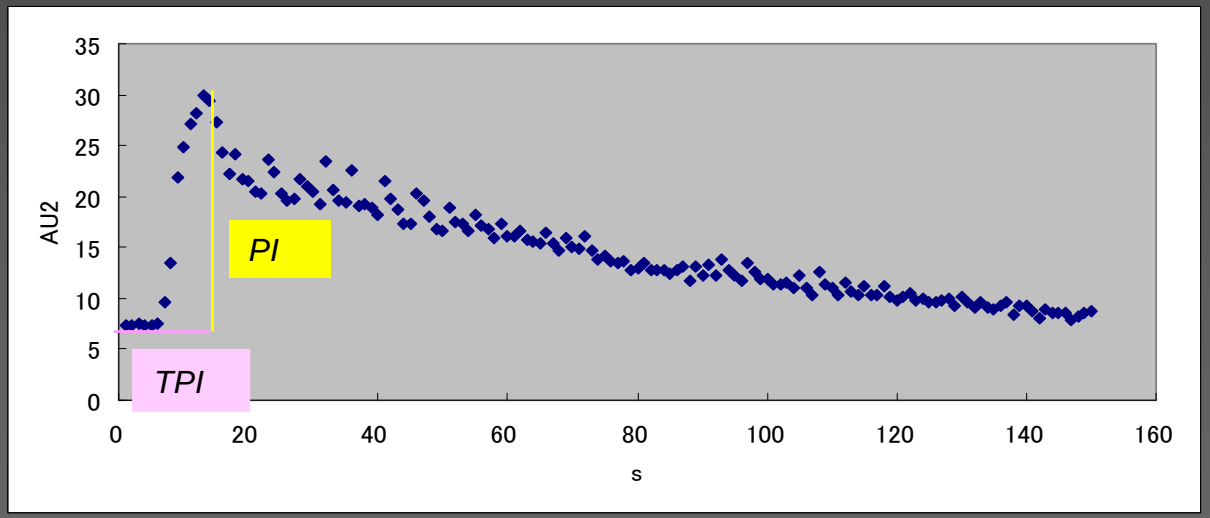
ACZ Vasoreactivity (PHI)

at rest





ACZ

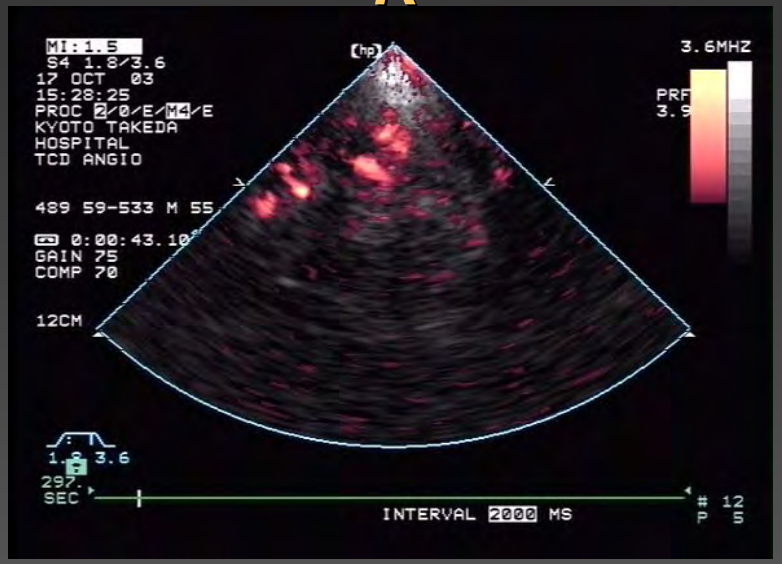


TO 55M ATI (L ICAO)

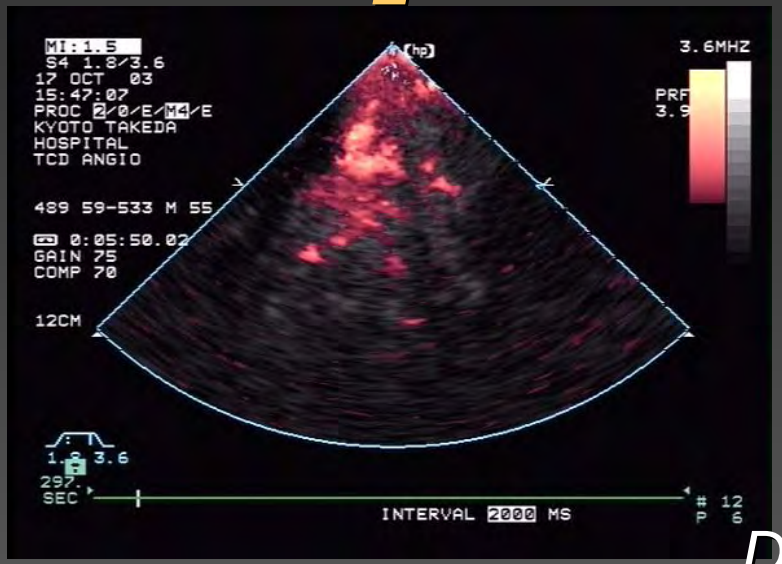
Shiogai et al. Acta Neurochir (submitting)

ACZ Vasoreactivity Test (PHI)

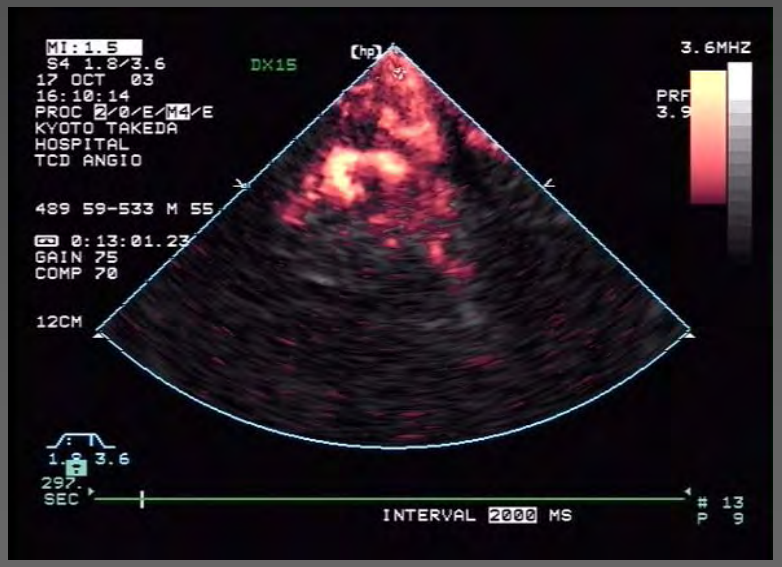
R



L



at rest



Diamox® 500mg IV

ACZ

TO 55M ATI (L ICAO) *5 months after onset*

Shiogai et al. Minimally Invasive Neurosurgery and Multidisciplinary Neurotraumatology Springer-Verlag, 2006, pp360-367

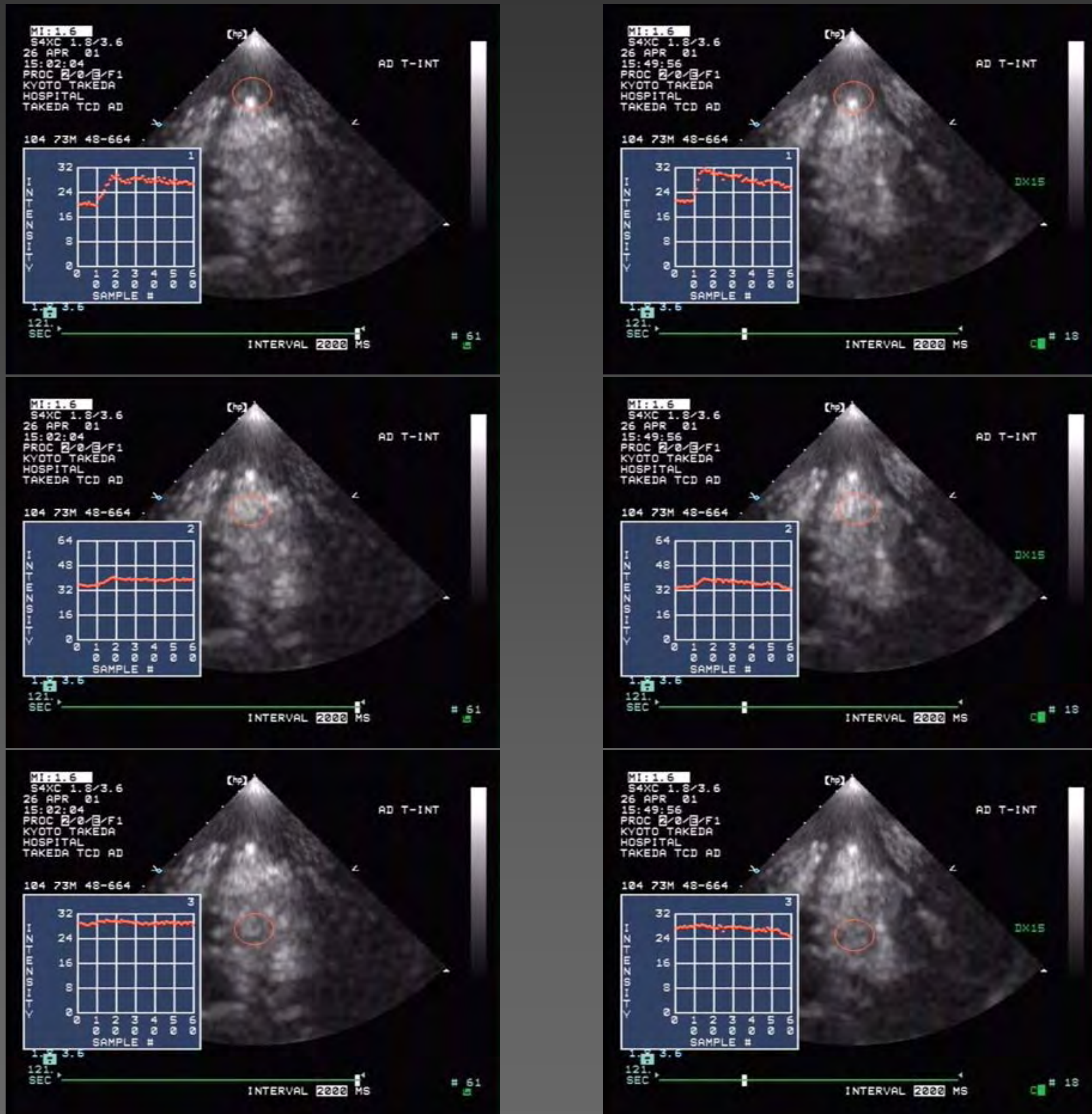
Correlation of Vasoreactivity between transcranial CDS and PHI parameters

	Correlation Coefficient (p value**)	
	Occlusive group (n = 15)	
Parameters*	Lesion side	Non-lesion side
MCA Vm vs. Contrast area	0.45 (ns)	0.69 (p < 0.01)
MCA Vm vs. PI	0.48 (ns)	0.64 (p < 0.05)
MCA Vm vs. TPI	- 0.17 (ns)	- 0.65 (p < 0.05)
PCA Vm vs. Contrast area	0.50 (ns)	0.67 (p < 0.05)
PCA Vm vs. PI	0.37 (ns)	0.66 (p < 0.05)
PCA Vm vs. TPI	- 0.36 (ns)	-0.48 (ns)

Shiogai et al. Acta Neurochir (submitting)

Acetazolamide Test (Bolus Kinetics)

at Rest | Acetazolamide



1.8/ 3.6MHz

SHI (IBS)

R

Temporal Lobe (TL)

Basal ganglia (BG)

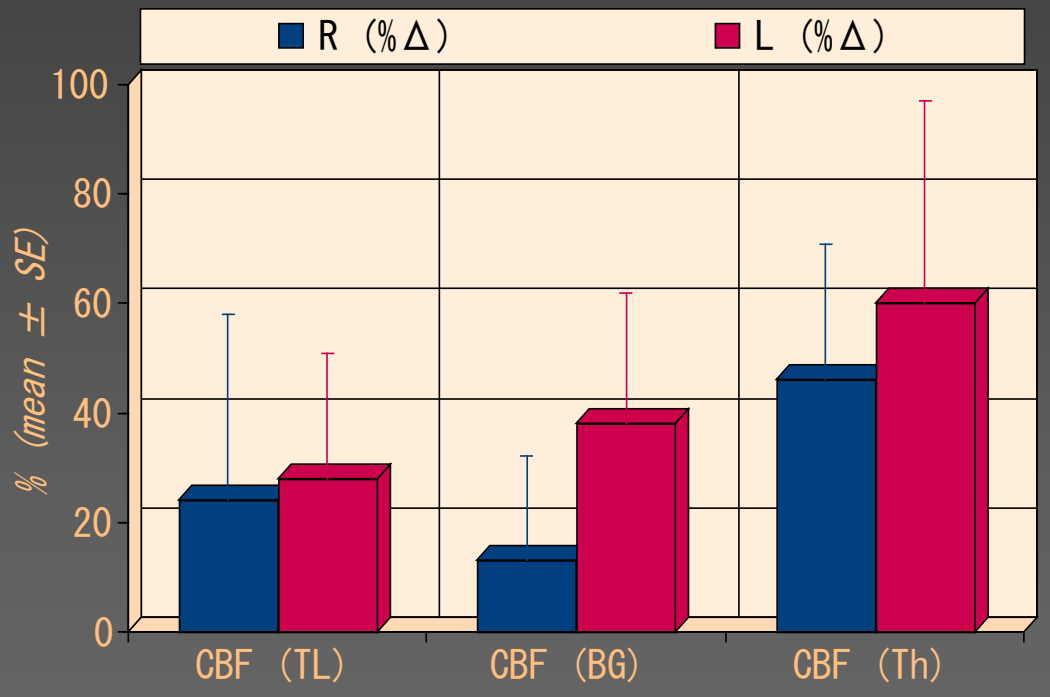
Thalamus (Th)

WY 73M L Cervical ICAS

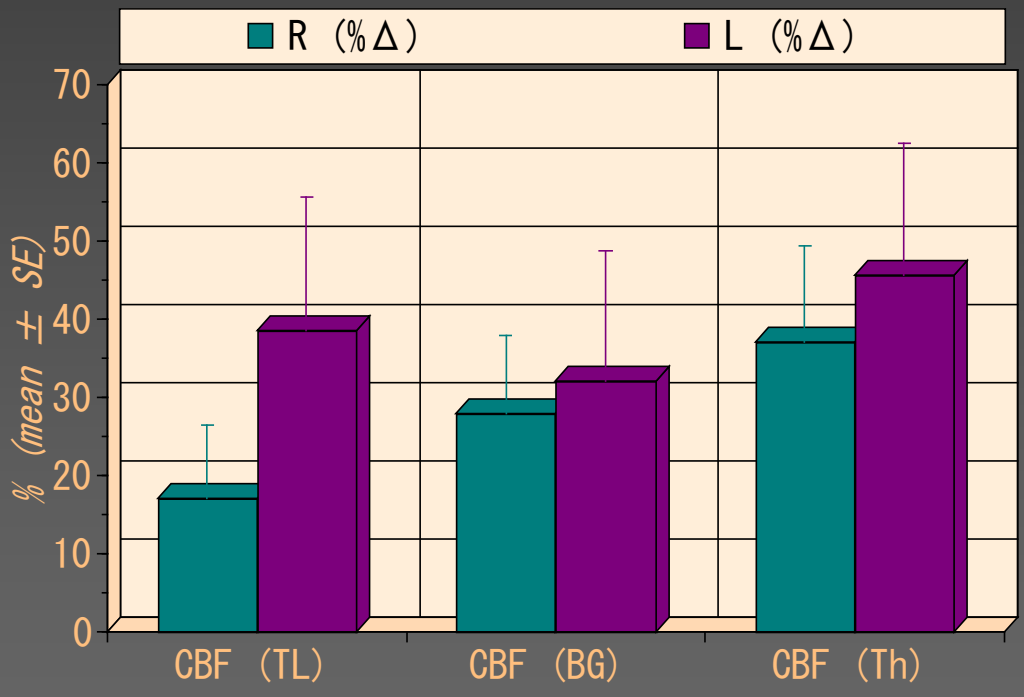
Shiogai et al. Acta Neurochir (Suppl) 86:59-63, 2003

Vasoreactivity (%Δ CBF) of Harmonic Perfusion Imaging (HPI) and Dynamic CT (DCT)

HPI %Δ CBF



DCT %Δ CBF



n = 12

Shiogai et al. Acta Neurochir (2003)[Suppl]86:57-62

Quantitative Measurements of Brain Tissue Perfusion II

b) Continuous Infusion of UCA

1) Refill kinetics (Wei et al 1998, Rim et al 2001, Seidel et al 2001, 2002, Shiogai et al 2005)

Intensity (I) and pulsing interval (t)

$I(t) = A(1-e^{-\beta t})$

A : plateau intensity (microvascular cross-sectional area: blood volume)

β : rise rate of intensity (microbubble velocity)

2) Diminution kinetics (Meyer and Seidel 2002, Meyer-Wiethe et al 2005, Kier et al 2007)

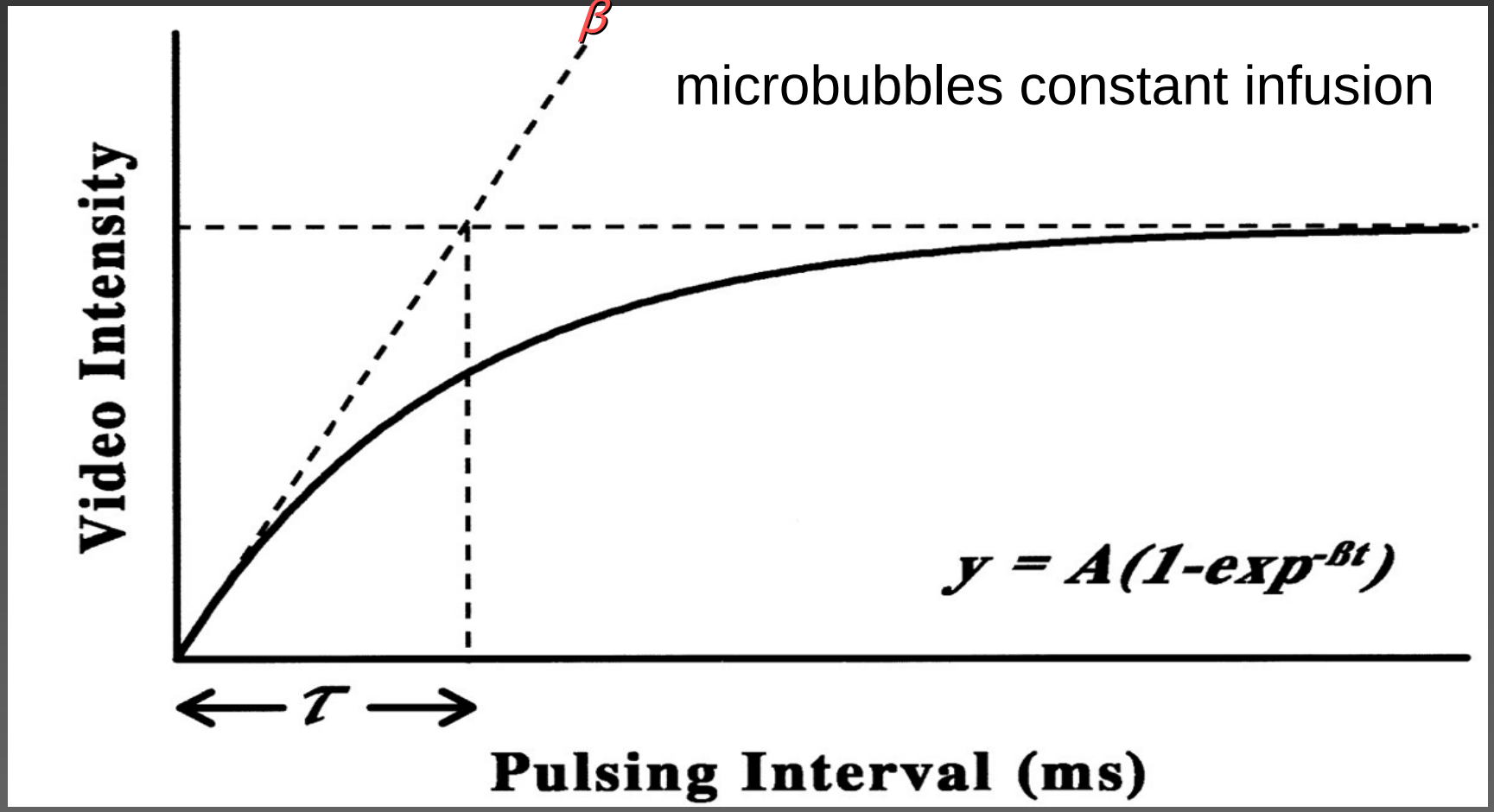
$I(t) = I_0 e^{-\beta t} + B$ *(baseline intensity)*

3) Contrast Destruction Imaging (Lucidarme et al 2003)

flow parameter ($1/\tau$), destruction factor (λ)

$C(n) = C0(X^{n-1} + Y*X^{n-1} - 1/X - 1)$, $X = e^{-\lambda \delta t} \cdot e^{-\Delta t/\tau}$, $y = (1-e^{-\Delta t/\tau})$

Refill Kinetics

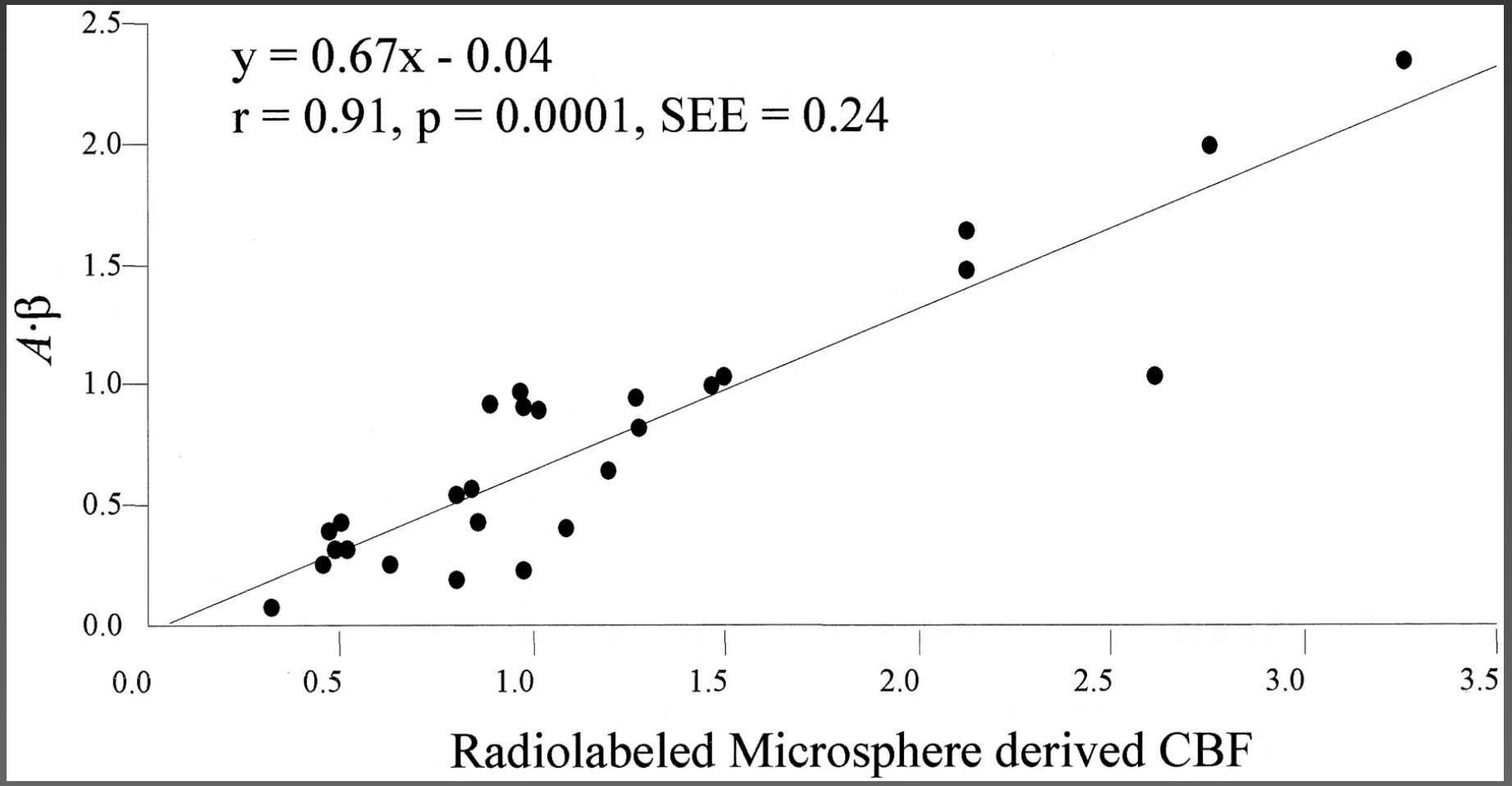


A : plateau intensity (microvascular cross-sectional area = blood volume)

β : rise rate of intensity (microbubble velocity)

(Wei et al. Circulation 97:473-483,1998, Rim S-J et al. Circulation 104:2582-2587, 2001, Seidel et al. Ultrasound Med Biol 27:1059-1064,2001, 28:183-189, 2002)

Correlation with CBF



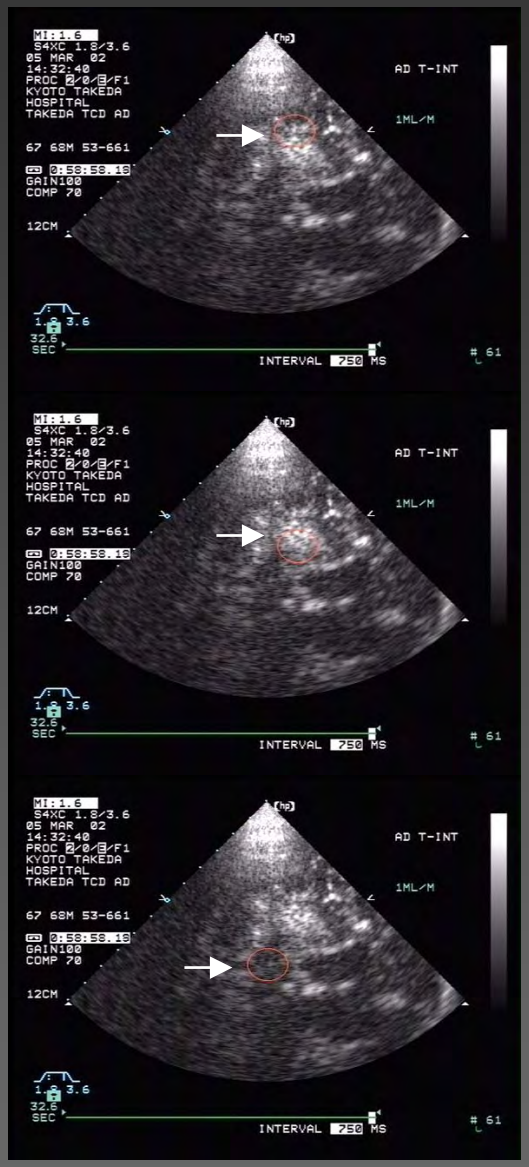
Rim S-J et al. Circulation 104:2582-2587, 2001

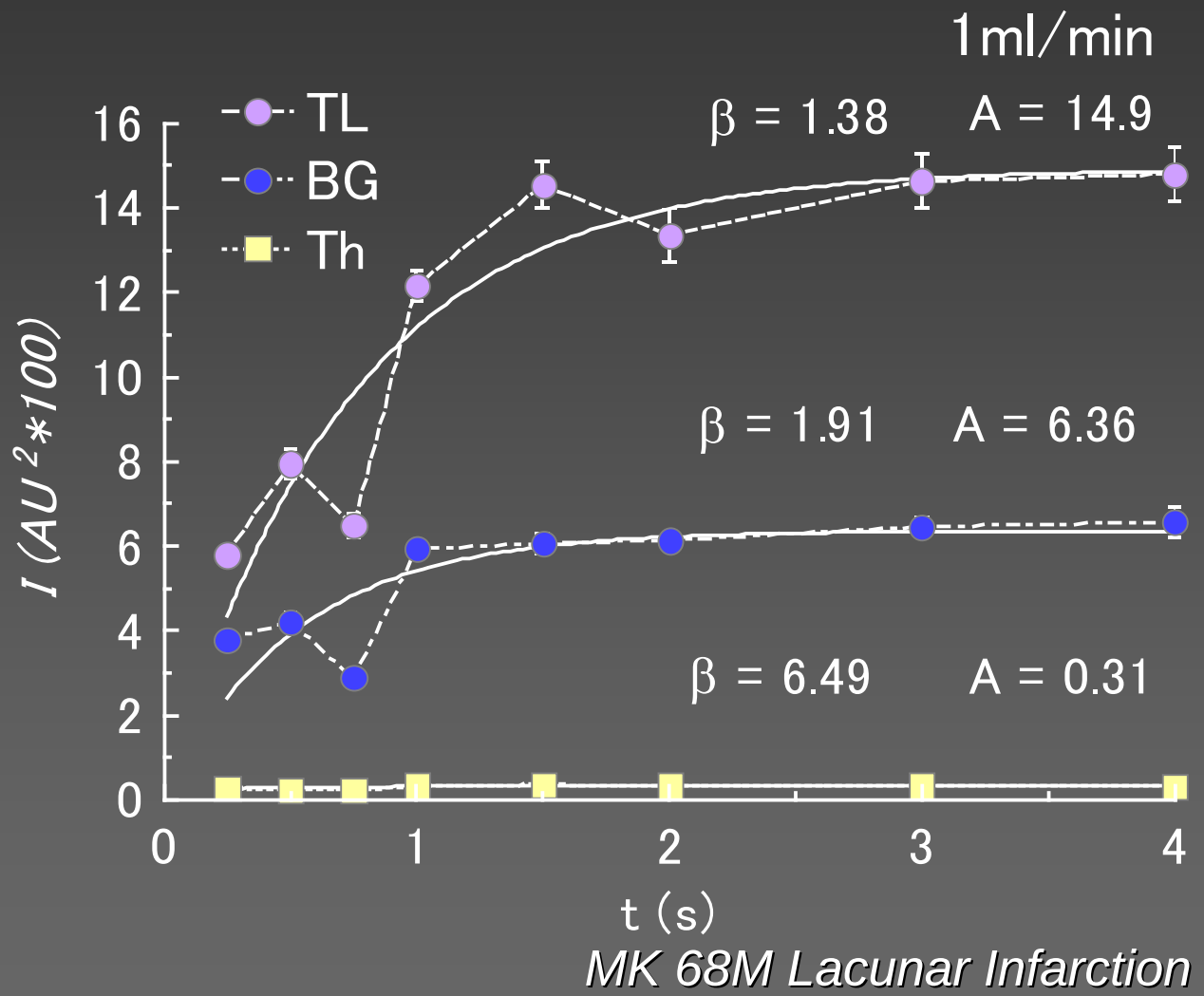
Refill Kinetics

TL

BG

Th

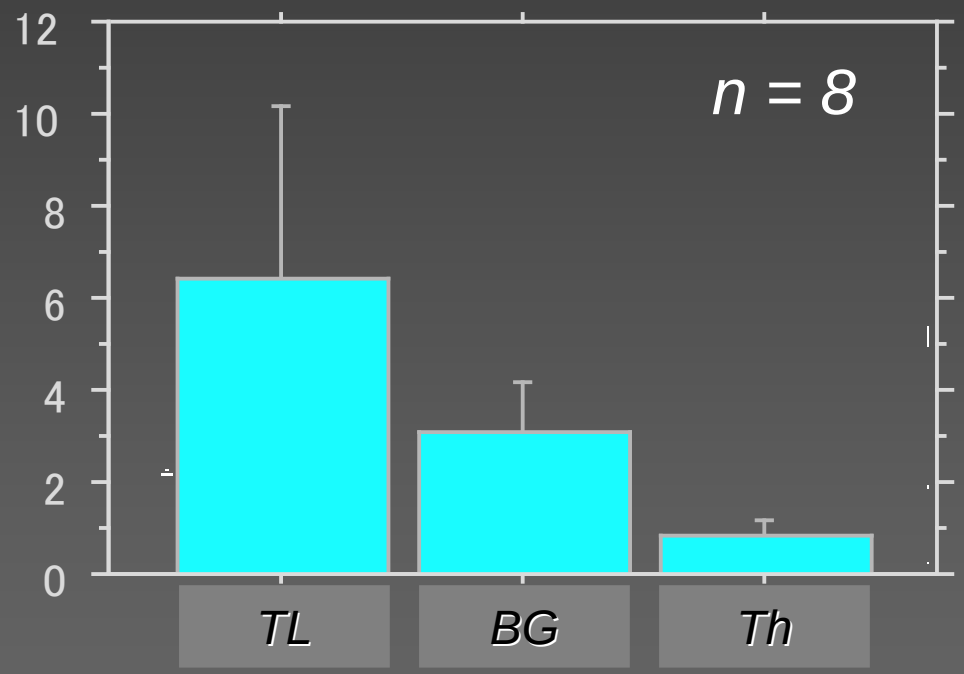




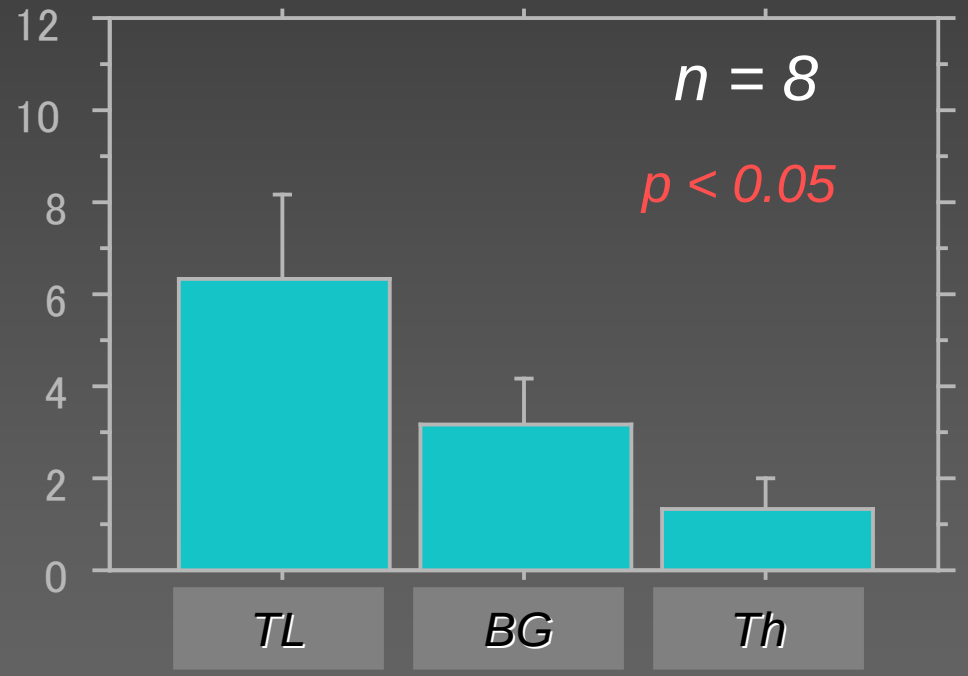
MK 68M Lacunar Infarction

Shiogai et al. Acta Neurochir 95:183-190, 2005

Parameter A in the 3 ROI Sites



0.5 ml/min

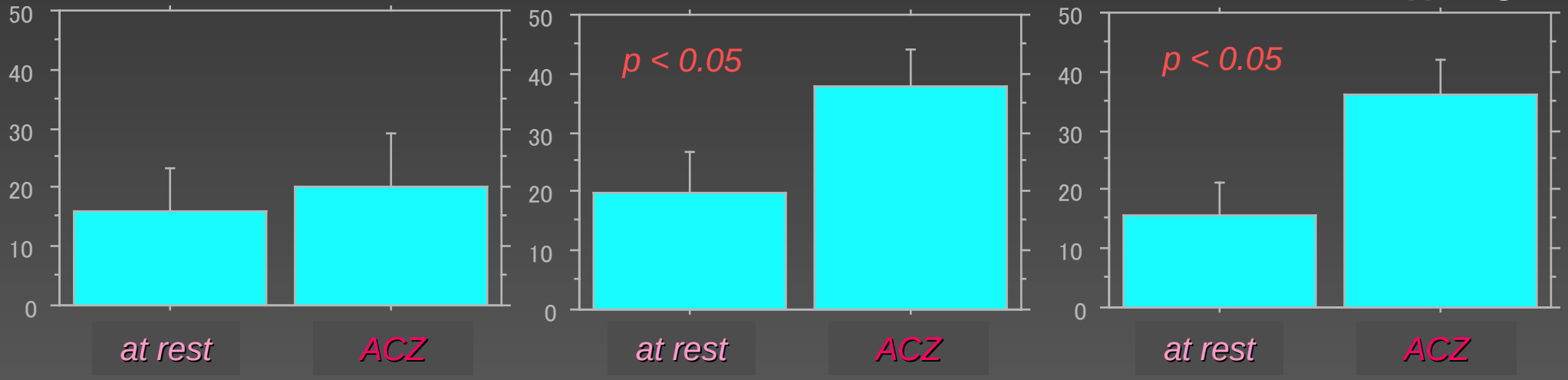


1 ml/min

ACZ Effects for β

0.5 ml/min

n = 8

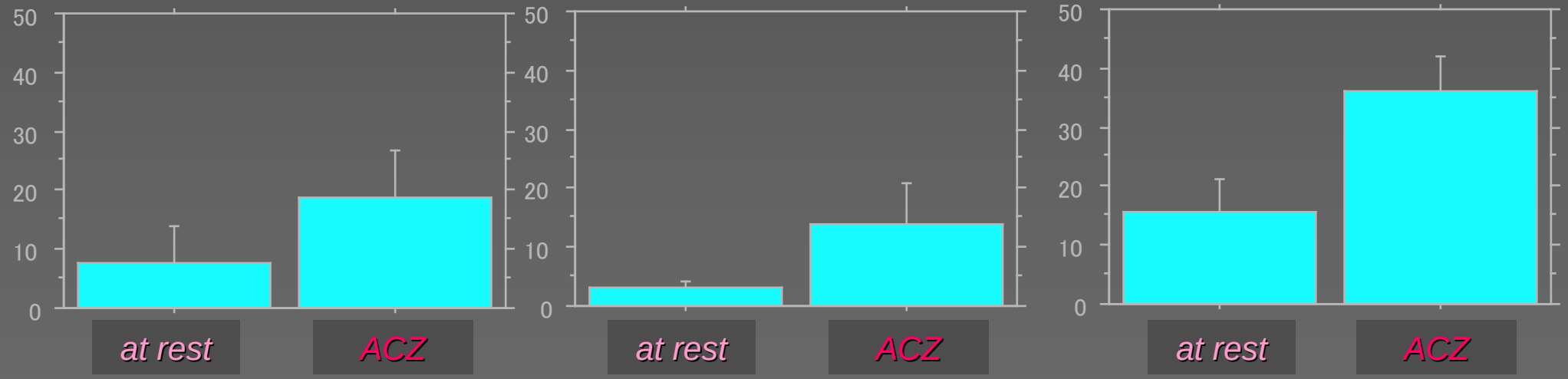


1 ml/min

TL

BG

Th



Related Factors of Optimal Transcranial Perfusion Imaging of the Brain

a) Signal processing and imaging procedures

- sufficient resolution and sensitivity (high S-N ratio)
- precise anatomical orientation
- simple and quicker visualization

1) Gray-scale imaging (IBS, B-mode, Pulse-inversion, etc)
   Color-coded imaging (PHI, Power Pulse-inversion, Parametric imaging, etc)
2) Harmonic imaging (2nd, ultra-, 1.5-, sub-harmonics?)
   Fundamental imaging (CBI, TVI, ADF, Dynamic flow, etc)
   CPS, Power modulation, Power modulated pulse-inversion
3) Transient response imaging
   Continuous (real-time) imaging
4) Transmitting and receiving frequencies
   less bone-dependent attenuation
5) Ultrasound contrast agents
   1. Levovist
   2. Sonazoid, SonoVue, Optison, Definity, etc

Optimal Transcranial Perfusion Imaging of the Brain

b) Evaluation

Qualitative or Quantitative (Semi-quantitative)

1) Methods:Bolus or Infusion
2) Transducer fixation (Sonopod)
3) Analysis (kinetics):

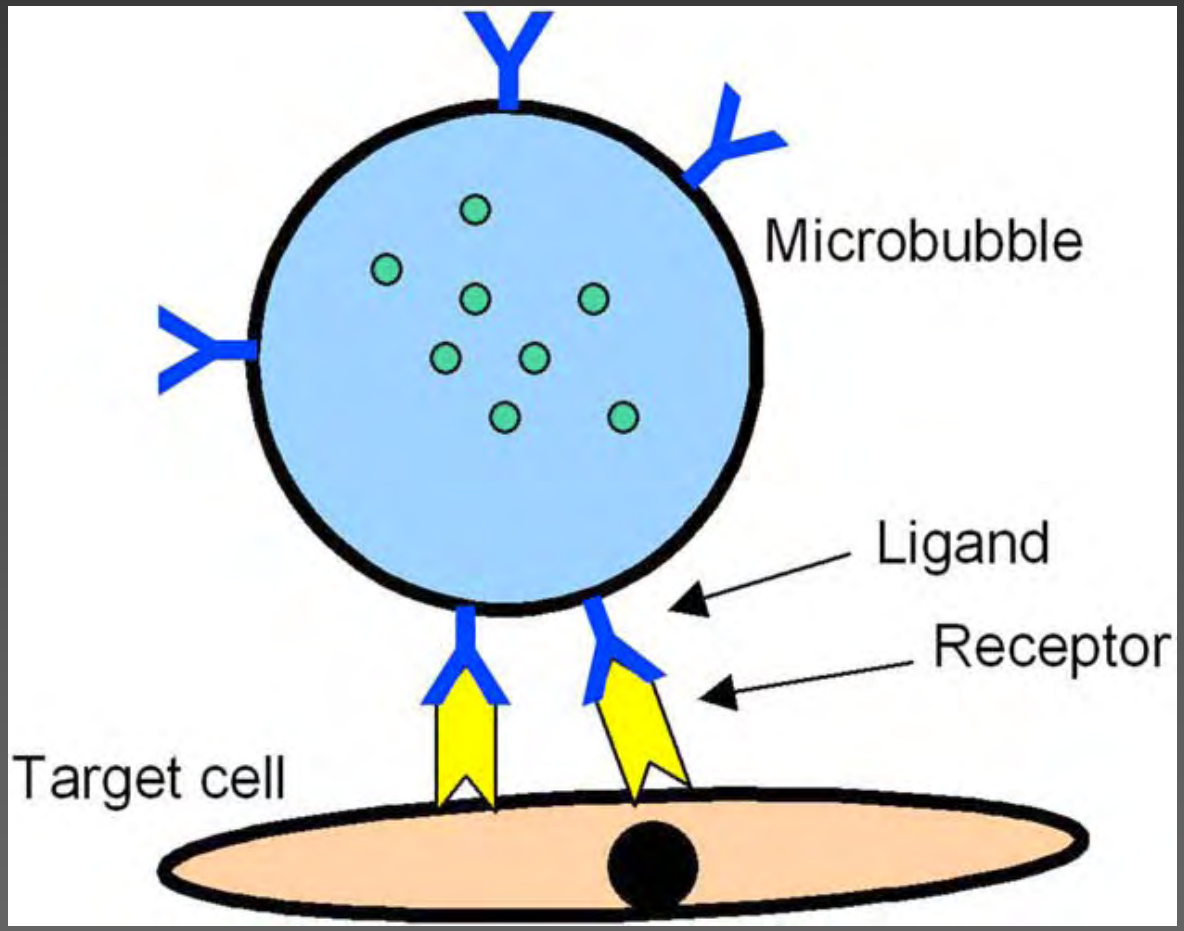
Bolus, Refill, and Depletion (Diminution, Destruction)

Therapeutic Application

1. Sonothrombolysis
   - Combined with t-PA (MCA/BA)
   - Levovist, SonoVue, Definity, MRX-801 (SonoLysis™)
2. Sonodynamic therapy
   - Sonoporation, BBB opening
   - Drug Delivery System, DDS
   - Apoptosis
   - Sonotransfection
     - Carotid stenosis, etc
3. Targeting Imaging

   endothelial cells, thrombus, inflamed tissue, angiogenesis
   - Molecular Imaging
     - Glycoprotein (GPIIb/IIIa):C_4F_{10} (MRX-408), C_3F_8, SF_6
     - Selectin, Integrin, ICAM-1, VEGFR2, etc

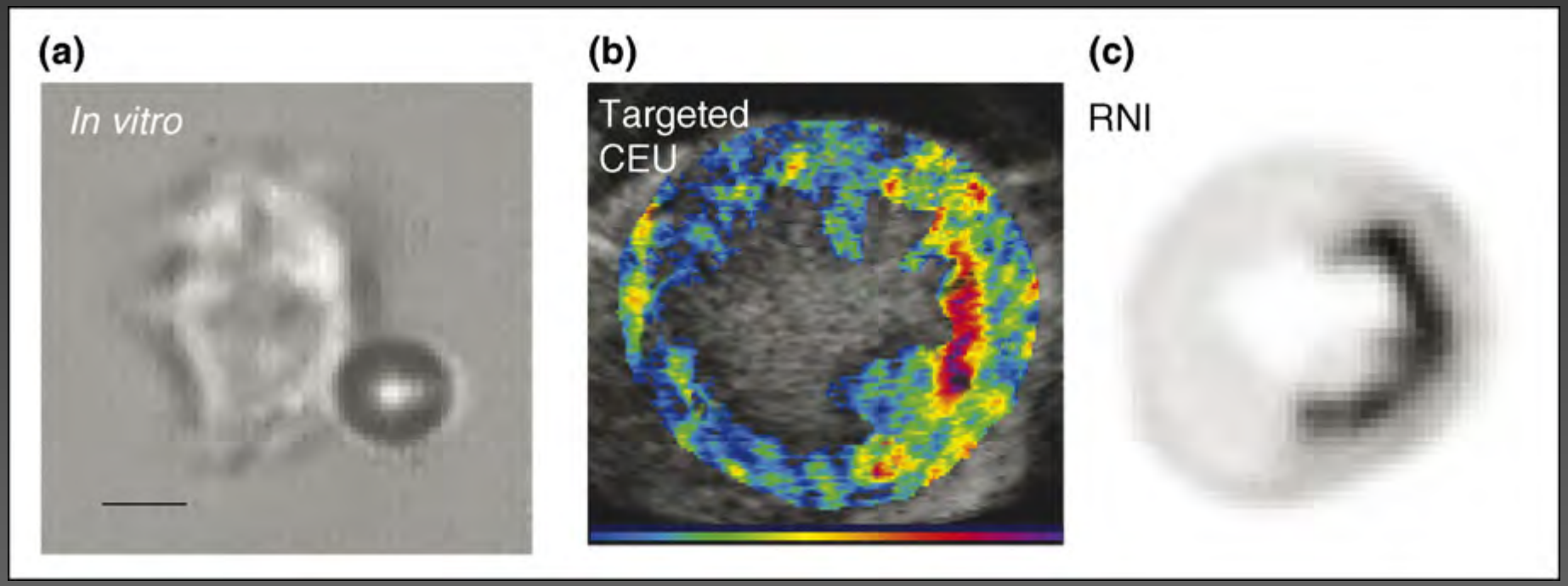
Targeted Microbubbles



endothelial cells
thrombus
inflamed tissue
angiogenesis

Dijkmans et al. Eur J Echocardiogr 5:245-256, 2004

Bubble Targeting Imaging



Leucocyte-targeted microbubbles

Post –ischemic myocardial inflammation

Kaufmann and Lindner Curr Opin Biotechnol 2007;18:11-16.

Conclusions

Further studies would be indispensable in establishing not only optimal transcranial perfusion imaging, but also therapeutic microbubble applications to the brain.