

# Introduction

Dementia of Alzheimer type (DAT) is characterized by progressive impairment of memory and cognitive function. In recent years, several studies have suggested that the early treatment of DAT using cholinesterase inhibitors such as donepezil hydrochloride could improve symptoms and might even delay progress. Cerebral blood flow (CBF) was imaged using a single scan with iodine-123-N-isopropyl-p-iodoamphetamine (IMP) perfusion tracer. Quantitative CBF data normalization was performed by means the auto-radiographic (ARG) method with one-point arterial blood sampling.

This study was undertaken to evaluate the use of 3D perfusion isosurface measures as a new method for providing 1) a rapid overall quantitative assessment of global CBF (gCBF) as compared to the conventional 2D ROI method and 2) a rapid, quantitative, and accurate assessment of the increase in gCBF as a measure of donepezil hydrochloride DAT treatment efficacy.



# Methods 1

## 23 DAT Patients

1. 8 male and 15 female patients
2. Mean age:  $71.7 \pm 5.0$  years
3. DAT diagnosis criteria: Diagnostic and Statistical Manual of Mental Disorders, 4th edition.
4. Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog.): 10-53
5. Mini-Mental State Examination (MMSE): 10-26

## Donepezil Treatment

Donepezil hydrochloride (Aricept™, Eisai, Tokyo): 5mg/day dose was administered to all patients after breakfast

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# Methods 2

## IMP SPECT: CBF using the ARG method

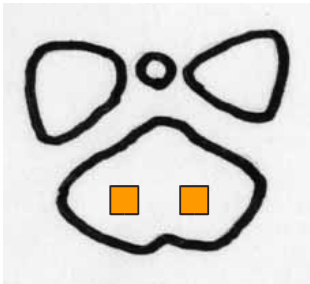
1. 167 MBq of I-123-IMP (Nihon Medi-Physics Co. Ltd., Japan) was injected intravenously over 1 minute.
2. Arterial blood sampling was done at 10 minutes after IMP injection.
3. In order to calculate CBF, the total blood count was measured with a well-type scintillation counter (ARC 300, Aloka Co. Ltd., Japan).
4. Three-headed gamma camera (GCA-9300A, Toshiba, Japan) equipped with a low energy super high resolution fan beam collimator used for data acquisition with an angular step of  $4^\circ$ , 30 steps at 60 sec/step and a  $128 \times 128$  matrix size.
5. Reconstruction performed using a Ramp filter and Butterworth-Low-Pass filter.
6. Attenuation correction applied using the Chang method to first order .



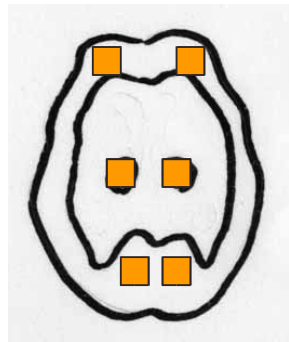
# Methods 3.1

## Regional CBF Analysis

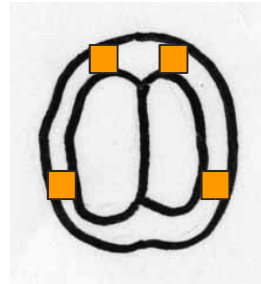
- Square regions of interest (ROIs) (9 X 9 pixels) were positioned, using the BrainGuide™ medical image analysis software (Advanced Biologic Corp., Toronto), in the following four brain structures



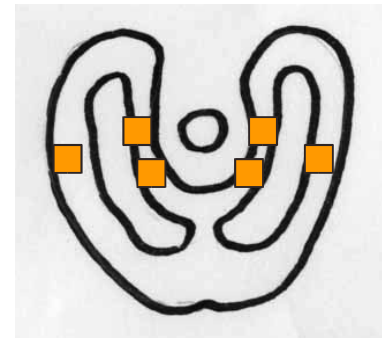
Cerebellar slice



Thalamic slice



Parietal slice



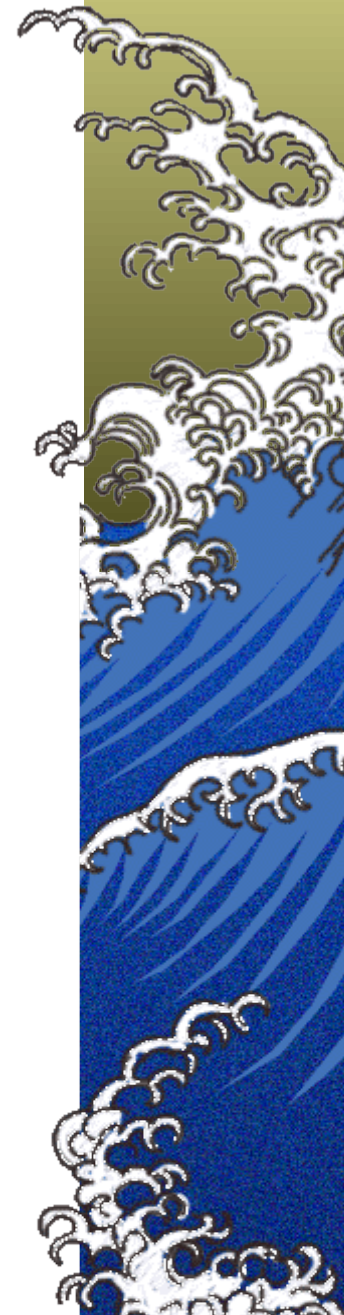
Hippocampal slice



# Methods 3.2

## Global CBF Analysis

- 3D perfusion isosurfaces (surfaces of constant perfusion) at 20, 30, 40, and 50 [ml/min/100g] were automatically generated using the BrainGuide™ medical image analysis software (Advanced Biologic Corp., Toronto, Canada).
- For each isosurface with a unique value, BrainGuide™ also generated
  - 1| 3D-PSA: the surface area associated with a isosurface value
  - 2| 3D-PSEV: the volume of brain tissue enclosed by the selected isosurface,
  - 3| the derived ratios:
    - $3D-PSR(1) = 3D-PSA / 3D-PSV,$
    - $3D-PSR(3/2) = (3D-PSA)^{3/2} / 3D-PSV,$  and
  - 4| 3D-PSIV: the integral of total blood flow within the enclosed isosurface.



# Methods 4

## CBF Evaluation of Donepezil Treatment

- Iodine-123-IMP SPECT patient baselines were acquired before treatment with donepezil hydrochloride.
- Iodine-123-IMP SPECT data was subsequently re-acquired for each subject at a mean interval of 4 and 10 months during treatment with donepezil hydrochloride.
- Changes in regional and global CBF in patient IMP SPECT were visually and quantitatively compared and the effect of donepezil hydrochloride on CBF was evaluated.

## Statistical Analysis of Data

- Data are shown as mean  $\pm$  SD. Wilcoxon's matched pairs signed-rank test was used in the analysis of two paired groups. P values less than 0.05 were considered statistically significant.



# Results 1

## Visual CBF Inspection for Each Patient

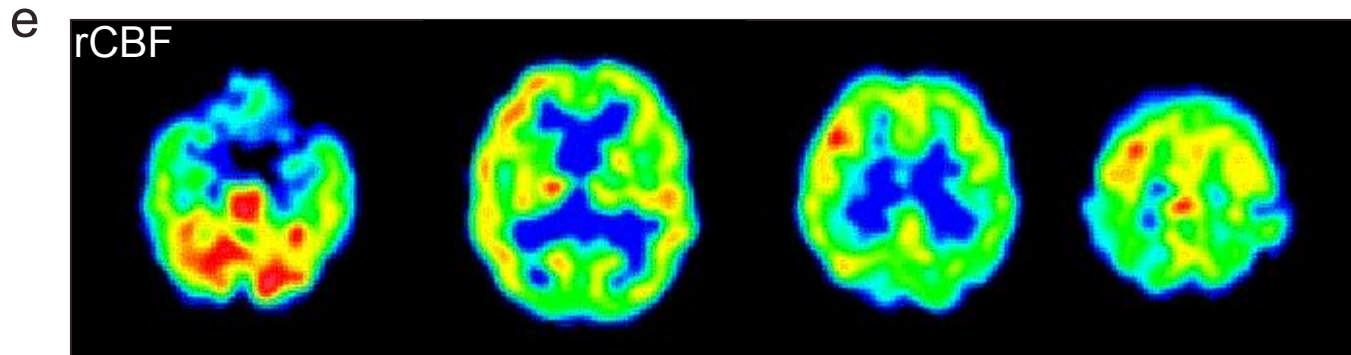
- For the 23 DAT patients, global CBF was observed to have
  - improved in eleven cases (47.8%)
  - exhibited no change in six cases (26.1%), and
  - deteriorated in six cases (26.1%).
- For the same patients, regional CBF was observed to have
  - improved in seven cases (30.4%),
  - exhibited no change in twelve cases (52.2%), and
  - deteriorated in four cases (17.4%).
- For 5 of the 23 patients (21.7%), no significant change in regional CBF was observed in any region , but 3D perfusion isosurface analysis revealed
  - increased 3D-PSA, 3D-PSIV, and 3D-PSEV in 3 cases and
  - decreased 3D-PSA, 3D-PSIV, and 3D-PSEV in 2 cases.



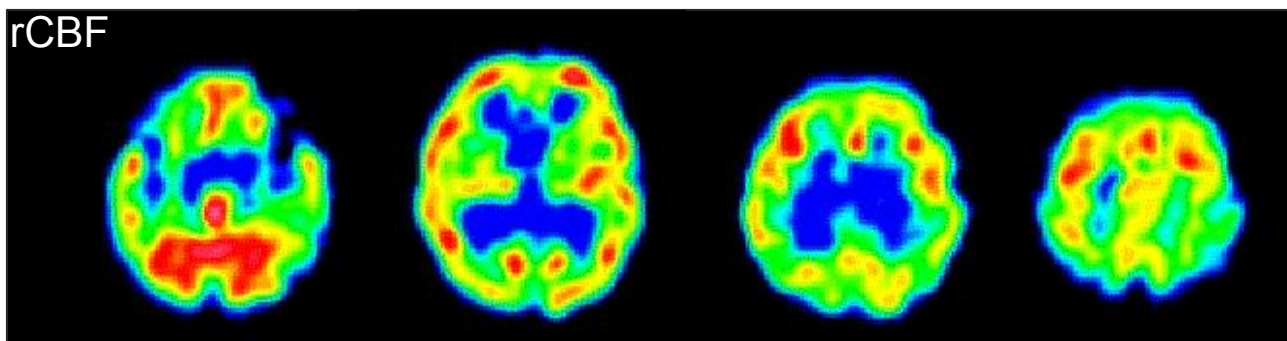
# Results 2.1

Improvement in both regional and global CBF

Regional CBF: **Before** treatment with donepezil hydrochloride



Regional CBF: **After** treatment with donepezil hydrochloride

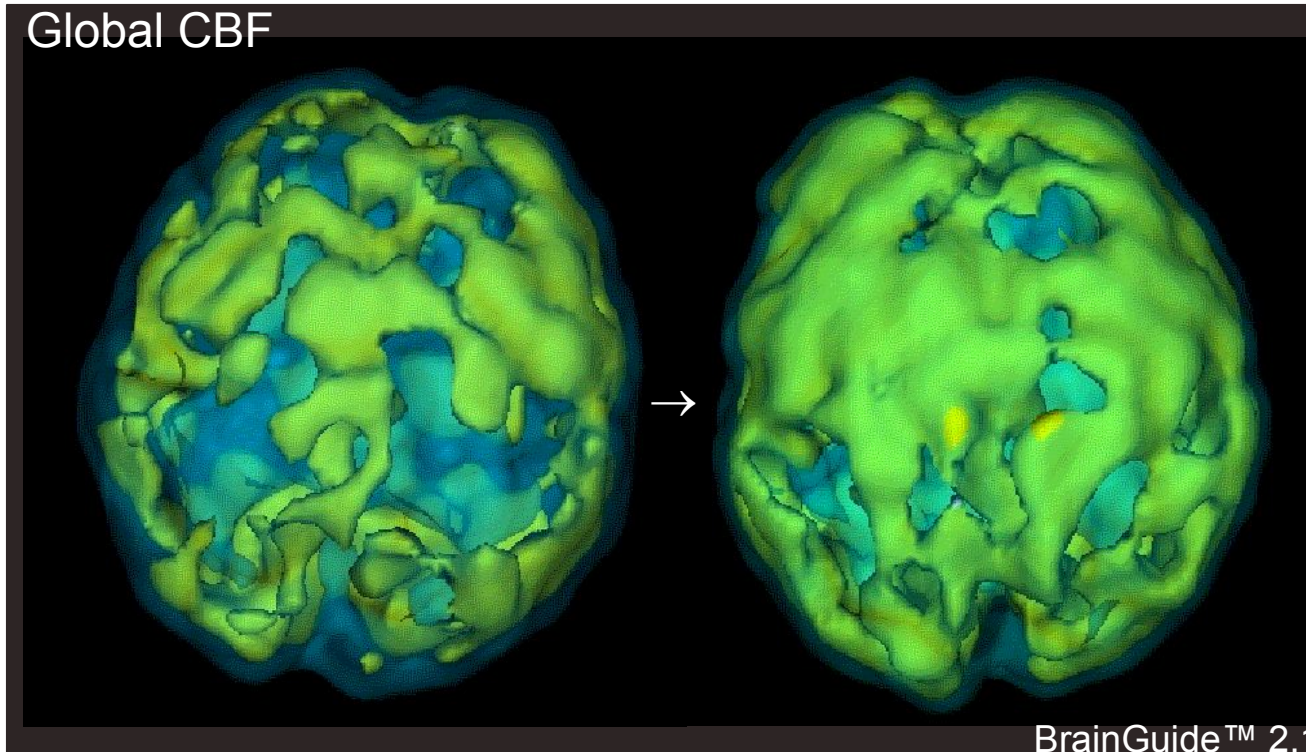


# Results 2.2

## Improvement in both regional and global CBF

|       | Before treatment |   | After treatment |
|-------|------------------|---|-----------------|
| ADAS: | 25.4             | → | 20.7            |
| MMSE: | 22               | → | 24              |

Global CBF



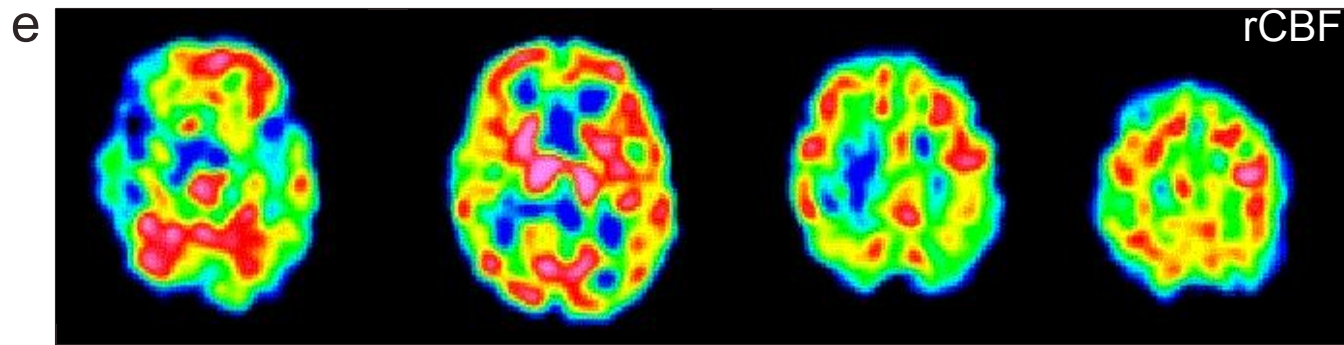
Perfusion Isosurface: 30 [ml/min/100g]



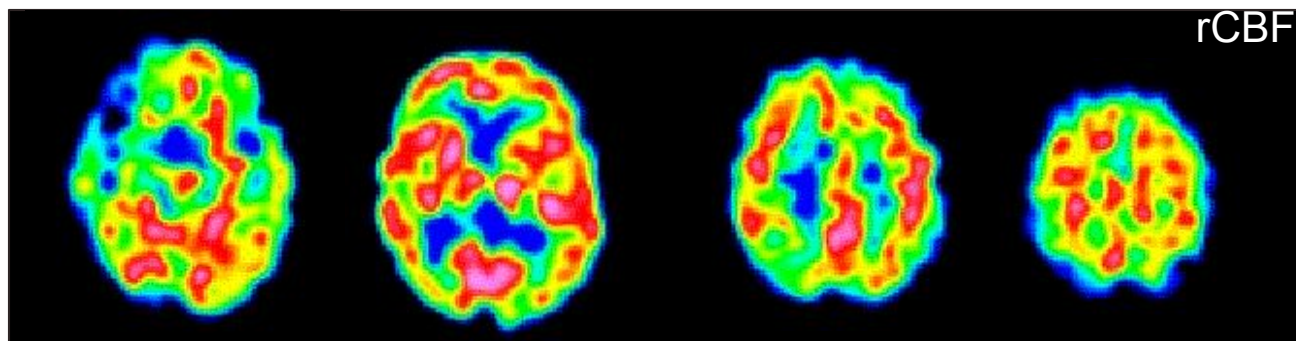
# Results 3.1

## Improvement in global CBF only - not rCBF

Regional CBF: **Before** treatment with donepezil hydrochloride



Regional CBF: **After** treatment with donepezil hydrochloride



No improvement in regional CBF. Neither ADAS (pre: 17.7) or MMSE (pre: 21.0) was examined after treatment. However, the caregiver's impression was that the patient's condition had improved.



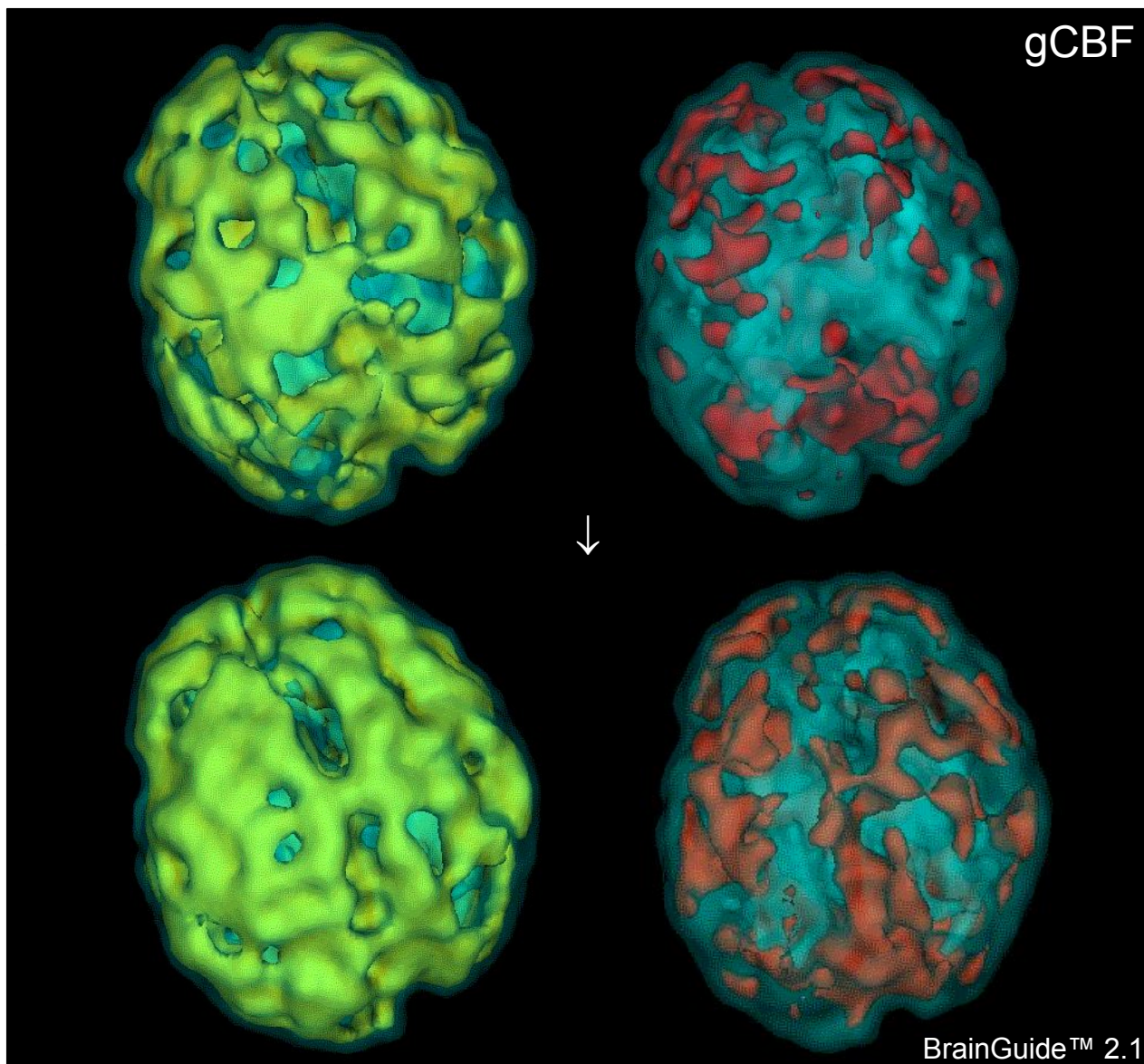
# Results 3.2 Improvement in gCBF only

Global CBF

Before Treatment

↓ Donepezil hydrochloride

After Treatment



Isosurface: 40 [ml/min/100g]

50 [ml/min/100g]



# Results 4.1

## Quantitative Assessment of Cerebral Blood Flow

**Regional CBF:** in the prefrontal (lower part), occipital, and parietal lobes rCBF increased significantly in the second follow-up IMP SPECT after donepezil hydrochloride treatment.

| Region                  | RH Before Treatment | RH After Treatment | LH Before Treatment | LH After Treatment |
|-------------------------|---------------------|--------------------|---------------------|--------------------|
| cerebellar hemisphere   | 32.9 ± 7.0          | 36.9 ± 5.3         | 32.9 ± 6.4          | 36.5 ± 6.4         |
| prefrontal lobe (upper) | 24.6 ± 5.7          | 26.9 ± 4.3         | 25.5 ± 7.7          | 27.2 ± 6.3         |
| prefrontal lobe (lower) | 26.4 ± 6.4          | <b>31.5 ± 6.3</b>  | 26.5 ± 7.2          | <b>29.5 ± 6.2</b>  |
| thalamus                | 40.8 ± 8.2          | 45.2 ± 7.9         | 42.0 ± 10.8         | 42.6 ± 8.2         |
| occipital lobe          | 27.8 ± 5.5          | <b>32.9 ± 6.6</b>  | 28.3 ± 4.8          | <b>34.5 ± 6.1</b>  |
| parietal lobe           | 21 ± 5.6            | <b>25.6 ± 6.9</b>  | 20.2 ± 5.5          | <b>25.1 ± 4.6</b>  |
| temporal lobe (lateral) | 21.3 ± 6.1          | 21.9 ± 4.1         | 21.6 ± 4.7          | 22.7 ± 4.8         |
| hippocampus             | 19.4 ± 5.3          | 20.6 ± 5.9         | 20.1 ± 4.7          | 19.4 ± 4.7         |
| parahippocampus         | 20.6 ± 5.8          | 21.1 ± 5.3         | 21.6 ± 5.9          | 22.4 ± 5.3         |

RH  
≡ Right Hemisphere

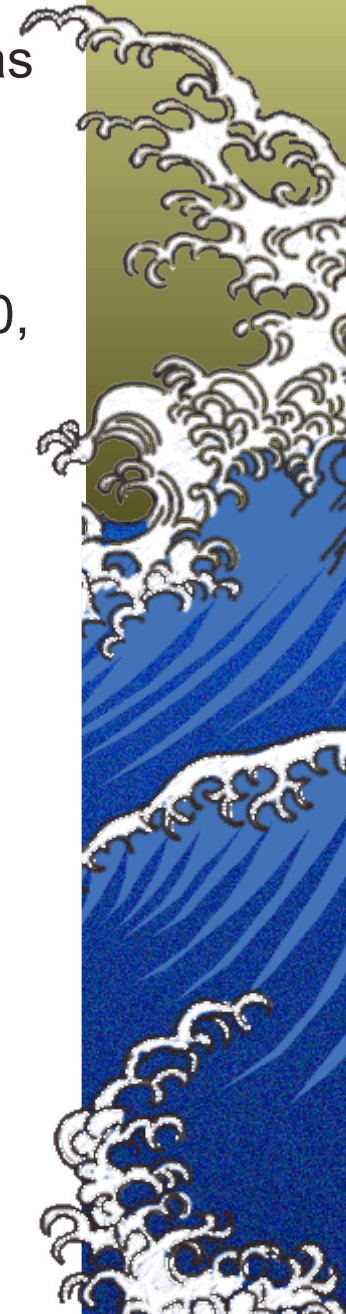
LH  
≡ Left Hemisphere



# Results 4.2 Quantitative Assessment of CBF

**Global CBF:** in follow-up SPECT, a statistically significant increase in gCBF was indicated by 3D perfusion isosurface measures ( $p < 0.01$ ). Values of PSA, PSEV, and PSIV in isosurfaces 30, 40, 50, and PSIV in isosurface 20 (all [ $\text{ml}^2/\text{min}/100\text{g}$ ]) increased significantly. Moreover, those of PSR(1) in isosurfaces 30 and 40, and PSR(3/2) of isosurface 20 (all [ $\text{ml}^2/\text{min}/100\text{g}$ ]) significantly decreased.

| Isosurface                           |      | 20        | 30        | 40        | 50        |
|--------------------------------------|------|-----------|-----------|-----------|-----------|
| PSA ( $\text{cm}^2$ )                | Pre  | 944±111   | 730±298   | 339±305   | 89.7±127  |
|                                      | Post | 951±104   | 814±219   | 398±299   | 119±138   |
| PSEV (ml)                            | Pre  | 799±164   | 381±235   | 107±117   | 19.4±30.4 |
|                                      | Post | 841±132   | 429±207   | 133±120   | 28.1±35.3 |
| PSIV ( $\times 10^3$ )<br>[min/100g] | Pre  | 24.8±7.58 | 14.4±9.57 | 4.93±5.51 | 1.08±1.70 |
|                                      | Post | 26.7±6.48 | 16.4±8.74 | 6.17±5.75 | 1.58±2.00 |
| PSR (1) (1/ml)                       | Pre  | 0.12±0.03 | 0.26±0.13 | 0.47±0.21 | 0.50±0.30 |
|                                      | Post | 0.12±0.02 | 0.23±0.09 | 0.40±0.15 | 0.54±0.23 |
| PSR (3/2)                            | Pre  | 38.1±10.3 | 60.3±11.8 | 59.3±22.7 | 36.8±27.6 |
|                                      | Post | 35.9±8.12 | 61.1±15.5 | 62.5±14.9 | 42.3±23.8 |



# Discussion

- From the visual and quantitative results, we find that the 3D perfusion isosurface method is a more sensitive measure than the 2D ROI method of the efficacy of DAT treatment with donepezil hydrochloride as measured by an increase in cerebral blood flow (CBF).
- This observation may be understood as follows:
  - If donepezil hydrochloride treatment resulted in strongly differential increases in regional CBF, then the 2D ROI method would prove superior for determining which regions were most affected.
  - However, in the present study, when an increase in CBF was observed, it was found to occur consistently in all regions where the 2D ROI measurements were made.
  - Thus, increases in CBF due to donepezil hydrochloride treatment are a global brain phenomenon, and are most sensitively measured using a single large 3D global measure of CBF as opposed to several smaller 2D regional measures (ROIs).
  - An integrative gCBF measure will reduce the statistically contaminating effects of noise better than sampling 2D ROIs.



# Conclusions

- Donepezil hydrochloride treatment increased both regional and global cerebral blood flow (CBF). As CBF reduction in DAT is usually progressive, this result suggests that donepezil hydrochloride is efficacious against DAT. However, the improvement in regional and / or global CBF was not observed in all patients. A prospective study would help reveal why CBF does not always increase after treatment.
- 3D perfusion isosurface measures may prove to be a set of useful techniques for
  - 1| the rapid, quantitative, clinical assessment of the global progress of DAT in patients and
  - 2| the rapid, quantitative, and accurate assessment of the efficacy of drug treatments.

