Increased Cerebrovascular Reactivity In Selected Brain Regions After Extracranial-Intracranial Bypass Improves The Speed of Visual Cancellation In Patients With Severe Steno-Occlusive Disease: A Preliminary Study

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Abstract

The effect of the change in cerebrovascular reactivity (CVR) in each brain area on cognitive function after extracranial-intracranial bypass was examined as a preliminary study in 20 patients with severe steno-occlusive disease. CVR studies and the visual cancellation task (VC) were performed before and after surgery. The Speed and Accuracy scores of the VC, which increased with improvement after the operation, were evaluated. CVR increased postoperatively both ipsilaterally and contralaterally to the surgery. Before surgery VC completion time was delayed, but accuracy was relatively maintained. In stepwise and least absolute shrinkage and selection operator (LASSO) regression models, two regions (right inferior frontal gyrus and right uncus) for the Speed score and one region (right superior occipital gyrus) for the Accuracy score were common brain regions associated with CVR change after surgery. The Speed and Accuracy scores of brain regions of the right cerebral hemisphere, which may be anatomically distant from the blood vessel anastomosis, were related to CVR change. Moreover, in the ischemic stage, with reduced CVR but no cerebral infarction, processing speed might decrease to maintain accuracy, and revascularization might increase the processing speed. In revascularization, the relationship between CVR change and the speed-accuracy trade-off in each brain region should be considered.

Introduction

The impaired cerebral hemodynamic status resulting from chronic hypoperfusion (i.e., severe steno-occlusive disease of an intracranial artery, Moyamoya disease) has been thought to cause cognitive decline [1, 4, 12]. If so, improving cerebral hemodynamics by surgical extracranial-intracranial (EC-IC) bypass should improve cognitive function. There are many previous reports on whether improving cerebral hemodynamics with extracranial-intracranial bypass improves cognitive function, since some showed improvements in processing speed, whereas others did not; the issue remains controversial [13, 17]. Thus, the relationship between cerebral hemodynamics and cognitive function may not simply be a link between the change in cerebral blood flow and the level of cognitive function.

Cerebrovascular reactivity (CVR) is a measure of the brain hemodynamic status and is defined as the change in cerebral blood flow (CBF) in response to a vasoactive stimulus; it reflects the ability of the cerebral vasculature to augment CBF when cerebral perfusion pressure is reduced and when neural activity is increased [8]. Surgical revascularization for severe steno-occlusive disease can improve CVR and reverse the paradoxical reduction in the ipsilateral hemisphere and often in the contralateral hemisphere; the areas of the brain where CVR improves after EC-IC bypass vary from case to case [10, 21]. In addition, cognitive function is classified into many types, each of which is associated with a specific brain region [2, 19]. From that perspective, when examining the effects of surgery, CVR and cognitive function should be examined in each brain region. In previous studies, however, the effects of surgery on cognitive function were not classified by brain region, although the areas where CVR improves differ from patient to patient.

It was hypothesized that examining CVR and cognitive function before and after EC-IC bypass in each brain region would show whether the improved CVR contributed to the improvement of cognitive function. We have previously investigated the relationship between lesion location and attention deficit after stroke, and we showed that the areas related to attention deficit differ depending on the type, and that the reaction time is related to the right cerebral hemisphere [19]. Attentional function is thought to cover a wide range of functions in the left and right cerebral hemispheres. Thus, this study focused on the completion time and accuracy of the visual cancellation task (VC), which is one of the widely used tests of attention function.

Material And Methods

Patients

This retrospective study was conducted as a preliminary study after approved by the Research Ethics Committee of Hiroshima City Asa Citizens Hospital and Hiroshima University (E-466-3, E-1554-2). Written, informed consent was obtained from all participants. In this study, 20 consecutive patients who underwent EC-IC bypass for severe steno-occlusive disease of the intracranial internal carotid artery (ICA) or middle cerebral artery (MCA) at Asa Citizens Hospital from September 2017 to April 2020 were reviewed. The inclusion criteria for this study were the following: 1) patients with symptomatic intracranial steno-occlusive disease who had rCBF of the ipsilateral MCA less than 32 mL/100 g/min (corresponding to 80% of the normal value), and a CVR less than 10% on a quantitative SPECT study with acetazolamide (ACZ) challenge [11]; and 2) patients with available preoperative and postoperative (3–6 months or later post surgery) CVR studies available. Exclusion criteria were as follows: 1) allergy to contrast media; 2) renal dysfunction (estimated glomerular filtration rate < 30 ml/min/1.73 m²); or 3) medical illness, physical disability, or speech impediment precluding the VC task. Twenty patients were selected on the basis of the inclusion criteria (5 women; mean age at the time of bypass 66.9 years). The etiology included atherosclerosis (n = 18) and Moyamoya disease (n = 2) (Supplemental Table 1).

Assessment of cognitive functions

To assess attention deficit, four kinds of VCs (Kana, Triangle, Symbol, Number) included in the Clinical Assessment for Attention (CAT), which is a standardized test for attention deficit, were used as previously described [19]. Participants used a pencil to cross out a target stimulus dispersed within rows of randomly placed interfering stimuli displayed on a sheet. These tasks were scored as speed (completion time) and accuracy. Accuracy was based on the ratio of the number of correct answers to the total number of items (% correct answers) or the number of accurate answers compared to the number of total responses (both correct and incorrect responses) (% accurate answer).

It is known that the scores of the VC depend on age. To correct by age, age-matched values were calculated as (VC score)/(age specific mean VC value); the lower the age matched % correct answer and

% accurate answer, the greater the attentional disturbance. Moreover, the higher the age-matched completion time, the greater the attentional disturbance.

The changes in the age-matched time and accuracy scores between before and after EC-IC bypass of each of the 4 VCs were scored as “1” for “improved (time was faster, and correct rate was increased)” and as “0” for “not improved (time was equal or slower, and the correct rate was equal or decreased)”. Then, the speed score was calculated as the sum of the speed values of the four VCs (score range from 0 to 4). The accuracy score was calculated as the sum of the values of the % correct answers and the % accurate answers of the VCs (score range from 0 to 8).

Measurement and analysis of cerebral blood flow

Scans for rCBF were performed just before and 10 minutes after injection of 1.0 g of acetazolamide. Regional cerebrovascular reactivity (rCVR) was calculated as follows: $rCVR(\%) = [(acetazolamide\ challenge\ rCBF - resting\ rCBF) / resting\ rCBF] \times 100$. A three-dimensional stereotactic surface profile program (3D-SSP, Nihon Medi-Physics, Tokyo, Japan) was used to spatially normalize the local distribution. The change of CVR (post-operative CVR – pre-operative CVR) was calculated, and the anatomical classification was evaluated using the stereotactic extraction estimation method: (SEE method LEVEL3) [18].

Operative procedure

Under general anesthesia, with continued antiplatelet medication perioperatively, a skin incision was made just over the superficial temporal artery (STA) frontal branch or parietal branch. Under microscopy, meticulous STA dissection was conducted. Then, the skin incision was extended toward the forehead, and a skin flap was reflected. The frontal branch of the STA was dissected. After craniotomy, an STA-MCA single or double anastomosis was performed between each STA branch and the recipient M4 (cortical MCA branch). Successful bypass was confirmed by microvascular Doppler evaluation.

Statistical analysis

Normality assumptions for each value were analyzed using the Shapiro-Wilk test, and mean (95% confidential interval: CI) was calculated for normal distribution and the median (interquartile range) were calculated for the non-normal distribution. To compare differences between two groups, Fisher’s exact test was used for categorical variables, and the Mann-Whitney U-test was used for quantitative variables. The level of significance was set at $p < 0.05$.

To test the correlations between the time or the accuracy score and the CVR change in the 31 brain areas on each side (62 in total), bivariate analysis (Spearman’s rank correlation coefficient, ρ) was performed. A cross-correlation matrix was constructed after calculation of Spearman’s rank correlation coefficient (ρ). Then, the hierarchical clustering was built from the bottom-up by joining the closest clusters at each step according to the defined distance and linkage functions [20]. The result was represented by a dendrogram.

Stepwise multiple linear regression analysis based on the Akaike information criterion (AIC) was used to estimate the independent effects of predictor variables on the Speed or Accuracy score (forward–backward selection method). These predictor variables were as follows: age, sex, laterality of the operation, and the CVR changes in the 31 brain areas on each side (62 in total). To assess multicollinearity, the variance inflation factor (VIF) was calculated.

A least absolute shrinkage and selection operator (LASSO) regression model was used to choose the optimized subset of brain regions related to CVR change to predict the Accuracy or the Speed score. First, 10-fold cross-validation was used to obtain the best hyperparameters, while all factors were degenerate. Thus, lambda was set up in ways that 6 values were residual through trial and error.

To compare the performance of the LASSO model, three metrics were calculated between the actual Speed or Accuracy score and the predicted Speed or Accuracy score obtained from all folds: the coefficient of determination (R^2), the squared correlation coefficient (r^2), and root-mean-square error (RMSE). The values were considered significant at $p < 0.05$. All data were analyzed using R (version 3.6.2).

Results

Baseline characteristics

A total of 20 consecutive patients were included in this study, all of whom underwent EC-IC bypass (laterality of operation: 9 were right and 11 were left) without adverse events. Magnetic resonance angiography (MRA) confirmed bypass patency in patients 3–6 month after surgery. The subjects consisted of 15 males and 5 females (age: 66.9 ± 2.3 years, etiology: 18 atherosclerosis and 2 Moya-Moya Disease).

Visual Cancellation Task

The age-matched completion time for all four VC tasks before EC-IC bypass was widely distributed in the range greater than 1, suggesting many cases to be slower than the average completion time (Fig. 1A). The median age-matched completion time of all 4 VCs tended to be closer to 1 after EC-IC bypass (completion time became faster), but no significant difference was observed (Fig. 1A, supplemental Table 1).

Compared with the age-matched completion time, the age-matched accuracy (% correct answer and % accurate answer) for all four VC tasks before EC-IC bypass tended to be distributed in a narrow range close to 1, and there was no remarkable change after extracranial-intracranial bypass (Fig. 1B, supplemental Table 1).

Therefore, the speed of the visual cancellation task tended to be slower, whereas accuracy was maintained before surgery.

CVR change after extracranial-intracranial bypass

Figure 2 and Supplemental Table 2 show the CVR change after EC-IC bypass. The cortical regions of the frontal, parietal, and temporal lobes, which are anatomically close to the blood vessel anastomosis, showed a marked CVR increase. In addition, CVR increased in the ipsilateral hemisphere, but it also increased to a lesser extent in the contralateral hemisphere, occipital lobe, and the deep brain region (i.e., thalamus, limbic system), which were anatomically distant from the blood vessel anastomosis.

Bivariate analysis: Cross-correlation matrix and hierarchical clustering

The correlation matrix of all parameters showed that the CVR changes in the 62 brain regions had strong correlations with each other (Fig. 3A). This suggests that multicollinearity is a problem when performing multivariate analysis.

The hierarchical clustering showed 8 clusters (Fig. 3B, C). Among them, clusters 1–3 showed right side dominance, cluster 4 showed left side dominance, and cluster 5 showed a mixture of right and left sides (but dominance anatomically distant from the blood vessel anastomosis).

Multivariate analysis

To identify the brain regions associated with the Speed score, a stepwise multiple regression model suggested 6 related regions (Table 1). Among them, 2 regions (right inferior frontal gyrus and right uncus) consisted of 2 of the 6 related regions detected with the LASSO regression models (Fig. 4A; Table 3).

To identify the brain regions associated with the Accuracy score, the stepwise multiple regression model suggested one related region (right superior occipital gyrus), which consisted of one of the 6 related regions detected with the LASSO regression models (Fig. 4B; Table 2, 3).

In the LASSO regression model, the correlation coefficients of the Accuracy and Speed scores were reversed positive and negative in the right precuneus, respectively (Table 3).

The scatter plot of the predicted Accuracy score or Speed score vs. the actual Accuracy score or Speed score of the LASSO regression model to predict the accuracy score showed a relatively low R^2 value (supplemental Fig. 1).

The results of the stepwise and LASSO regression models showed that the related regions of clusters 3 and 5 occupied a large part, and the brain region common to both models was the right cerebral hemisphere. Therefore, it was considered that the Speed and Accuracy scores involved the brain region of the right cerebral hemisphere, which may be anatomically distant from the blood vessel anastomosis.

Discussion

In this study, the change in cognitive function after revascularization surgery was evaluated by dividing the results of VC into speed and accuracy scores, and the relationships with the change in CVR were investigated for each brain region. CVR was increased not only in the cortical region near the anastomotic site on the ipsilateral hemisphere, but also in the occipital lobe, deep brain region, or contralateral hemisphere far from the anastomotic site. This was consistent with previous reports [10, 21]. Therefore, the effect of changes in CVR after surgery on cognitive function should be examined separately for each brain region. Then, multivariate analysis showed that the brain region where changes in CVR affect speed and accuracy is mainly in the right hemisphere, including the region far from the anastomotic site.

We previously demonstrated that right hemisphere damage led to a delay in cognitive processing speed after stroke [24]. Delay of the processing speed was thought to be related to a deficit of arousal or sustained attention, which was affected with damage of specific brain regions of the right hemisphere; i.e., temporo-parietal junction or frontal lobe) [5, 9, 14]. Moreover, the network systems coordinating motor control and visual signals were thought to be associated with inferior parietal systems and the temporal lobe [7]. From these observations, the brain regions related to speed were thought to cover a large territory of the right hemisphere (mainly the cortical region). Therefore, regardless of whether revascularization was performed on the left or right, it was thought that increased CVR in the right hemisphere would lead to an increase in processing speed.

In this study, before revascularization, the completion time of VC was delayed, but the accuracy (% correct answer and % accurate answer) was relatively maintained. Previous reports examined the processing speed and accuracy of elderly people, showing a tendency to slower processing speed and maintained accuracy compared with young people [3]. However, our previous study and others showed that brain damage increased false recognition (reduced accuracy) after stroke [4, 24, 25]. There might be one possibility that accuracy was preferentially maintained at the cost of speed (slow down) under the condition of CVR reduction (ischemia before infarction). This relationship between speed and accuracy has been called the “speed-accuracy trade-off” in the area of human kinematics (kinesiology) [6].

In the many previous studies of the “speed-accuracy trade-off”, inhibition of ongoing thought and action was focused when a mistake was noticed: if the stopping process wins, thought and action are inhibited (slow but more accurate); if the ongoing process wins, thought and action are executed (fast but less accurate) [15]. This inhibition mechanism has been thought to be related to the cortical-basal ganglia circuit; the basal ganglia output an inhibitory signal on the thalamus like a brake and control the speed and accuracy of some action initiated by cerebral cortical activity [16, 22, 26, 27].

In the right precuneus of the LASSO regression model, the positive and negative correlation coefficients of Speed and Accuracy were reversed, and it might be considered that the increase in CVR in this region contributed to slowing speed and improving accuracy. Moreover, the inclusion of the left thalamus in the remaining factors of the stepwise regression analysis of the speed score may suggest a speed-accuracy trade-off. Revascularization is thought to improve the CVR in the cortical area more than in the deep brain region (i.e., basal ganglia, thalamus), suggesting that the brain area associated with inhibitory function of

the speed-accuracy trade-off is less likely to be effective after surgery than the cortical area, resulting in an increase in processing speed. However, the speed-accuracy trade-off mechanism may be adjusting so that the accuracy does not decrease even if the speed increases. Therefore, it may be difficult to obtain a significant improvement in cognitive function after EC-IC bypass for patients with severe steno-occlusive disease in previous studies.

The present result demonstrated that the effect of CVR improvement on the processing speed was mainly related to the right hemisphere. Our previous study that examined the cognitive function related to car driving showed the negative impact of right hemisphere damage on the processing speed in stroke patients, suggesting the importance of preservation of the right hemisphere function for maintaining quality of life [23, 24]. Traditionally, in EC-IC bypass, greater attention has been paid to preservation of the dominant hemisphere than the nondominant hemisphere. However, given the results of the present study, it is also necessary to consider whether the function of the right hemisphere is preserved.

Study Limitations

The number of subjects in the present study was small, and statistical analysis issues could have been a problem due to the large number of explanatory variables for the objective variable, the problem of multicollinearity, and overfitting. To solve these problems, the LASSO regression model was used, and it showed the factors common to these two models, suggesting that these problems were minimized. Moreover, many previous papers examined the effect of EC-IC bypass on cognitive function with long-term follow up (6 months to 2 years or more), but the present study had relatively short follow-up (3 months). In the future, it will be necessary to carry out analyses using data obtained from more cases with longer-term follow-up.

Conclusions

This study suggested the following. In the ischemic stage, when CVR is reduced but there is no cerebral infarction, processing speed decreases to maintain accuracy, and revascularization increases the processing speed. However, processing speed might be adjusted so that accuracy would not be lowered by the speed-accuracy trade-off mechanism. More data will be needed before the clinical implications of these findings become clear. However, we have pointed out the possibility for the first time that it is necessary to pay attention to the “speed-accuracy trade-off” for each brain region when investigating the effect of revascularization surgery on cognitive function. Therefore, considering the results of the present study, a different concept in the discussion of the relationship between cerebral hemodynamics and cognitive function is proposed.

Declarations

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Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Availability of data and material: The datasets generated and/or analysed in the current study are available from the corresponding author upon reasonable request.

Code availability: Not applicable.

Authors' contributions: KS and SH conceived and designed the study. SH, AF, and TT performed the statistical analysis and interpreted the results. AY participated in data collection. AK, HA, SY, and TM interpreted the results. All authors reviewed and edited the manuscript.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review boards and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Research Ethics Committee of Hiroshima City Asa Citizens Hospital and Hiroshima University (E-466-3, E-1554-2).

Consent to participate: Written, informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable.

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Tables

Due to technical limitations, table 1, 2 & 3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Box plots and dot plots of differences in age-matched completion time (A), and % correct answers and % accurate answers (B) between pre- (grey) and post-(white) extracranial-intracranial bypass for each of the 4 VCs. Box plots show medians, quartiles, and 10th and 90th percentiles. The dotted line shows the average. Dash-dot-dash line shows the average pre- and post-operation completion time or % correct and % accurate of 4 VCs. Score=1 indicates the age-matched average.

Figure 2

Box plots and dot plots of differences in CVR change between pre- and post-operation (vertical lines indicate standard deviation) classified by treatment side (right: gray dots and left: white dots) of each brain region. Box plots show medians, quartiles, and 10th and 90th percentiles. The dotted line shows the average.

Figure 3

Correlation matrix for the correlation features of all parameters. The direction and strength of the linear relationship between the parameters including CVR change of 62 brain areas, age, sex, and laterality are represented by Spearman's rank correlation coefficient (ρ) (ranging from -1 to +1; coded in red and blue, respectively) (A). Hierarchical clustering was performed based on Spearman's correlation coefficient, and each factor is shown in a heat map (B) and a dendrogram (C), suggesting 8 clusters.

Figure 4

LASSO regression model analysis. (A) is the path change chart of the regression coefficient of the speed score, and (B) is the path change chart of the regression coefficient of the accuracy score. The vertical dashed line indicates the value of lambda determined by trial and error so that six variables remain.

Supplementary Files

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