Does Hemispheric Lateralization Influence Functional and Cardiovascular Outcomes After Stroke?

An Analysis of Placebo-Treated Patients From Prospective Acute Stroke Trials

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Background and Purpose—The influence of stroke lateralization on functional and cardiovascular outcome after stroke is not well established. We evaluated the influence of hemispheric lateralization among patients enrolled in prospective acute stroke trials.

Methods—We obtained data from the VISTA database for acute stroke trials which reported lateralization. Baseline data, cardiac adverse events, and 90-day outcomes were compared between right and left hemisphere stroke patients. A “hemisphere unbiased” subscore of the NIHSS which omitted items strongly associated with lateralized cognitive deficits was also compared for trials which reported individual NIHSS item scores. A multivariable analysis of outcome predictors was performed.

Results—Three acute stroke trials met the prespecified inclusion criteria. 1644 placebo-treated patients with documented hemispheric lateralization were included in the analysis. Baseline NIHSS was higher for left hemisphere patients (mean 16.2, versus 12.8 right, \(P<0.001\)); there was no difference in the “hemisphere unbiased” NIHSS subscore (10.88 left, 11.08 right, \(n=687, P=0.49\)). There was no difference between hemispheres in 90-day modified Rankin Score (3.43 left, 3.29 right, \(P=0.13\)), mortality (22.1% left, 19.5% right, \(P=0.20\)), or cardiac adverse events (\(P=0.71\)). Hemispheric lateralization was not an independent predictor of outcome in the multivariable analysis after controlling for the hemispheric bias intrinsic to the NIHSS.

Conclusions—There is no difference in functional outcome between patients with right or left hemisphere stroke. Use of the baseline NIHSS score to predict stroke outcome must take hemispheric lateralization into account. Stroke lateralization is not an important predictor of cardiac adverse events or 90-day mortality. (Stroke. 2008;39:3335-3340.)

Key Words: cardiac arrhythmia ■ clinical trials ■ functional recovery ■ stroke outcome ■ scales

The lateralization of specialized cortical functions such as language and spatial orientation result in important clinical differences between right and left hemisphere stroke. There is some evidence of a systematic bias in routine clinical practice against patients presenting with right hemisphere stroke, which may not be justifiable. Patients with right hemisphere stroke present later to hospital, are not treated with thrombolysis as frequently as patients with left hemisphere stroke,\(^1,2\) and are underrepresented in trials of other stroke interventions such as carotid endarterectomy.\(^3\) Standard clinical scales of severity of stroke impairments such as the NIHSS emphasize comprehension dependent tasks associated with left-hemisphere lesions more than tasks dependent on right hemisphere functions.\(^4,5\) Imaging studies show that patients with right hemisphere stroke can have a low NIHSS score despite substantial infarct volume.\(^4,6\) But do patients with right hemisphere stroke have better or worse long-term outcome than patients with left hemisphere stroke? The results of studies comparing the functional outcome of patients with right-hemisphere and left-hemisphere stroke have been inconclusive. Some studies of outcome of patients admitted to rehabilitation units have found that patients with right-hemisphere lesions do more poorly than those with left-hemisphere lesions,\(^7-10\) but this has not been found by others.\(^11-13\) Poorer functional outcome for patients with right-hemisphere stroke has been shown in some studies of incident stroke patients,\(^14,15\) but not others.\(^16\)

The role of the insular cortex in autonomic and cardiovascular function and the lateralization of these functions is another area of clinical uncertainty. The role of the insula in cardiovascular autonomic functions is supported by strong experimental evidence,\(^17-19\) and a role of insula infarction in...
causing cerebrogenic arrhythmia and sudden cardiac death has been suggested, particularly right insula infarction.\textsuperscript{20–25} However, others have found no association of insula infarction and sudden death in the acute phase,\textsuperscript{6} or long-term.\textsuperscript{26} Although detailed imaging analysis is required to investigate the specific role of the insula in cardiovascular outcome, the question of association with stroke lateralization can be addressed without this requirement.

Although there should be a wealth of information from well-designed prospective stroke trials available to inform these questions, the majority of stroke studies simply do not report outcomes for right- and left-sided stroke separately. The Virtual International Stroke Trials Archive (VISTA) is a collaborative venture which collects standardized data from placebo-treated patients from numerous clinical stroke trials into a single academic database.\textsuperscript{27} Analysis of data from the VISTA database of from randomized acute stroke trials which have prospectively recorded stroke lateralization provides an opportunity to address the influence of lateralization on clinically important outcomes.

### Methods

At July 2006, the VISTA database contained data from 21 stroke trials.\textsuperscript{27} The database was searched for trials of acute stroke which met the following criteria: (1) hemispheric lateralization of stroke recorded, (2) recruitment within 24 hours of stroke onset, (3) baseline NIHSS score recorded, (4) modified Rankin score (mRS) recorded at 90 days. Three trials met the inclusion criteria. Baseline data extracted for the current study included demographic data and baseline clinical features, including baseline NIHSS score. The mRS at 90 days (mRS90) was considered the primary outcome measure. Favorable functional outcome was defined as mRS less than or equal to 2 (fully independent). Secondary outcome measures included 90-day mortality, NIHSS at 90 days (NIHSS90), and recorded cardiac adverse events during the study period. Patients who died were assigned a NIHSS90 score of 42.

### Baseline Data

Baseline demographic and clinical observation data and outcome data were compared between patients with right and left hemisphere stroke. Student $t$ test was used for continuous variables, Mann–Whitney U test for ordinal variables, and Chi-squared or Fisher Exact tests for categorical variables (Table 1).

### Hemispheric Bias in the NIHSS

A difference in NIHSS scores dependent on stroke lateralization was anticipated because of bias in the NIHSS itself, where a greater number of points may be scored for comprehension-dependent deficits associated with left-hemisphere lesions (eg, dysphasia) than right-hemisphere lesions (eg, inattention).\textsuperscript{5} Two methods were planned to enable the effect of hemispheric lateralization to be examined independent of the hemispheric bias of the NIHSS, while controlling for stroke severity. First, a “hemisphere unbiased” stroke score was constructed by deleting the scores from NIHSS items 1b (LOC questions), 1c (LOC commands), 9 (dysphasia), and 10 (dysarthria), which are strongly biased toward left hemisphere stroke,\textsuperscript{5} and item 11 (extinction and inattention), which is strongly associated with right hemisphere stroke.\textsuperscript{5} The “unbiased” NIHSS score for R and L hemisphere was then compared. This approach was limited, however, by the lack of availability of scores for individual items of the NIHSS from the largest of the 3 randomized controlled trial datasets being studied, which recorded only the total NIHSS scores for each patient. A second method was to use ranked NIHSS scores in a multivariable analysis, described below.
Cardiac Adverse Events
Adverse events were recorded prospectively for all patients within 7 days of stroke onset. All recorded cardiovascular adverse events were categorized into 6 categories: bradycardia, ventricular tachycardia, atrial fibrillation, other nonventricular tachycardia, myocardial infarction, and other. The number and type of cardiac adverse event were compared between patients with right- and left-hemisphere stroke.

Multivariable Analysis of Stroke Outcomes
The univariate relationship of baseline NIHSS score and functional outcome (mRS) for right and left hemisphere patients was examined with Pearson correlation coefficient. The association of baseline demographic variables and clinical observations (including hemispheric laterality) with mRS, NIHSS, and mortality at 90 days was then tested using forward stepwise multiple linear and logistic regression analyses. Baseline variables included in the multivariable analysis were limited to those for which recorded data were available for at least 1500 patients. An exploration of the expected interaction between NIHSS and hemispheric lateralization was planned. To further control for the anticipated hemispheric bias in NIHSS score, the scores were ranked within each hemisphere to provide comparable scales of “relative” stroke severity for each hemisphere, and a multivariable analysis then performed including ranked NIHSS score, lateralization, and outcome.

Results
The complete dataset contained data from 1891 placebo-treated patients with anterior circulation stroke from 3 acute stroke trials, including 1717 ischemic strokes, 163 intracerebral hemorrhage, and 11 “other” or unspecified strokes. Hemispheric lateralization was recorded for 1644 patients, 839 with stroke affecting the left hemisphere, 805 right-sided (P=0.21, binomial distribution).

Baseline Characteristics
A significant difference between hemispheres was present for baseline NIHSS score (L: median 17, mean 16.2; R: median 13, mean 12.8; P<0.001), and for a past history of myocardial infarction (16.0% L, 11.7% R, P=0.041). The distribution of baseline NIHSS scores for patients with right- and left-hemisphere stroke is shown in Figure 1. No other significant differences in baseline variables were detected (Table 1). Missing data are largely explained by differences in parameters recorded for each of the 3 trials. Baseline Oxfordshire Clinical Stroke Project (OCSP) classification28 was available for 826 patients from a single clinical trial and was used for an exploratory subgroup analysis. There was a trend toward a difference in OCSP between hemispheres (P=0.059), with a greater number of patients with left-hemisphere stroke being classified as “total anterior circulation syndrome” (TACS, 41.3%) than right-hemisphere stroke (33.4%; comparison of “TACS” versus non-“TACS” P=0.018, Fisher Exact test).

The “hemisphere unbiased” subset of the NIHSS score could be calculated for 687 patients (356 L, 331 R, P=0.18) and did not differ between right and left hemisphere (median 11 both R and L, mean 10.88 L, 11.08 R, P=0.49). Of these patients, normal scores for all of the motor items of the NIHSS (motor arm, motor leg, facial palsy) were recorded for only 2 patients with left hemisphere stroke and for no patient with right hemisphere stroke (P=0.50).

Cardiac Adverse Events
Two hundred seventy-two cardiac adverse events were recorded within 7 days of stroke onset among 86 (10.3%) patients with left-hemisphere stroke and 87 (10.8%) patients with right-hemisphere stroke (P=0.71). The cardiac adverse events recorded were atrial fibrillation (96 events), other nonventricular tachycardias (70), bradycardia (70), ventricular tachycardia (23), and myocardial infarction (13). There was no significant difference in the distribution of these events between right- and left-hemisphere patients, with 129 events recorded among the left-hemisphere patients, and 143 right (χ²=4.076, P=0.40). Cardiac AE were significantly associated with a past history of MI, but adjustment for baseline imbalance in MI between L and R hemisphere stroke did not change the analysis result.

Stroke Outcome
Modified Rankin Scale score at 90 days (mRS90) was available for 1591 patients with documented stroke lateralization. The mRS90 did not differ between patients with right or left hemisphere stroke: mean 3.43 L, 3.29 R (P=0.13); median mRS was 4 for both L and R. Independent outcome (mRS 0 to 2) was recorded for 271 (33.6%) patients with left hemisphere stroke compared with 274 (34.9%) patients with right hemisphere stroke (P=0.60). Choice of definition for “good outcome” did not affect the analysis: there was no difference between hemispheres if a definition of mRS 0 to 1 was used (23.9% L, 24.2% R, P=0.91).

A statistically significant linear relationship was found between baseline NIHSS score and mRS90 for both left- and right-hemisphere patients: left hemisphere slope 0.171 (SE 0.012), intercept 0.652 (SE 0.152), P<0.001, adjusted r²=0.33; right hemisphere slope 0.214 (SE 0.012), intercept 0.692 (SE 0.152), P=0.006. The significant difference in NIHSS-mRS relationship between left and right hemispheres could not be attributed to age or NIHSS score (P=0.28).


distribution of NIHSS scores at baseline for left and right-hemisphere stroke.
0.548 (SE 0.169), \(P<0.001\), adjusted \(\bar{r}^2=0.28\). The proportion of right- and left-hemisphere patients who achieved an independent outcome at 90 days (mRS90 0 to 2) for each point on the presenting NIHSS score is shown in Figure 2A. The functional outcome of right hemisphere patients presenting at or below their median NIHSS score of 13 was similar to that of left hemisphere patients presenting at or below their median NIHSS score of 17 (figure 2).

Mortality data were available for all but one patient. There was no difference in mortality between left and right hemisphere patients: 22.1% L, 19.5% R, \(P=0.20\).

NIHSS90 was available for 1554 patients. The median NIHSS90 was 9 (mean 15.68) for left-hemisphere and 7 (mean 13.52) for right-hemisphere patients \((P=0.007)\). A “hemisphere unbiased” NIHSS90 score could be calculated for 754 patients. This score was no different between hemispheres: median 4, mean 5.00 L; median 4, mean 5.18 R \((P=0.60)\).

### Multivariable Analysis

Results of the multivariable analyses are shown in Table 2. Right hemisphere stroke appeared as an independent predictor of adverse outcome for mRS90, NIHSS90, and mortality, but inclusion of hemispheric lateralization was dependent on an interaction with baseline NIHSS, being absent from all predictive models when NIHSS was “forced” out. Hemispheric lateralization was not a predictor of outcome when ranked NIHSS scores were used. Age was an independent predictor of all 3 outcome variables. Other independent predictors of adverse outcome were: presence of diabetes and baseline systolic blood-pressure for mRS90; male gender, presence of diabetes and presence of AF for NIHSS90; and male gender and presence of AF for mortality.

### Discussion

We found no difference in overall functional outcome between patients presenting with acute right hemisphere stroke compared with left hemisphere stroke, as measured by the modified Rankin Score at 90 days. The modified Rankin score (mRS) is an outcome measure used frequently in acute stroke trials.29,30 The mRS is a measure of disability, with a focus on functional independence, ambulation, and level of assistance required. Criteria that are used to determine assignment of mRS grade include assessment of presence of symptoms, ability to carry out usual duties and activities, ability to look after own affairs without assistance, requirement of help, ability to walk without assistance, ability to attend to bodily needs without assistance, and requirement for constant nursing care and attention.31 These criteria are simple and meaningful to patients and clinicians, and the mRS is strongly associated in a graded fashion with length of institutional care and associated economic costs.29 Our finding that there is no difference in these outcomes between patients with right and left hemisphere stroke is therefore clinically important.

Previous studies directly comparing the functional outcome of patients with right-hemisphere and left-hemisphere stroke have been inconclusive.7–13,32 Studies of outcome of patients admitted to rehabilitation units rather than incident stroke patients may be subject to selection bias if patients with language deficits gain rehabilitation admission more easily.7 A tendency for patients with left hemisphere stroke to remain in rehabilitation longer may also contribute to an apparently better ADL ability measured at discharge.12 We found no association of stroke lateralization with cardiac adverse events within the first week of stroke or with

| Table 2. Multivariable Analysis of Predictors of 90-Day Outcome |
|---------------------------------|----------------|------------|----------|------------|
| Outcome Measure                  | Predictor      | B          | SE       | \(P\)       | Odds Ratio |
|---------------------------------|----------------|------------|----------|------------|
| A. mRS 90                        | Baseline NIHSS | 0.172      | 0.007    | <0.001     |            |
|                                 | Age            | 0.038      | 0.003    | <0.001     |            |
|                                 | Right hemisphere | 0.425   | 0.085    | <0.001     |            |
|                                 | Diabetes       | 0.292      | 0.102    | 0.004      |            |
|                                 | SBP            | 0.003      | 0.002    | 0.047      |            |
| B. NIHSS 90                      | Baseline NIHSS | 1.235      | 0.061    | <0.001     |            |
|                                 | Age            | 0.251      | 0.031    | <0.001     |            |
|                                 | Male gender    | 2.482      | 0.705    | <0.001     |            |
|                                 | Right hemisphere | 2.051 | 0.724    | 0.005      |            |
|                                 | Diabetes       | 1.964      | 0.866    | 0.024      |            |
|                                 | AF             | 1.874      | 0.832    | 0.024      |            |
| C. Mortality                     | Baseline NIHSS | 0.148      | 0.014    | <0.001     | 1.159      |
|                                 | Age            | 0.046      | 0.007    | <0.001     | 1.047      |
|                                 | Male gender    | 0.488      | 0.139    | <0.001     | 1.630      |
|                                 | AF             | 0.316      | 0.146    | 0.031      | 1.371      |
|                                 | Right hemisphere | 0.408 | 0.148    | 0.006      | 1.505      |

SBP indicates systolic blood pressure.
90-day mortality. Previous evidence regarding the influence of stroke lateralization on cardiovascular outcome is conflicting.\(^3\) Infarction of the right insular cortex has been associated with reduced cardiac parasympathetic innervation\(^24,25\) and more frequent and complex arrhythmia and sudden death.\(^20\) By contrast, there was a trend toward greater risk of sudden death among NASCET patients with CT evidence of left-sided brain infarcts when compared with those with right-sided infarcts after 5 years of follow-up.\(^26\) Our study, which uses data collected from patients enrolled in acute pharmaceutico-technical stroke trials, has the advantage of detailed recording of cardiovascular adverse events within the first week of stroke for a relatively large group of acute stroke patients and reliable 90-day mortality data, however long-term outcome data are lacking from the current study.

The strengths of the current study are that patients were recruited in the acute phase without bias related to hemispheric lateralization, and they were assessed prospectively with regard to overall functional outcome. However, although we have shown that functional outcome is not affected by stroke lateralization, we are not able to assess whether there may be an effect on quality of life. To our knowledge, no studies have yet adequately addressed this issue. Assessment of quality of life is complicated by inability of patients with severe dysphasia to reliably complete questionnaires for themselves.\(^34\) The opinions of relatives or carers may not necessarily be a true reflection of the patients’ own perceptions, however the magnitude of such bias is likely to be small to moderate.\(^35\) Although some evidence suggests there may not be a substantial difference in the presence and severity of emotional and cognitive changes between survivors of right- and left-hemisphere stroke overall, those with right-hemisphere stroke underestimate these changes compared with their partners’ observations.\(^36\)

Previous evidence suggests that patients with right-hemisphere stroke are less likely to be admitted to hospital, treated with TPA, or offered carotid endarterectomy compared with patients with left-hemisphere stroke.\(^1,3\) In contrast, we found no difference in the number of patients recruited with right-hemisphere stroke compared with left-hemisphere stroke in this cohort representing patients from 3 randomized trials of acute stroke therapy, nor any difference in onset to treatment time. Mild right-hemisphere stroke is under-recognized, probably because symptoms attributable to right hemisphere dysfunction may be perceived as less severe by patients, their relatives, and their physicians.\(^1,6\) Regardless of hemispheric lateralization, few patients with very mild stroke and NIHSS score <4 were included in our cohort because of restrictive entry criteria in clinical trials, and even fewer were included with cortical signs only in the absence of any motor deficit. The exclusion of some patients with either very mild or very severe stroke may limit the generalizability of our results, which does not represent the full spectrum of patients with acute stroke in the community. On the other hand, the data summarized here do represent a large cohort of patients for whom acute stroke treatments are being actively considered over a broad range of stroke severity.

Our finding that patients actually enrolled in trials of acute stroke therapies are not routinely excluded because of hemispheric lateralization of stroke is reassuring. The difference in baseline NIHSS recorded for right- and left-hemisphere stroke may be explained by the structural bias inherent in the NIHSS itself. Whereas the NIHSS may award up to 7 of a possible maximum of 42 points for tests directly related to language function (orientation questions, 2 points; commands, 2 points; aphasia, 3 points), it awards only 2 points directly related to inattention/neglect.\(^4,5,37\) The “dysarthria” item has also been found to be biased toward left-hemisphere stroke.\(^5\) Imaging studies indicate that baseline NIHSS scores are higher for left-hemisphere stroke than right-hemisphere stroke when adjusted for stroke lesion volume.\(^3,5\) We calculated a “hemisphere unbiased” NIHSS score for patients for whom the scores of the individual items of the NIHSS were available by subtracting the values of the above items from the overall NIHSS score. This adjusted score was not affected by hemispheric lateralization in our cohort, suggesting that there was no true difference in underlying stroke severity at onset for patients with right- and left-hemisphere stroke. Likewise, analysis using ranked NIHSS scores showed no influence of lateralization on functional outcome or mortality.

Although there is no overall difference in outcome between patients with right- and left-hemisphere stroke, the multivariable analysis confirms that if baseline NIHSS score is to be used as a prognostic indicator, then hemispheric lateralization must also be taken into account. We found that although the strength of the association of baseline NIHSS score with outcome was similar for both hemispheres, the median baseline NIHSS score was 4 points lower for right-hemisphere patients\(^13\) compared with left-hemisphere patients.\(^17\) Despite this difference in baseline NIHSS score, the probability of favorable outcome was very similar for right- and left-hemisphere patients. As the NIHSS score is the standard assessment of neurological impairment for clinical stroke trials, established methods for analysis of outcomes which control for side of lesion should be preferred.\(^38,39\)

There was a nonsignificant trend toward a difference in Oxfordshire Clinical Stroke Project (OCSP) classification among the subset of patients for whom this classification was prospectively applied. This difference appeared to be attributable to a greater number of patients with left-hemisphere stroke than right-hemisphere stroke being classified as “total anterior circulation syndrome” (TACS). We suspect that this is also attributable to a bias in the clinical classification system, rather than any true difference among our patients. TACS is defined as patients presenting with a combination of new-onset higher cerebral dysfunction (eg, dysphasia, dyscalculia, visuospatial disorder); homonymous visual field defect; and ipsilateral motor or sensory deficit of at least 2 areas of the face, arm, and leg.\(^28\) All 3 components of this definition are required for TACS classification to be assigned. As dysphasia is more readily recognized clinically than dyscalculia or visuospatial disorder, it is likely that some patients with right-hemisphere stroke would have been classified as TACS if more detailed cognitive function testing had been routinely performed.

The only other difference between left- and right-hemisphere stroke patients at baseline was past history of myocardial infarction. We believe that this finding is most likely attributable to the effects of chance alone. Correction for this imbalance did not alter the study findings.
We conclude that there is no difference in functional outcome between patients with acute right hemisphere stroke compared with those with left hemisphere stroke. While the baseline NIHSS score is strongly associated with functional outcome for patients with both right- and left-hemisphere stroke, patients with right-hemisphere stroke are awarded lower scores and the prognostic implication of the NIHSS score is different for each hemisphere. As a result, clinicians should take care not to underestimate the rehabilitation needs of their patients with right-hemisphere stroke. Analyses of outcomes in clinical trials which adjust for baseline NIHSS scores should also adjust for stroke lateralization. Stroke lateralization does not appear to be an important predictor of cardiac adverse events within 7 days or mortality within 90 days of stroke onset.

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Disclosures
None.

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