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Several studies of intravenous digital subtraction angiography (IVDSA)[1-5] suggested that some parameters of time-density curve, time course of regional absorption value, reflect transition of iodinated contrast media, and their laterality detects the asymmetric cerebral perfusion. In patients with ischemic stroke, this technique may provide information about the state of residual blood flow. We here report a study, which shows the laterality of time-density curve in cranial IVDSA well correlates with the asymmetric blood flow determined by positron emission tomography (PET).

Theoretical Backgrounds

In a vascular system, a transition of an ideal bolus of non-diffusible indicator has a distribution of transit time, rather than a single transit time[6]. When a region contains a volume, V, of vascular bed, and blood enters and exits at a constant flow rate, F, and a bolus indicator has a mean, t, of a distribution of transit time (mean transit time), then

$$V = F\, t..$$

This equation[6] is transformed as

$$t = (F / V)^{-1}. \qquad (1)$$

Thus, the mean transit time of a non-diffusible indicator including iodinated contrast media is an equivalent to the reciprocal of vascular blood flow (blood flow rate per unit volume of vascular bed). However, we can not directly obtain mean transit time with intravenous injection of contrast media, because they pass through pulmonary circulation, and arrive at arteries with a non-bolus distribution. Nagata and Basugi[7] studied a theoretical model for cerebral transition of non-bolus contrast media, using a computer simulation method. They showed that time from intravenous injection to the peak of regional time-density curve (peak time: PT) has a linear correlation to the mean transit time, that is

$$PT = a\,t + b,$$

where the constant, *b*, corresponds to the mean arrival time of non-bolus contrast media. This constant is uniform in a pair of symmetric regions in left and right cerebral hemispheres, and disappears in a subtraction to obtain peak time laterality. Now we indicate the right- and left-sided parameters of symmetric regions by $_r$ and $_l$, then

$$PT_r - PT_l = a\,(t_r - t_l). \qquad (2)$$

From *equations 1 and 2*,

$$PT_r - PT_l = a\,[\,(F / V)_r^{-1} - (F / V)_l^{-1}\,], \qquad (3)$$

which indicates that the laterality of peak time correlates the laterality of the reciprocal of regional cerebral vascular blood flow (1/rCVBF). We can not obtain absolute values of rCVBF or regional cerebral blood flow (rCBF) from this study, as shown in *equation 3*. A unilateral reduction of rCBF in a region, however, results in prolonged peak time, and the laterality of peak time will reflect the degree of the reduction in certain extent. Thus, we examine the peak time laterality obtained from IVDSA study, and its correlation with the lateralities of 1/rCVBF and rCBF determined by PET studies.

Subjects and Methods

We examined 5 stroke patients, 3 males and 2 females, aged 44-67 years. Angiogram in acute phase had revealed the unilateral occlusion of their internal carotid or middle cerebral artery (three left- and two right-sided). All patients underwent IVDSA and PET with one day interval, in the third month after the last stroke episode.

In IVDSA, we introduced a straight catheter with multiple side holes via an antecubital vein, and placed the tip in superior vena cava. Patients received a bolus injection of 40 ml of ioxaglic acid (Hexabrix, 320 mg I/ml, Gueret S. A., Aulnay, France) in 2 seconds. With 4-8 seconds of delay time, cranial images of Towne's view were obtained at a rate of 7.5/sec, with a 512 by 512 matrix. We studied time density curve of subtracted cranial images with an image analyzing minicomputer (RPF-40A, Toshiba, Tokyo, Japan) and its software for function analyses. A pair of 4 adjacent square regions of interest (ROIs) was placed in cerebral hemispheres (figure 1). The bottoms of lower ROIs were just above the horizontal portion of MCA, and the tops of upper ROIs located at the level of distal anterior cerebral artery. The analyzing system plotted the change of mean density over time for each ROI, and fitted a g-curve to the graph (figure 2, A-C). We obtained the peak time as the time from injection to the positive peak of the g-curve.

A PET scanner (PT931, CTI, Knoxville, Tenn., USA) performed a 15-minute transmission scan with a retractable germanium-68-gallium-68 ring source before the study.

The patients underwent rCBF study by $C^{15}O_2$ steady state inhalation methods, and regional cerebral blood volume (rCBV) study by $C^{15}O$ bolus inhalation, with sufficient washout interval. In each study, the scanner collected emission data for 7 minutes with arterial blood samplings, and the data were reconstructed to 14 plains parallel to the orbito-meatal line with an 8 mm axial and transaxial resolution. We selected 8 continuous slices from just above chiasmatic cistern to the ceiling of lateral ventricles. In each slice, 4 adjacent ROIs, 2 medial rectangular and 2 lateral half-elliptic, covered the medial and lateral halves of bilateral hemispheres. The reported methods[8),9)] provided rCBF and rCBV for each ROI. Then, we calculated the rCBF and rCBV values corresponding to the 8 ROIs in IVDSA study as follows: the mean rCBF of right lateral ROIs in the lower 4 slices is for the right lateral lower ROI in IVDSA, etc. We defined rCVBF as rCBF/rCBV in each region.

Right-to-left subtraction calculated the lateralities of peak time, rCBF and 1/rCVBF for 4 pairs of symmetric regions in 5 patients. Statistical analyses were performed with Statflex statistical package (JIP, Tokyo, Japan). We evaluated the goodness to fit to normal distribution for each variable by kurtosis and skewness, and then analyzed the relation between variables by Pearson correlation coefficients, and linear regression analysis, as appropriate.

The Research Ethics Committee of Tohoku University School of Medicine approved this study. The patients, or their spouses and siblings, gave written informed consents.

Results

The ranges (mean ± SD) of right-to-left lateralities of peak time (sec), 1/rCVBF ($1/ml/cm^3/min$), and rCBF (ml/100g/min) were -2.3 to 1.5 (-0.5 ± 1.0), -0.065 to 0.101 (0.007 ± 0.039), and -14.6 to 20.8 (-0.6 ± 8.6), respectively. The kurtosis and skewness of each variable did not deny the normal distribution. Peak time laterality significantly correlated with laterality of 1/rCVBF (figure 3; left). The relation has linear nature as *equation 3* predicted. Peak time laterality also showed a significant negative correlation with laterality of rCBF (figure 3; right). Figure 3 exhibits the comparable degree of these two correlations.

Discussion

The linear correlation of the lateralities of peak time and 1/rCVBF (figure 3: left) is consistent with *equation 3*, and underlines our theoretical considerations. This equation, however, dose not predict the relation of the lateralities of peak time and rCBF itself, so we directly examined the relation of these two variables. The result shows comparable linear correlation (figure 3; right). These facts reveal the sensitivity of peak time laterality in IVDSA study as an indicator of unilateral rCBF reduction. We can apply the methodology of time-density curve to dynamic CT[10)] and "ultra-fast" magnetic resonance imaging[11)].

Peak time laterality may also be useful to evaluate asymmetric rCBF in tomographic images.

Spatial resolution of IVDSA limits its current indication, but the quality of the image is sufficient to detect significant stenoses and occlusions in carotid arteries[12]. The combination of conventional projection images and time-density curve study in IVDSA may provide useful information, for example, in thrombolytic interventions in acute ischemic strokes, which need to exclude carotid occlusion and evaluate residual blood flow[13].

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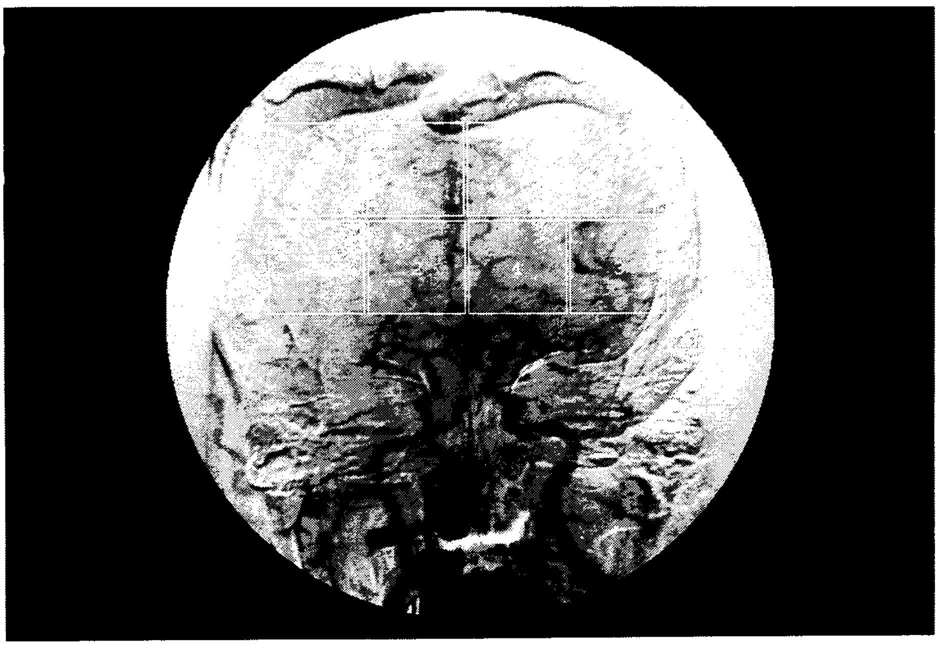

Fig. 1. Regions of interest placed on an IVDSA image of Towne's view.

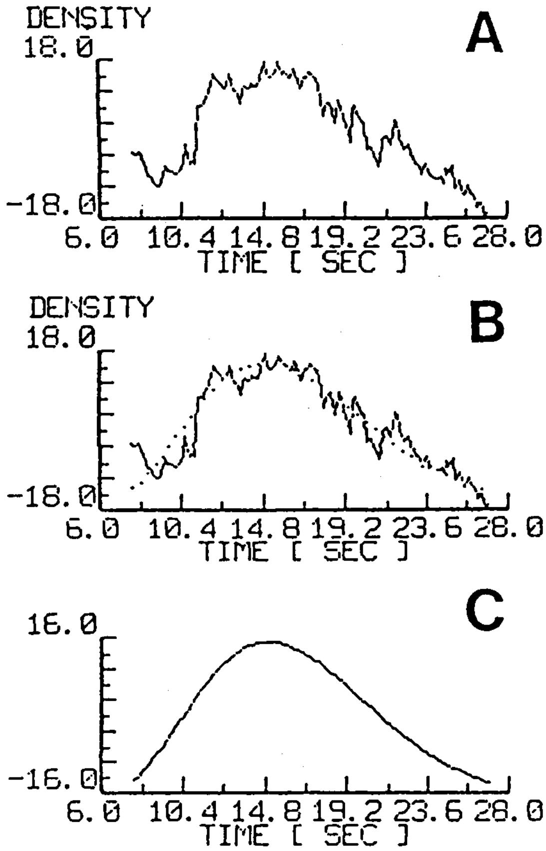

Fig. 2. An example of time-density curve study in IVDSA. Low data of mean density over time for each ROI (A) were subject for g-fitting (B). We defined peak time as the time from injection to the positive peak of the g-curve (C).

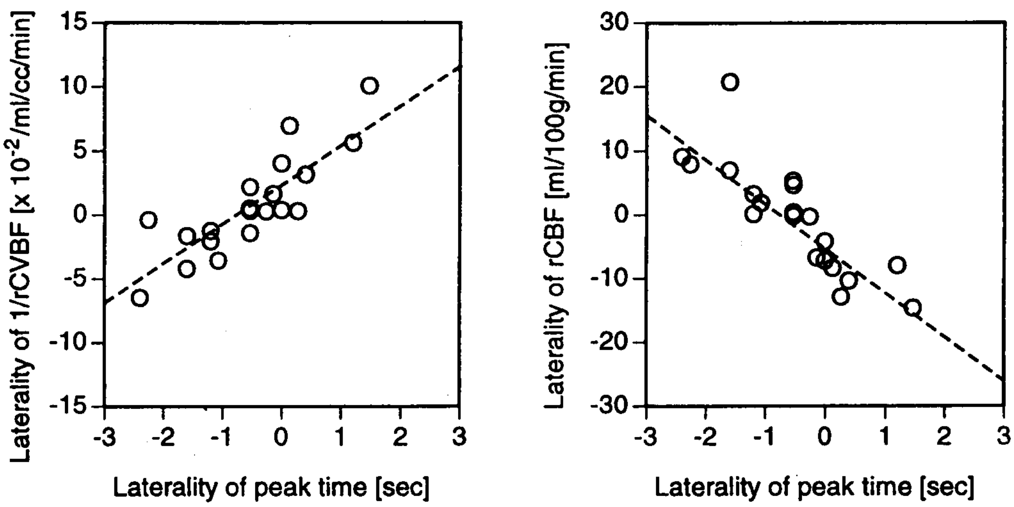

Fig. 3. Peak time laterality shows significant linear correlation both with laterality of 1/rCBVF (left; $r = 0.85$, $p < 0.001$) and with laterality of rCBF (right; $r = -0.84$, $p < 0.001$). Dotted lines indicate the results of linear regression analyses ($y = 0.03\,x + 0.02$, and $y = -7.15\,x - 4.31$, respectively).