Acute right insular ischaemic lesions and poststroke left ventricular dysfunction

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ABSTRACT

Introduction Myocardial injury related to acute ischaemic stroke is common even without primary cardiac disease. We intended to determine associations between values of left ventricular ejection fraction (LVEF) and ischaemic stroke lesion sites.

Methods Of a local database, patients with acute first-ever ischaemic stroke confirmed by brain imaging but without pre-existing heart disease were included. The cardiac morphology and LVEF were obtained from transthoracic or transesophageal echocardiography, and impaired LVEF was categorised as mild (35%–50%), moderate (34%–25%) and severe (<25%). Patient age, stroke severity, ischaemic lesion volume, prevalence of troponin I increase (>0.1 ng/mL), atrial fibrillation and cardiac wall motion abnormalities were assessed and compared between patients with and without impaired LVEF after stroke (significance: p<0.05). A multivariate voxelwise lesion analysis correlated LVEF after stroke with sites of ischaemic lesions.

Results Of 1209 patients who had a stroke, 231 (mean age 66.3±14.0 years) met the inclusion criteria; 40 patients (17.3%) had an impaired LVEF after stroke. Patients with impaired LVEF had higher infarct volumes (53.8 mL vs 30.0 mL, p=0.042), a higher prevalence of troponin increase (17.5% vs 4.2%, p=0.006), cardiac wall motion abnormalities (42.5% vs 5.2%, p<0.001) and atrial fibrillation (60.0% vs 26.2%, p<0.001) than patients with LVEF of >50%. The multivariate voxelwise lesion analysis yielded associations between decreased LVEF and damaged voxels in the insula, amygdala and operculum of the right hemisphere.

Conclusion Our imaging analysis unvels a prominent role of the right hemispheric central autonomic network, especially of the insular cortex, in the brain–heart axis. Our results support preliminary evidence that acute ischaemic stroke in distinct brain regions of the central autonomic network may directly impair cardiac function and thus further supports the concept of a distinct stroke-heart syndrome.

INTRODUCTION

Cardiovascular complications are common after ischaemic stroke even without primary cardiac disease and comprise troponin increase,2 cardiac arrhythmia,3 4 left ventricular (LV) dysfunction4-6 and sudden cardiac death.4-7 Cardiovascular complications following an ischaemic stroke are associated with significantly worse prognosis in terms of major adverse cardiovascular events.8 Particularly impaired LV function (ie, ejection fraction (EF) <50%) after acute ischaemic stroke is a well-recognised post-stroke cardiovascular complication occurring in up to 31% of patients and contributes to poor outcome.9 These cardiac abnormalities associated with stroke are called the stroke-heart syndrome.4 6 A major pathophysiological mechanism seems to be a dysfunction of the brain–heart axis triggered by brain lesions in the master controllers of autonomic cardiovascular control.4 6 10-12

Acute lesions of brain areas involved in central autonomic control lead to autonomic imbalance with increased sympathetic tone and release of catecholamines.1 3 7-14 Catecholamines mediate toxic effects on cardiomyocytes, explaining part of the cardiac
dysfunction, that is, LV dysfunction observed among patients who had an acute stroke.\(^\text{15}\)

We hypothesised that LV dysfunction may also result from ischaemic stroke lesions within specific master controllers of the autonomic nervous system. Therefore, we assessed LV function by means of cardiac ultrasound and applied voxelwise lesion-symptom mapping (VLSM) to determine associations between the supratentorial stroke lesion site and altered LV function.\(^\text{15,16}\)

**METHODS**

For this study, consecutive patients presenting from 2006 to 2016, who received treatment for acute ischaemic stroke, that is, intravenous thrombolysis or mechanical recanalisation, were entered in a prospective database and screened. We excluded patients with following criteria: (1) pre-existing heart failure, history of myocardial infarction and valvular disease; (2) medication influencing cardiac inotropic function; (3) ultrasonographic EF not available; (4) imaging not revealing an acute ischaemic lesion or with other brain pathology; (5) presence of infratentorial stroke; and (6) pre-existing cerebral ischaemic lesions. Since the VLSM analysis is primarily validated for supratentorial infarcts, we excluded infratentorial infarcts.\(^\text{15,17}\)

Supratentorial infarctions in the vertebrobasilar vascular territory were not excluded. We included also patients with infarctions in the posterior cerebral artery territory. Hence, patients with infarctions in the hippocampus, thalamus and visual cortex were included in the VLSM analysis but only if they had no infarctions in the infratentorial areas. Patients with a significant haemorrhagic transformation of the infarct area with mass effect were excluded from the study because it would compromise the delineation and spatial normalisation process of the VLSM analysis. The left ventricular ejection fraction (LVEF) was assessed by experienced cardiologists from transthoracic or transesophageal echocardiography within 24 hours after stroke. The examination followed the recommendations of international guidelines.\(^\text{19}\)

The impairment of LVEF was categorised as mild (with an LVEF of 35%–50%), moderate (between 34% and 25%) and severe (<25%). Wall motion abnormalities including hypokinesis, dyskinesis or akinesis of the myocardium were assessed during echocardiography. Troponin I measurements at baseline were performed as a part of routine general care; increased troponin was classified as >0.1 ng/mL.\(^\text{1}\)

Figure 1  Process of lesion delineation and spatial normalisation. (A) DWI or FLAIR-weighted MR images in original space. (B) The DWI or FLAIR-weighted axial image was used to define the area of ischaemic lesions shown as a red contour and below the red lesion shape. (C) The ischaemic lesion shape and the T1-weighted MRI scans were then transformed into stereotaxic space which generated the normalised map. The normalised lesion map was also applied to the normalised T1-weighted brain to qualitatively demonstrate the accuracy of image normalisation. DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

The troponin assay used in the present study was the sensitivity assay (Siemens Healthcare) was obtained in all patients. Patients who had a CT but no MRI were only included when a CT scan was available which was acquired more than 24 hours after stroke onset and clearly showed demarcation of the ischaemic infarct. In patients who had MRI only, the ischaemic lesion was delineated on diffusion-weighted imaging sequences on MRI performed ≤4 days after stroke onset and on fluid-attenuated inversion recovery sequences on an MRI performed 4–7 days post stroke.

**Lesion analysis and spatial normalisation**

Ischaemic lesion boundaries were manually determined on anonymised axial MRI or CT scans with MRICron software.\(^\text{20}\)

The CT and MRI scans and the lesion shape were transferred into stereotaxic space.\(^\text{20}\)

We transformed the MRI-derived lesion shape and the MR images to the standardised T1 template with the MR-segment-normalise algorithm of the Clinical Toolbox. The normalised lesion map was analysed with non-parametric mapping (NPM) software.\(^\text{20}\)

The process of lesion delineation and normalisation is illustrated in figure 1.

**Statistical analysis**

We created the lesion overlap by overlaying lesion shapes of all 231 patients who fulfilled the inclusion criteria. In a first univariate voxelwise analysis, we compared patients’ continuous LVEF values voxel by voxel between patients with and without a lesion in a given voxel using t-test statistics.\(^\text{21}\)

To control for multiple comparisons, we implemented a false discovery rate (FDR) correction of q<0.01. Since increasing ischaemic lesion volume might be associated with an increased risk of afflicting brain areas that are...
strategically relevant modulators of the brain–heart axis, we calculated the ischaemic lesion volume using the NPM software. In the next step, we conducted a multivariate voxelwise logistic regression analysis adjusting associations between impaired LVEF and cerebral ischaemic lesion site for confounding variables. We, therefore, categorised our variable of interest, that is, LVEF, into normal (>50%), mild impairment (between 35% and 50%), moderate (between 34% and 25%) and severe (<25%). The binary dependent variable was whether a voxel was lesioned or not. For the multivariate voxelwise logistic regression analysis, we applied an FDR correction of q<0.05 to control for multiple comparisons. Only voxels that were lesioned in at least 5% of the patients were included in the analyses. To determine damaged brain regions, affected voxels were overlaid on the automated anatomical labelling atlas.

To further include parameters possibly contributing to stroke-related LVEF impairment, we compared age, NIHSS scores, infarct volume, prevalence of troponin increase, atrial fibrillation and cardiac wall motion abnormalities between patients with and without impairment of LVEF after stroke and used the Mann-Whitney U test or the Fisher exact test, as appropriate. We used the Shapiro-Wilk test to test for normal distribution of data. Statistical significance was assumed for p values of <0.05. For statistical calculations, we used a statistic programme (SPSS V.24.0).

RESULTS

Patient characteristics

Of 1209 patients admitted, 978 patients were excluded because of (1) history of heart failure, newly diagnosed or history of myocardial infarction, or valvular disease (304 patients); (2) medication influencing cardiac inotropic function (129 patients); (3) ultrasonographic EF not available (72 patients); (4) no detection of ischaemic lesion or other pathology in imaging (350 patients); (5) presence of infratentorial stroke (75 patients); and (6) pre-existing ischaemic lesions (48 patients). A total of 231 patients met the criteria and were included.

Median patient age was 68 years (IQR 56–77 years) and 95 (41.1%) were women. The median NIHSS score on admission was 13 (IQR 8–18). The mean blood pressure was 112.9 mm Hg (IQR 101.5–126.1 mm Hg). Fifteen patients (6.5%) had increased troponin I of >0.1 ng/mL on admission. The median volume of ischaemic lesions was 33.1 mL (IQR 7.9–106.1 mL). Forty patients (17.3%) had newly diagnosed impaired LVEF after stroke (LVEF <50%). Table 1 illustrates baseline clinical parameters of the patients with and without LVEF impairment after stroke.

Patients with reduced LVEF had wall motion abnormalities in 17 cases (42.5%) vs 10 cases (5.2%) (p<0.001). Patients with reduced LVEF had a higher ischaemic lesion volume, a higher prevalence of troponin increase of >0.1 ng/mL and atrial fibrillation than patients with LVEF of ≥50% (p<0.05). Four of the 40 patients (10.0%) with deteriorated EF had severely reduced EF of <25%. Three patients (7.5%) had moderately reduced EF (25%–34%), and 33 patients (82.5%) had slightly reduced EF (35%–50%). In 95 patients (41.1%), MRI was used, and in 136 patients (58.9%), CT scans were used. Figure 2 comprises the lesion distribution and lesion overlap of all patients (with a threshold with inclusion of voxels lesioned in at least 5% of the patients).

Voxel-based lesion symptom mapping

Figure 3A points out brain regions where lesioned voxels were associated with LVEF impairment after stroke as a continuous variable. Overall correlations between continuous LVEF and ischaemic lesions were detected in 6626

| Table 1 | Demographic and clinical characteristics of the patients who had an ischaemic stroke with and without decreased LVEF after stroke |
|-----------------|-------------------------|-------------------------|-----------------------|
| Parameter        | Decreased EF (n=40) | Normal EF (n=191) | P value  |
| Age (years), median (IQR) | 71.5 (58.3–79.8) | 67 (55–76) | n.s.* |
| M/F              | 25/15                  | 111/80                | n.s.†    |
| NIHSS score, median (IQR) | 13 (10.0–19.5) | 14 (7.0–18.0) | n.s.†    |
| MBP on admission (mm Hg), median (IQR) | 108.7 (96.5–117.3) | 113.5 (101.7–126.5) | n.s.*    |
| LVEF, n (%)       | 45 (40–50)            | 60 (55–60)           | <0.001*  |
| Troponin I >0.1 ng/mL, n (%) | 7 (17.5) | 8 (4.2) | 0.005†    |
| Wall motion abnormalities, n (%) | 17 (42.5) | 10 (5.2) | <0.001†    |
| Atrial fibrillation, n (%) | 24 (60.0) | 50 (26.2) | <0.001†    |
| Infarct volume (mL), median (IQR) | 53.8 (16.8–147.6) | 30.0 (6.4–104.7) | 0.042*    |

* Mann–Whitney U test.  † Fisher’s exact test.
EF, ejection fraction; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; M/F, male-to-female ratio; NIHSS, National Institutes of Health Stroke Scale; n.s., not significant.
Figure 2  Overlap and distribution of ischaemic stroke lesions of all 231 patients thresholded to include only voxels that were lesioned in at least 5% of the patients. The number of overlapping lesions is illustrated by different colours coding increasing frequencies from dark red to yellow. Regions with higher lesion overlap counts are found in the insular and adjacent opercular regions. Montreal Neurological Institute) coordinates of axial, coronal and sagittal sections are given. L, left hemisphere; N, number of individuals with a lesion in a given voxel; R, right hemisphere.

Figure 3  Results of the voxelwise univariate and multivariate logistic regression analysis showing lesion sites associated with impaired LVEF after stroke. (A) Results of the voxelwise t-test statistics comparing the continuous LVEF parameter between patients who had a stroke with and without lesions in a given voxel. Lesioned voxels in the right insula, amygdala and hippocampus were most prominently associated with decreased LVEF after stroke. An FDR correction of q<0.01 was applied (z-score=3.7). (B) Results of the voxelwise logistic regression analysis comparing LVEF as a categorical parameter adjusted between patients who had a stroke with and without lesions in a given voxel (adjusted for lesion volume and atrial fibrillation). Lesioned voxels in the right insula, adjacent amygdala and hippocampus remained associated with LVEF deterioration after stroke. The independent variable of interest, LVEF, was categorised as normal (>50%), mild impairment (between 35% and 50%), moderate (between 34% and 25%) and severe (<25%). The regressors were ischaemic lesion volume and whether the patient had atrial fibrillation or not. An FDR correction of q<0.05 was applied (z-score=3.3). Only voxels that were damaged in at least 5% were included in the analysis. FDR, false discovery rate; L, left hemisphere; LVEF, left ventricular ejection fraction; R, right hemisphere; z, z-score.

voxels; 4664 voxels were situated in the cortex and 1662 voxels in the subcortex. Decreased LVEF correlated with ischaemic right hemispheric lesions in the posterior insula, hippocampus, parahippocampal gyrus, amygdala, fusiform gyrus, temporal pole and temporal opercular region. The peak z-scores predicting decreased LVEF were found in the right insula (z-score=5.2; peak coordinates x=39, y=−4, z=−9), in the right hippocampus (z-score=5.9; peak coordinates x=37, y=−13, z=−17), right amygdala (z-score=5.2; peak coordinates x=32, y=−2, z=−19) and right fusiform gyrus (z-score=5.3; peak coordinates x=39, y=−16, z=−19). The multivariate logistic regression analysis adjusted for ischaemic lesion volume and atrial fibrillation yielded similar lesion sites, especially in the right hemispheric insular, amygdala, hippocampus, and adjacent opercular areas to be associated with deterioration of LVEF after stroke (figure 3B). The peak z-scores predicting decreased LVEF were found in the right insula (z-score=4.9; peak coordinates x=39, y=−4, z=−9), the right hippocampus (z-score=4.6; peak coordinates x=37, y=−13, z=−17), the right amygdala (z-score=4.0; peak coordinates x=32, y=−2, z=−19), the right fusiform gyrus (z-score=4.3; peak coordinates x=39, y=−16, z=−19) and the right superior temporal gyrus (z-score=4.2; peak coordinates x=43, y=−6, z=−8).

DISCUSSION

Our VLSM analysis demonstrates associations between poststroke impaired LVEF and ischaemic lesions most prominently in the right posterior insular, amygdala and adjacent opercular region. To isolate the effect of ischaemic strokes on LV dysfunction, we excluded patients who had a prior stroke, patients with acute or pre-existing chronic myocardial infarction, as well as patients with a history of heart failure or valvular disease, and patients on drugs influencing LV function, such as calcium antagonists or catecholamines. The association between stroke-related LV dysfunction and right hemispheric ischaemic lesions remained robust even after adjustment for confounding variables, that is, atrial fibrillation and ischaemic lesion volume.

While impaired LV function (ie, EF <50%) after acute ischaemic stroke, a cardiovascular complication occurring in up to 31% of patients, contributes to poor outcome,6 9 systematic imaging studies evaluating the impact of lesion-location on cardiac LV function are lacking. Two previous lesion studies linked myocardial damage as evidenced by increased serum troponin to ischaemic stroke in the right insular region.12 Using VLSM, Krause et al12 showed associations between increased levels of cardiac troponin and ischaemic stroke lesions in the right dorsal anterior insular cortex. The authors concluded that lesions in this structure contributed to a shift towards increased sympathetic output, myocardial injury and cardiac troponin elevation.2 To the best of our knowledge, our VLSM study is the first that assessed associations between LVEF after...
stroke and the ischaemic lesion site in a large well-defined patient cohort with first-ever ischaemic strokes.

Our findings affirm the importance of the insular cortex as a master controller of the brain–heart axis. The insular cortex integrates visceral arousal states via organotopic viscerosensory representation to ensure proper cardiovascular autonomic control. Cardiac afferent feedback, that is, afferent visceral information from the myocardium and baroreceptors, allows the cardiovascular system to adjust autonomic output. Signals are conveyed to brainstem areas and relayed via the thalamus to the posterior insular cortex and processed in the mid- and anterior insular cortex. Evidence from previous research showed a hemispherical specialisation of the cerebral representation of autonomic cardiovascular arousal with a right hemispheric dominance of sympathetically mediated modulation and the left hemisphere being primarily involved in parasympathetic modulation.

Even within insular subcomponents, there are differential effects of cardiovascular autonomic modulation. Insular cortex stimulation in animals and humans showed different representations of sympathetically mediated cardiovascular modulation. The anterior subcomponent of the right insula seems to exert the most impact on sympathetic parameters. Lesion research in rats showed lesions set in the cortex of the insula induced cardiovascular autonomic imbalance, depending on the lesion side and site. In this study, Zhang et al. demonstrated an enhanced sympathetic output after damage applied to the right posterior insular cortex. Butcher and Cechetto draw the conclusion that the right posterior insula has sympathoinhibitory control on the predominantly sympathoexcitatory right hemispheric central autonomic network. Thus, lesions in the right posterior insula, as seen in our study, may lead to loss of sympathoinhibitory control with consecutive sympathetic disinhibition as a possible mechanism for catecholamin-related myocardial toxicity, explaining in part the impairment of LVEF after stroke. In humans, several studies confirmed associations between right hemiplegic insular lesions and autonomic dysfunction with sympathoexcitatory effects, hyperglycaemia and myocardial damage. Notably, Krause et al. found that lesions in the right anterior, not posterior, insula are associated with rise in troponin levels after stroke. We assume that ischaemic lesions in the more posterior insular region might have more impact on decreasing LVEF, as found in our study, while ischaemic lesions in the more anterior portion of the right insular might have more effect on troponin increase.

Moreover, our VLSM analysis yielded associations between decreased LVEF and lesions in the amygdala, hippocampus and temporal pole, areas that are functionally closely linked to the insular cortex and known to be critically involved in cardiovascular sympathetic control.

Patients with decreased LVEF after stroke had higher prevalence of troponin increase (≥0.1 ng/mL) and cardiac wall motion abnormalities on cardiac ultrasound, known as common phenomena of the stroke-heart syndrome pathology even in the absence of primary cardiac disease. Furthermore, patients with reduced LVEF had higher prevalence of atrial fibrillation (60.0% vs 26.2%), which has also been reported in association with ischaemic stroke especially in the right hemispheric central autonomic network.

Limitations
Although we defined strict inclusion and exclusion criteria, we cannot definitely rule out that single patients had impaired LVEF before the study. Hence, our results demonstrate correlations between decreased LVEF and ischaemic stroke lesions, yet we cannot conclude that LVEF is decreased as a result of the stroke. Since no specific measure of autonomic function or catecholamine metabolism was performed, it remains speculative whether autonomic tone or higher catecholamine levels mediated the observations. The use of both CT and MRI may have biased our results, as CT may underestimate the extent of stroke lesions. We believe that this effect is negligible. One can postulate that cerebral infarct volume may be the major force in stroke-related LV dysfunction. However, our VLSM results clearly remained stable even after regressing out ischaemic lesion volume.

CONCLUSION
In conclusion, our results show an association between decreased LVEF and acute lesions in the right hemispheric insula, amygdala, hippocampus and opercular region. Our findings support preliminary evidence that acute ischaemic stroke in these distinct brain regions may directly impair cardiac function and, thus, further support the concept of a distinct stroke-heart syndrome. The results of the present study have a significant impact on clinical implications. Since patients with right-sided ischaemic stroke lesions had significantly higher probability for cardiac dysfunction, that is, impaired pump function, cardiac arrhythmia and myocardial damage, we recommend that patients with lesions in these regions should be monitored closely for cardiac dysfunction.

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REFERENCES